in the ultracentrifuge,[8,41] as are polysaccharides generally.

With respect to immunological homogeneity it has been established by several investigators that proteins which are non-homogeneous in the ultracentrifuge,[42] electrophoretically[43] and in amino acid composition[31] may be immunochemically uniform.

The relationship of amino acid composition to specificity among the blood group substances is not clear from the data presented. Work on the inhibition by oligosaccharides of the precipitation of blood group substances with specific antibody suggests that the carbohydrate presents binding sites for the immunological reaction.[44] In view of the general similarity of amino acid composition, it is possible that the amino acids function to maintain the structure of the blood group substances.[45] This assumes that the samples are molecularly homogeneous. Because of the differences in amino acid composition among samples belonging to the same group, it is more likely that at least a part of the amino acids found are remnants of enzymatic digestion and play no role in specificity. A less appealing possibility is that a variety of protein–carbohydrate molecules are identically specific as blood group substances. The isolated samples would thus be molecules having a variety of compositions. Further elucidation of the function of the amino acids in blood group substances will have to await the preparation of more uniform materials or a demonstration of their inherent heterogeneity.

(41) R. A. Kekwick, *Biochem. J.*, **46**, 438 (1950).

(42) E. A. Kabat and J. P. Murray, *J. Biol. Chem.*, **182**, 251 (1950).

(43) B. V. Jager, E. L. Smith, M. Nickerson and D. M. Brown, *ibid.*, **176**, 1177 (1948).

(44) E. A. Kabat and S. Leskowitz, THIS JOURNAL, **77**, 5159 (1955).

(45) W. T. J. Morgan, First Macy Conference on "Polysaccharides in Biology," April 27–29, 1955.

NEW YORK 32, N. Y.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES AND THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

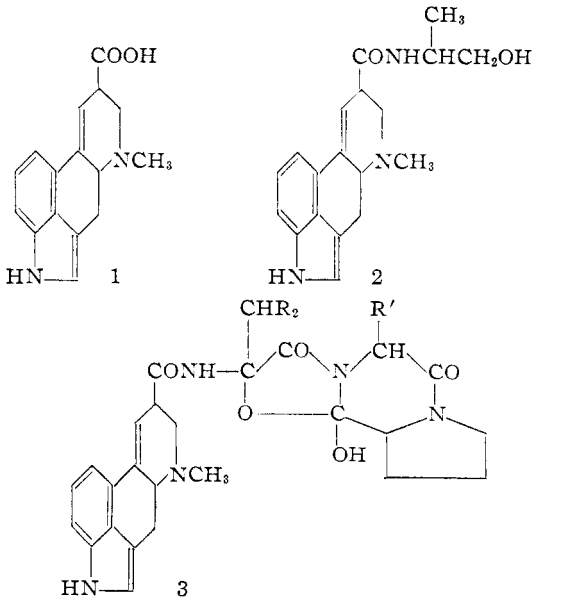
The Total Synthesis of Lysergic Acid

BY EDMUND C. KORNFELD, E. J. FORNEFELD, G. BRUCE KLINE, MARJORIE J. MANN, DWIGHT E. MORRISON, REUBEN G. JONES AND R. B. WOODWARD[1]

RECEIVED DECEMBER 24, 1955

Lysergic acid, the basic fragment derived from the ergot alkaloids, has been synthesized in a fifteen-stage sequence beginning with 3β-carboxyethylindole. The starting material was converted to the intermediate 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (4), containing three of the four rings present in lysergic acid. This ketone in turn was transformed into the tetracyclic compound, 9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4.3-*fe*]quinoline (69), and thence to lysergic acid. The synthetic acid was converted to *dl*-isolysergic acid hydrazide which had previously been resolved and converted to ergonovine. The present work, therefore, completes also the synthesis of this ergot alkaloid.

The striking physiological properties of ergot early directed attention to this remarkable product of the growth of the fungus *Claviceps purpurea* on rye grain. Pre-Christian allusions to its effects have been recorded, and it was identified in 1676 as the causative agent of the dreaded medieval gangrenous scourge, St. Anthony's Fire. The therapeutic powers of ergot were likewise recognized during the middle ages. Its capacity to induce uterine contractions was recorded as early as 1582, and crude preparations were introduced into orthodox medicine early in the nineteenth century.[2] However, its present important position in medical practice was made possible only by the extensive researches of the past forty years on the isolation and characterization of the pure active principles. These elegant investigations, in which Arthur Stoll has played a dominant role,[3] have led to the isolation of no less than six related bases all of which have been shown to be amides of the same key substance, lysergic acid (1).[4] Of the natural bases, ergonovine (2) is a particularly simple representative; the others—ergotamine (3, R = H; R′ = —CH_2-



(1) Harvard University; other authors, The Lilly Research Laboratories.

(2) G. Barger, "Ergot and Ergotism," Gurney and Jackson, London, 1931.

(3) A. Stoll, *Chem. Revs.*, **47**, 197 (1950).

(4) W. Jacobs and L. Craig isolated lysergic acid [*J. Biol. Chem.*, **104**, 547 (1934) and **106**, 393 (1934)] and deserve the major credit for the determination of its structure. Their deductions were incomplete only in respect to the placing of one double bond, and stereochemical points. These final details were established by Stoll [A. Stoll, A. Hofmann and F. Troxler, *Helv. Chim. Acta*, **32**, 506 (1949); A. Stoll, Th. Petrzilka, J. Rutschman A. Hofmann and Hs. Günthard, *ibid.*, **37**, 2039 (1954)]. A compre ısive account of the structural work is given in a review by A. Glenn *uart. Revs.*, **8**, 192 (1954)].

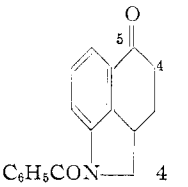
Ph), ergosine (3, R = H; R′ = —CH_2CHMe_2), ergocristine (3, R = Me; R′ = —CH_2Ph), ergokryptine (3, R = Me; R′ = —CH_2CHMe_2), ergocornine (3, R = Me; R′ = Pr^{β})—terminate in common in an unusual polypeptide array.[5]

Widespread interest in the synthesis of lysergic acid was stimulated even before the structural issues were resolved in 1949. This attention was evoked by the unique polycyclic system present in the acid and by the medical applications of the derived natural bases. The synthesis of dihydrolysergic acid by Uhle and Jacobs[6] was the first major accomplishment in the synthetic studies, and this was followed by a number of attempts[7] directed at lysergic acid itself. More recently, interest in the synthesis has been heightened by the discovery of the startling capacity of the corresponding diethylamide (LSD) to induce abnormal psychic states.[8] In this communication we describe the synthesis of lysergic acid.[9]

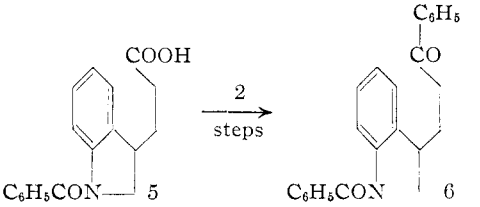
The presence within the lysergic acid skeleton of a β-substituted indole system and the ready availability of simple β-substituted indoles suggested such compounds as starting materials for synthetic work. However, the very high reactivity of the hetero-ring of indole compounds seemed incompatible with further extensive synthetic operations. Moreover, we were aware of the possibility that many tricyclic indole intermediates (*viz.* various benz[*cd*]indoles) would be susceptible to ready and irreversible isomerization to the more stable naphthalenoid isomers.[10]

In order to circumvent such problems we adopted at the very outset the artifice of using dihydroindole derivatives.

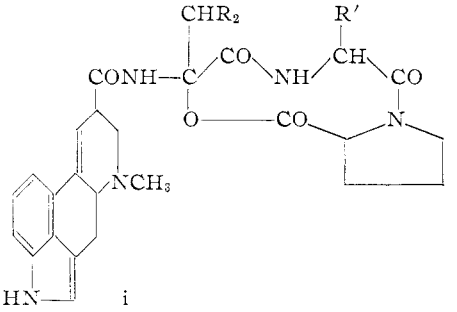
Synthesis of the Tricyclic Ketone (4).—N-



Benzoyl-3-(β-carboxyethyl)-dihydroindole (5)[11] was converted by thionyl chloride in ether solution to the corresponding acid chloride, and thence directly, by the action of aluminum chloride in carbon disulfide or ethylene dichloride, to the ketone 4. It is of some interest that when the Friedel–Crafts reaction was carried out in benzene solution, the sole product was the phenyl ketone 6. Attempts to effect direct cyclization of the acid 5 to 4 with sulfuric acid or hydrogen fluoride were unsuccessful; with polyphosphoric acid only a very small conversion was obtained. In another attempt to obtain useful tricyclic intermediates the oxalyl



(5) This structure, which was deduced by Stoll on the basis of extensive and thorough reductive studies [A. Stoll, Th. Petrzilka and B. Becker, *Helv. Chim. Acta*, **33**, 57 (1950); A. Stoll and A. Hofmann, *ibid.*, **33**, 1705 (1950); A. Stoll, A. Hofmann and Th. Petrzilka, *ibid.*, **34**, 1544, (1951)], is unusual in that it represents the alkaloids as *ortho* amide derivatives *containing a free hydroxyl group*. No other authentic members of this class are known, and it may be questioned whether factors are present in these molecules which would confer on the *ortho* amide structures stability *vis-a-vis* the ring chain tautomeric isomers (i). It is of interest that the large-ring lactone structure (i),



earlier considered favorably by Stoll was first suggested by Barger as long ago as 1938 (Barger, "Handbuch der experimentellen Pharmakologie," suppl. Vol. VI, 1938, pp. 84, 221). Attention may be directed here to the presence of large lactone rings in a number of other metabolic products of microörganisms [enneatin A and B: Pl. A. Plattner and V. Nager, *Helv. Chim. Acta*, **31**, 2192 (1948); picromycin: H. Brockmann and R. Oster, *Naturwissenshaften*, **42**, 155 (1955); erythromycin: P. Wiley, K. Gerzon, E. Flynn, M. Sigal and U. Quarck, THIS JOURNAL, **77**, 3677 (1955); magnamycin: unpublished observations by R. B. W.]

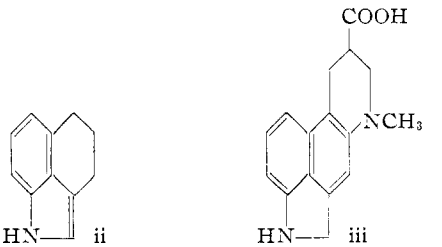
(6) F. Uhle and W. Jacobs, *J. Org. Chem.*, **10**, 76 (1945).

(7) (a) F. Uhle, THIS JOURNAL, **71**, 761 (1949); **73**, 2402 (1951); (b) A. Stoll and J. Rutschmann, *Helv. Chim. Acta*, **33**, 67 (1950); **34**, 382 (1951); (c) A. Stoll, Th. Petrzilka and J. Rutschmann, *ibid.*, **33**, 2254 (1950); (d) A. Stoll and Th. Petrzilka, *ibid.*, **36**, 1125 (1953); (e) F. Atherton, F. Bergel, A. Cohen, B. Heath-Brown and A. Rees, *Chemistry & Industry*, 1151 (1953); (f) C. Grob and co-workers, *Helv. Chim. Acta*, **33**, 1796 (1950); **33**, 1955 (1950); **35**, 2095 (1952); **36**, 839 (1953); (g) H. Plieninger and co-workers, *Ber.*, **86**, 25 (1953); **86**, 404 (1953); **87**, 228 (1954); **87**, 882 (1954); **88**, 370 (1955); **88**, 550 (1955); (h) E. Hardegger and co-workers, *Helv. Chim. Acta*, **38**, 463 (1955); **38**, 468 (1955); (i) J. Barltrop and D. Taylor, *J. Chem. Soc.*, 3399 (1954); 3403 (1954); (j) P. Julian and H. Printy, THIS JOURNAL, **75**, 5301 (1953); (k) A. Berrie, G. Newbold and F. Spring, *J. Chem. Soc.*, 2042 (1952); (i) A. Glenn, "Synthetic compounds structurally related to the ergot alkaloids," Ph.D. Thesis, London, 1951.

(8) W. A. Stoll, *Schweiz. Arch. Neurol. Psychiat.*, **60**, 279 (1947).

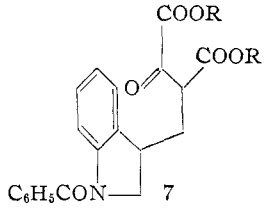
(9) Preliminary communication: E. Kornfeld, E. Fornefeld, G. B. Kline, M. Mann, R. G. Jones and R. Woodward, THIS JOURNAL, **76**, 5256 (1954).

(10) We considered that this possibility would apply generally to any intermediate containing the tricyclic system (ii), and *one additional double bond*. Our presumption of the greater stability of the naphthalenoid isomers was based on the fact that the resonance energy of naphthalene is much greater than that of indole [L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1942]. It has been amply justified by subsequent events. Thus, lysergic acid itself falls into the above category, and has recently been found to suffer ready irreversible isomerization to iii in the presence of acids (ref. 7d). Furthermore, at least two attempts by other groups (ref. 7d and 7e) to synthesize lysergic acid were based apparently on the opposite presumption, *i.e.* isomerization of iii to 1, but such an isomerization could not be effected after iii had been obtained by synthesis.

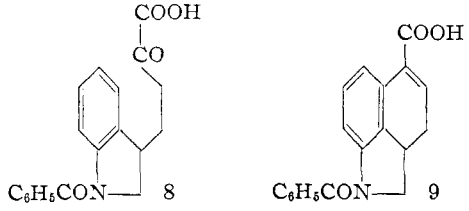


(11) B. Blount and R. Robinson, *J. Chem. Soc.*, 3158 (1931). In our hands, the hydrogenation of 3-(β-carboxyethyl)-indole proceeded most smoothly using Raney nickel in aqueous solution.

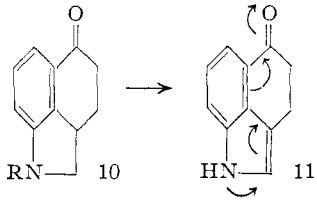
derivatives (7, R = Me or Et) were prepared by condensation of the appropriate oxalic ester with

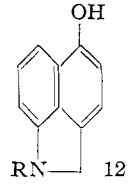


the corresponding ester of 5 in the presence of alkoxides. When these esters were heated with 80% sulfuric acid, hydrolysis and decarboxylation occurred smoothly, with the formation of the α-keto acid 8, but no cyclization to a dihydronaphthalene (*cf.* 9) was observed.[12]



The tricyclic ketone 4 was hydrolyzed readily by aqueous hydrochloric acid to the free base (10, R = H), which was dehydrogenated by palladium–charcoal in *p*-cymene to the known 5-keto-1,3,4,5-tetrahydrobenz[*cd*]indole (11).[7a,f] On the other hand, 4 itself, and the corresponding N-acetyl ketone (10, R = Ac), which was prepared either by acetylation of 10 (R = H), or by aluminum chloride-catalyzed cyclization of the chloride of N-acetyl-3-(β-carboxyethyl)-dihydroindole, were dehydrogenated under similar conditions to the naphthalenoid compounds (12, R = Bz or Ac). The stabilization of





the naphthalene system in the N-acetylated series as a result of the suppression of interaction between the nitrogen atom and the carbonyl group in the ketonic isomers (*cf.* 11, arrows) has been commented upon by Grob.[13] These dehydrogenation studies early in the work tended to confirm the soundness of the synthetic approach based on dihydroindole derivatives. In addition they indicated that the conversion to the indole system would have to be carried out using compounds in which the nitrogen function was in the free base form.

Most of the substances described in the present work fell into one or another of several well-defined structural classes, which could be recognized readily by characteristic ultraviolet and infrared spectra, and liberal use was made of this valuable control. *The chromophoric systems present in 4 gave rise to absorption at 5.91 (ketone carbonyl) and 6.07μ (amide carbonyl) in the infrared, and at 235 and 326 mμ in the ultraviolet* (*cf.* Fig. 1).

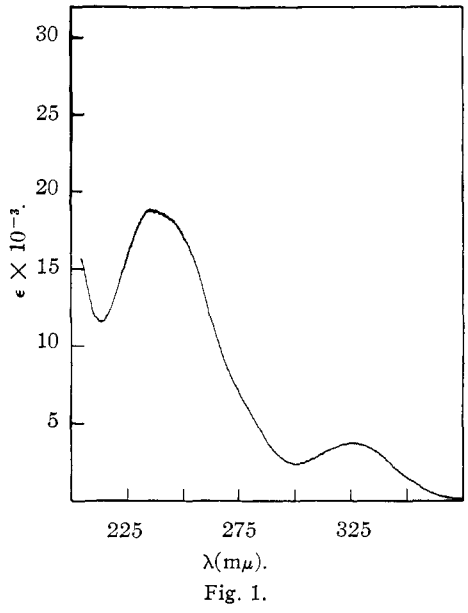
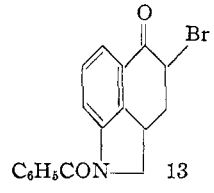


Fig. 1.

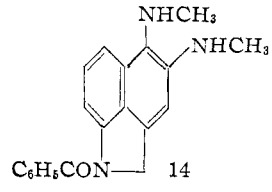
All of our subsequent synthetic experiments were based upon the tricyclic ketone 4.

Direct Introduction of Nitrogen at C.4.—The presence, in the tricyclic ketone 4, of an activated methylene group at C.4, suggested that the construction of ring D of lysergic acid might be initiated by the attachment of the requisite nitrogen atom at the reactive position.

The 4-bromo derivative 13, an obvious intermediate for such studies, was obtained in excellent



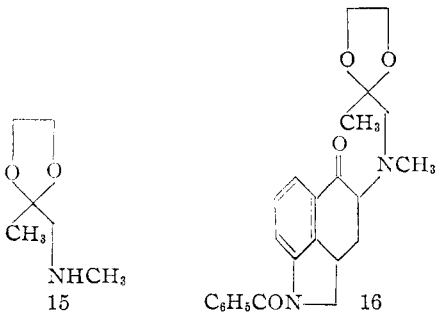
yield by bromination of the tricyclic ketone with either bromine or pyridine hydrobromide perbromide. However, early attempts to utilize this compound in the alkylation of amines were unpromising. For instance, the reaction of the bromo ketone 13 with methylamine, even at room tem-



(12) Contrast the behavior of simpler compounds of the type 7: L. Fieser and E. Hershberg, THIS JOURNAL, **58**, 2314 (1936); L. Fieser and H. Holmes, *ibid.*, **58**, 2319 (1936).

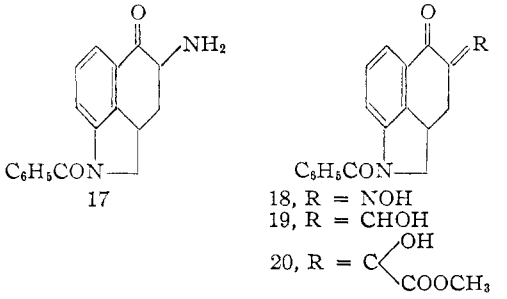
(13) C. Grob and P. Payot, *Helv. Chim. Acta*, **36**, 839 (1953).

perature, took a complicated course and led in fairly good yield to the naphthalene derivative 14. In addition, initial experiments designed to obtain the potentially useful ketal-ketone 16 by alkylation of methylaminoacetone ethylene ketal 15 were like-

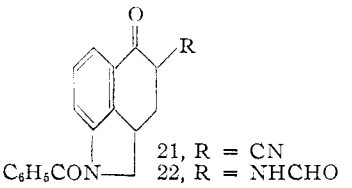


wise unsuccessful. The side chain amine 15 was obtained by reaction of methylamine with either chloro- or bromoacetone ethylene ketal.[14] Further discussion of these alkylations and of the ketal-ketone 16 will be deferred until a later section.

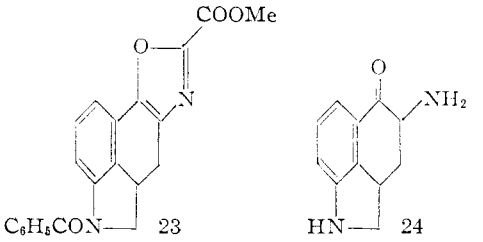
Meanwhile, much of the early effort was directed toward the synthesis of the α-amino ketone 17. The preparation of the α-oximinoketone 18 by condensation of 4 with butyl nitrite in the pres-



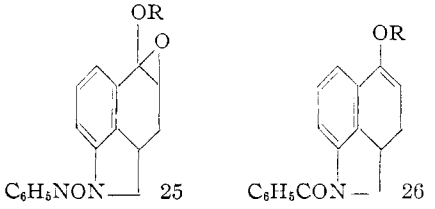
ence of potassium ethoxide proceeded smoothly, but the desired reduction of 18 could not be brought about. On the other hand, treatment of the O-toluenesulfonyl derivative of the oxime of 4 with potassium ethoxide, followed by acid, gave the desired 17, as hydrochloride, in good yield.[15] The free base, however, decomposed immediately on liberation from its salt, and in our hands was of little further synthetic utility. Another sequence of reactions which led into the 4-amino series was initiated by condensation of 4 with ethyl formate, or methyl oxalate, in the presence of sodium methoxide. These reactions afforded 19 and 20, respectively.[16] When the hydroxymethylene compound 19 was treated with hydrazoic acid in trifluoroacetic acid[17] in the presence of sulfuric acid, the major product was the cyano-ketone 21, though the desired 4-formylamino ketone 22 was formed concomitantly in low yield. Similar treatment of the



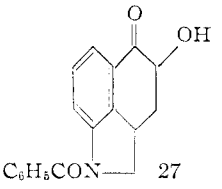
methoxalyl compound 20 gave the oxazole 23 in poor yield; the Schmidt reaction had evidently proceeded normally with subsequent cyclodehydration. Hydrolysis of either the ester 23, or the formylamino compound 22, gave the simple aminoketone 24, which like 17 was deemed too sensitive to be useful.

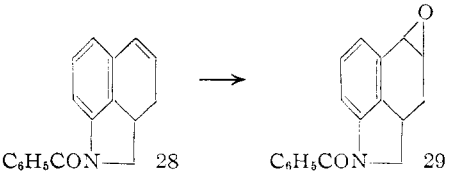


In the hope that 4-alkylamino ketones might be prepared by the action of amines on oxides of the type 25, the ketone 4 was converted into the enol acetate (26, R = Ac) and the enol ethyl ether (26. R = Et) by the action of isopropenyl acetate and



ethyl orthoformate, respectively. When these enol derivatives were treated with peracids, however, the product isolated was the hydroxyketone 27.[18]





The simpler oxide 29 was prepared, however, by peroxidation of the olefin 28. The latter in turn was prepared from 4 by reduction to the alcohol (30, R = OH) with sodium borohydride, conversion to the bromide (30, R = Br) with phosphorus tribromide, and dehydrohalogenation with collidine. The olefin 28 contains the basic chromophoric system present in many subsequent compounds; *its maxi-*

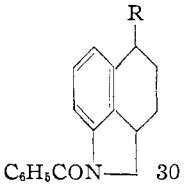
(14) M. Kuhn, *J. prakt. Chem.*, **156**, 103 (1940).

(15) The Neber reaction, of which this is an example, has been studied recently by D. Cram and M. Hatch, THIS JOURNAL, **75**, 33 and 38 (1953).

(16) Another acyl compound, the 4-acetyl derivative of **4**, was prepared by condensation of the ketone with acetic anhydride in the presence of boron fluoride etherate, but was not further investigated.

(17) It was hoped that trifluoroacetic acid would bring about the Schmidt reaction without the strong mineral acid, but no reaction set in until the latter was added.

(18) Some oxides of the type 25 have been reported [N. Leeds, D. Fukushima and T. Gallagher, THIS JOURNAL, **76**, 2943 (1954)] to be formed by the action of peracids on the enol acetates of the 17-keto-steroids.



mum absorption in the ultraviolet is at 264 mμ (Fig. 2, curve A). The corresponding saturated compound

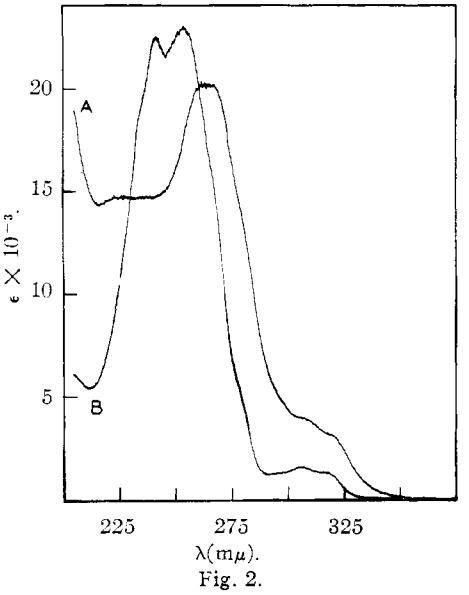
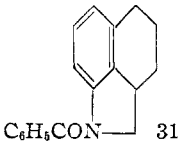
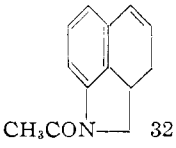


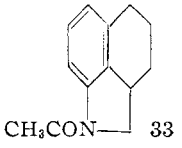
Fig. 2.

31, prepared from 28 by hydrogenation, *absorbs at 267 and 292 mμ (Fig. 3, curve A).* We further took

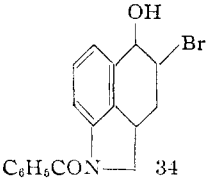


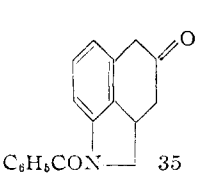
advantage of having in hand these simple compounds of known structure by replacing the N-benzoyl groups by N-acetyl functions. *The resulting amide 32 possesses bands at 241, 254, 307 and 316 mμ (Fig. 2, curve B), while the bands of the saturated analog 33 are at 213, 253, 279 and 289 mμ (Fig. 3, curve B).*





The oxide 29 was typical of its class in that it was readily converted to a bromohydrin 34 with hydrogen bromide in benzene–ether, and rearranged to the β-tetralone (35) by magnesium bromide.[19]





(19) F. Straus and A. Rohrbacher, *Ber.*, **54**, 40 (1921); M. Stoll and A. Commarmont, *Helv. Chim. Acta*, **31**, 1077 (1948).

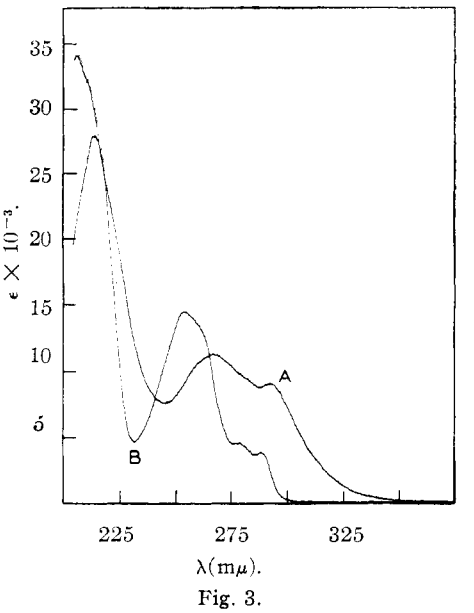
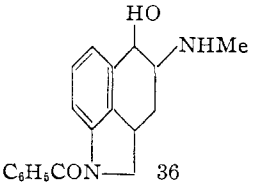
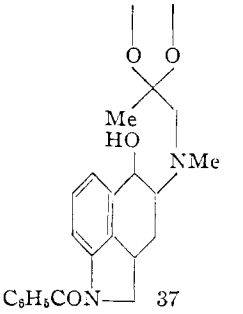
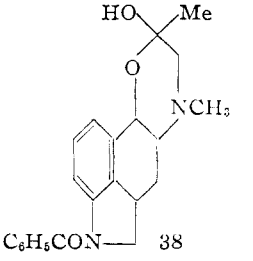


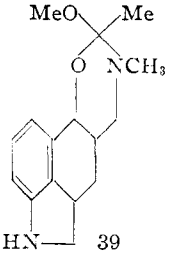
Fig. 3.

Of greater synthetic interest was the smooth reaction of 29 with amines. With methylamine at 100°, for example, the simple alkanolamine 36 was produced, while under similar conditions, methylaminoacetone ethylene ketal 15 gave the ketal alcohol 37.[20] Numerous attempts to effect the oxidation of 37 to the corresponding amino-ketone 16 were unsuccessful. Reaction of 36 with bromoacetone gave a substance which we formulate as the hemiketal 38 in view of the absence of a carbonyl band below 6 μ in its infrared spectrum, and its ready conversion to a methyl ether 39 with methanolic hydrogen chloride. The ether 39 was obtained also from 37 by treatment with hydrogen chloride in methanol. Like 37, 38 could not be oxidized to any well-defined product.





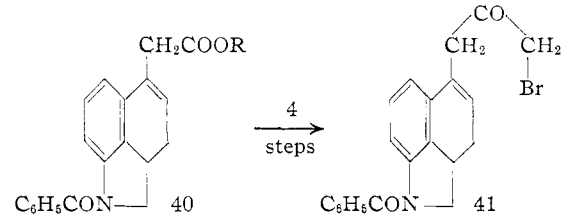




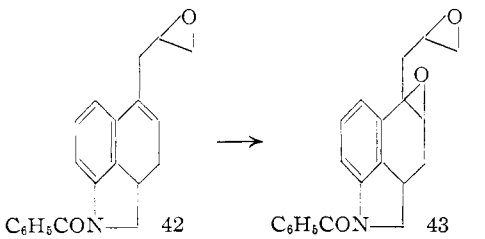
(20) No rigorous proof of the direction of opening of this oxide with amines was obtained. However, in the 5-substituted-4,5-epoxy series described below reaction with amines takes place at the 4-position.

Addition of a Carbon Chain at C.5.—An obvious alternative for building ring D of lysergic acid involved the elaboration of a carbon chain at C.5. The capacity of the carbonyl group in the tricyclic ketone 4 to undergo addition reactions was therefore utilized.

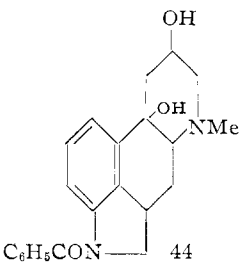
The initial attempt in that direction involved the Reformatsky reaction. When 4 was treated with methyl or ethyl bromoacetate in the presence of zinc, and the resulting crude hydroxy-ester was warmed with formic acid, the unsaturated ester (40, R = Me or Et) was obtained. The β,γ-position of the double bond in these esters was easily demonstrated by ultraviolet measurements (*vide supra*). It is of some interest that only the unconjugated isomers were isolated. The acid (40, R = H), obtained by careful alkaline hydrolysis of either ester



(40, R = Me or Et), was then converted to the bromoketone 41 in excellent yield through successive treatments with oxalyl chloride in toluene, diazomethane in methylene chloride, and aqueous hydrobromic acid. Reduction of the bromoketone with sodium borohydride furnished directly the oxide 42; clearly the medium was sufficiently basic to effect dehydrobromination of the intermediary bromohydrin. Perbenzoic acid was then used to effect addition of an oxygen atom to the isolated double bond of 42, and the dioxide 43 was obtained.



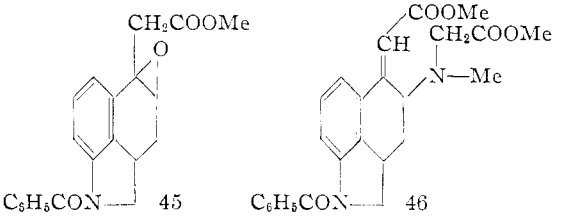
With methylamine at 100°, the latter yielded an amorphous, tertiary, tetracyclic base, characterized as the crystalline methiodide. There is little doubt that the substance possesses the structure 44, and in view of its close relation to other tetracyclic sub-



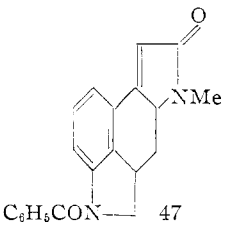
stances, described below, it seems likely that intensive further investigation should have enabled us to connect this series with our other synthetic routes. However, the low over-all yield in the conversion of 4 to 44, which may be attributed in the main to an insufficient opportunity for stereochemical control, and the availability of superior paths, led us not to make the effort.

Another attempt to utilize the Reformatsky ester (40, R = Me) foundered early on a point of sufficient interest to merit description.

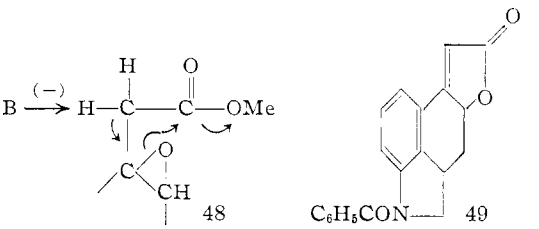
Conversion to the corresponding oxide 45 was easily effected by monoperphthalic acid. We hoped that 45 would yield the diester 46 on treatment with sarcosine methyl ester and were encouraged by the



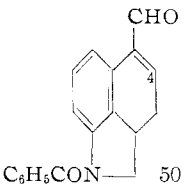
observation that methylamine at 100° gave the lactam 47. However, the changes depicted in (48,



arrows) occurred so readily in the experiment with sarcosine ester that the lactone 49 was the sole product.

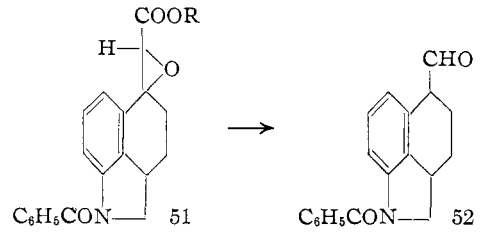


The Unsaturated Aldehyde 50.—The unsaturated



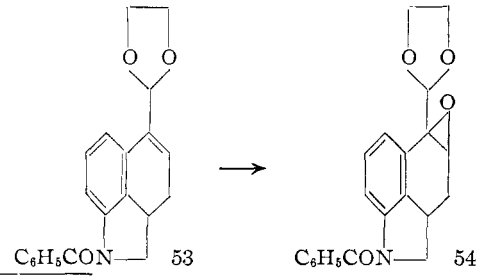
aldehyde 50 containing as it does a very reactive carbonyl group, and a point of entry for the introduction of substituents at C.4, occupied a central position in many schemes for the elaboration of ring D. Furthermore, it was found to be readily preparable from the tricyclic ketone 4, through the corresponding glycidic ester (51, R = Et) obtained from the ketone by treatment with ethyl chloroacetate in the presence of potassium *t*-butoxide.[21] The ester was smoothly hydrolyzed to the sodium salt (51, R = Na), which was converted to the saturated aldehyde 52 with mineral acids, or

(21) W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt have independently discovered the superiority of this catalyst in the Darzens reaction [THIS JOURNAL, **75**, 4995 (1953)].

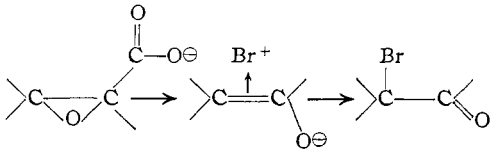


directly to derivatives of that compound with appropriate carbonyl reagents. Our major interest in the sodium salt, however, was excited by the observation that it gave the semicarbazone of 50 simply and in high yield when it was treated successively, *in acetonitrile solution, with pyridine hydrobromide perbromide and semicarbazide.*[22] The free aldehyde 50 was readily obtained from the derivative by exchange of the semicarbazide residue to pyruvic acid.[23]

The synthetic opportunities presented by the unsaturated aldehyde were exploited, *inter alia*, in at least three directions[24]: i. With ethylene glycol and toluenesulfonic acid, the aldehyde was converted to the ethylene acetal 53, which was smoothly oxidized by perbenzoic acid to the oxide 54. The latter reacted with methylamine at 120°



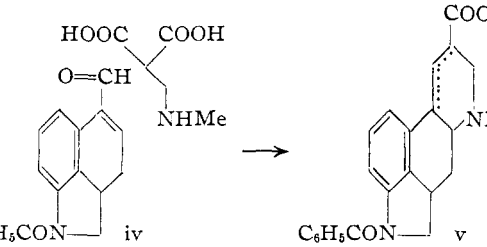
(22) So far as we are aware, there are no previous instances of this reaction sequence, in which advantage is taken of the intermediacy of an enolate in the decarboxylation of glycidates:



The dehydrobromination, induced by semicarbazide, follows well-explored paths [W. McGuckin and E. Kendall, THIS JOURNAL, **74**, 5811 (1952)].

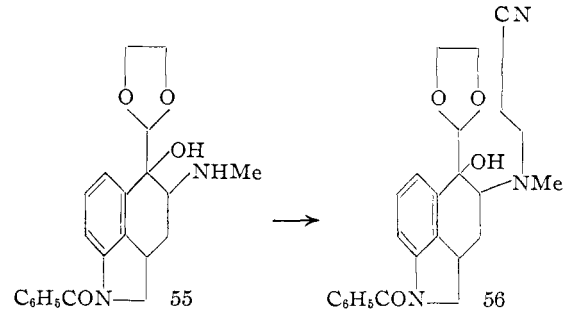
(23) E. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(24) We contemplated the possibility of constructing the desired system in a single step, using the aldehyde 50 in a "quasi-physiological" reaction with methylaminomethylmalonic acid (*cf.* iv → v) or suitable

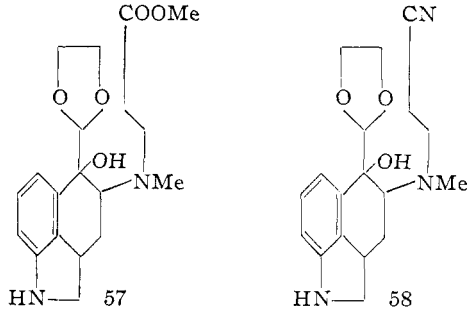


components for, or equivalents of that substance. However, a number of attempts to reduce this conception to practice were uneventful. Indeed, the aldehyde was uniformly disappointing in all reactions with simple amines or with active methylene compounds; in the former case, prior reaction at the aldehyde group, rather than at C.4, seemed to be the rule and, in all cases, dehydrogenation (or disproportionation) with formation of naphthalene derivatives was a complicating factor.

to give the base 55, which in turn combined readily with acrylonitrile to give 56. It will not be difficult to imagine the uses to which we wished to put the nitrile 56; but the recalcitrance of the acetal function stood in the way of all of them. With

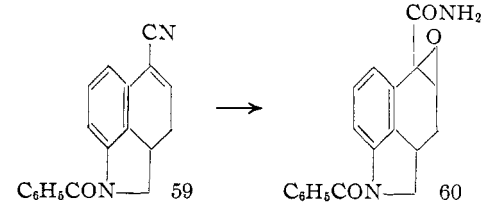


methanolic hydrogen chloride, for example, the ester 57 was formed, while 6 *N* hydrochloric acid gave 58; hot 90% acetic acid removed the β-cyanoethyl chain, and gave the familiar 55. Attempts to re-



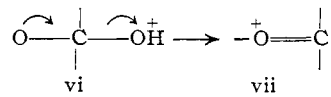
move the offending function by more brutal means led only to deep-seated changes of no utility.[25]

ii. The unsaturated nitrile 59 was easily obtained from the aldehyde 50, through treatment of the corresponding oxime with thionyl chloride. Conversion of the 4,5-double bond to an oxide function, by means of alkaline hydrogen peroxide, was



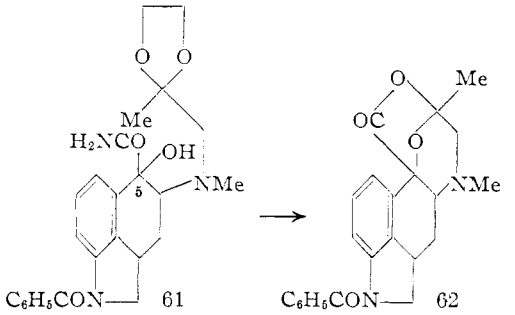
accompanied by hydration of the nitrile group, and the epoxyamide 60 was obtained in substantially quantitative yield. Like other 4,5-oxides, 60 was susceptible to attack by amines; with methylamino-

(25) Other instances are available of the difficulty of hydrolyzing acetals and ketals neighbored by a basic nitrogen atom [R. Moggridge and A. Neuberger, *J. Chem. Soc.*, 745 (1938); C. Grob and H. Utzinger, *Helv. Chim. Acta*, **37**, 1256 (1954)]. The basis for such behavior is reasonable: the usual easy heterolytic cleavage of the C–O bond in such substances involves the generation of a stabilized cation (*cf.* vi → vii) the formation of which is strongly suppressed by a proximate N+. In the case at hand the positive pole engendered by the presence of a hydroxyl group,



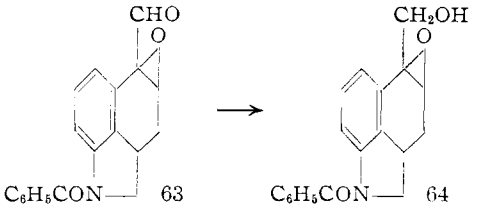
and perhaps also steric and hindrance effects, must enhance the difficulty. It will be noted, nevertheless, that an important later stage in our synthesis involves the hydrolysis of a basic ketal [*vide infra*, (16 → 68)].

acetone ethylene ketal, the base 61 was readily obtained. The remaining task in this series is the

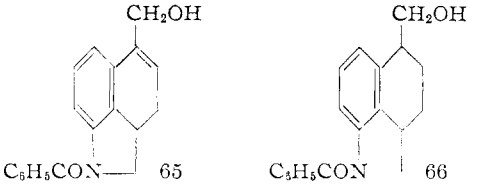


conversion of the α-hydroxyamide function to a carbonyl group. It remains undone; the most novel of the various results obtained in this effort was the formation of the pentacyclic lactone 62 when the amide was treated with red lead oxide in acetic acid, in an attempt to bring about oxidative cleavage of the group at C.5.

iii. The aldehyde 50 was converted to the epoxyalcohol 64 by either of two methods. In the first, and preferred method, alkaline hydrogen peroxide



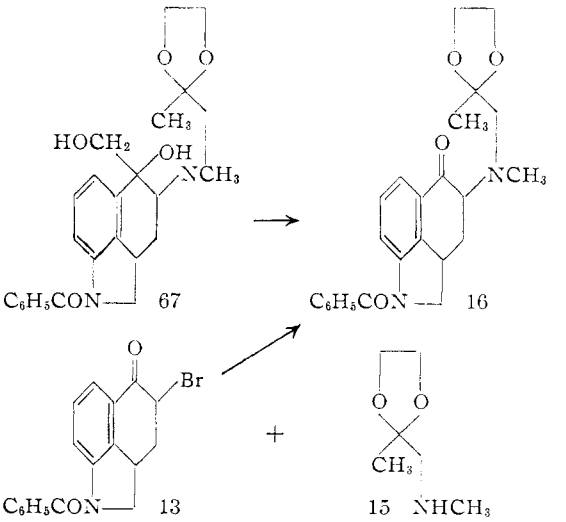
was used to convert the aldehyde to the corresponding oxide 63, which was then reduced with sodium borohydride. Alternatively, the latter reagent was used to convert 50 to the unsaturated alcohol 65, which was oxidized to 64 by perbenzoic acid. This



method suffered from the concomitant formation of a certain amount of the dihydro alcohol 66 in the reduction step. Although this difficulty was overcome by the use of Ponndorf reduction, the oxidation stage was relatively inefficient.

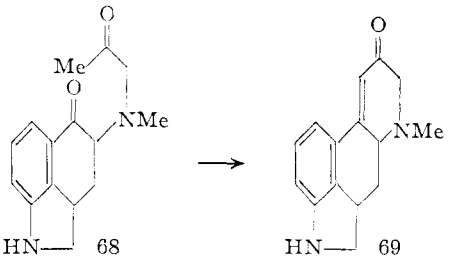
Reaction of the epoxyalcohol 64 with methylaminoacetone ethylene ketal 15 gave, although in poor yield, the desired amino glycol 67, which was very smoothly oxidized to the ketone 16 by slightly more than one mole of periodate in acid solution.

The important intermediate ketal-ketone 16 thus became available in an eleven-stage sequence from the tricyclic ketone 4. However, both the length and the inefficiency of this route led us once again to re-examine the possible *direct* preparation of 16 from the bromoketone 13. In a new series of experiments it was discovered that reaction of 13 with methylaminoacetone ethylene ketal 15 *in a nonpolar solvent* afforded the ketal-ketone 16 in excellent yield. The cumbersome earlier route, therefore, could be abandoned.



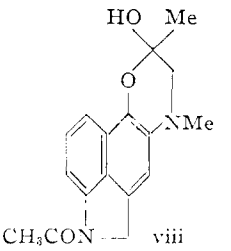
The Tetracyclic Series.—With the obtention of the ketone 16, the stage was set for entry into the tetracyclic phase of our work. Thus, it may be noted that the intermediate contains, actually or potentially, all of the functions necessary for closure of ring D, and for attachment of the lysergic acid carboxyl group as well.

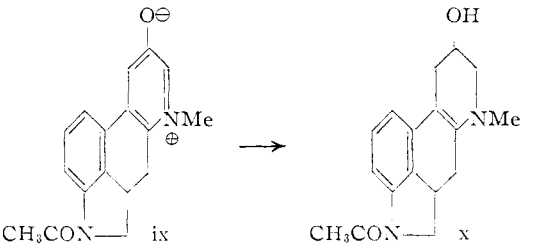
The first step was taken with the hydrolysis of 16 to the diketone 68, best effected by treatment with 6 *N* hydrochloric acid.[25] The diketone was then smoothly cyclized, by sodium methoxide in absolute

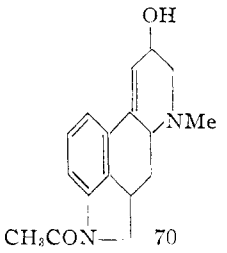


ethanol, to the tetracyclic unsaturated ketone 69, which in turn was converted to the protected unsaturated alcohol 70, by successive treatments with acetic anhydride and sodium borohydride, or *vice versa*.[26]

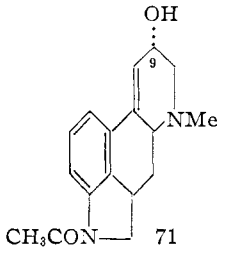
(26) It is worthy of note that the ketones of this series are susceptible to very ready aerial oxidation. Thus, in an attempt to effect the acetylation of 68 with acetic anhydride in methanol, the sole product isolated was viii. Special attention may be directed to the facile dehydrogenation of the N-acetyl derivative of the tetracyclic ketone 69 to the interesting betaine (ix), and the reduction of the latter by sodium borohydride to an unsaturated alcohol x isomeric with 70.



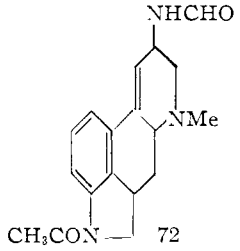


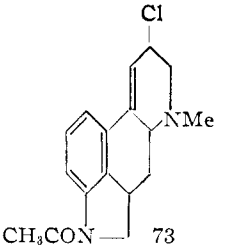


It was now necessary to replace the hydroxyl function in 70 by a carboxyl group. An initial attempt in that direction was based on the observation of Price and Krishnamurti[27] that allyl alcohol is easily and directly converted to allyl cyanide by treatment with cuprous cyanide in concentrated hydrochloric acid. However, when the allylic alcohol 70 was treated under similar conditions with the aim of exchanging –OH for –CN, it was transformed simply into the epimeric alcohol 71.[28]



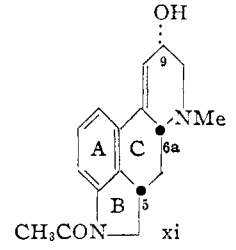
Nevertheless, the result was encouraging insofar as it suggested that carbonium ion reactions at C.9 were practicable. We next treated the alcohol 70 with liquid hydrogen cyanide in the presence of boron fluoride etherate. Perhaps not without analogy,[29] this reaction led to the very smooth production of the formylamino compound 72.





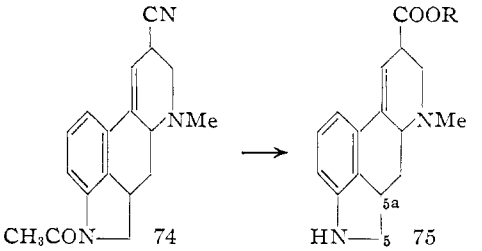
(27) C. Price and I. Krishnamurti, THIS JOURNAL, **72**, 5334 (1950).

(28) The stereochemistry implied in the formulas 70 and 71, and the complete solution, symbolized for 71 in xi, may be developed as follows: (a) The tightly fused A/B/C ring system can be constructed only with a *quasi*-axial hydrogen atom at C.5a. (b) C.6a will enjoy the stabler of the two possible orientations, *i.e.*, that containing a *quasi*-equatorial C–N bond; since opportunities for equilibration have been provided in both the tricyclic and tetracyclic classes (*cf.* 68 and 69), by the proximity of a carbonyl or a vinylogous carbonyl function. (c) Sodium borohydride reduction of carbonyl groups ordinarily leads to equatorial alcohols (*cf.* 70); furthermore, the relative basicity of 70, (pK_a, 6.02) and 71 (pK_a, 6.68) confirms our assignment, in that stabilization of the conjugate acid by hydrogen bonding is possible in the stronger base 71, but not in 70. A related case, that of quinine and epiquinine, is discussed by R. Turner and R. Woodward (R. Manske and H. Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1953, p. 32). Assignment of the configurations of the epimeric 10-hydroxydihydrodesoxycodeines was recently made in a similar fashion [H. Rapoport and S. Masamune, THIS JOURNAL, **77**, 4330 (1955)].

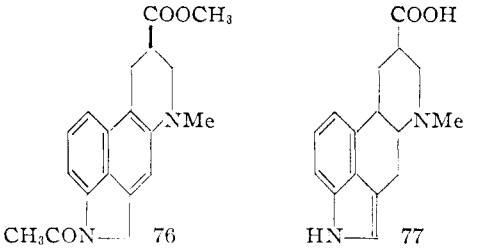


(29) J. Ritter and J. Kalish, *ibid.*, **70**, 4048 (1948).

Our attention was then directed to the preparation of the chloride 73, and after a series of experiments in a number of solvents it was found to be readily prepared as its hydrochloride, by the action of thionyl chloride on 70 in liquid sulfur dioxide. The chloride was extraordinarily susceptible to hydrolysis to the alcohol 71, and initial attempts to replace the chlorine atom by a cyano group in hydroxylic solvents were seriously complicated by the formation of the alcohol 71 and corresponding ethers. The difficulty was surmounted by treating the hydrochloride of 73 with excess sodium cyanide in anhydrous liquid hydrogen cyanide, under which conditions the desired nitrile 74 was formed in good yield. Methanolysis of 74 catalyzed by sulfuric acid gave the ester (75, R = Me), which was hydrolyzed by hydrochloric acid or by sodium hydroxide to the corresponding acid (75, R = H).



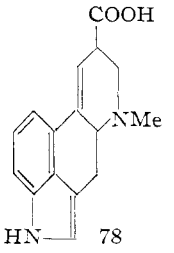
Two hydrogen atoms, placed by design at C.5 and C.5a to deprive our synthetic operations of the dangers attendant upon the presence of an indole ring, now alone remained to be eliminated. The position of these atoms, as components of a dihydroaromatic system, provided a basis for supposing that they should be relatively readily removed, and dehydrogenation studies were taken in hand. As was the case in our earlier experiences with related N-acyl derivatives (*vide supra*, 10 → 12), the N-acetyl derivative of the ester (75, R = Me) was converted by palladium–charcoal in boiling xylene to the known naphthalenoid compound 76.[30] On the other hand, when the sodium salt of the acid (75, R = H) was treated in boiling water with Raney nickel, disproportionation occurred, with formation of 77. Under these conditions generation of the desired indole system was accomplished, but reduction of the double bond in ring D took place as well.



Subsequent studies obviated these difficulties; in similar experiments in which heat-deactivated Raney nickel was used as dehydrogenation catalyst in the presence of sodium arsenate,[31] *dl*-lysergic acid (78) was the sole product isolated.

(30) References 7d and 7e.

(31) E. Kleiderer and E. Kornfeld, *J. Org. Chem.*, **13**, 455 (1948), and P. Ruggli and E. Girod, *Helv. Chim. Acta*, **27**, 1464 (1944).



78

The synthetic *dl*-lysergic acid was converted, through its methyl ester, into *dl*-isolysergic acid hydrazide.[32] The acid and the hydrazide were shown to be identical with samples prepared[32,33] from natural materials by comparison of melting points, mixture melting points, infrared and ultraviolet spectra, X-ray powder diagrams, pK_a's, and paper chromatographic behavior.

Since *dl*-isolysergic acid hydrazide has already been resolved and converted to ergonovine 2,[34] the present work completes the synthesis of that alkaloid as well as that of lysergic acid.

Acknowledgments.—We wish to express our warmest appreciation to a number of people whose very cordial assistance during the course of the work was to a large measure responsible for its ultimate success: (1) to Drs. H. L. Breunig, A. W. Hubert and associates who provided more than adequate supplies of several of the early intermediates; (2) to Mr. W. L. Brown, Mr. G. Maciak, Mr. H. L. Hunter, Miss G. Beckmann and Mr. L. S. Hatfield who carried out all of the many analyses; (3) to Dr. H. E. Boaz, Mr. J. M. Forbes, Mr. D. O. Woolf, Miss M. Hofmann, Mrs. H. Arndt and Dr. H. A. Rose who recorded the numerous and very useful physical measurements; (4) to Dr. E. R. Shepard for helpful suggestions; and finally (5) to Dr. T. P. Carney for continued patient encouragement.

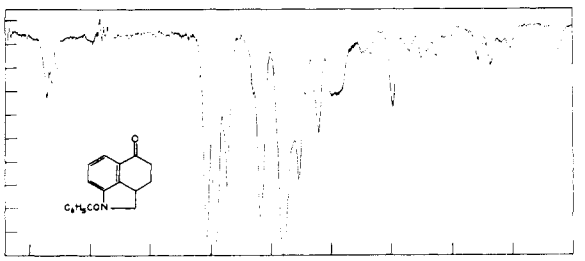
Experimental

Melting points were determined in soft glass capillary tubes and are uncorrected. Ultraviolet and infrared measurements were used for control purposes throughout the investigation, and spectra of all pure substances prepared were determined. However, in the sequel, spectra are recorded ordinarily only for the substances in the main line of the synthesis and for key model compounds. In each case in the infrared measurements, the abscissa is plotted in wave lengths (2.6–12 μ) and the ordinate in percentage transmission (0 to 100%). The measurements were made on a Beckman IR 2-T automatic recording spectrophotometer. Determinations were run at 0.15 molar concentration in chloroform solution except those designated with an "M" on the curve. In the latter a mineral oil mull was used. Ultraviolet data were obtained in methanol solution using a Cary model 11 automatic recording spectrophotometer.

1-Benzoyl-3-(β-carboxyethyl)-2,3-dihydroindole (5).—This was prepared by a modification of the method of Blount and Robinson.[35] 3-Indolepropionic acid, 94.6 g. (0.5 mole), was dissolved in 600 ml. of water containing 20 g. of sodium hydroxide. The solution was mixed with about 100 g. of Raney nickel catalyst and hydrogenated at room temperature in a steel hydrogenation bomb at 3000 to 4000 pounds per square inch pressure. Reduction was usually complete in 20 to 30 hours, after which the catalyst was filtered and washed with a little water. Concentrated hydrochloric acid, 85 ml., was added to the filtrate, and the solution was cooled. If the reduction was incomplete, unreacted indolepropionic acid separated at this point and was removed by filtration. The filtrate was then benzoylated by the usual Schotten–Baumann procedure using 210 ml. of 12 *N* sodium hydroxide and 180 ml. of benzoyl chloride. The solution was kept alkaline throughout the benzoylation, and the temperature was kept below 40° by cooling. When the benzoyl chloride was completely reacted, the mixture was cooled and acidified with 300 ml. of concentrated hydrochloric acid. The crude product was filtered and washed with water, after which it was extracted with four 1-l. portions of hot water to remove benzoic acid. The hot sirupy product, after decantation of the aqueous extract, was crystallized from a few volumes of methanol. The acid was filtered and washed with a little cold methanol; yield 103 g. (70%), m.p. 151–153°.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (4).—1-Benzoyl-3-(β-carboxyethyl)-2,3-dihydroindole, 118 g. (0.4 mole), was mixed with 200 ml. of pure thionyl chloride. The solution was allowed to stand for one-half hour, after which it was warmed gently for 15–20 minutes on the steam-bath. Excess thionyl chloride was evaporated completely below 30° *in vacuo*, and the crude acid chloride was dissolved in 200 ml. of dry carbon disulfide. The solution of the acid chloride was then added in a thin stream to a vigorously stirred suspension of 240 g. of aluminum chloride in 1750 ml. of carbon disulfide contained in a 5-l. flask (hood!). A complex separated, and stirring became difficult. The mixture was heated under reflux and stirred for one hour to complete the reaction, after which it was decomposed very carefully by adding 500 g. of ice, 250 ml. of concentrated hydrochloric acid and 500 ml. of water. During the decomposition, stirring was maintained, and cooling was effected by periodic distillation of the carbon disulfide *in vacuo*. When the decomposition was complete, any carbon disulfide remaining was removed completely *in vacuo*, and the product was extracted with 2 l. of benzene. The extract was washed thoroughly with 500 ml. of 2 *N* sodium hydroxide in three portions and then with water. It was dried over magnesium sulfate and then evaporated to small volume *in vacuo*. Slow addition of several volumes of ether caused the yellow ketone to crystallize. It was filtered and washed with ether; yield 85.3 g. (77%), m.p. 146–147°. A sample was recrystallized for analysis from benzene–ether.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.81; H, 5.29; N, 5.15.



1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Semicarbazone.—A mixture of 1.5 g. of N-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 1.5 g. of semicarbazide hydrochloride and 2.25 g. of anhydrous sodium acetate in 25 ml. of ethanol and 10 ml. of water was warmed under reflux on a steam-bath for 1.25 hours. The solution was cooled, and the product was filtered and washed with water, ethanol and ether; yield 1.7 g. (94%), m.p. 260–262° dec. It was recrystallized from dilute acetic acid.

Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.05; H, 5.64; N, 16.08.

1-Benzoyl-3-β-benzoylethyl-2,3-dihydroindole (6).—In the above Friedel–Crafts cyclization procedure, if benzene was used as solvent in place of carbon disulfide, acylation of the benzene took place rather than cyclization. The product was crystallized from ethanol; m.p. 101–102°, yield 52%.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.19; H, 6.14; N, 4.10.

1-Benzoyl-α-oxo-3-indolinebutyric Acid (8).—Diazomethane was prepared from 55 g. of nitrosomethylurea and 150 ml. of 40% potassium hydroxide in 500 ml. of ether in the

(32) A. Stoll and A. Hofmann, *Z. physiol. Chem.*, **250**, 7 (1937).

(33) S. Smith and G. Timmis, *J. Chem. Soc.*, 1440 (1936).

(34) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922, 944 (1943).

(35) B. K. Blount and R. Robinson, *J. Chem. Soc.*, 3158 (1931).

usual way. The ether solution was dried over solid potassium hydroxide. Methanol (10 ml.) was added, and 60 g. of 1-benzoyl-3-[β-carboxyethyl]-2,3-dihydroindole was then added in portions with shaking and cooling in an ice-bath. When reaction was complete, the solution was concentrated *in vacuo* below 25°, and the residue was dissolved in 400 ml. of ether. The solution was washed well with dilute hydrochloric acid and with 5% aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The 1-benzoyl-3-[β-carbomethoxyethyl]-2,3-dihydroindole so obtained did not crystallize but was adequately pure for use in the oxalation reaction below; yield 62.5 g. (99%).

The methyl ester was mixed with 300 ml. of dry ether, 36 g. of methyl oxalate and 12.5 g. of sodium methoxide, and the mixture was heated under reflux and stirred for 22 hours. Ice-water was added with stirring, and the aqueous layer was separated from the neutral ether layer and then acidified with 7 ml. of concentrated sulfuric acid. The oil which separated was extracted with 300 ml. of ether in two portions, and the extracts were dried over magnesium sulfate. The ether was distilled, and the 1-benzoyl-3-[β-methoxalyl-β-carbomethoxyethyl]-2,3-dihydroindole was obtained as a sirup which did not crystallize; yield 44.2 g. (55%). Unchanged starting material (32 g.) was recovered from the neutral ether layer above.

The methoxalyl ester was dissolved in 265 ml. of 77% sulfuric acid and heated on a steam-bath for 20 minutes, during which time the temperature was in the range of 68 to 92°. The solution was poured onto an excess of ice, and the product was filtered, washed with water, and dried *in vacuo*. It was crystallized from a mixture of benzene and dioxane; yield 18.4 g. (51%), m.p. 160–161° dec.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.84; H, 4.89; N, 4.40.

The methyl ester was prepared in dioxane solution by adding an ether solution of diazomethane. It was crystallized from a mixture of benzene and ether, m.p. 146.5–147.5°.

Anal. Calcd. for $C_{20}H_{19}NO_4$: N, 4.15. Found: N, 4.02.

5-Keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (10).—1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 30 g., was mixed with 300 ml. of concentrated hydrochloric acid and 225 ml. of glacial acetic acid, and the solution was heated under reflux for 16 hours. It was evaporated to dryness *in vacuo*, and the residue was dissolved in water. The solution was treated with carbon, filtered and excess ammonium hydroxide was added to the filtrate. The crude yellow ketone was filtered and recrystallized from 60 ml. of methanol; yield 13.6 g. (73%), m.p. 124–126°. An analytical sample recrystallized from methanol separated as golden yellow plates, m.p. 126–127°; ultraviolet λ_{max} 244 mμ (ε 17000), 355 mμ (ε 1900).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.97; H, 6.60; N, 8.43.

The hydrochloride prepared in ethanol–ether had a melting point of 195–200° dec.

Anal. Calcd. for $C_{11}H_{11}NO \cdot HCl$: C, 63.01; H, 5.77. Found: C, 63.21; H, 6.01.

The hydrobromide prepared in similar fashion had a melting point of 212–215° dec.

Anal. Calcd. for $C_{11}H_{11}NO \cdot HBr$: N, 5.51; Br, 31.45. Found: N, 5.43; Br, 31.74.

1-Acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—5-Keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 1 g., was dissolved in a mixture of 12.5 ml. of pyridine and 12.5 ml. of acetic anhydride. After the solution had stood for 0.5 hour, it was warmed on the steam-bath for 15 minutes. Excess acetic anhydride was decomposed with methanol, and the solution was evaporated to small volume *in vacuo*. Water was added to the residue, and the acetyl derivative was filtered and washed with dilute hydrochloric acid and water; yield 0.9 g. (73%). It was recrystallized from ethanol, m.p. 177.5–178.5° (yellow prisms).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.22; H, 6.23; N, 6.70.

The infrared spectrum had bands at 5.96, 6.03, 6.28, 6.82, 7.14 and 7.49 μ.

1-Butyryl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—This was prepared like the acetyl derivative using one gram of the ketone, and 5 ml. each of pyridine and butyric anhydride; yield 90%, m.p. 137.5–138.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.43; H, 7.18; N, 5.70.

1-Acetyl-3-[β-carboxyethyl]-2,3-dihydroindole.—In a 1-l. bomb was placed 71.0 g. (0.375 mole) of 3-indolepropionic acid, 15.0 g. (0.375 mole) of sodium hydroxide, seven teaspoonsful (about 71 g.) of Raney nickel catalyst, and distilled water to make the volume 450 ml. This mixture was hydrogenated for about 20 hours at a pressure of 4300 lb. per square inch at room temperature. The catalyst was filtered, and the filtrate was acidified with 65 ml. of concentrated hydrochloric acid. Unreduced 3-indolepropionic acid, 12.9 g., was recovered by filtration. The aqueous acid solution containing 58.6 g. (0.307 mole) of 3-[β-carboxyethyl]-2,3-dihydroindole was placed in a 3-l., three-necked flask equipped with a mechanical stirrer, two dropping funnels, a thermometer and a cooling bath. To the stirred mixture was added, through one dropping funnel, a solution of 92 g. (2.3 moles) of sodium hydroxide in 250 ml. of distilled water. When the reaction mixture became basic, simultaneous addition of 94 g. (0.921 mole) of acetic anhydride was begun, with continued stirring and cooling. At the completion of the additions, the reaction mixture was acidified with 100 ml. of concentrated hydrochloric acid, and the mixture was refrigerated overnight. The product which was collected on a funnel weighed 77.7 g. Recrystallization of the acid from 700 ml. of methanol gave 45.3 g. (63%), m.p. 157–158°.

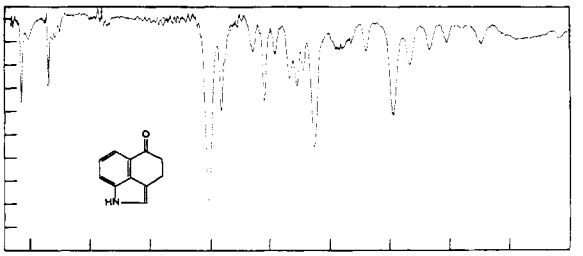
Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.52; H, 6.92; N, 5.84.

1-Acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole by Cyclization.—The acid chloride was prepared in the customary manner from 23.3 g. (0.1 mole) of 1-acetyl-3-[β-carboxyethyl]-2,3-dihydroindole and 50 ml. (0.698 mole) of thionyl chloride. After the excess thionyl chloride had been removed *in vacuo*, the residual acid chloride was dissolved in 75 ml. of dry nitrobenzene. The solution was then added to 60 g. (0.452 mole) of aluminum chloride suspended in 300 ml. of dry nitrobenzene while cooling the reaction mixture to keep the temperature below 20°. The mixture was stirred about four hours at 25°, after which it was cooled in a chloroform–Dry Ice-bath and decomposed by adding crushed ice, 200 ml. of distilled water and 100 ml. of concentrated hydrochloric acid. A heavy precipitate was removed by filtration. The nitrobenzene layer was separated and washed with three 50-ml. portions of 2 *N* sodium hyroxide solution, and then with distilled water until the washings were neutral. The nitrobenzene was steam distilled, and the residual crystalline product was filtered; yield 3.3 g. (15%), m.p. 175–177°. It was purified by recrystallization from ethanol.

5-Keto-1,3,4,5-tetrahydrobenz[*cd*]indole (11) from 5-Keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (10).—The indoline derivative, 2.0 g., was mixed with 3 g. of 5% palladium-on-carbon and 30 ml. of *p*-cymene. The mixture was refluxed for one hour, after which the solvent was removed *in vacuo*, and the residue was taken up in 200 ml. of benzene. The solution was filtered and washed with dilute hydrochloric acid and water and dried over magnesium sulfate. On concentration *in vacuo* to about 10 ml., the indole derivative crystallized; yield 0.3 g. (15%), m.p. 157–158°. Recrystallization from a few ml. of benzene gave the pure ketone, m.p. 159.5–160.5°.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.25; N, 8.04.

The ultraviolet absorption spectrum was identical with that reported by Uhle.[36]



(36) F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

1-Benzoyl-5-hydroxy-1,2-dihydrobenz[*cd*]indole (12).—A mixture of 20 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 20 g. of 5% palladium-on-carbon in 350 ml. of xylene was heated under reflux for 16 hours. The catalyst was filtered and washed with ethyl Cellosolve. The filtrate was concentrated, and the product was filtered; yield 8.45 g. (42%), m.p. 229–231° dec. Recrystallization from a mixture of chloroform and methanol raised the melting point to 231–235° dec.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.67; N, 5.09. Found: C, 78.12; H, 4.86; N, 5.56.

1-Benzoyl-5-acetoxy-1,2-dihydrobenz[*cd*]indole.—1-Benzoyl-5-hydroxy-1,2-dihydrobenz[*cd*]indole, 6.2 g., was dissolved in a mixture of 60 ml. of acetic anhydride and 60 ml. of pyridine. The solution was warmed on a steam-bath for one hour, and the solvents were distilled under reduced pressure. The ester was crystallized from ethyl acetate; yield 4.25 g. (60%), m.p. 168–169°; ultraviolet λ_{max} 233 mμ (ε 43900), 321 mμ (ε, 16200), 329 mμ (ε, 14900).

Anal. Calcd. for $C_{20}H_{15}NO_3$: C, 75.69; H, 4.76; N, 4.41. Found: C, 75.29; H, 4.01; N, 4.62.

1-Acetyl-5-hydroxy-1,2-dihydrobenz[*cd*]indole (12).—A mixture containing 2.0 g. of 1-acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 3.0 g. of 5% palladium-on-carbon in 30 ml. of *p*-cymene was heated under reflux for one hour. The solvent was distilled *in vacuo*, and the residue was extracted with hot methanol and chloroform. The extracts were evaporated, and the residue was taken up in chloroform. The product was filtered (0.25 g.) and recrystallized from a mixture of acetic acid and methanol, m.p. 239–247° dec.

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.19; H, 5.20; N, 6.57. Found: C, 73.51; H, 4.70; N, 7.18.

The ultraviolet absorption spectrum was identical to that reported by Grob and Voltz.[71]

1-Acetyl-5-acetoxy-1,2-dihydrobenz[*cd*]indole.—One gram of the 5-hydroxy compound was dissolved in a mixture of 10 ml. of acetic anhydride and 10 ml. of pyridine, and the solution was warmed on a steam-bath for 0.5 hour. The mixture was evaporated *in vacuo*, and the residual product was taken up in water, filtered and recrystallized from acetone; m.p. 156–161°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.09; N, 5.49. Found: C, 71.03; H, 5.29; N, 5.90.

1-Benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (13).—A solution of 304.7 g. (1.1 moles) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole in 2200 ml. of glacial acetic acid was warmed to 40°. While the reaction mixture was illuminated with a 250 watt bulb, 352 g. (1.1 moles) of pyridine hydrobromide perbromide was added in portions during 5 minutes with shaking. The solution was warmed to 60° and was kept at 55–60° for 0.5 hour. The mixture was treated with carbon and concentrated to small volume *in vacuo*. The residue was taken up in 2200 ml. of chloroform, and the solution was washed several times with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from 2200 ml. of 1:1 acetic acid–ether; m.p. 180.5–181.5°, yield 270 g. (69%). A second crop (31 g.) of less pure material was obtained by concentrating the filtrates.

Anal. Calcd. for $C_{18}H_{14}BrNO_2$: N, 3.93; Br, 22.44. Found: N, 3.94; Br, 22.14.

1-Benzoyl-4,5-di-[methylamino]-1,2-dihydrobenz[*cd*]indole (14).—1-Benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (19.0 g.) was dissolved in 300 ml. of liquid methylamine, and the solution was sealed in an autoclave and kept at 25° for two days. Methylamine was allowed to evaporate, and the residue was crystallized from about 10 ml. of ethanol; yield 9.5 g. (56%), m.p. 197–202° dec. A sample for analysis was recrystallized twice from toluene, m.p. 205–209° dec.; ultraviolet λ_{max} 248 mμ (ε, 21000), 278 mμ (ε, 31300), 370 mμ (ε, 4400).

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.68; H, 6.03; N, 13.24. Found: C, 75.91; H, 6.18; N, 12.75.

Methylaminoacetone Ethylene Ketal (15).—A mixture of 3718 g. of chloroacetone ethylene ketal[37] and 7150 g. of liquid methylamine was heated at 155–170° for 48 hours (pressure 750 to 950 pounds per square inch). Methylamine was vented, and the residue was mixed with several volumes of ether. A warm solution of 1400 g. of potassium hydroxide in 650 ml. of water was then added slowly with thorough agitation, after which excess solid potassium hydroxide was added to form a thick sludge as a bottom layer. The ether solution was decanted and dried over potassium hydroxide to remove all water, and the ether was distilled. The crude product was distilled to yield 3210 g., b.p. 50–80° at 12 mm., of a mixture still containing 25–30% of unchanged chloroacetone ethylene ketal, which was removed as follows. The crude product was dissolved in 20 l. of dry ether, and the hydrochloride of the product was precipitated with hydrogen chloride. The salt was filtered and washed thoroughly with ether to remove all chloroketal; m.p. 165–167°.

Anal. Calcd. for $C_6H_{13}NO_2 \cdot HCl$: N, 8.36. Found: N, 8.11.

The hydrochloride was then suspended in ether and converted to the free base with potassium hydroxide exactly as above. The pure amino ketal had a b.p. of 160–162°, yield 2165 g. (61%).

Anal. Calcd. for $C_6H_{13}NO_2$: N, 10.68. Found: N, 10.93.

A similar preparation using 1450 g. of bromoacetone ethylene ketal[37] and 2750 g. of liquid methylamine heated at 162–173° for 24 hours gave 843 g. (80%) of the methylaminoacetone ethylene ketal. In this case the product was halogen-free, and purification through the hydrochloride salt was unnecessary.

1-Benzoyl-4-isonitroso-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Potassium Salt.—A mixture of 100 ml. of anhydrous toluene and 6.5 ml. of absolute alcohol was placed in a flask protected from atmospheric moisture. To this was added 0.9 g. (0.023 atom) of potassium with stirring and warming to speed solution.

At this point, 5.55 g. (0.02 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole suspended in 75 ml. of anhydrous toluene was added, and the mixture was warmed until the ketone had dissolved. Immediately the solution was cooled; 5 ml. (0.0436 mole) of butyl nitrite was added, and the reaction mixture was stirred for 4 hours at room temperature, and allowed to stand for three days.

The solid product obtained by filtration weighed 6.8 g. (100%) after washing with anhydrous ether, m.p. 145–150° dec. A sample was recrystallized from absolute ethanol, m.p. 167–169° dec.

Anal. Calcd. for $C_{18}H_{13}N_2O_3K$: N, 8.14; K, 11.35. Found: N, 8.49; K, 11.10.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Oxime.—A mixture of 41.7 g. (0.15 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 17.4 g. (0.25 mole) of hydroxylamine hydrochloride, 12.6 g. (0.0915 mole) of anhydrous potassium carbonate, 750 ml. of methanol and 20 ml. of distilled water was stirred and heated for one hour, cooled and placed in the refrigerator for a few days. The product was filtered and washed with ice-cold distilled water. Dilution of the filtrate with water gave additional product. After drying *in vacuo* at 50°, the combined product had a m.p. of 210–211°, yield 41.6 g. (95%).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.47; H, 5.61; N, 9.31.

1-Benzoyl-5-isonitroso-1,2,2a,3,4,5-hexahydrobenz[*cd*]-indole Tosylate.—Dry pyridine (1000 ml.) and 87.0 g. (0.30 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole oxime were cooled in an ice-bath. To the reaction mixture was added with stirring a cold solution prepared by dissolving 228 g. (1.2 moles) of *p*-toluenesulfonyl chloride in 500 ml. of dry pyridine while cooling in an ice-bath. Addition was at such a rate that the temperature remained at 1–2°. When the addition was complete, stirring was continued at 0° for 2 hours, and the reaction mixture was placed in the refrigerator overnight. The solution was poured onto ice, and the product was filtered, washed with water, and recrystallized from ethanol; yield 100.7 g. (76%), m.p. 152–155°.

Anal. Calcd. for $C_{25}H_{22}N_2O_4S$: C, 67.25; H, 4.97; N, 6.28. Found: C, 67.23; H, 5.05; N, 6.26.

4-Amino-1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole Hydrochloride (17).—Potassium metal, 0.86 g. (0.022 gram atom), was added to 50 ml. of absolute ethanol protected from atmospheric moisture, and the mixture was stirred until solution was complete. After the reaction

(37) M. Kuhn, *J. prakt. Chem.*, **156**, 103 (1940).

mixture was cooled in ice to 10°, a suspension of 8.8 g. (0.02 mole) of 1-benzoyl-5-isonitroso-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole tosylate in 200 ml. of absolute ethanol was added, and stirring and cooling were continued for eight hours, after which the reaction mixture was placed in the refrigerator for three days. Unchanged starting material, 3.69 g., was recovered by filtration, m.p. 156–157°. The filtrate was poured into 600 ml. of absolute ether, and the solution was extracted with a total of 225 ml. of 6 *N* hydrochloric acid solution in several portions. The acid extract was concentrated to dryness *in vacuo*, and the residue was taken up in 250 ml. of hot absolute alcohol, from which the amino ketone hydrochloride, m.p. 240° dec., crystallized. Additional product from the mother liquors brought the yield to 2.30 g. (60%, based on starting material consumed). Material for analysis had a m.p. of 248–250° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O_2 \cdot HCl$: C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.86; H, 5.23; N, 8.56; Cl, 10.50.

The infrared spectrum (mull) had bands at 5.83, 6.08, 6.27, 6.34, 6.60, 6.78 and 7.19 μ.

1-Benzoyl-4-formyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (19).—Sodium methoxide, 6.0 g., and 15 ml. of ethyl formate were added to 150 ml. of cold, dry benzene. The mixture was stirred in an ice-bath, and 27.7 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was added. The reaction mixture was stirred in the cold for 15 minutes and then at 25° for two hours. The sodium enolate which separated was filtered and washed with benzene and ether; yield 28.0 g. (85%). A sample of the salt was dissolved in water, and the solution was acidified with hydrochloric acid. The aqueous solution was decanted, and the gummy product was crystallized from a mixture of dimethylformamide and methanol; m.p. 142–145° dec.

Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.96; N, 4.59. Found: C, 73.85; H, 4.91; N, 4.62.

1-Benzoyl-4-formamido-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (22) and 1-Benzoyl-4-cyano-5-keto-1,2,2a,-3,4,5-hexahydrobenz[*cd*]indole (21) from 1-Benzoyl-4-formyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—The crude sodium enolate of the 4-formyl derivative, 20 g., was dissolved in 270 ml. of trifluoroacetic acid, and 4.6 g. of sodium azide was added with stirring. The flask was fitted with a reflux condenser and thermometer, and 18 ml. of concentrated sulfuric acid was added dropwise with stirring during 12 minutes. The temperature was kept at 45° during the addition and for an additional 15 minutes. The reaction mixture was concentrated below 30° *in vacuo* to a volume of about 75–100 ml. Chloroform, 200 ml., and 250 ml. of ice-water were added, and the organic layer was separated and washed twice with water. Acidic material was then extracted from the mixture using an excess of cold dilute sodium hydroxide solution. The neutral chloroform fraction was washed with water, dried over magnesium sulfate, and the solvent was distilled under reduced pressure. The 4-formamido derivative was crystallized from a little methanol; yield 2.23 g. (11.4%), m.p. 178–180°. The ultraviolet spectrum was like that in Fig. 1.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.09; H, 5.08; N, 8.49.

The aqueous sodium hydroxide extract above, containing the acidic fraction, was acidified with hydrochloric acid and extracted with 150 ml. of chloroform. The chloroform solution was dried; the solvent was distilled, and the 4-cyano compound was crystallized from methanol; yield 5.83 g. (32%), m.p. 190–191°. A sample was recrystallized from a mixture of dimethylformamide and methanol; m.p. 190–191°.

Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.73; H, 5.10; N, 9.01.

1-Benzoyl-5-keto-4-methoxalyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (20).—To a solution of 30 g. of methyl oxalate in 800 ml. of cold benzene was added 15 g. of sodium methoxide powder with stirring and cooling in ice. A warm solution of 55.5 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole in 350 ml. of toluene was then added dropwise with continued stirring and cooling during 10 minutes. Stirring was maintained with the cooling bath removed for two hours, after which 400 ml. of ice-water was added. The aqueous solution containing the sodium enolate was separated and acidified with 30 ml. of concentrated hydrochloric acid. The product was extracted with 500 ml. of chloroform, and the solvent was distilled *in vacuo*. The residue was crystallized from a few volumes of ethanol; yield 52.3 g. (72%), m.p. 202–204° dec. A sample was recrystallized from a mixture of acetic acid and methanol.

Anal. Calcd. for $C_{21}H_{17}NO_4$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.20; H, 4.77; N, 3.53.

Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindole[4,3-*fg*]benzoxazole-8-carboxylate (23).—1-Benzoyl-5-keto-4-methoxalyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 3.63 g., was dissolved in 15 ml. of concentrated sulfuric acid, and 1.0 g. of sodium azide was added with stirring. The mixture was warmed to 40°, at which point the reaction became exothermic, and the temperature rose spontaneously to 50°. The solution was cooled to 40° and kept at that temperature for 15 minutes, after which it was poured onto ice. The amorphous product was filtered, washed with water, and crystallized from ethanol; yield 0.69 g. (19%), m.p. 230° dec. Purification was effected by recrystallization from a mixture of dimethylformamide and methanol; m.p. 237–238° dec.

Anal. Calcd. for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 70.05; H, 4.46; N, 7.70.

The infrared spectrum had carbonyl bands at 5.75 (ester) and 6.07 μ (amide).

Methyl 4,5,5a,6-Tetrahydroindolo[4,3-*fg*]benzoxazole-8-carboxylate Hydrochloride.—A mixture of 1 g. of the 4-benzoyl derivative above and 50 ml. of methanol was saturated with 12 g. of dry hydrogen chloride while cooling. The reaction mixture was kept for four days at 25°, after which time 0.34 g. (34%) of unchanged starting material was filtered. The filtrate was decolorized with carbon, and evaporated to dryness *in vacuo*. The residue was crystallized from methanol; yield 0.26 g. (49% based on ester not recovered), m.p. 226–227° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O_3 \cdot HCl$: Cl, 12.11; N, 9.57. Found: Cl, 12.07; N, 9.78.

4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-*fg*]benzoxazole-8-carboxylic Acid Hydrazide.—One-half gram of the corresponding methyl ester was dissolved in 5.5 ml. of hot dimethylformamide. Pure hydrazine (7 ml.) was added, and in a few seconds the hydrazide crystallized. The mixture was diluted with an equal volume of methanol, and the product was filtered, 0.43 g. (86%), m.p. 270° dec. It was insoluble in all the usual solvents.

Anal. Calcd. for $C_{20}H_{16}N_4O_3$: N, 15.55. Found: N, 15.97.

4-Amino-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Dihydrochloride (24). A. By Hydrolysis of Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-*fg*]benzoxazole-8-carboxylate.—A mixture of the oxazole ester, 7.6 g., in 400 ml. of methanol was saturated with dry hydrogen chloride, and the solution was heated at reflux while a continuous stream of dry hydrogen chloride was bubbled in during 4.5 hours. The solution was decolorized with carbon, and the solvent and hydrogen chloride were evaporated under reduced pressure. The product was taken up in methanol, filtered and washed with methanol and ether; yield 3.4 g. (62%), m.p. above 300°.

Anal. Calcd. for $C_{11}H_{12}N_2O \cdot 2HCl$: N, 10.73; Cl, 27.15. Found: N, 10.30; Cl, 27.76.

Hydrolysis of the ester in aqueous hydrochloric acid gave about the same result.

B. By Hydrolysis of 1-Benzoyl-4-amino-5-keto-1,2,2a,-3,4,5-hexahydrobenz[*cd*]indole Hydrochloride.—A solution of 1.11 g. of the amino ketone hydrochloride in 50 ml. of concentrated hydrochloric acid was heated under reflux overnight. The mixture was treated with carbon, and the solvent was distilled *in vacuo*. The residual product was digested with a little ethanol, filtered, and washed with ethanol and ether; yield 0.6 g. (68%), m.p. above 300°.

Anal. Calcd. for $C_{11}H_{12}N_2O \cdot 2HCl$: N, 10.73; Cl, 27.15. Found: N, 10.19; Cl, 27.96.

X-Ray diffraction patterns of the samples prepared by methods A and B were identical.

C. From 1-Benzoyl-4-formamido-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—The hydrolysis in this case was run in hydrochloric acid exactly as above. Once again the m.p. was indistinct in the region of 280–300° dec., and identity was proved by comparison of X-ray diffraction patterns.

1-Benzoyl-4-acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A mixture of 13.8 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole in 100 ml. of acetic anhydride was cooled in an ice-bath. Boron trifluoride gas was bubbled into the solution for 20 minutes with stirring and continued cooling, during which time the temperature of the reaction mixture rose to 40°. The solution was kept at 25° for 1.5 hours, after which it was concentrated to small volume *in vacuo*. The residue was dissolved in chloroform, and the solution was washed successively with water, 6 *N* sodium hydroxide, concentrated hydrochloric acid and water. It was dried over magnesium sulfate and concentrated under reduced pressure. The residual ketone was crystallized from benzene; yield 6.0 g. (38%), m.p. 172–175°.

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.43; H, 5.71; N, 4.47.

1-Benzoyl-5-acetoxy-1,2,2a,3-tetrahydrobenz[*cd*]indole (26, R = Ac).—1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 100 g., was added to 500 ml. of isopropenyl acetate and 2 g. of *p*-toluenesulfonic acid. The flask was fitted with a glass-helix packed column about 12–15 inches long. The reaction mixture was heated, and the rate of heating was regulated so that about 250 ml. distilled during about 26 hours. Isopropenyl acetate was added periodically to replace that which had distilled. The solution was then treated with decolorizing carbon, filtered and concentrated under reduced pressure until a thick slurry of crystals had deposited. The mixture was cooled, and the product was filtered and washed with cold ethyl acetate and ether; yield 74 g. (65%). A sample was recrystallized from ethyl acetate for analysis, m.p. 145–146°.

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.34; H, 5.76; N, 4.67.

The infrared spectrum had an ester carbonyl band at 5.70 μ; ultraviolet λ_{max} 263 mμ (ϵ 21500), 309 mμ (ϵ 4200), 319 mμ (ϵ 3660).

1-Benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (13) from 1-Benzoyl-5-acetoxy-1,2,2a,3-tetrahydrobenz[*cd*]indole.—The enol acetate, 63.9 g., was dissolved in 250 ml. of chloroform, and the solution was cooled in ice. A mixture of 10.5 ml. of bromine and 50 ml. of chloroform was then added dropwise during 10–15 minutes with stirring and continued cooling. The solution was warmed to about 55°, after which 50 ml. of methanol was added in portions during five minutes to decompose the acetyl bromide. The mixture was cooled, washed twice with water, dried over magnesium sulfate, and the solvent was distilled *in vacuo*. The bromo ketone was recrystallized from 1:1 acetic acid–ether; yield 64 g. (90%), m.p. 178–180°.

1-Benzoyl-5-ethoxy-1,2,2a,3-tetrahydrobenz[*cd*]indole (26, R = Et).—A mixture of 5.0 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 50 ml. of ethyl orthoformate, 45 ml. of absolute alcohol and 2 drops of concentrated sulfuric acid was heated at reflux for 4 hours. The volatile materials were removed *in vacuo*, leaving an oil which crystallized on standing. The oil was triturated with ethyl acetate–petroleum ether and allowed to stand overnight in a refrigerator. The crystalline product, 3.0 g. (55%), was collected on a funnel and washed with petroleum ether. Several crystallizations from ethyl acetate–petroleum ether gave the enol ether, m.p. 97.5–102°.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.48; H, 5.99; N, 4.54.

1-Benzoyl-4-hydroxy-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (27). A. From 1-Benzoyl-5-acetoxy-1,2,2a,3-tetrahydrobenz[*cd*]indole.—The enol acetate (10 g., 0.031 mole) was dissolved in 250 ml. of dry benzene, and to it was added a solution of 7.3 g. (0.040 mole) of monoperphthalic acid in 135 ml. of dry ether. The mixture was allowed to stand at room temperature for three days. The supernatant solution was decanted from the crystalline phthalic acid which had collected on the sides of the flask, and it was washed with three 50-ml. portions of saturated sodium bicarbonate solution. The addition of anhydrous magnesium sulfate to the benzene–ether solution caused the product to separate. Several volumes of chloroform were added, and the magnesium sulfate was separated by filtration. The solvents were removed *in vacuo* leaving 8 g. (85%) of the crude hydroxy ketone. Crystallization from ethyl acetate gave analytically pure material, m.p. 205–206°.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.61; H, 5.07; N, 4.79.

The infrared spectrum had carbonyl bands at 5.91 (ketone) and 6.07 μ (amide); ultraviolet λ_{max} 244 mμ (ϵ 23300), 330 mμ (ϵ 4400).

B. From 1-Benzoyl-5-ethoxy-1,2,2a,3-tetrahydrobenz[*cd*]indole.—A solution of 1.6 g. (0.0052 mole) of the enol ether in 15 ml. of chloroform was cooled in an ice-bath, and mixed with 22 ml. of cold chloroform containing 0.86 g. (0.0062 mole) of perbenzoic acid. The solution was allowed to stand in the refrigerator overnight, after which it was washed with two 15-ml. portions of saturated sodium bicarbonate solution, and then with 15 ml. of water. It was then dried over anhydrous magnesium sulfate, and the chloroform was removed *in vacuo* leaving an oil, which crystallized on trituration with 1:1 benzene–petroleum ether. Recrystallization from ethyl acetate gave the hydroxy ketone, m.p. 205–207°. A mixture melting point with a sample of hydroxy ketone prepared from the enol acetate showed no depression.

1-Benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—Twenty-five grams of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was dissolved in 200 ml. of hot absolute ethanol. The solution was stirred and heated at reflux while a solution of 2.5 g. of sodium borohydride in 120 ml. of absolute alcohol was added dropwise during about 0.5 hour. Refluxing was continued for one hour, after which 50 ml. of 10% aqueous sodium hydroxide was added, and heating was continued for 0.5 hour. The solution was cooled and then poured into 250 ml. of 6 *N* hydrochloric acid. Most of the ethanol was distilled *in vacuo*, and the product was extracted from the residue with 3 200-ml. portions of 1:1 ether–benzene. The extracts were washed with water, treated with carbon and the solvents were removed. The crude alcohol, 20 g. (80%), was sufficiently pure to be used in the subsequent reaction. A sample was crystallized from ethyl acetate–petroleum ether, m.p. 182–183°.

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 76.57; H, 5.96; N, 5.24.

In another experiment the extraction was omitted, and the crude product was simply filtered and then washed with water, cold methanol and ether. The yield of crystalline material was 72%, m.p. 182–183°.

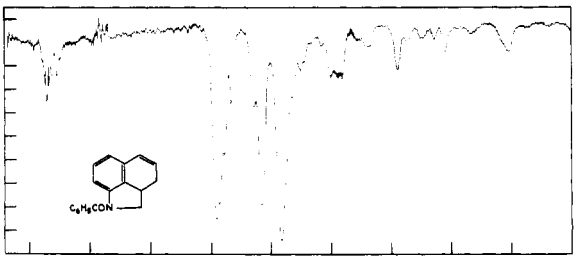
Oxidation of 1-Benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole to 1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—To a mixture of 2.79 g. of the tricyclic alcohol in 100 ml. of acetic acid was added with shaking a solution of 0.73 g. of chromic acid in 7 ml. of water and 9 ml. of acetic acid. The reaction mixture was kept at 25° for two days, after which it was warmed on a steam-bath for four hours. The solvents were evaporated under reduced pressure, and the residue was dissolved in chloroform and washed well with water. The solution was dried over magnesium sulfate; the solvent was distilled, and the ketone was crystallized from ethanol; yield 1.3 g. (47%), m.p. 138–141°. Recrystallization from a mixture of benzene and ether gave ketone with m.p. 145–146°. A mixture melting point with authentic tricyclic ketone was not depressed.

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (28).—Thirty-nine and one-half grams of crude 1-benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was dissolved in 400 ml. of benzene, and the mixture was cooled in ice while 25 ml. of phosphorus tribromide was added slowly with swirling. The solution was kept overnight at room temperature and was then boiled gently under reflux for four hours. It was cooled and poured onto ice. The organic layer was separated, and the aqueous layer was washed with a mixture of ether and benzene. The combined extracts were washed well with water and 5% sodium carbonate solution, and the solvents were evaporated *in vacuo*. The residue of 1-benzoyl-5-bromo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole weighed 36 g. (74%) and was pure enough for use in the next step.

The bromide was mixed with 150 ml. of 2,6-lutidine, and the solution was heated at reflux for 4 hours. The mixture was cooled and poured into 400 ml. of ice-cold 6 *N* hydrochloric acid. The product was extracted with 1:1 ether–benzene, and the extract was washed with aqueous sodium carbonate, dilute hydrochloric acid and finally with water. The solution was treated with decolorizing carbon, and the solvents were distilled *in vacuo*. The residual 1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole was crystallized from benzene–petroleum ether; yield 15.2 g. (32%, based on the

tricyclic ketone), m.p. 91–95°. An analytical sample melted at 95.5–96.5°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 82.72; H, 5.78; N, 5.36. Found: C, 82.66; H, 5.61; N, 5.37.



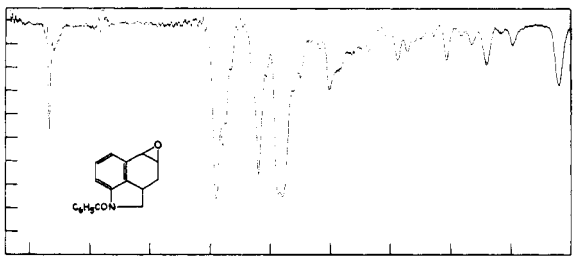
1-Acetyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—1-Acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 3.0 g., was dissolved in 50 ml. of hot absolute alcohol, and to the solution was added 4 ml. of 4% sodium borohydride in absolute ethanol. The mixture was heated under reflux for ten minutes, after which another 4 ml. of the sodium borohydride solution was added, and heating was continued for 0.5 hour. Water, 25 ml., was added, and the solution was heated for ten minutes, cooled, acidified with 2 ml. of concentrated hydrochloric acid and then diluted with several volumes of water. The product was extracted with 75 ml. of chloroform, and the extract was washed with dilute hydrochloric acid and with 5% sodium bicarbonate solution. The solution was dried over magnesium sulfate, decolorized with carbon, and concentrated to small volume. Petroleum ether was added, and the product was filtered; yield 2.7 g. (89%), m.p. 147–149°. Recrystallization from benzene raised the melting point to 150–151°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.90; H, 7.02; N, 6.11.

The ultraviolet type was like that in Fig. 3, curve B.

1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (29).—A solution of perbenzoic acid in chloroform was prepared in the usual fashion and standardized against sodium thiosulfate. Twenty-four grams of 1-benzoyl-1,2,2a,-3-tetrahydrobenz[*cd*]indole was added in portions with swirling to a cold solution of perbenzoic acid containing a 20% excess of the oxidizing agent. The solution was allowed to stand for 44 hours at 0°, after which it was washed several times with 5% sodium hydroxide solution and then with water. It was dried over sodium sulfate, and the solvent was removed *in vacuo*. The epoxy compound was crystallized from a mixture of ethyl acetate and petroleum ether; yield 20.6 g. (81%), m.p. 95–100°. Repeated recrystallization from benzene–petroleum ether raised the m.p. to 104–105°; ultraviolet λ_{max} 217 mμ (ε 34500), 265 mμ (ε 14600), 295 mμ (ε 9350).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 77.95; H, 5.45; N, 5.05. Found: C, 78.17; H, 5.72; N, 5.33.



1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (31).—1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole, 8.2 g., was hydrogenated at three atmospheres pressure in 150 ml. of ethanol using 4.1 g. of 5% palladium-on-carbon catalyst. The catalyst was filtered, the ethanol was distilled, and the residue was crystallized from a mixture of benzene and petroleum ether; yield 6.1 g. (74%), m.p. 107–108°. A sample for analysis was recrystallized from methanol.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.45; H, 6.66; N, 4.88.

The infrared spectrum had bands at 6.11, 6.20, 6.31, 6.85, 7.15, 7.47 and 7.72 μ.

1-Acetyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (32).—A solution containing 2.61 g. of 1-benzoyl-1,2,2a,3-tetrahydrobenz-[*cd*]indole and 4.0 ml. of 50% aqueous sodium hydroxide in 25 ml. of ethanol was heated under reflux for two hours. About half of the alcohol was distilled, and several volumes of water were added. The mixture was extracted with 100 ml. of ether, and the extract was washed with water. The ether solution was then extracted with dilute hydrochloric acid, and the acid extract was neutralized with sodium bicarbonate. The crude 1,2,2a,3-tetrahydrobenz[*cd*]indole was extracted with 100 ml. of ether, and the extract was dried over magnesium sulfate and concentrated to a volume of about 25 ml. Methanol, 25 ml., and 4.0 ml. of acetic anhydride were added, and the solution was kept at 25° for 16 hours. The solvents were distilled, and the acetyl derivative was crystallized from a benzene–petroleum ether mixture; yield 1.55 g. (78%), m.p. 120.5–121.5°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.27; H, 6.59; N, 6.73.

The infrared spectrum had bands at 6.05, 6.13, 6.37, 6.85 and 7.12 μ.

1-Acetyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (33).—A solution of 2.63 g. of 1-benzoyl-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole in 25 ml. of ethanol and 5 ml. of 50% aqueous sodium hydroxide solution was heated under reflux for 2.25 hours. The solution was concentrated to about 10 ml., and the residue was diluted with 100 ml. of ether and 25 ml. of water. The ether layer was separated and washed with water. It was then extracted with dilute hydrochloric acid to remove basic material, and the extract was separated and neutralized with excess sodium bicarbonate. The crude 1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was extracted with 100 ml. of ether, and the solution was dried and concentrated to 25 ml. Methanol, 25 ml., and 5 ml. of acetic anhydride were added, and the mixture was kept at 25° for 18 hours. Solvents were distilled, and the acetyl derivative was crystallized from an ether–petroleum ether mixture; yield 1.54 g. (77%), m.p. 104–105°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40; H, 7.61; N, 6.68.

The infrared spectrum had bands at 6.04, 6.21, 6.28, 6.86 and 7.14 μ.

1-Benzoyl-4-bromo-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (34). A. From 1-Benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A mixture of 3.6 g. of the bromoketone in 25 ml. of warm dioxane was treated with a solution of 0.28 g. of sodium borohydride in 6.7 ml. of absolute alcohol, and the solution was stirred for 1.5 hours. Water, 20 ml., was added, the mixture was cooled, and the bromohydrin was filtered; yield 2.12 g. (54%). It was purified by recrystallization from methanol, m.p. 87° dec. When mixed with a sample prepared by method B below the melting point was unchanged.

B. From 1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—The epoxide, 5.0 g., was dissolved in a mixture of 100 ml. each of benzene and dry ether. Dry hydrogen bromide was passed into the solution with cooling until 23 g. had been absorbed. After standing for 5.5 hours at 25°, the mixture was concentrated to small volume *in vacuo*, and the residue was taken up in a mixture of chloroform and ether. The bromohydrin was filtered, washed with ether, and recrystallized from a few volumes of methanol. It deposited as crystals containing one molecule of methanol of crystallization; m.p. 80° dec., yield 4.0 g. (57%).

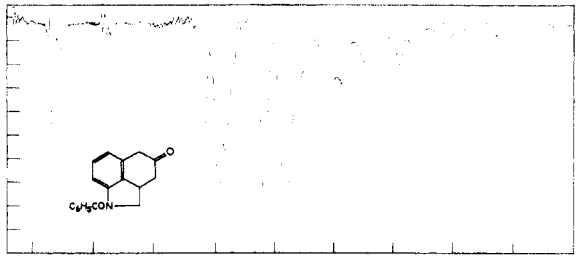
Anal. Calcd. for $C_{18}H_{16}BrNO_2 \cdot CH_4O$: C, 58.47; H, 5.17; N, 3.59; Br, 20.48. Found: C, 58.09; H, 4.68; N, 3.77; Br, 20.64.

1-Benzoyl-4-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (35).—A suspension of 40 g. of magnesium turnings in 4 l. of absolute ether was prepared in a 12-l. three-neck flask fitted with a stirrer and reflux condenser. Bromine, 40 ml., was added dropwise with stirring while cooling in ice to moderate the reaction. Two layers formed, and the reaction was completed by warming until the mixture was colorless. The solution was decanted from unreacted magnesium into a 22-l. three-neck flask containing 5 l. of dry ether. To the resulting mixture was added with stirring a solution of 20 g. of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole in 1 l. of dry benzene. Stirring was continued for 1.5 hours, after which the mixture was allowed to stand for 18 hours at 25°. The solvent was evaporated to dry-

ness *in vacuo*. Dry toluene, 3 l., was added to the residue, and the resulting mixture was stirred and heated under reflux for 4 hours. It was then cooled and washed with ice-water. The organic layer was dried over magnesium sulfate, and the toluene was distilled under reduced pressure. The ketone was crystallized from a mixture of benzene and ether; yield 11.4 g., m.p. 147–149°; second crop, 3.7 g., m.p. 143–146°; total, 15.1 g. (75%). A sample for analysis had a m.p. of 149.5–151.5°; a mixture m.p. with the isomeric 5-keto compound was 120–141°.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.80; H, 5.61; N, 5.01.

The ultraviolet type was like Fig. 3, curve A.



The semicarbazone of the ketone was prepared in the usual way and was obtained as colorless prisms by recrystallization from aqueous acetic acid; m.p. 225–226°.

Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.75. Found: C, 68.00; H, 5.95; N, 16.11.

1-Benzoyl-4-methylamino-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (36).—Twenty grams of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was placed in an autoclave with 200 ml. of liquid methylamine, and the reaction mixture was heated at 100° for 16 hours. Excess methylamine was evaporated, and the residue was crystallized from benzene. The product was filtered and washed with benzene and petroleum ether; yield 25 g. (90%), m.p. 93–95°. The amino alcohol crystallized from benzene with one mole of solvent of crystallization.

Anal. Calcd. for $C_{19}H_{20}N_2O_2 \cdot C_6H_6$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.71; H, 6.85; N, 7.26.

The ultraviolet type was like Fig. 3, curve A.

1-Benzoyl-4-acetylmethylamino-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—Two-hundredths of a mole of the methylamino alcohol was dissolved in a mixture of 12 ml. of methanol and 60 ml. of ether, and 3 ml. of acetic anhydride was added. The mixture was kept at room temperature for one hour, cooled, and the product was filtered and washed with ether; yield 6.0 g. (86%), m.p. 158–160°.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00; CH_3 on N, 4.28. Found: C, 71.77; H, 6.40; N, 8.20; CH_3 on N, 4.12.

A one-tenth mole run gave an 89% yield. The ultraviolet type was like Fig. 3, curve A.

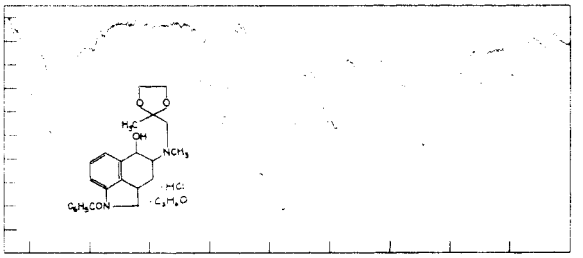
4-Methylamino-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A mixture of 1.54 g. (0.005 mole) of 1-benzoyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 0.5 g. (0.013 mole) of sodium hydroxide, 10 ml. of ethanol and 5 ml. of water was heated under reflux for eight hours. The mixture was cooled and extracted with benzene. The extract upon concentration gave material of m.p. 184–185° dec. Further purification using the same solvent raised the m.p. to 185.5–186.5° dec., yield 0.5 g. (49%).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.72. Found: C, 70.83; H, 7.91; N, 13.90.

1-Benzoyl-4-[N-methyl-N-acetonylamino]-5-hydroxy-1,2,-2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal Hydrochloride (37).—One-hundredth of a mole of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was mixed with 5.0 g. of methylaminoacetone ethylene ketal, and the mixture was warmed on the steam-bath for 19 hours. Excess amine was distilled *in vacuo*, and the product was dissolved in a few volumes of benzene. It was precipitated as a gum by addition of a few volumes of petroleum ether, and the solvents were removed by decantation. The gum was dissolved in 10 ml. of acetone, and dry hydrogen chloride was passed into the solution. The hydrochloride crystallized and was filtered and washed with cold acetone and ether; yield 81%, m.p. 156–158° dec. It contained one mole of acetone of crystallization.

Anal. Calcd. for $C_{24}H_{28}N_2O_4 \cdot HCl \cdot C_3H_6O$: N, 5.57; Cl, 7.05. Found: N, 5.54; Cl, 7.22; pK'_a in 66% dimethylformamide, 4.4.

Larger runs gave yields up to 88%.



For isolation of the compound as the free base the following procedure was used.

1-Benzoyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,-2,2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal (37).—A mixture of 155.5 g. of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 310 ml. of methylaminoacetone ethylene ketal was heated on the steam-bath for 17 hours. Excess amine was recovered by distillation under reduced pressure, and the residue was dissolved in a little benzene. Several volumes of petroleum ether were added to precipitate the product, and the supernatant solution was decanted. The residue was crystallized from 200 ml. of acetone; yield 98.5 g. (43%), m.p. 126–129°.

Anal. Calcd. for $C_{24}H_{28}N_2O_4$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.75; H, 7.23; N, 6.76.

The filtrates were treated with dry hydrogen chloride, and the hydrochloride of the product was filtered and recrystallized from a mixture of ethanol and acetone; yield 88 g. (31%), m.p. 159–160° dec. The total yield of product as free base and salt was thus 74%.

The sulfuric acid addition salt was prepared from the above free base in ethanol solution and was recrystallized from dilute ethanol, from which it deposited as crystals containing one mole of ethanol of crystallization, m.p. 184–185° dec.

Anal. Calcd. for $C_{24}H_{28}N_2O_4 \cdot H_2SO_4 \cdot C_2H_6O$: N, 5.07; S, 5.80. Found: N, 5.10; S, 6.00.

5-Hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal Dihydrochloride.—1-Benzoyl-5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole ethylene ketal hydrochloride, 15.0 g., was dissolved in 250 ml. of ethanol, and 75 ml. of an aqueous solution containing 30 g. of sodium hydroxide was added. The mixture was kept at 25° for 16 hours, after which it was concentrated *in vacuo* to small volume. The residue was mixed with water and extracted three times with benzene. The extracts were dried over magnesium sulfate, and the hydrochloride was precipitated with dry hydrogen chloride. The solvent was decanted, and the gummy product was crystallized from a mixture of ethanol and acetone; yield 5.2 g. (40%). A sample was recrystallized from the same solvents, m.p. 166–167° dec. It crystallized with one molecule of acetone of crystallization.

Anal. Calcd. for $C_{17}H_{24}N_2O_3 \cdot 2HCl \cdot C_3H_6O$: N, 6.44; Cl, 16.29. Found: N, 6.64; Cl, 16.37.

The same debenzoylated ketal-alcohol dihydrochloride was isolated in about 35% yield in an attempt to oxidize the benzoylketal-alcohol by a modified Oppenauer procedure using potassium *t*-butoxide and benzophenone.[38]

1-Acetyl-5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,-2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal.—One gram of the dihydrochloride salt of 5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole ethylene ketal was dissolved in 10 ml. of methanol, and 0.5 g. of anhydrous sodium acetate, 5 ml. of ether and 1 ml. of acetic anhydride were added. The reaction mixture was kept at 25° for three days, after which it was evaporated to dryness *in vacuo*, and the residue was mixed with excess aqueous sodium bicarbonate. The acetyl derivative was

(38) R. B. Woodward, N. L. Wendler and F. J. Brutschy, THIS JOURNAL, **67**, 1425 (1945).

extracted with chloroform, and the extract was dried over magnesium sulfate and concentrated *in vacuo*. The product was taken up in ether, and filtered; yield, 0.705 g. (89%), m.p. 150–151°. A sample was recrystallized from acetone; m.p. 152–153°.

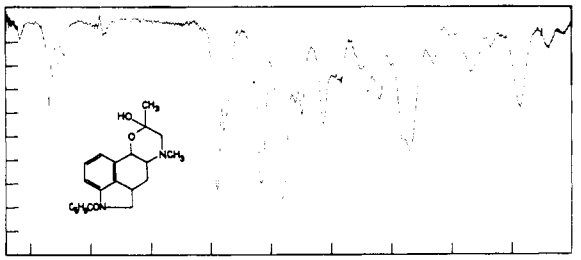
Anal. Calcd. for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.62; H, 7.49; N, 8.18.

The ultraviolet type was like Fig. 3, curve B.

4-Benzoyl-4,5,5a,6,6a,8,9,10a-octahydro-7,9-dimethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazin-9-ol (38). A. From 1-Benzoyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A solution of 14.8 g. of the amino alcohol, 2.64 g. of bromoacetone and 125 ml. of benzene was heated at reflux for one hour. The supernatant liquid was decanted from the insoluble material and washed well with water and aqueous sodium bicarbonate. The benzene solution was dried, concentrated, and cooled, and the crystalline hemiketal was filtered; yield 2.8 g. (40% based on bromoacetone), m.p. 153–155°. A sample was recrystallized from aqueous acetone, m.p. 158–160°.

Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.42; H, 6.60; N, 7.64.

The ultraviolet type was like Fig. 3, curve A.



B. From 1-Benzoyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal.—A solution of 0.5 g. of the ketal in 20 ml. of 90% acetic acid was warmed on a steam-bath for four and two-thirds hours. The acetic acid was evaporated under reduced pressure, and the residue was crystallized from a mixture of acetone and ether; yield 40 mg. (9%), m.p. 150–151°. A mixture melting point determination with a sample prepared by method A, above, showed no depression.

4,5,5a,6,6a,8,9,10a-Octahydro-7,9-dimethyl-7*H*-indolo-[3,4-*gh*][1,4]-benzoxazin-9-ol.—A solution of 1.0 g. of the 1-benzoyl derivative above in 40 ml. of 6 *N* hydrochloric acid was kept at room temperature for five days. The mixture was cooled, and 0.19 g. of benzoic acid was removed by filtration. The filtrate was concentrated *in vacuo* to small volume, and the residue was dissolved in water and neutralized with sodium bicarbonate. The product was extracted with chloroform; the solution was dried over magnesium sulfate, and the solvent was distilled. The hemiketal was crystallized from ethanol; yield 0.13 g., m.p. 120–122°.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.31; H, 7.98; N, 10.32.

4,5,5a,6,6a,8,9,10a-Octahydro-7,9-dimethyl-9-methoxy-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (39). A. From 4-Benzoyl-4,5,5a,6,6a,8,9,10a-octahydro-7,9-dimethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazin-9-ol (38).—A solution of 1.0 g. of the hemiketal in 40 ml. of methanol was saturated with dry hydrogen chloride and kept at 25° for 16 hours. The mixture was evaporated *in vacuo*, and the residue was washed with ether to remove methyl benzoate. The crude dihydrochloride was then crystallized from a mixture of absolute ethanol and ether; yield 0.3 g. (31%), m.p. 193–195° dec. An analytical sample recrystallized from the same mixture had a m.p. of 199–201° dec.

Anal. Calcd. for $C_{16}H_{22}N_2O_2 \cdot 2HCl$: C, 55.33; H, 6.97; N, 8.09; Cl, 20.42. Found: C, 54.74; H, 7.16; N, 8.22; Cl, 19.82.

B. From 1-Benzoyl-5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal.—One gram of the ketal-alcohol was treated exactly as above with methanol–hydrogen chloride. One hundred and fifty milligrams (18%) of the dihydrochloride was obtained, m.p. 193° dec. A mixture m.p. with the sample prepared by method A above was not depressed; ultraviolet λ_{max} 245 mμ (ε 6800), 292 mμ (ε 2200).

1-Benzoyl-5-carbethoxymethyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—In a flask protected from atmospheric moisture were placed 16.6 g. (0.06 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 30 g. of activated zinc, 300 ml. of anhydrous benzene and 15 ml. of ethyl bromoacetate, and the mixture was stirred and heated to reflux. A small amount of ethylmagnesium iodide along with a crystal of iodine were added to initiate the reaction. At the end of 0.5 hour from the start of the reaction, 15 g. of zinc and a crystal of iodine were added, and this was repeated twice more at 0.5-hr. intervals. One hour after the last addition, 15 g. of zinc and 7.5 ml. of ethyl bromoacetate were added. At the end of another hour, 15 g. of zinc and a crystal of iodine were added, and the reaction mixture was stirred and heated under reflux for an additional hour, after which it stood at room temperature.

After 200 ml. of benzene had been added, the whole was poured into 300 g. of ice and water, and the mixture was acidified with a solution of 25 g. of concentrated sulfuric acid in 50 ml. of water. This dissolved all of the precipitate except the unreacted zinc. The benzene layer was separated, and the aqueous layer was extracted twice with benzene. The extracts were combined and washed with water, dilute acetic acid solution, dilute ammonium hydroxide and finally with water, and dried over anhydrous magnesium sulfate. Concentration at reduced pressure gave an oily residue which deposited crystals on standing overnight at room temperature; yield 7.7 g. (35%), m.p. 136–138°.

Recrystallization from ethyl acetate gave an analytical sample, m.p. 142–143°

Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.35; N, 3.83. Found: C, 72.15; H, 6.64; N, 3.88.

1-Benzoyl-5-carbomethoxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (40, R = Me).—A mixture of 300 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 300 g. of activated zinc, 1.0 g. of mercuric chloride, 6 l. of dry benzene and 90 g. of methyl bromoacetate was prepared in a 12-l. three-neck flask fitted with a stirrer, reflux condenser and heating mantle. The mixture was heated under reflux and stirred, and after an induction period of 10–30 minutes the reaction started, and the solution became cloudy. After 3.5 hours 90 g. of methyl bromoacetate and 20 g. of zinc were added, and after five hours 75 g. of the bromoester and 60 g. of zinc were added. Refluxing and stirring were maintained for a total of six hours, after which the reaction mixture was allowed to cool and stand overnight. Two normal hydrochloric acid (1500 ml.) was then added with stirring. The organic layer was separated and washed with 1500 ml. of 2 *N* hydrochloric acid, once with water, three times with 2 *N* ammonium hydroxide, and again with water. The solution was dried over magnesium sulfate and concentrated to about 1200 ml. *in vacuo*. Petroleum ether was added slowly until the solution became cloudy; the mixture was cooled, and the crude ester was filtered. A solution of the crude hydroxy ester in 2250 ml. of 98% formic acid and 500 ml. of acetic anhydride was warmed for one hour on a steam-bath. The dehydration mixture was poured into 6 l. of cold water, and the product was extracted with about 5 l. of benzene in two portions. The extract was washed several times with water and 5% aqueous sodium bicarbonate, and the solvent was distilled under reduced pressure. The product was recrystallized twice from methanol using decolorizing carbon. The yield (two crops) was 300.4 g. (83%), m.p. 114–126°.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.12; H, 5.74; N, 4.26.

The infrared carbonyl bands were at 5.75 (ester) and 6.08 μ (amide).

1-Benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]-indole (40, R = H).—A mixture of 190 g. of 1-benzoyl-5-carbomethoxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole and 1100 ml. of absolute alcohol was brought to reflux, and with efficient stirring 250 ml. of 3 *N* sodium hydroxide was added over a period of 3 hours. After heating for an additional 1.5 hours, the mixture was concentrated to about 600 ml. *in vacuo* and diluted with 2 l. of water. After extraction of unreacted starting material with two 250-ml. portions of chloroform, the aqueous solution was acidified with 75 ml. of concentrated hydrochloric acid, and the product was extracted with four 250-ml. portions of chloroform. The combined chloroform extracts were washed with 250 ml. of water and dried over anhydrous magnesium sulfate.

After removal of the chloroform *in vacuo*, 550 ml. of hot ethyl acetate and several grams of decolorizing carbon were added to the residual oil, and the mixture was allowed to boil for 20 minutes. The carbon was filtered, and the filtrate was allowed to stand in a refrigerator overnight. The crystalline product was collected and washed with a small amount of cold ethyl acetate. The yield of acid, m.p. 166–170° dec., was 157 g. (86%). A second crop of less pure acid raised the yield to 96%. Several recrystallizations from ethyl acetate gave an analytical sample, m.p. 168.5–170° dec.

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.21; H, 5.37; N, 4.39. Found: C, 75.06; H, 5.53; N, 4.00.

1-Benzoyl-5-[γ-bromoacetonyl]-1,2,2a,3-tetrahydrobenz[*cd*]indole (41).—1-Benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (50 g.) was suspended in 750 ml. of dry toluene in a flask protected from moisture. Oxalyl chloride (40 ml.) and pyridine (1 ml.) were added, and the mixture was allowed to stir at room temperature until it was homogeneous (2 hours). A small amount of insoluble oil was separated from the reaction mixture by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residual oil was dissolved in dry benzene and again concentrated to dryness *in vacuo*. The crude acid chloride was dissolved in 1 l. of dry benzene, and the solution was added dropwise over a period of 2 hours to an ice-cold well-stirred solution of diazomethane (from 75 g. of nitrosomethylurea) in methylene chloride. The reaction mixture was allowed to stir at room temperature overnight. After adding 500 ml. of chloroform (to diminish emulsion formation), 300 ml. of 48% hydrobromic acid was added over a period of one hour with ice-bath cooling and vigorous stirring. The mixture was allowed to stir an additional 3 hours at room temperature, and then the layers were separated. The organic layer was washed with two 500-ml. portions of water and 500 ml. of saturated sodium bicarbonate solution. It was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a tan solid. The yield of crude bromoketone, m.p. 127–129°, was 48 g. (77%). The best analysis was obtained from material, m.p. 128–132°, recrystallized from benzene–petroleum ether.

Anal. Calcd. for $C_{21}H_{18}BrNO_2$: C, 63.64; H, 4.58; N, 3.53. Found: C, 64.56; H, 4.91; N, 3.72.

The ultraviolet type was like Fig. 2, curve A.

1-Benzoyl-5-(β,γ-epoxypropyl)-1,2,2a,3-tetrahydrobenz[*cd*]indole (42).—To a solution of 20 g. of sodium borohydride in 960 ml. of methanol and 40 ml. of water was added 20 g. of 1-benzoyl-5-(γ-bromoacetonyl)-1,2,2a,3-tetrahydrobenz[*cd*]indole in several portions. When the spontaneous reaction had subsided, the mixture was heated under reflux for one hour. It was then poured into several volumes of water, and the white precipitate which separated was extracted with two 300-ml. portions of chloroform. The combined chloroform extracts were washed successively with 150 ml. of 1 *N* hydrochloric acid, 150 ml. of 1 *N* sodium hydroxide and water. The solution was dried over anhydrous magnesium sulfate and concentrated to dryness *in vacuo*. The residual oil was dissolved in a minimum amount of hot ethanol and allowed to stand at 0°. The yield of epoxide, m.p. 108–111°, was 9.5 g. (59%). Several crystallizations from aqueous ethanol gave an analytical sample, m.p. 115–117°.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.49; H, 6.03; N, 4.41. Found: C, 78.83; H, 6.13; N, 4.67.

The ultraviolet type was like Fig. 2, curve A.

1-Benzoyl-4,5-epoxy-5-[β,γ-epoxypropyl]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (43).—A mixture of 9.5 g. (0.029 mole) of 1-benzoyl-5-[β,γ-epoxypropyl]-1,2,2a,3-tetrahydrobenz[*cd*]indole and 6.1 g. (0.0435 mole) of perbenzoic acid in 90 ml. of chloroform was allowed to stand overnight at 0°. The chloroform solution was washed with dilute sodium hydroxide and water and then dried over anhydrous magnesium sulfate. The chloroform was evaporated *in vacuo*, leaving an oil which crystallized upon trituration with aqueous ethanol. The yield of crude diepoxide, m.p 150–170°, was 4.7 g. (42%). Crystallization from ethanol gave an analytical sample, m.p. 186–187°, which contained one mole of ethanol of crystallization.

Anal. Calcd. for $C_{21}H_{19}NO_3 \cdot C_2H_5OH$: C, 72.80; H, 6.64. Found: C, 72.94; H, 6.19.

The ultraviolet type was like Fig. 3, curve A.

4-Benzoyl-9,10a-dihydroxy-7-methyl-4,5,5a,6,6a,7,8,9,-10,10a-decahydroindolo[4,3-*fg*]quinoline (44).—A mixture of 3.8 g. of 1-benzoyl-4,5-epoxy-5-[β,γ-epoxypropyl]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and about 100 ml. of liquid methylamine was heated at 100° in an autoclave for 24 hours. The methylamine was allowed to evaporate, and the residual oil was dissolved in chloroform and extracted with two 50-ml. portions of dilute hydrochloric acid. The combined acid extracts were washed with two 25-ml. portions of chloroform. The acid solution was made alkaline with sodium hydroxide, and the basic product was extracted with three 40-ml. portions of chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo* leaving 3.3 g. of crude, amorphous tetracyclic dialcohol, m.p. 95–105°. Secondary amine impurities were removed by dissolving the product in about 100 ml. of ice-cold 6 *N* hydrochloric acid and adding slowly and with stirring 70 ml. of 20% sodium nitrite solution. The insoluble neutral material which formed was extracted with chloroform, and the aqueous layer was made basic with cold sodium hydroxide solution. The product (free of secondary amine) was extracted with three 50-ml. portions of chloroform, and the solution was washed with water and dried over potassium carbonate. The solvent was removed, and the product was triturated with petroleum ether and filtered, m.p. 102–110°. It was not obtained in crystalline form.

Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 71.25; H, 6.77; N, 6.63.

The ultraviolet type was like Fig. 3, curve A.

Although the product was not analytically pure, it was suitable for conversion to the crystalline methiodide below.

4-Benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,-9,10,10a-decahydroindolo[4,3-*fg*]quinolinium Iodide.—When a solution of 0.205 g. (0.000564 mole) of 4-benzoyl-9,10a-dihydroxy-7-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[4,3-*fg*]quinoline in 10 ml. of ethyl acetate and two drops of benzyl alcohol was treated with 4.56 g. (0.032 mole) of methyl iodide with warming overnight, the crystalline methiodide was obtained. It was filtered and purified by recrystallization from ethanol–ethyl acetate solution; m.p. 200–202° dec.

Anal. Calcd. for $C_{23}H_{27}IN_2O_3$: C, 54.55; H, 5.38; N, 5.53. Found: C, 54.53; H, 5.64; N, 5.61.

1-Benzoyl-5-carbomethoxymethyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (45).—A mixture of 3.5 g. (0.0105 mole) of 1-benzoyl-5-carbomethoxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole, 30 ml. of chloroform, and a solution of 2.2 g. (0.012 mole) of monoperphthalic acid in 37 ml. of ether was allowed to stand at room temperature for one week. The supernatant solution was decanted and washed successively with saturated sodium bicarbonate solution and water. The organic solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to a viscous oil, which solidified upon trituration with benzene. The yield of the epoxide was 2.0 g. (55%). Crystallization from benzene gave an analytical sample, m.p. 181–182°.

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.91; H, 5.66; N, 3.93.

The ultraviolet type was like Fig. 3, curve A.

4-Benzoyl-5,5a,6,6a-tetrahydro-7-methyl-4*H*-indolo[6,5,-4-*cd*]indol-8(7*H*)-one (47).—A mixture of 1 g. of 1-benzoyl-4,5-epoxy-5-carbomethoxymethyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and a large excess of liquid methylamine (about 100 ml.) was heated at 100° for 6 hours in an autoclave. The methylamine was allowed to evaporate, and the residual oil was dissolved in chloroform. The chloroform solution was washed with dilute hydrochloric acid and water and then dried over anhydrous magnesium sulfate. The chloroform was removed *in vacuo* leaving a viscous oil which, on standing, deposited a crystalline solid. The mixture was triturated with ethanol, and the solid was collected on a filter. Several crystallizations from ethanol gave a pure sample of the lactam, m.p. 201–202°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 75.72; H, 6.09; N, 8.35.

Infrared carbonyl bands were at 6.00 (lactam) and 6.08 μ (amide).

1-Benzoyl-2,2a,3,4-tetrahydro-4-hydroxybenz[*cd*]indole-Δ⁵(1*H*), α-Acetic Acid Lactone (49).—A mixture of 1.0 g. of 1-benzoyl-4,5-epoxy-5-carbomethoxymethyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 4 ml. of sarcosine methyl ester was heated at 100° for 2.5 hours. Sarcosine ester was

distilled *in vacuo*, and the residual oil was crystallized from aqueous ethanol. The unsaturated lactone crystallized with one molecule of water of crystallization, m.p. 160–161°.

Anal. Calcd. for $C_{20}H_{15}NO_3 \cdot H_2O$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.87; H, 5.69; N, 4.11.

Infrared carbonyl bands were at 5.84 (lactone) and 6.09 μ (amide).

Sodium Salt of 1-Benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (51, R = Na).—Potassium metal, 179 g., was added to a mixture of 3700 ml. of dry *t*-butyl alcohol and 4900 ml. of dry benzene contained under nitrogen in a 22-l. round-bottom flask. After the potassium had dissolved the solution was evaporated to dryness *in vacuo*, and the cake of potassium *t*-butoxide was mixed with 3700 ml. of dry benzene and 4900 ml. of toluene. The cake was broken up by mechanical stirring, and while keeping the reaction mixture protected continuously under an atmosphere of nitrogen it was cooled to −5°. Precooled 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 750 g., and 593 g. of ethyl chloroacetate were then added as rapidly as possible. Stirring in the cooling bath was maintained for 15 minutes during which time the temperature rose to 9–10° and fell again to −5°. The cooling bath was removed, and the mixture was heated to 75° with stirring during 40–45 minutes. At this point it was cooled rapidly to room temperature or below. The mixture was then washed twice with ice-water, twice with cold, dilute sulfuric acid, once with water, and twice with aqueous sodium bicarbonate solution. It was dried over magnesium sulfate, and the solvents were distilled under reduced pressure. The sirupy glycidic ester was dissolved in 5900 ml. of commercial absolute ethanol, and 350 ml. of 50% aqueous sodium hydroxide was added. The mixture was warmed rapidly to 70–75° and was kept at that temperature for a few minutes. It was then cooled rapidly below room temperature by evaporation *in vacuo* without external heating. The sodium salt crystallized, and the mixture was kept at 0° for 16 hours. The product was filtered and washed well with absolute ethanol and ether; yield 774 g. (80%). A further crop of less pure material, 109 g. (11%), was obtained by dilution of the filtrates with a few volumes of dry ether. A sample of the first crop was recrystallized from a mixture of methanol, ethanol and ether; m.p. 230–232° dec.

Anal. Calcd. for $C_{20}H_{16}NNaO_4$: N, 3.92; Na, 6.44. Found: N, 3.85; Na, 6.65.

1-Benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (52).—One-tenth mole (35.7 g.) of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was dissolved in 150 ml. of water and mixed with a solution containing 100 g. of sodium bisulfite in 200 ml. of water. The resulting mixture was filtered, kept at 25° for two hours, and then cooled. The bisulfite addition product of the aldehyde was filtered and washed with a little ice-water, alcohol and ether; yield 35 g. (88%), m.p. 128–130°.

Anal. Calcd. for $C_{19}H_{18}NO_5SNa$: N, 3.54; S, 8.11. Found: N, 4.07; S, 7.66.

The bisulfite product was dissolved in 350 ml. of water and decomposed by addition of 25 ml. of acetic acid and 35 ml. of concentrated hydrochloric acid. After long cooling 17.0 g. of the amorphous aldehyde was deposited, m.p. 90–100° dec. It was never obtained in crystalline form.

Anal. Calcd. for $C_{19}H_{17}NO_2$: N, 4.81. Found: N, 4.91.

Similar results were obtained simply by acidifying aqueous solutions of the Darzens sodium salt.

1-Benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Semicarbazone.—A solution containing 5 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 5 g. of semicarbazide hydrochloride and 5 g. of anhydrous sodium acetate in 250 ml. of 50% aqueous ethanol was heated at reflux for 1.25 hours, and then concentrated under reduced pressure to a volume of 75 ml. Five per cent. sodium carbonate solution (100 ml.) was added, and the semicarbazone was filtered and recrystallized from 200 ml. of methanol; yield 2.2 g. (45%), m.p. 200–202° dec.; ultraviolet λ_{max} 235 mμ (ϵ 18800), 267 mμ (ϵ 12100), 293 mμ (ϵ 8050).

Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.09. Found: C, 68.63; H, 5.44; N, 15.57.

1-Benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Oxime.—A solution containing 17.9 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 21.9 g. of hydroxylamine hydrochloride, and 21.9 g. of anhydrous sodium acetate in 270 ml. of water and 180 ml. of ethanol was heated at reflux for two hours. It was then concentrated to about 250 ml., and 500 ml. of cold water was added. The product was filtered, washed with water and crystallized from methanol; yield 8.5 g. (55%), m.p. 168–170°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.15; H, 6.16; N, 9.20.

1-Benzoyl-5-acetoxymethylene-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A mixture of 71.5 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 25 g. of anhydrous sodium acetate in 800 ml. of acetic anhydride and 100 ml. of acetic acid was refluxed for one hour and then concentrated to small volume *in vacuo*. An excess of methanol was added slowly to decompose any remaining acetic anhydride, and the solution was decolorized and again evaporated. Water (2 l.) was added slowly with shaking, and the product was filtered and then recrystallized from acetic acid; yield 49.6 g. (74.5%). The compound showed a double melting point at 125–130° and 166–168°. The higher melting form could be obtained by recrystallization from ethanol.

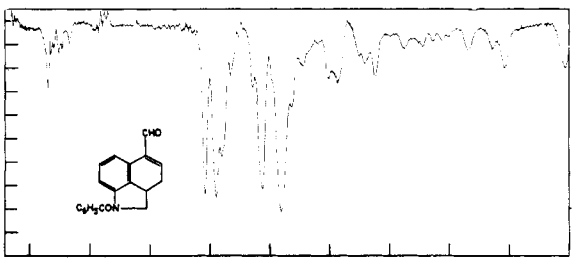
Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.50; H, 5.77; N, 4.45.

The infrared carbonyl bands were at 5.70 (ester) and 6.10 μ (amide).

The enol acetate could be prepared also, but less conveniently, from either 1-benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole or its sodium bisulfite addition product.

1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (50).—Three hundred and thirty-five grams of 1-benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole semicarbazone was mixed with 4400 ml. of chloroform, 1050 ml. of pure, freshly distilled pyruvic acid and 15 ml. of water. The solution was kept at 25° for 18 hours, after which it was diluted with 1 l. of chloroform and washed three times with 1500-ml. portions of water and once with 1000 ml. of 5% sodium bicarbonate. The chloroform solution was dried over magnesium sulfate, and the solvent was distilled *in vacuo*. The crystalline aldehyde was digested with a little hot methanol, and the mixture was cooled, and the product was filtered and washed with methanol and ether; yield 234.3 g. (83.5%), m.p. 179.5–180.5°. Similar runs gave yields in the range of 80 to 89%. A sample for analysis was recrystallized from ethanol.

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.40; H, 5.67; N, 4.44.



1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole Semicarbazone.—Ten liters of acetonitrile in a 22-l. round-bottom flask was warmed to 58°. The solvent was stirred while 500 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 448 g. of pyridine perbromide hydrobromide was added. The reaction mixture was illuminated with two 250-watt heat lamps and stirred for 12–15 minutes, during which time the temperature rose to about 63°. The illumination was removed, and 468 g. of semicarbazide hydrochloride and 460 g. of anhydrous sodium acetate was added, and the mixture was digested on a steam-bath for three hours with frequent agitation. The solvent was then removed by distillation under reduced pressure, and the residue was mixed with about 12 l. of water. The crude semicarbazone was filtered and washed well with water. It was purified by recrystallization from a mixture of acetic acid and methanol; yield 426 g. (87%), m.p. 231–232° dec., ultraviolet λ_{max} 257 mμ (ϵ 24200).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.15; H, 5.54; N, 16.20.

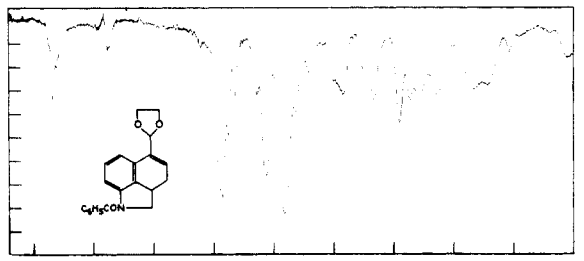
The unsaturated semicarbazone was also prepared by an exactly similar procedure starting with 1-benzoyl-5-acetoxymethylene-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, but the yield was inferior.

1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole Phenylhydrazone.—This was prepared from the aldehyde and phenylhydrazine in ethanol solution using a little acetic acid as catalyst. It was recrystallized from a benzene–ethanol mixture; m.p. 210–212°.

Anal. Calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.08. Found: C, 78.89; H, 5.88; N, 11.02.

1-Benzoyl-5-[2′-dioxolanyl]-1,2,2a,3-tetrahydrobenz[*cd*]-indole (53).—A mixture of 140 g. of 1-benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole, 250 ml. of ethylene glycol, 480 ml. of toluene and 0.4 g. of *p*-toluenesulfonic acid was heated under reflux for 7.5 hours using a water separator to collect water formed in the reaction. The reaction mixture was washed thoroughly with aqueous sodium bicarbonate, and the aqueous wash was extracted once with chloroform. The chloroform extract was combined with the original toluene solution, and the mixture was dried over magnesium sulfate. The solvents were distilled under reduced pressure, and the residual acetal was taken up in methanol, chilled and filtered; yield 130 g. (80%), m.p. 150–153°. An analytical sample recrystallized from a mixture of ethyl acetate and petroleum ether melted at 153–155°.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.54; H, 5.88; N, 4.24.

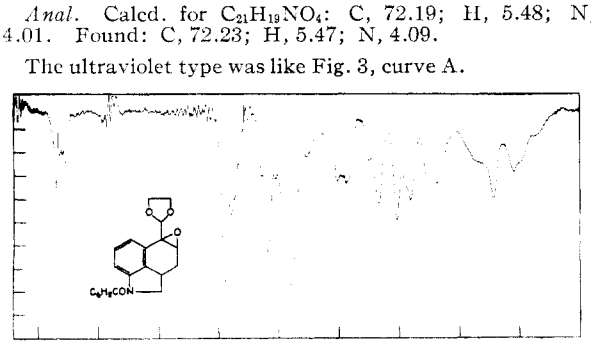


1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole from 1-Benzoyl-5-[2′-dioxolanyl]-1,2,2a,3-tetrahydrobenz-[*cd*]indole.—The acetal, 0.5 g., in 20 ml. of 90% acetic acid was warmed for 0.5 hour on a steam-bath. Water was added until the mixture became cloudy; the solution was cooled, and 0.35 g. (82%) of the unsaturated aldehyde was filtered, m.p. 176–179°. A mixture melting point with authentic aldehyde was unchanged.

1-Benzoyl-5-[2′-dioxolanyl]-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (54).—1-Benzoyl-5-[2′-dioxolanyl]-1,2,2a,3-tetrahydrobenz[*cd*]indole, 83.5 g. (0.25 mole), was dissolved in a cold solution containing 0.3 mole of perbenzoic acid in 600 ml. of chloroform. The reaction mixture was kept at 0–5° for 23 hours, after which it was washed twice with 5% aqueous sodium bicarbonate solution. It was then dried over magnesium sulfate, and the solvent was distilled under reduced pressure. The epoxyacetal was crystallized from methanol; yield 75.5 g. (87%), m.p. 174–176°. Recrystallization from methanol raised the melting point to 178–180°.

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.23; H, 5.47; N, 4.09.

The ultraviolet type was like Fig. 3, curve A.



1-Benzoyl-5-[2′-dioxolanyl]-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (55). A. From 1-Benzoyl-5-[2′-dioxolanyl]-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A mixture of 15 g. of the epoxy acetal and 500 ml. of liquid methylamine was heated in an autoclave at 120° for 14 hours. The methylamine was evaporated completely, and the dark amorphous product was dissolved in 250 ml. of methanol, and the solution was decolorized with carbon. The filtrate after removal of carbon was then mixed with a hot solution of 9.3 g. of picric acid in 60 ml. of ethanol. The picrate salt which crystallized was filtered and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. A sample was recrystallized for analysis from a mixture of dimethylformamide and methanol; m.p. 240° dec.

Anal. Calcd. for $C_{22}H_{24}N_2O_4 \cdot C_6H_3N_3O_7$: C, 55.17; H, 4.47; N, 11.49. Found: C, 55.51; H, 4.82; N, 10.61.

The picrate from several runs, 52.0 g., was dissolved by shaking in a mixture of 500 ml. of 40% aqueous ethanolamine and 300 ml. of chloroform. The chloroform was separated, and the aqueous amine layer was washed with two 200-ml. portions of chloroform. The combined chloroform extracts were washed three times with aqueous ethanolamine solution, after which they were dried over magnesium sulfate, and the chloroform was distilled. The residual amino alcohol was crystallized from ethyl acetate; yield 23.7 g. (71%), m.p. 150–152°. A smaller run gave an 80% conversion. A sample after recrystallization from a mixture of ethyl acetate and petroleum ether had a melting point of 151–153°. The pK'_a in 66% dimethylformamide was 8.6.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.10; H, 7.10; N, 7.57.

The ultraviolet type was like Fig. 3, curve A.

The rather hygroscopic hydrochloride salt was prepared and crystallized from a mixture of ethanol and ethyl acetate; m.p. 221° dec. It gave analyses indicating a monohydrate.

Anal. Calcd. for $C_{22}H_{24}N_2O_4 \cdot HCl \cdot H_2O$: C, 60.75; H, 6.26; N, 6.44. Found: C, 60.38; H, 6.41; N, 6.10.

B. From 1-Benzoyl-5-[2′-dioxolanyl]-5-hydroxy-4-[methyl-β-cyanoethylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—The cyanoethyl derivative below, 3.0 g., in 100 ml. of 90% acetic acid was heated on a steam-bath for 17 hours. The solution was decolorized with carbon and evaporated *in vacuo*. The residue was dissolved in chloroform, and the chloroform solution was extracted with dilute hydrochloric acid. The acid extract was neutralized with excess sodium bicarbonate and extracted with chloroform. The solution was dried; the solvent was distilled, and the amino alcohol was crystallized from ethyl acetate; yield 0.4 g. (15%), m.p. 150–152°. A mixture melting point with a sample of the starting material was depressed, but a mixture melting point with an authentic sample prepared as above showed no depression.

1-Benzoyl-5-[2′-dioxolanyl]-5-hydroxy-4-[N-methyl-*p*-toluenesulfonamido]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—A solution of 2.0 g. of 1-benzoyl-5-[2′-dioxolanyl]-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 1.2 g. of *p*-toluenesulfonyl chloride in 8 ml. of dry pyridine was kept at 25° for 16 hours. It was then poured into water, and the product was extracted with chloroform. The chloroform solution was dried, and the solvent was distilled. The derivative was crystallized from acetone; yield 1.43 g. (51%), m.p. 200–205°. A sample was recrystallized from a dimethylformamide–methanol mixture; m.p. 204–206°.

Anal. Calcd. for $C_{29}H_{30}N_2O_6S$: N, 5.25. Found: N, 5.08.

5-[2′-Dioxolanyl]-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole. A. By Alkaline Hydrolysis.—1-Benzoyl-5-[2′-dioxolanyl]-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 1.0 g., in 20 ml. of ethanol was treated with 1 ml. of 50% aqueous sodium hydroxide, and the solution was refluxed for 0.5 hour and then kept at 25° for 16 hours. The ethanol was distilled under reduced pressure, and the residue was taken up in water and extracted with chloroform. The extracts were dried over magnesium sulfate and evaporated to dryness. The residual amino alcohol was taken up in alcohol and filtered; yield 0.35 g. (48%), m.p. 207–210°. It was recrystallized from a mixture of dimethylformamide and methanol.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.18; H, 7.31; N, 9.94.

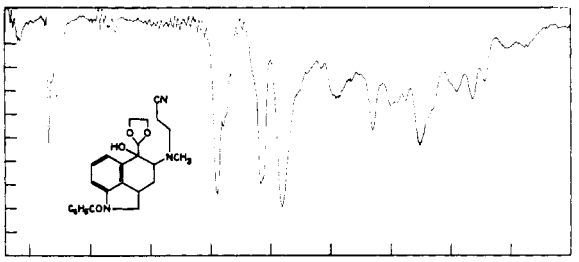
The dihydrochloride salt was prepared and crystallized from a methanol–acetone mixture; m.p. 250° dec.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot 2HCl$: C, 51.58; H, 6.35; N, 8.02. Found: C, 51.56; H, 6.52; N, 8.18.

B. By Acid Hydrolysis.—A solution of 1.0 g. of the 1-benzoyl-5-hydroxy-4-methylamino-5-acetal in 50 ml. of methanol containing 1 ml. of concentrated sulfuric acid was refluxed for 16 hours. Most of the methanol was distilled, and the residue was mixed with 20 ml. of 6 *N* sodium hydroxide. The product was extracted with chloroform in three portions and isolated as above; yield 0.3 g. (41%), m.p. 208–211°. A mixture m.p. with a sample obtained by alkaline hydrolysis showed no depression. Hydrolysis of the benzoyl compound with aqueous acid gave similar results.

1-Benzoyl-5-(2′-dioxolanyl)-5-hydroxy-4-(methyl-β-cyanoethylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (56).—A mixture of 6.5 g. of 1-benzoyl-5-(2′-dioxolanyl)-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 50 ml. of acrylonitrile was warmed briefly to 50° until homogeneous and then kept at 25° for 16 hours. Excess acrylonitrile was distilled *in vacuo*, and the residue was crystallized from ethyl acetate; yield 5.6 g. (88%), m.p. 130–132°. A sample recrystallized from a mixture of ethyl acetate and petroleum ether melted at 135–138°.

Anal. Calcd. for $C_{25}H_{27}N_3O_4$: C, 69.26; H, 6.28; N, 9.69. Found: C, 69.12; H, 6.50; N, 9.72.



The hydrochloride salt recrystallized from an alcohol–ether mixture melted at 184–186° dec.

Anal. Calcd. for $C_{25}H_{27}N_3O_4 \cdot HCl$: C, 63.89; H, 6.01; N, 8.94. Found: C, 63.94; H, 6.02; N, 8.64.

5-(2′-Dioxolanyl)-5-hydroxy-4-(methyl-β-carbomethoxyethylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (57).—Twenty ml. of methanol was saturated with dry hydrogen chloride, and 0.5 g. of 1-benzoyl-5-(2′-dioxolanyl)-5-hydroxy-4-(methyl-β-cyanoethylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole was added. The solution was kept at 25° for four days, after which it was concentrated *in vacuo* to dryness. The residue was taken up in chloroform and water, and the aqueous layer was separated and neutralized with excess sodium bicarbonate. The product was extracted with chloroform; the extract was dried, and the solvent was distilled. The residual ester was crystallized from ethyl acetate; yield 0.1 g. (24%), m.p. 138–140°.

Anal. Calcd. for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 63.07; H, 7.21; N, 7.55.

The infrared carbonyl band was at 5.76 μ (ester).

5-(2′-Dioxolanyl)-5-hydroxy-4-(methyl-β-cyanoethylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (58).—A solution of 2.0 g. of the 1-benzoyl derivative above in 40 ml. of 6 *N* hydrochloric acid was kept at 25° for four days. Benzoic acid that precipitated from the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was crystallized from absolute ethanol; yield 1.3 g. (63%), m.p. 173–175° dec. The dihydrochloride recrystallized from dilute alcohol contained one mole of ethanol of crystallization.

Anal. Calcd. for $C_{18}H_{23}N_3O_3 \cdot 2HCl \cdot C_2H_6O$: N, 9.37; Cl, 15.81. Found: N, 9.37; Cl, 16.06.

The free base was obtained by dissolving the salt in water and adding excess sodium bicarbonate. It was extracted with chloroform and the solution was dried over magnesium sulfate and concentrated *in vacuo*. The product was crystallized from benzene; m.p. 130–132°.

Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.85; H, 7.31; N, 12.87.

The compound had an infrared band at 4.38 μ (nitrile).

1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole Oxime.—A solution containing 20 g. of 1-benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole, 24 g. of hydroxylamine hydrochloride and 24 g. of anhydrous sodium acetate in 400 ml. of alcohol and 300 ml. of water was heated under reflux with stirring for five hours. The mixture was cooled overnight, and the product was filtered and recrystallized from benzene–methanol; m.p. 195–197° dec., yield 12.5 g. (62%).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.29; H, 5.93; N, 9.05.

1-Benzoyl-5-cyano-1,2,2a,3-tetrahydrobenz[*cd*]indole (59).—To a suspension of 12.5 g. of 1-benzoyl-5-formyl-1,2,-2a,3-tetrahydrobenz[*cd*]indole oxime in 200 ml. of dry benzene was added 20 ml. of thionyl chloride dropwise during 15 minutes while stirring and cooling in an ice-bath. Stirring at 0–5° was continued for 0.5 hour, after which the solvent was distilled *in vacuo* at room temperature. The residue was dissolved in benzene, and the solution was again concentrated *in vacuo*. The product was crystallized from a benzene–petroleum ether mixture; yield 10.7 g. (91%), m.p. 142–144°.

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.79. Found: C, 80.33; H, 5.04; N, 9.56.

The infrared spectrum had bands at 4.48, 6.05, 6.15, 6.82, 7.16 and 7.34 μ.

1-Benzoyl-5-carbamyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (60).—To 2.86 g. (0.01 mole) of 1-benzoyl-5-cyano-1,2,2a,3-tetrahydrobenz[*cd*]indole was added 11.3 g. of 30% hydrogen peroxide (0.1 mole H_2O_2), in 22.6 g. of water, 150 ml. of acetone and 2.7 ml. of 10% sodium carbonate. Stirring was continued for 10 hours at room temperature, after which the reaction mixture was refluxed for 2.5 hours. Then, after concentration *in vacuo* on the steam-bath, 50 ml. of water was added to dissolve all sodium carbonate, and the crude product, m.p. 224.5–225.5° dec., was filtered; yield 3.12 g. (94.8%). Crystallization from methanol gave the analytical sample, m.p. 229.5–230° dec., containing 0.5 mole of water of crystallization.

Anal. Calcd. for $C_{19}H_{16}N_2O_3 \cdot {}^1/_2H_2O$: C, 69.29; H, 5.20; N, 8.51. Found: C, 69.56; H, 5.47; N, 7.97.

The ultraviolet type was like Fig. 3, curve A. The infrared spectrum had carbonyl bands at 5.89 (unsubstituted amide) and at 6.07 μ (substituted amide).

1-Benzoyl-5-carbamyl-5-hydroxy-4-methylamino-1,2,2a,-3,4,5-hexahydrobenz[*cd*]indole.—A mixture of 24.5 g. of 1-benzoyl-5-carbamyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 650 ml. of liquid methylamine was sealed in a steel autoclave and heated in a steam-bath for 18 hours. The methylamine was vented, and the residue was digested with a few volumes of hot methanol. The mixture was cooled, and the product was filtered and washed with methanol and ether; yield 25.4 g. (89%), m.p. 140–142° dec. A sample was recrystallized from a mixture of dimethylformamide and methanol, m.p. 141–143° dec. The amide contained one mole of methanol of crystallization.

Anal. Calcd. for $C_{20}H_{21}N_3O_3 \cdot CH_4O$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.89; H, 6.03; N, 10.69.

The solvent-free form was obtained by drying *in vacuo* and recrystallizing from benzene, m.p. 191–193°.

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.03; N, 11.96. Found: C, 68.61; H, 6.29; N, 12.27.

Carbonyl bands in the infrared were at 5.93 (unsubstituted amide) and 6.08 μ (substituted amide).

5-Carbamyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Dihydrochloride.—To 100 ml. of methanol saturated with dry hydrogen chloride was added 1.0 g. (0.0028 mole) of 1-benzoyl-5-carbamyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, and the mixture was allowed to stand for three days. Crystals had formed, m.p. 223–226° dec., yield 0.46 g. (51%). Recrystallization from a methanol–ether mixture gave an analytical sample, m.p. 223–226° dec.

Anal. Calcd. for $C_{13}H_{17}N_3O_2 \cdot 2HCl$: N, 13.12. Found: N, 12.69.

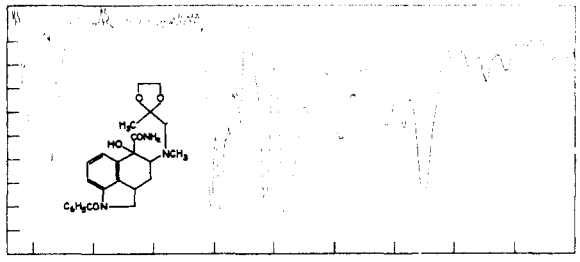
1-Benzoyl-5-carbamyl-4-dimethylamino-5-hydroxy-1,2,-2a,3,4,5-hexahydrobenz[*cd*]indole.—In a glass autoclave liner was placed 1.0 g. (0.003 mole) of 1-benzoyl-5-carbamyl-

4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 150 ml. of anhydrous dimethylamine. The liner and contents were placed in the bomb, which was sealed and heated on the steam-bath at 100° for 16 hours. After the bomb was opened and the excess dimethylamine was evaporated, the residue was recrystallized from benzene to give the product, m.p. 204–205.5°, yield 0.7 g. (61%).

Anal. Calcd. for $C_{21}H_{23}N_3O_3$: N, 11.50. Found: N, 11.71.

1-Benzoyl-5-carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal (61).—A mixture of 1.0 g. (0.003 mole) of 1-benzoyl-5-carbamyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 40.0 g. (0.3 mole) of methylaminoacetone ethylene ketal was heated on the steam-bath overnight. Excess ketal was distilled *in vacuo*, and 1.0 g. (71%) of crude amide, m.p. 198–200° dec., was obtained. Recrystallization from benzene gave the analytical sample, m.p. 200.5–203° dec.

Anal. Calcd. for $C_{25}H_{29}N_3O_5$: C, 66.50; H, 6.47; N, 9.31. Found: C, 67.28; H, 6.80; N, 8.40.



The ultraviolet type was like Fig. 3, curve A. The pK'_a in 66% dimethylformamide was 4.7.

5-Carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole Ethylene Ketal.—A mixture of 0.450 g. (0.001 mole) of 1-benzoyl-5-carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole ethylene ketal and 10 ml. of 100% hydrazine hydrate was heated under reflux for two hours and then kept at room temperature for one week. The crude crystalline product melted at 253° dec. This was raised to 255° dec. after recrystallization from a mixture of dimethylformamide and ethanol.

Anal. Calcd. for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.35; H, 7.32; N, 12.01.

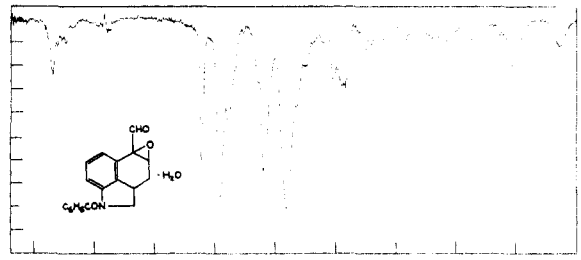
4-Benzoyl-4,5,5a,6,8,9-hexahydro-9-hydroxy-7,9-dimethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine-10a(6a*H*)-carboxylic Acid Lactone (62).—Treatment of 1.8 g. (0.004 mole) of 1-benzoyl-5-carbamyl-5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole ethylene ketal dissolved in 55 ml. of acetic acid with 2.74 g. (0.004 mole) of red lead oxide at room temperature for 18 hours gave a homogeneous solution. Glycerol (1 ml.) and 3.5 g. of concentrated sulfuric acid were then added. The mixture was filtered, and the filtrate was neutralized with sodium bicarbonate. The precipitate which formed was collected and recrystallized from methanol; m.p. 249–250° dec., yield 0.94 g. (58%).

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.56; H, 6.04; N, 7.22. Found: C, 70.75; H, 5.68; N, 7.18.

The ultraviolet spectrum was like that in Fig. 3, curve A. The infrared spectrum had carbonyl bands at 5.57 (lactone) and 6.08 μ (amide) and no bands in the OH or NH regions.

1-Benzoyl-5-formyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (63).—1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole, 100 g., was dissolved in 5 l. of acetone. The solution was cooled to 5° while stirring in ice, and 400 ml. of cold 30% aqueous hydrogen peroxide and 175 ml. of cold 5% sodium carbonate solution were added. The mixture was stirred in ice for 5 hours, after which 2 l. of ice-water and 10 ml. of acetic acid were added. The solution was concentrated *in vacuo* at 20° to a volume of about 5 l., and ice-water was added until the solution became cloudy. The mixture was cooled for a few days, and the product was filtered, washed well with water, triturated with ether and refiltered; yield 98.6 g., m.p. 150–153° dec.; second crop, 4.6 g.; total 92%. The compound was a monohydrate. The sample for analysis was recrystallized from methanol.

Anal. Calcd. for $C_{19}H_{15}NO_3 \cdot H_2O$: C, 70.57; H, 5.30; N, 4.33; active hydrogen, 2.00. Found: C, 70.20; H, 5.70; N, 4.20; active hydrogen, 1.88.



The anhydrous epoxyaldehyde could be obtained by vacuum drying of the hydrate at 140° or better as follows: A mixture of the hydrate, 0.98 g., in 2.5 g. of ethyl orthoformate and 0.45 ml. of absolute ethanol containing a trace of sulfuric acid was refluxed for 2.5 hours. The solution was cooled, and the aldehyde was filtered and washed with ether; yield 0.5 g. (54%), m.p. 168–171°. A sample was recrystallized from ethyl acetate; m.p. 173–174°.

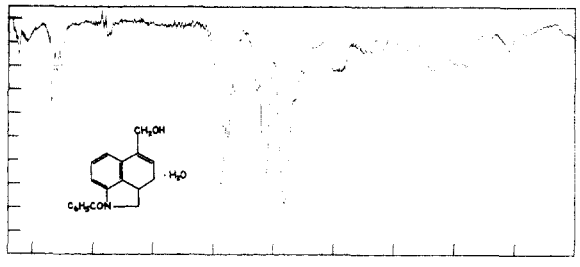
Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.57; H, 4.88; N, 4.47.

The ultraviolet spectrum was very similar to that in Fig. 3, curve A.

A larger run (100 g.) gave a 60% yield of the anhydrous form from the hydrate, and the filtrates on evaporation left a sirup which gave a 2% yield of 1-benzoyl-4-hydroxy-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole on crystallization from ethanol; melting point and mixture melting point 203–205° dec.

1-Benzoyl-5-hydroxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]-indole (65).—1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole, 76.5 g., was dissolved in 350 ml. of hot dioxane. The solution was then added during 20 minutes to a stirred solution of 7.32 g. of sodium borohydride in 330 ml. of absolute ethanol. The warm mixture was then stirred at room temperature for two hours, after which 800 ml. of water was added. The product which separated upon cooling was filtered and washed with acetone; yield 64.5 g. (74%), m.p. 108–110° dec. The compound was a monohydrate.

Anal. Calcd. for $C_{19}H_{17}NO_2 \cdot H_2O$: C, 73.76; H, 6.19; N, 4.53; loss on drying at 120°, 5.82. Found: C, 73.93; H, 6.06; N, 4.56; loss on drying at 120°, 6.46.



The ultraviolet type was like that in Fig. 2, curve A.

1-Benzoyl-5-hydroxymethyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (66).—Filtrates from the preparation of 1-benzoyl-5-hydroxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole in the sodium borohydride reduction above on further dilution with water gave a 10% yield of a second compound, m.p. 135–137°. Recrystallization from acetone raised the m.p. to 136–138°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.58; H, 6.40; N, 4.41.

The ultraviolet type was like that in Fig. 3, curve A.

1-Benzoyl-5-hydroxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]-indole by Ponndorf Reduction.—A solution of 2.89 g. of 1-benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[*cd*]indole in 100 ml. of dry isopropyl alcohol and 50 ml. of 1.0 molar aluminum isopropoxide in isopropyl alcohol was refluxed for 3.5 hours with very slow distillation of about 25 ml. of the solvent through a 10-inch fractionating column. The reaction mixture was then concentrated to small volume, and 200 ml. of chloroform, 100 ml. of cold water, 15 ml. of concentrated hydrochloric acid and 20 ml. of acetic acid were added. The chloroform layer was separated and washed

with water and dilute sodium bicarbonate solution, after which it was dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken up in wet ether, and the crystalline alcohol-hydrate was filtered and washed with ether; yield 2.66 g. (89%). Recrystallization from dilute acetic acid gave pure alcohol with m.p. 108–111° dec. A mixture melting point with a sample prepared by sodium borohydride reduction showed no depression.

1-Benzoyl-5-acetoxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole.—1-Benzoyl-5-hydroxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole hydrate (2.0 g.) was dried at 120° *in vacuo*. The resulting amorphous product was dissolved in 10 ml. of acetic anhydride and treated with six drops of boron fluoride etherate. The mixture was kept at room temperature for three days and was then concentrated *in vacuo* below 40°. The product was taken up in chloroform, and the solution was washed with aqueous sodium bicarbonate. The chloroform was removed, and the acetyl derivative was crystallized from ethyl acetate–petroleum ether; m.p. 95–98°, yield 0.8 g. (37%).

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74. Found: C, 75.90; H, 6.18.

Carbonyl bands in the infrared were at 5.74 (ester) and at 6.09 μ (amide).

1-Benzoyl-5-trifluoroacetoxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole.—The alcohol-hydrate, 2.0 g., was mixed with 1.0 g. of sodium trifluoroacetate and 40 ml. of trifluoroacetic anhydride. The mixture was refluxed for two and two-thirds hours, concentrated to dryness *in vacuo*, and the residue was taken up in a mixture of carbon tetrachloride and ether. The insoluble material was filtered, and the solvent was evaporated. The residual product was crystallized from ether, yield 1.05 g. (42%), m.p. 157–158° dec., and recrystallized from a mixture of chloroform and ether, m.p. 161–163° dec.

Anal. Calcd. for $C_{21}H_{16}F_3NO_3$: C, 65.11; H, 4.16; N, 3.62. Found: C, 64.63; H, 4.42; N, 4.00.

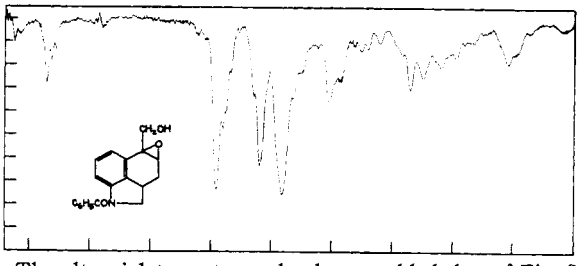
The ester carbonyl band in the infrared was at 5.62 μ.

1-Benzoyl-5-benzoxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole.—One gram of 1-benzoyl-5-hydroxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole hydrate was heated *in vacuo* at 120° to remove the water of hydration. The dry alcohol was dissolved in 3 ml. of pyridine, and 0.8 ml. of benzoyl chloride was added. After a few minutes the mixture was warmed to 60° and kept at that temperature for five minutes. It was then poured into cold water, and the gummy product was dissolved in chloroform, and the chloroform solution was washed with dilute sodium carbonate solution. The chloroform was dried over magnesium sulfate, and the solvent was distilled. The benzoate ester was crystallized from an ethyl acetate–petroleum ether mixture; yield 0.8 g. (63%), m.p. 133–135°.

Anal. Calcd. for $C_{26}H_{21}NO_3$: C, 78.96; H, 5.35; N, 3.54. Found: C, 78.37; H, 5.51; N, 3.68.

1-Benzoyl-4,5-epoxy-5-hydroxymethyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (64).—1-Benzoyl-4,5-epoxy-5-formyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole hydrate, 48.4 g. (0.15 mole), was dissolved in 180 ml. of hot dioxane. A solution of 4.13 g. (0.11 mole) of sodium borohydride in 180 ml. of ethanol was then added slowly with stirring. The reaction mixture was stirred for 0.5 hour, after which time 500 ml. of water was added. The crude product which separated on cooling had a m.p. of 167–170°, yield 34.6 g. (75%). It contained inorganic impurities which were removed after repeated recrystallization from methanol; m.p. 174–177°.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.43; H, 5.60; N, 4.81. Found: C, 74.25; H, 5.58; N, 4.56.



The ultraviolet spectrum closely resembled that of Fig. 3, curve A.

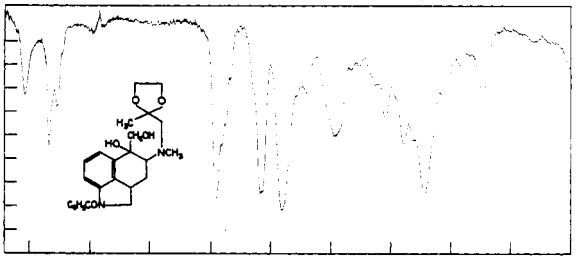
The epoxy alcohol was also prepared by treatment of 1-benzoyl-5-hydroxymethyl-1,2,2a,3-tetrahydrobenz[*cd*]indole with perbenzoic acid in chloroform solution; however, the yield was unsatisfactory.

1-Benzoyl-5-acetoxymethyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole.—1-Benzoyl-5-acetoxymethyl-1, 2,2a,-3-tetrahydrobenz[*cd*]indole, 8.0 g., was dissolved in 60 ml. of chloroform containing 4.14 g. of perbenzoic acid. The solution was kept at 0–5° for 16 hours, after which it was washed with aqueous sodium bicarbonate solution and dried over magnesium sulfate. The chloroform was distilled, and the epoxy ester was crystallized from an ethyl acetate–petroleum ether mixture; yield 2.03 g. (24%). A sample for analysis was recrystallized from a mixture of ethyl acetate and methanol; m.p. 177–179°.

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48. Found: C, 72.22; H, 5.74.

1-Benzoyl-5-hydroxy-5-hydroxymethyl-4-[N-methyl-N-acetonylamino] - 1,2,2a,3,4,5 - hexahydrobenz[*cd*]indole Ethylene Ketal (67).—A mixture of 12.0 g. of 1-benzoyl-4,5-epoxy-5-hydroxymethyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 50 ml. of methylaminoacetone ethylene ketal was heated under nitrogen in an oil-bath at 125° for 16 hours. Excess amine was distilled *in vacuo*, and the residue was taken up in a little benzene. The crude product was precipitated as a gum by addition of petroleum ether. The supernatant liquid was decanted, and the gum was taken up in chloroform. The resulting solution was extracted with cold dilute hydrochloric acid to remove all the basic material, and the acid extracts were neutralized with sodium bicarbonate. The product was extracted with chloroform; the solution was dried over magnesium sulfate, and the solvent was distilled. The residual amino-glycol was crystallized from ethyl acetate; m.p. 148–150° yield 1.2 g. (7.0%).

Anal. Calcd. for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.54; H, 7.14; N, 6.55.



The picrate prepared in methanol melted at 185–186° dec.

Anal. Calcd. for $C_{25}H_{30}N_2O_5 \cdot C_6H_3N_3O_7$: C, 55.77; H, 4.98; N, 10.49. Found: C, 55.05; H, 5.14; N, 10.38.

1-Benzoyl-2,2a,3,4-tetrahydro-4-[methyl-(2-methyl-1,3-dioxolan-2-yl-methyl)-amino]benz[cd]indol-5(1*H*)-one (16).

A. By Oxidation of the Glycol (67).—A mixture , 0.88 g. (0.002 mole) of 1-benzoyl-5-hydroxy-5-hydroxymethyl-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole ethylene ketal and 0.44 g. (0.0022 mole) of sodium periodate in 10 ml. of water was treated with 0.2 ml. of concentrated sulfuric acid. The mixture was shaken occasionally during 0.5 hour at 25–30°. The solution was neutralized with sodium bicarbonate, and the amorphous product was filtered and washed with water; yield almost theoretical. The crude product was crystallized from acetone, m.p. 135–136°.

Anal. Calcd. for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.49; N, 6.95.

The hydrochloride was prepared using dry hydrogen chloride in acetone. The salt crystallized with one mole of acetone; m.p. 138–139°.

Anal. Calcd. for $C_{24}H_{26}N_2O_4 \cdot C_3H_6O \cdot HCl$: C, 64.72; H. 6.64; N, 5.59. Found: C, 65.27; H, 6.51; N, 5.61.

The sulfuric acid addition salt, prepared in methanol containing a little water, analyzed for a trihydrate, m.p. 153–155° dec.

Anal. Calcd. for $C_{24}H_{26}N_2O_4 \cdot H_2SO_4 \cdot 3H_2O$: C, 51.61; H, 6.14; N, 5.02; S, 5.74. Found: C, 51.24; H, 6.09; N, 4.78; S, 5.46.

B. By Alkylation with the Bromo Ketone 12.—A solution of 270 g. (0.76 mole) of 1-benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole and 307 g. (2.35

moles) of methylaminoacetone ethylene ketal in 4500 ml. of dry benzene was refluxed under nitrogen for 21 hours. The mixture was cooled, and 151 g. (93.5%) of methylaminoacetone ethylene ketal hydrobromide was filtered, m.p. 158–159°.

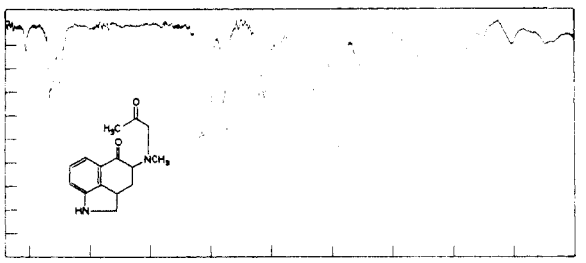
Anal. Calcd. for $C_6H_{13}NO_2 \cdot HBr$: N, 6.60; Br, 37.68. Found: N, 6.07; Br, 36.55.

The filtrate was washed several times with ice-water, after which it was extracted with 2.5 liters of cold dilute hydrochloric acid containing 150 ml. of the concentrated acid. The acid extracts were immediately added to an excess of ice-cold dilute sodium hydroxide. The product was extracted with one liter of chloroform, and the chloroform solution was dried over magnesium sulfate, treated with carbon and concentrated *in vacuo*. The residual ketal-ketone was crystallized from acetone; m.p. and mixture m.p. 135–136°, yield 220 g. (71%).

The ultraviolet curve was like that in Fig. 1.

5-Keto-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (68).—Twenty grams of 1-benzoyl-2,-2a,3,4-tetrahydro-4-[methyl-(2-methyl-1,3-dioxolan-2-ylmethyl)-amino]benz[*cd*]indol-5(1*H*)-one was dissolved in a mixture of 250 ml. of concentrated hydrochloric acid and 250 ml. of water, and the solution was kept under nitrogen at 37° for five days. The mixture was cooled, treated with carbon, filtered and the filtrate was concentrated *in vacuo* to small volume. The residue was treated with excess sodium bicarbonate; the product was extracted with cold chloroform, and the solvent was removed *in vacuo* at room temperature. The crude diketone was powdered, slurried with about 75 ml. of 1:1 benzene–ether, and filtered; yield 9.8 g. (77%), m.p. 105–107°. A sample for analysis was recrystallized from benzene–ether or ethanol; m.p. 109–110°; ultraviolet λ_{max} 241 mμ (ε 17700), 346 mμ (ε 2200).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 70.00; H, 7.41; N, 10.91.



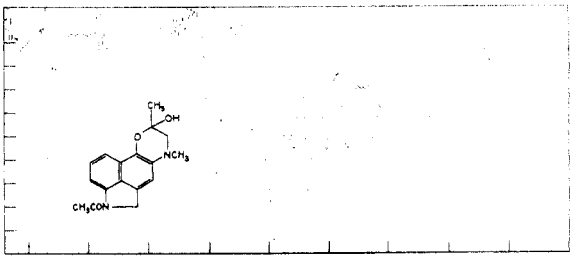
A monohydrochloride was obtained from dilute ethanol; m.p. 200° dec.

Anal. Calcd. for $C_{15}H_{18}N_2O_2 \cdot HCl$: N, 9.50. Found: N, 9.33.

4-Acetyl-4,5,8,9-tetrahydro-7,9-dimethyl-7*H*-indolo[3,4-*gh*][1,4]-benzoxazin-9-ol (viii).—5-Keto-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole, 0.15 g., was dissolved in 5 ml. of methanol, and 0.5 ml. of acetic anhydride was added. The solution was kept at room temperature for 2.5 hours and was then diluted with an equal volume of ether. The acetyl derivative which separated 0.075 g. (43%), had a m.p. of 160–162°.

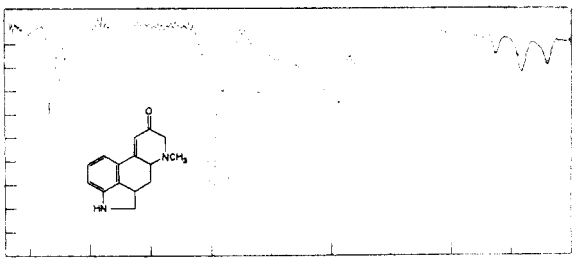
Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 67.60; H, 6.63; N, 9.68.

The compound shows an OH band and a single amide carbonyl band in the infrared and must, therefore, be formulated as the cyclic hemiketal. Ultraviolet absorption indicated the naphthalene system: λ_{max} 236 mμ (ε 20000), 273 mμ (ε 36500), 279 mμ (ε 35000), 314 mμ (ε 7060), 326 mμ (ε 7500), 357 mμ (ε 3900), and 363 mμ (ε 4000).



9-Keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline (69).—Twenty-five grams of 5-keto-4-[N-methyl-N-acetonyl]amino-1,2,2a,3,4,5-hexahydrobenz[*cd*]-indole was mixed with 550 ml. of absolute ethanol. The mixture was stirred under nitrogen and cooled to −15°. Sodium methoxide, 16.9 g., was then added, and the mixture was stirred at −10 to −12° for ten minutes. The reaction mixture was cooled to −25°, and the product was filtered on a 6.5-inch büchner funnel and washed with a little cold ethanol and ether. With the very minimum exposure to air (contains sodium methoxide!) the crude ketone was immediately slurried with a little ice-water and refiltered. It was washed with ice-water, ethanol and ether; yield 16.2 g. (69%), m.p. 145–147°. An analytical sample was recrystallized from dilute ethanol; m.p. 155–157°; ultraviolet λ_{max} 210 mμ (ε 10000), 266 mμ (ε 13000), 306 mμ (ε 20000).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.08; H, 6.95; N, 11.78.



The dihydrochloride was prepared and recrystallized from aqueous acetone; m.p. 270° dec.

Anal. Calcd. for $C_{15}H_{16}N_2O \cdot 2HCl$: C, 57.51; H, 5.79; N, 8.95. Found: C, 57.03; H, 6.18; N, 8.65.

The oxime was prepared in dilute ethanol and was recrystallized from a mixture of dimethylformamide and ether, m.p. 235–236° dec.

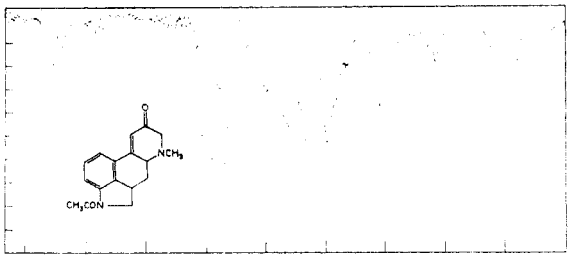
Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.60; H, 6.72; N, 16.49. Found: C, 70.43; H, 6.55; N, 16.30.

The semicarbazone recrystallized likewise from dimethylformamide–ether melted at 225° dec.

Anal. Calcd. for $C_{16}H_{19}N_5O$: N, 23.55. Found: N, 22.77.

4-Acetyl-9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—9-Keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline, 24 g., was added to 80 ml. of cold acetic anhydride. The mixture was kept at 25° for about five minutes, after which it was thoroughly cooled, and the product was filtered and washed with ether; yield 20.5 g. (76%), m.p. 167–170°. A second crop was obtained by evaporation of the filtrate; this raised the total yield to 82%. A sample was recrystallized from acetone–ethanol; m.p. 169–170°; ultraviolet λ_{max} 216 mμ (ε 6400), 259 mμ (ε 21000), 301 mμ (ε 17600); pK'_a in 66% dimethylformamide, 4.30.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.60; H, 6.63; N, 9.68.



The hydrochloride was prepared in ethanol and was recrystallized from aqueous ethanol; m.p. 250° dec.

Anal. Calcd. for $C_{17}H_{18}N_2O_2 \cdot HCl$: N, 8.79. Found: N, 8.52.

The oxime was prepared in the usual fashion, m.p. 250° dec., after recrystallization from dimethylformamide–ether.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.74; H, 6.70; N, 14.41.

The semicarbazone melted at 245–246° dec. after crystallization from aqueous ethanol.

Anal. Calcd. for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.71; H, 6.18; N, 20.58.

9-Hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—Ten grams of 9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline in a mixture of 200 ml. of methanol and 10 ml. of water was treated with 1.5 g. of sodium borohydride. The mixture was stirred for two hours, after which it was diluted with 150 ml. of methanol and 25 ml. of water, heated to boiling, treated with carbon, and concentrated *in vacuo*. The product was filtered and washed with water and methanol; 8.6 g. (85%), m.p. 210–220° dec. A sample was recrystallized from alcohol; ultraviolet λ_{max} 242 mμ (ε 22000), 318 mμ (ε 1900).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 75.07; H, 7.58; N, 11.42.

The infrared spectrum (mull) had bands at 3.15, 6.27, 6.86 and 7.03 μ.

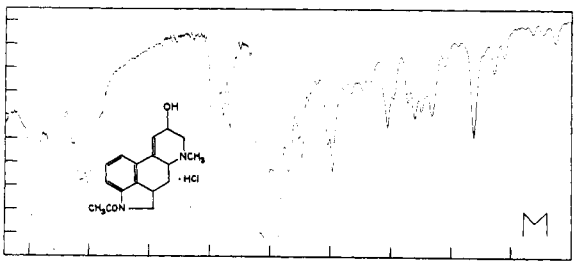
The dihydrochloride was prepared in ethanol and was recrystallized from aqueous ethanol; m.p. 242–243° dec.

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot 2HCl$: N, 8.89. Found: N, 8.97.

Acetylation of the free base in alcohol solution gave the 4-acetyl derivative described below.

4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline (70).—Ten grams of 4-acetyl-9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]-quinoline was added to a mixture of 150 ml. of methanol and 10 ml. of water. Sodium borohydride, 1.5 g., was added, and the reaction was allowed to proceed at room temperature for about two hours. The solution was then concentrated to small volume, and a mixture of 15 ml. of concentrated hydrochloric acid and 60 ml. of water was added. The hydrochloride which separated on cooling was filtered and washed with methanol, 9.0 g. (79%). A sample was recrystallized from dilute ethanol; m.p. 245–246° dec.

Anal. Calcd. for $C_{17}H_{20}N_2O_2 \cdot HCl$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.47; H, 6.81; N, 8.96.



The free base was obtained by neutralization of the hydrochloride with aqueous sodium bicarbonate. It was extracted with chloroform; the solution was dried over magnesium sulfate, and the chloroform was distilled. The crude product was crystallized from ethyl acetate; m.p. 182–184°; ultraviolet λ_{max} 243 mμ (ε 33400), 251 mμ (ε 38700), 306 mμ (ε 3500), 316 mμ (ε 3000); pK'_a in 66% dimethylformamide, 6.02.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.72; H, 7.20; N, 9.73.

The hydrobromide was prepared and recrystallized from dilute ethanol; m.p. 243–244° dec.

Anal. Calcd. for $C_{17}H_{20}N_2O_2 \cdot HBr$: C, 55.90; H, 5.80; N, 7.67. Found: C, 55.83; H, 5.84; N, 8.23.

The acetate ester of the alcohol was prepared using excess acetic anhydride (15 ml.) with 0.5 g. of the alcohol at 25° for 12 hours. The acetic anhydride was distilled *in vacuo*, and the hydrochloride of the acetate was prepared in methanol and recrystallized from dilute ethanol; m.p. 186–187° dec.

Anal. Calcd. for $C_{19}H_{22}N_2O_3 \cdot HCl$: C, 62.89; H, 6.39; N, 7.72. Found: C, 62.71; H, 6.36; N, 7.72.

The methiodide of the unsaturated alcohol was obtained using 1.5 parts of methyl iodide in 1:1 nitromethane–methanol as solvent. It was recrystallized from water, m.p. 257–258° dec.

Anal. Calcd. for $C_{18}H_{23}IN_2O_2$: C, 50.71; H, 5.44; N, 6.57; I, 29.77. Found: C, 50.25; H, 5.12; N, 6.68; I, 29.93.

The methochloride was obtained by treating the methiodide with silver acetate, filtering the silver iodide, and then adding hydrochloric acid to the filtrate. It was crystallized from a mixture of methanol and ethyl acetate; m.p. 240–241° dec.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2$: C, 64.67; H, 6.92; N, 8.36; Cl, 10.58. Found: C, 64.47; H, 7.15; N, 8.44; Cl, 10.34.

4-Acetyl-4,5,5a,6-tetrahydro-9-hydroxy-7-methylindolo[4,3-*fg*]quinolinium Hydroxide Betaine (ix).—A mixture of 1.0 g. of 4-acetyl-9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline, 10 g. of 5% palladium-on-carbon, and 35 ml. of xylene was heated under reflux for four hours. The catalyst was filtered and extracted with hot methanol and chloroform. The combined filtrates were evaporated under reduced pressure, and the residue was recrystallized from water; yield 0.61 g. (57%), m.p. 255–256° dec. The compound was a monohydrate; ultraviolet λ_{max} 246 mμ (ε 29000), 351 mμ (ε 6900); pK'_a in 66% dimethylformamide, 6.06; pK'_a in water, 4.82.

Anal. Calcd. for $C_{17}H_{16}N_2O_2 \cdot H_2O$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.47; H, 6.33; N, 9.39.

The acetic acid salt was prepared by crystallization from acetic acid; m.p. 175°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2 \cdot CH_3COOH$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.78; H, 6.28; N, 8.25.

The hydrochloride crystallized from water as a hemihydrate, m.p. 267–268° dec.

Anal. Calcd. for $C_{17}H_{16}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$: C, 62.70; H, 5.58; N, 8.60. Found: C, 62.13; H, 5.48; N, 8.49.

9-Hydroxy-7-methyl-4,5,5a,6-tetrahydroindolo[4,3-*fg*]-quinolinium Chloride Hydrochloride.—A mixture of 1 g. of the betaine above in 10 ml. of concentrated hydrochloric acid and 10 ml. of acetic acid was heated under reflux for 2.5 hours. The mixture was cooled, and the product was filtered and washed with ethanol and ether; yield 0.9 g. (77%). It was recrystallized from ethanol containing a little aqueous hydrochloric acid, m.p. 284–285° dec.; ultraviolet λ_{max} 235 mμ (ε 20000), 284 mμ (ε 5600), 324 mμ (ε 9900).

Anal. Calcd. for $C_{15}H_{14}N_2O \cdot 2HCl$: C, 57.89; H, 5.18; N, 9.00. Found: C, 57.37; H, 5.66; N, 9.04.

4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,7,8,9,10-octahydroindolo[4,3-*fg*]quinoline (x).—One gram of the betaine above in a mixture of 20 ml. of ethanol and 5 ml. of water was treated with 0.081 g. of sodium borohydride, and the solution was refluxed for 10 minutes and kept at 25° for one hour. The solvent was distilled, and the residue was taken up in a mixture of chloroform and water. The chloroform solution was separated, dried over magnesium sulfate and the solvent was distilled. The residue was recrystallized twice from a nitromethane–ethyl acetate mixture; yield 0.2 g. (21%), m.p. 193–196° dec ; ultraviolet λ_{max} 252 mμ (ε 2060), 328 mμ (ε 1500). In acid solution the 328 mμ band was absent.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.97; H, 7.23; N, 9.89.

Four-tenths of a gram of starting betaine was recovered from the aqueous layer.

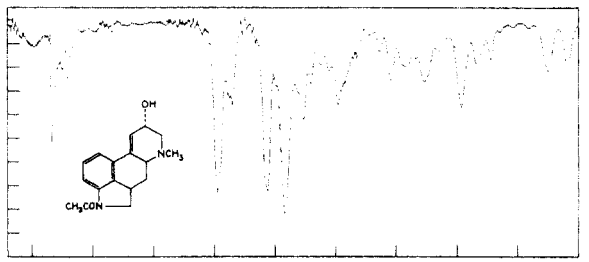
4-Acetyl-9-β-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline (71). A. From the 9-Chloro Compound.—One gram of 4-acetyl-9-chloro-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline hydrochloride below was dissolved in 2 ml. of water, and the solution was refrigerated overnight. The crystalline product which separated was filtered and washed with cold water and ethanol; yield 0.4 g. (42%). It was recrystallized from aqueous ethanol; m.p. 195° dec.

Anal. Calcd. for $C_{17}H_{20}N_2O_2 \cdot HCl$: N, 8.73; Cl, 11.05. Found: N, 8.82; Cl, 10.42.

The free base was obtained by neutralization of the hydrochloride with aqueous sodium bicarbonate. It was crystallized from ethanol or ethyl acetate; m.p. 195–197° dec. The ultraviolet spectrum was like the epimeric alcohol above; pK'_a in 66% dimethylformamide, 6.68.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.11; H, 7.11; N, 9.81.

B. From 4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—One-half gram of the α-alcohol hydrochloride was dissolved in 15 ml. of concentrated hydrochloric acid, and the solution was kept at 25° for 2 hours. Excess acid was removed *in vacuo*, and the residue was neutralized with aqueous sodium bicarbonate. The product was extracted with chloroform, and the solution was dried over magnesium sulfate. The solvent was distilled, and the residue was crystallized from ethyl acetate; yield 0.33 g. (75%), m.p. 194–196° dec. When mixed with the epimeric alcohol, the melting point was 163–165° dec. Concentrated sulfuric acid likewise caused epimerization of the α-alcohol, although in slightly lower yield.



4-Acetyl-9-β-acetoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline Hydrochloride.—4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]-quinoline, 1.0 g., was dissolved in 25 ml. of acetic acid, and to the mixture was added 10 ml. of a saturated solution of boron fluoride in acetic acid. The mixture was warmed briefly until it was homogeneous, and it was then kept at 25° for two hours. The solvent was distilled *in vacuo*, and the residue was taken up in water and chloroform. Excess sodium bicarbonate was added; the chloroform extract was separated and dried, and the solvent was distilled. The crude acetate ester was dissolved in methanol, and the hydrochloride was precipitated with dry hydrogen chloride. It was recrystallized from methanol–ethyl acetate, m.p. 176–177° dec., and the melting point was depressed when mixed with the α-epimer described above.

Anal. Calcd. for $C_{19}H_{22}N_2O_3 \cdot HCl$: N, 7.72. Found: N, 7.79.

9-Formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—Five grams of 9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline was suspended in 500 ml. of liquid hydrogen cyanide, and 200 ml. of boron fluoride etherate was added slowly while cooling in ice. The solution was kept at 25° for 16 hours, after which it was concentrated *in vacuo* to a thick sirup. Water and chloroform were added, and the mixture was neutralized with excess solid sodium bicarbonate. The product crystallized and was filtered and then digested with hot water and refiltered and washed with water; yield 4.67 g. (84%), m.p. 242–244° dec. A sample was recrystallized from dimethylformamide–methanol; ultraviolet λ_{max} 243 mμ (ε 29000), 320 mμ (ε 2000).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.19; H, 7.04; N, 15.65.

The infrared spectrum (mull) had bands at 3.09, 6.00, 6.24, 6.57, 6.83, 6.88 and 7.13 μ.

4-Acetyl-9-formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline (72).—Five grams of 4-acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline was suspended in 500 ml. of liquid hydrogen cyanide, and to the mixture was added slowly and while cooling in an ice-bath, 200 ml. of boron fluoride etherate. The solution was kept at 25° for about 20 hours, after which it was concentrated *in vacuo* to a thick sirup. The residue was then mixed with chloroform and cold water, and excess solid sodium bicarbonate was added to neutralize the acid. The chloroform layer was separated, and the aqueous layer was extracted twice with chloroform. The combined extracts (300 ml.) were dried over magnesium sulfate, and the chloroform was distilled. The residue was crystallized from 50 ml. of methanol; yield 4.5 g. (85%). It was recrystallized from a mixture of dimethylformamide and methanol; m.p. 225–226° dec.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.11; H, 6.92; N, 13.44.

When the epimeric β-alcohol was used as starting material in place of the normal alcohol above, the same amide was obtained in the same yield, m.p. 227–228° dec. A mixture m.p. showed no depression.

The infrared spectrum (mull) had bands at 3.15, 6.03, 6.32, 6.57, 6.83 and 7.13 μ.

4-Acetyl-9-amino-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—A mixture of the 4-acetyl-9-formamido compound, 0.5 g., and 10 ml. of anhydrous hydrazine was heated under reflux for 75 minutes. Water, 5 ml., was added slowly, after which refluxing was continued for 15 minutes. The solution was evaporated to dryness under reduced pressure, and the residue was crystallized from methanol–ether; yield 0.11 g. (24%). It was then recrystallized from water; m.p. 178–179° dec.; ultraviolet λ_{max} 243 mμ (ε 38000), 249 mμ (ε 41000), 304 mμ (ε 3100), 315 mμ (ε 2760).

Anal. Calcd. for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 71.53; H, 7.50; N, 14.95.

9-Amino-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline. A. By Acid Hydrolysis of the 9-Formamido Compound.—A solution of 5 g. of 9-formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline in 125 ml. of concentrated hydrochloric acid was heated at reflux under nitrogen for 4.5 hours. The solution was decolorized with carbon and concentrated *in vacuo* until a thick slurry of crystals was deposited. The product was filtered and washed with alcohol and ether; yield 5.2 g. (81%), m.p. 303–305° dec. A sample was recrystallized from aqueous ethanol; ultraviolet λ_{max} 245 mμ (ε 27600), 296 mμ (ε 1500), 330 mμ (ε 1240).

Anal. Calcd. for $C_{15}H_{19}N_3 \cdot 3HCl$: C, 51.32; H, 6.32; N, 11.92. Found: C, 51.21; H, 6.31; N, 11.69.

B. By Acid Hydrolysis of the 4-Acetyl-9-formamido Compound.—A solution of 2 g. of the formamido compound in 50 ml. of concentrated hydrochloric acid was heated at reflux under nitrogen for 18 hours. The solution was evaporated to dryness under reduced pressure, and the residual trihydrochloride salt was recrystallized from aqueous methanol; m.p. 291–292° dec., yield 2.1 g. (93%).

The salt from either A or B (2.3 g.) was dissolved in water, and the solution was treated with excess sodium bicarbonate. The free base which separated was filtered and washed with water, methanol and ether; yield 1.6 g. (90%). After recrystallization from ethyl acetate it melted at 165–166°.

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.43; H, 7.64; N, 17.43.

C. By Basic Hydrolysis of the 9-Formamido Compound.—A mixture of 2.5 g. of the formamido compound, 5.6 g. of potassium hydroxide and 100 ml. of water was heated at reflux under nitrogen for 17 hours. The solution was cooled, and the product was filtered and washed with water; yield 1.99 g. (89%), m.p. 165–166°. A mixture melting point with the sample obtained by acid hydrolysis above showed no depression.

9-Acetamido-4-acetyl-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—The 9-amino-4-desacetyl compound, 0.4 g., was dissolved in 10 ml. of acetic anhydride, and the solution was kept at 25° for 0.5 hour. Excess acetic anhydride was removed *in vacuo*, and the residue was crystallized from methanol–ether; yield 0.44 g. (82%). The diacetyl derivative was recrystallized from aqueous methanol, m.p. 215–217° (dec.); ultraviolet λ_{max} 243 mμ (ε 42000), 250 mμ (ε 45000), 305 mμ (ε 3200), 315 mμ (ε 2800).

Anal. Calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 69.78; H, 7.27; N, 12.87.

7-Methyl-4-[3′,4′,5′-trimethoxybenzoyl]-9-[3′,4′,5′-trimethoxybenzamido]-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—To a solution of 0.88 g. of 9-amino-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline in 11 ml. of pyridine was added 0.88 g. of 3,4,5-trimethoxybenzoyl chlo-

ride. The solution was kept at 0° for 17 hours, after which it was poured into an excess of aqueous sodium bicarbonate solution. The mixture was extracted three times with chloroform, and the extracts were washed with water and dried over magnesium sulfate. The solvent was distilled, and the product was crystallized from methanol; yield 0.9 g. (57%). A sample for analysis was recrystallized from a mixture of dimethylformamide and methanol; m.p. 275–280° dec.

Anal. Calcd. for $C_{35}H_{39}N_3O_8$: C, 66.76; H, 6.24; N, 6.67. Found: C, 66.93; H, 6.30; N, 6.48.

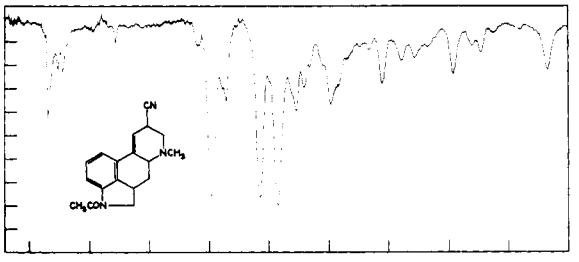
4-Acetyl-9-chloro-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline Hydrochloride (73).—4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline hydrochloride, 3.1 g., was dissolved in 75 ml. of liquid sulfur dioxide contained in a glass liner in a steel autoclave. Thionyl chloride, 1.2 ml., was added, and the vessel was sealed and kept at 25° for 6 hours. The autoclave was vented, and the reaction mixture was removed. Sulfur dioxide was allowed to evaporate while the volume of the solution was kept constant by slow addition of dry ether. The amorphous chloro hydrochloride was filtered, washed with ether, and dried *in vacuo*, m.p. 130–135° dec., yield 3.5 g.

Anal. Calcd. for $C_{17}H_{19}ClN_2O\cdot HCl$: Cl, 20.95; N, 8.26. Found: Cl, 21.61; N, 7.79.

Use of the 9β-epimeric alcohol in this reaction gave the same chloride in comparable yield.

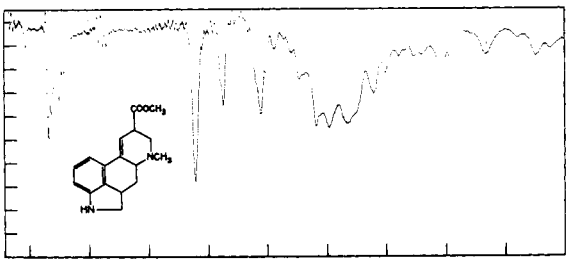
4-Acetyl-9-cyano-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline (74).—Dry, powdered sodium cyanide, 40 g., was added to 300 ml. of ice-cold liquid hydrogen cyanide. The mixture was stirred and cooled in ice, and 7.5 g. of the crude amorphous 4-acetyl-9-chloro-7-methyl-4,5,5a-6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline hydrochloride above was added. Stirring was continued for 30 minutes, after which the hydrogen cyanide was quickly distilled under reduced pressure below about 10°. The residue was mixed with chloroform and ice-water, and the resulting mixture was filtered. The organic layer was separated, and the aqueous phase was extracted twice with chloroform. The combined extracts were dried over magnesium sulfate, decolorized and the solvent was distilled *in vacuo*. The product was crystallized from ethyl acetate; yield 3.3 g. (54% over-all based on the alcohol hydrochloride), m.p. 172–174°. Recrystallization from the same solvent raised the m.p. to 181–182°; ultraviolet λ_{max} 243 mμ (ε 37000), 249 mμ (ε 40000), 306 mμ (ε 3300), 316 mμ (ε 2900).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.50; N, 14.33. Found: C, 73.41; H, 6.53; N, 14.17.



9-Carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline (75, R = Me).—4-Acetyl-9-cyano-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline, 1 g., was mixed with 15 ml. of methanol and 0.25 ml. of water. The mixture was cooled and 2 ml. of concentrated sulfuric acid was added slowly. The solution was sealed in a glass tube under nitrogen and heated at 100° for 23–24 hours. The mixture was treated with decolorizing carbon and then concentrated *in vacuo* to about 10 ml. It was poured onto a mixture of chloroform (30 ml.), ice and 10 g. of sodium bicarbonate. The chloroform layer was separated, and the aqueous phase was extracted with three 10-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, evaporated to dryness, and the product was crystallized from benzene; yield 0.51 g. (53%), m.p. 159–160°. It was recrystallized from ethyl acetate; m.p. 160–161°; ultraviolet λ_{max} 242 mμ (ε 10600), 318 mμ (ε 1920); pK'_a in 66% dimethylformamide, 6.20.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.86; H, 7.19; N, 10.05.



Methanolysis under the same conditions using hydrogen chloride as catalyst gave the ester in lower yield. Methanolysis under milder conditions gave mixtures containing the above ester along with some deacetylated nitrile, m.p. 170–171°.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.05; H, 6.97; N, 16.15.

4-Acetyl-9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—Acetylation of one part of the tetracyclic ester using four parts of acetic anhydride in about 25 parts of methanol gave the acetyl derivative, m.p. 140–142° (from benzene–ether).

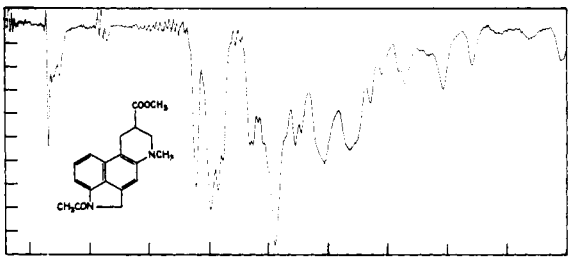
Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.06; H, 6.83; N, 8.70.

4-*p*-Toluenesulfonyl-9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline.—9-Carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]-quinoline, 0.5 g., and 0.38 g. of *p*-toluenesulfonyl chloride were mixed in 10 ml. of pyridine while cooling in an ice-bath. The mixture was kept below 25° for 3 hours, after which most of the excess pyridine was distilled under reduced pressure at room temperature. Chloroform and excess aqueous sodium bicarbonate solution were added to the residue. The chloroform layer was separated, and the aqueous layer was again extracted with chloroform. The combined extracts were dried over magnesium sulfate, and the solvent was distilled *in vacuo*. The residue was crystallized from ethanol; m.p. 172–173°, yield 0.31 g. (40%).

Anal. Calcd. for $C_{24}H_{26}N_2O_4S$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.51; H, 6.19; N, 6.20.

4-Acetyl-9-carbomethoxy-7-methyl-4,5,7,8,9,10-hexahydroindolo[4,3-*fg*]quinoline (76).—A mixture of 0.575 g. of 4-acetyl-9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline, 15 ml. of xylene and 0.5 g. of 5% palladium-on-carbon was heated at reflux under nitrogen for 16 hours. The catalyst was filtered, and the filtrate was cooled. The first crop of yellow crystalline product was collected and washed with benzene; yield 0.20 g. (35%). Some less pure ester could be obtained by concentrating the filtrates. The melting point after recrystallization from benzene was 177–178°.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.25; H, 6.35; N, 8.64.



The ultraviolet spectrum was identical to that reported by Stoll[7d] and by Atherton.[7e]

9-Carboxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-[4,3-*fg*]quinoline (75, R = H).—A solution of 1.0 g. of 9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-[4,3-*fg*]quinoline in 30 ml. of concentrated hydrochloric acid and 5 ml. of water was heated under reflux for three hours. The light yellow solution was evaporated completely to dryness under reduced pressure. A sample of the dihydrochloride salt, obtained thus in quantitative yield, was dissolved in a little water, and the solution was passed through a column of ion exchange resin IR 45 to remove hydrochloric

acid. The eluate was evaporated to give the amino acid, m.p. above 300°. A sample was recrystallized from water for analysis.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.76; H, 6.87; N, 10.40.

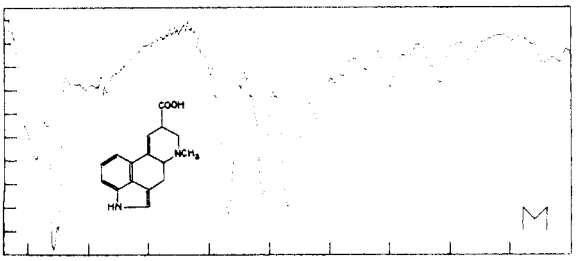
9-Carboxy-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo-[4,3-*fg*]quinoline (77).—A mixture of 1.0 g. of 9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]-quinoline and 40 ml. of *N* sodium hydroxide solution was heated under reflux for 19 hours. The solution was treated with decolorizing carbon, filtered and 10 g. of wet Raney nickel was added. Refluxing was continued for three hours under nitrogen. The catalyst was filtered, and the *p*H was adjusted to 5.8 by addition of dilute hydrochloric acid. The crude product which separated, 0.5 g., containing inorganic impurities was purified by reprecipitation from dilute ammonium hydroxide solution with carbon dioxide, m.p. 315–316° dec. The compound retained water of crystallization when dried at 120°, and was not completely anhydrous after drying at 180°.

Anal. Calcd. for $C_{16}H_{18}O_2N_2 \cdot H_2O$: C, 66.64; H, 6.99; N, 9.72. Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.09; H, 6.71; N, 10.36. Found, dried at 120°: C, 67.49; H, 7.10; N, 9.79. Found, dried at 180°: C, 69.20; H, 6.77.

The same dihydrolysergic acid was formed when 4-acetyl-9-cyano-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline was hydrolyzed with alkali and the hydrolysate was treated with Raney nickel.

The infrared spectrum (mull) had bands at 2.9, 3.1, 6.20, 6.38, 6.89 and 7.30 μ. The ultraviolet spectrum was that of an unconjugated indole system; λ_{max} 222 mμ (ϵ 30000), 281 mμ (ϵ 6200), 291 mμ (ϵ 5100).

Synthetic *dl*-Lysergic Acid (78).—A mixture of 9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline, 3.9 g., and 78 ml. of 1.5% potassium hydroxide solution was refluxed for 30 minutes under nitrogen. Hydrated sodium arsenate, 8.5 g., and Raney nickel (16 g. wet), previously deactivated by boiling in xylene suspension,[31] was added, and the mixture was heated under reflux and stirred in a nitrogen atmosphere for 20 hours. The solution was treated with carbon, and the crude lysergic acid was precipitated by neutralization to *p*H 5.6. It was filtered and washed with water; yield 1.04 g., m.p. 240–242° dec. A second crop, 0.16 g., m.p. 233–235° dec., was also obtained; total yield 30%. The acid could be purified by dissolving it in dilute ammonium hydroxide, treating with decolorizing carbon, and reprecipitating with carbon dioxide,



m.p. 242–243° dec.; a mixture m.p. with *dl*-lysergic acid made from natural *d*-lysergic acid[39] was likewise 242–243° dec.

Anal. Calcd. for $C_{16}H_{16}N_2O_2 \cdot H_2O$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.07; H, 6.59; N, 9.91.

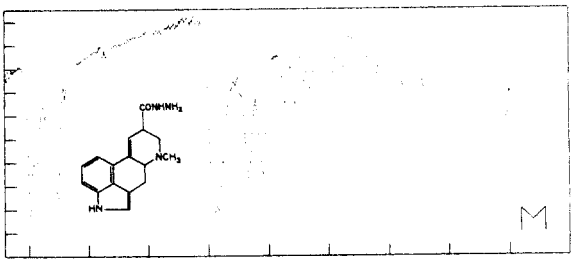
The anhydrous acid was obtained by drying *in vacuo* for several hours at 150°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.32.

The ultraviolet spectrum in dilute aqueous alkaline solution was identical with that of the sample derived from natural sources, λ_{max} 223 mμ (ϵ 20400), 238 mμ (ϵ 20500), 310 mμ (ϵ 9100). The pK'_a in 66% dimethylformamide (4.92 and 8.04) was the same for both samples, and the X-ray diffraction patterns and paper chromatographic behavior were identical.

***dl*-Isolysergic Acid Hydrazide from Ergocristine.**—A sample was obtained by reaction of anhydrous hydrazine with ergocristine in the usual manner.[32] It was recrystallized from a mixture of dimethylformamide and methanol; 225–228° dec.; λ_{max} 229 mμ (ϵ 18000), 240 mμ (ϵ 18300), 310 mμ (ϵ 7630).

Anal. Calcd. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85. Found: C, 67.90; H, 6.52; N, 19.62.



Synthetic *dl*-Isolysergic Acid Hydrazide.—Crude synthetic *dl*-lysergic acid, 0.4 g., was powdered and mixed with 23 ml. of benzene, 2 ml. of methanol and 25 ml. of approximately 2.5% diazomethane in cold ether. The mixture was shaken periodically during 45 minutes. Solvents were evaporated under reduced pressure, after which the residue was taken up in about 20 ml of 1:1 benzene–methanol and decolorized with carbon. Solvents were again evaporated, and the crude *dl*-methyl lysergate was dissolved in 10 ml. of methanol and 2 ml. of anhydrous hydrazine. The solution was heated at reflux under nitrogen for 1.5 hours, after which solvents were removed *in vacuo*, and the *dl*-isolysergic acid hydrazide was crystallized from methanol; yield 0.050 g., m.p. 224–227° dec. A mixture melting point with natural *dl*-isolysergic acid hydrazide showed no depression. Ultraviolet and infrared spectra and X-ray diffraction patterns for natural and synthetic specimens were identical in every respect.

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(39) S. Smith and G. M. Timmis, *J. Chem. Soc.*, 1440 (1936).