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Concerning 2-Carbomethoxytropinone*

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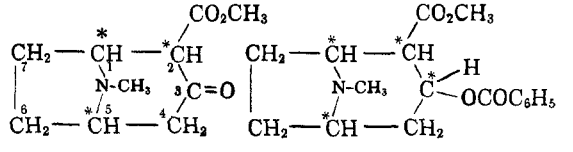
Racemic 2-carbomethoxytropinone is obtainable by the partial saponification of 2,4-dicarbomethoxytropinone and, more conveniently, by the condensation of monomethyl β-ketoglutarate, got from β-ketoglutaric anhydride, with succindialdehyde and methylamine. 2-Carbomethoxytropinone can conceivably exist in three racemic and six optically active forms. Of these only one has been obtained heretofore. The configurational relation of *d*-(2-carbomethoxytropinone) and its *l* antipode to *l*-cocaine is established by the Kiliani chromic acid oxidation of pseudoecgonine methyl ester to the former. Previous methods of preparing racemic 2-carbomethoxytropinone, the properties of 2,4-dicarbomethoxytropinone, and incidental experimental data are discussed.

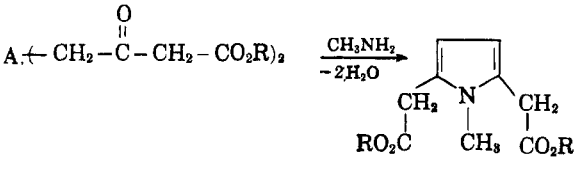
In any synthetic scheme for cocaine (II) and its stereoisomers, 2-carbomethoxytropine (I) is an obvious and probably the best key intermediate and has indeed been used to prepare *d*- and *l*-cocaine and racemic pseudococaine.[1,2] In connection with the synthesis of the other two isomers, allococaine and allopseudococaine, unreported until recently,[3] relatively large amounts of this β-keto ester were needed, and it was accordingly desirable to ascertain the most efficient method of its preparation.

Of the four synthetic methods recorded, one (Sequence A) is rather involved, and the cyclization of 1-methyl-2,5-dicarboethoxypyrrolidine (III, R = C_2H_5) to 2-carboethoxytropinone (IV, R = C_2H_5) difficult.[1,4,5] Another (Sequence B), in principle the simplest, is reported to give only a twenty per cent yield of product.[6] Hence, only the remaining two (Sequences C[7] and D[2]), which are relatively simple and claimed to proceed in good yield, came into consideration.

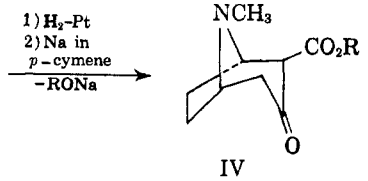
On the basis of the yields reported and the availability of the starting materials Sequence C seemed preferable. Tropinone (V), the components for the Robinson Synthesis of which are now obtainable commercially (see Experimental), can be made in high yield (~ 75%)[8,9] and, according to Preobrashenski,[7] is readily convertible (70–80%) by sodium or potassium and dimethyl carbonate in boiling benzene or xylene to 2-carbomethoxytropinone. It was here found, however, that, although the reported yields of tropinone are not exaggerated, this base is thus transformed to 2-carbomethoxytropinone only in rather low yield (~ 35%). For such a process many side reactions are conceivable, and in fact some or all of them do occur and produce large amounts of resinous by-products.



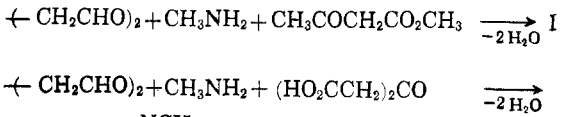
I II

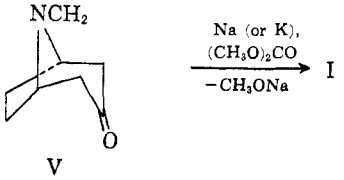


III



IV





V

Certain variations of the reaction were also tried. Substituting sodium methoxide in toluene did not alter the outcome appreciably. Sodium methoxide in a small volume of methanol gave a somewhat lower yield. By increasing the relative amount of methanol and prolonging the time of reaction correspondingly the product is markedly reduced and

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) R. Willstätter and M. Bommer, *Ann.*, **422**, 15 (1921).

(2) R. Willstätter, O. Wolfes, and H. Mäder, *Ann.*, **434**, 111 (1923).

(3) S. P. Findlay, *J. Org. Chem.*, **21**, 711 (1956).

(4) R. Willstätter and A. Pfannenstiehl, *Ann.*, **422**, 1 (1921).

(5) The use of the dimethyl ester (R = CH_3) would presumably not improve the over-all yield of sequence A appreciably.

(6) German Patent **345,759**.

(7) N. A. Preobrashenski, M. N. Schtschukina, and R. A. Lapina, *Ber.*, **69**, 1615 (1936).

(8) C. Schöpf and G. Lehmann, *Ann.*, **518**, 1 (1935).

(9) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).

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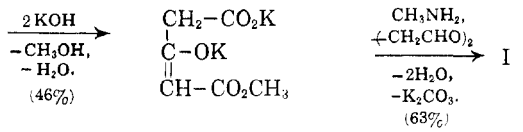
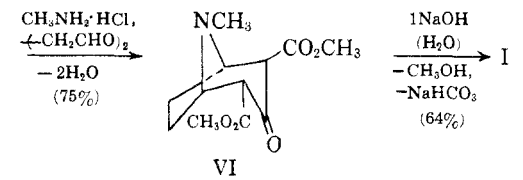
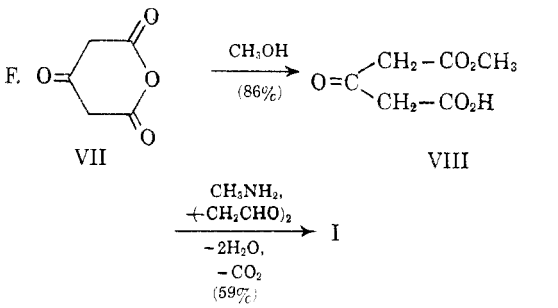
much unreacted tropinone is recoverable, excess solvent reversing the reaction presumably.[10]

D. $(CH_3O_2CCH_2)_2CO$



E. $(CH_3O_2CCH_2)_2CO$





In these circumstances Willstätter's synthesis[2] (Sequence D) or some modification thereof promised to be more satisfactory. The chief difficulty of Willstätter's method lies in preparing the pure dipotassium salt of monomethyl β-ketoglutarate, the yield being less than 50%. Although it was found that treatment of dimethyl β-ketoglutarate with methanolic potassium hydroxide affords a high yield of somewhat impure dipotassium salt, also convertible to 2-carbomethoxytropinone, no essential improvement of Willstätter's over-all yield (~30%) of the keto ester was realized in this manner. The formation of other potassium salts of lesser solubility and the ease with which β-ketoglutarates undergo self-condensation in the presence of basic catalysts[11] are probably the chief factors contributory to the low harvest of pure dipotassium salt.

By a reversal (E) of Willstätter's sequence one might hope to avoid some or all of the foregoing complications. Indeed the Robinson Synthesis of 2,4-dicarbomethoxytropinone (VI) appears to proceed in high yield; and its partial saponification is, moreover, effected more readily than that of the parent compound.

This procedure is, however, tedious, and another variation (F) of Willstätter's synthesis, consisting in the use of monomethyl β-ketoglutarate as its methylammonium salt, was therefore investigated. β-Ketoglutaric anhydride (VII),[4,12] which was obtained in excellent amount by a modification of Kaushall's procedure, is converted to the requisite monomethyl β-ketoglutarate by dissolving it in methanol. Although the optimum conditions for its condensation subsequently with succindialdehyde and methylamine were not determined, racemic 2-carbomethoxytropinone was thus obtained in satisfactory quantity (52–59%). Unlike the condensation, discussed in more detail below, of dimethyl β-ketoglutarate this proceeds with fewer side reactions in alkaline solution. For both simplicity and yield this sequence is very likely superior to all others presently known and probably represents also a convenient means of synthesizing certain derivatives of cycloheptane.

2,4-Dicarbomethoxytropinone (VI) which may be the first isolated dicarboalkoxy derivative of tropinone is a sufficiently unusual compound to merit some description. Its formation in high yield is contingent on the use of methylamine as its hydrochloride or similar salt: the greater the proportion of free amine used, the larger the quantity of dark, polymeric by-products. In his classical article on the synthesis of tropinone, Robinson prepared a solution of the 2,4-dicarboethoxy analog by a similar procedure. His use of free methylamine may account for the apparently low yield of tropinone obtained therefrom by acid hydrolysis.[13] The large number of isomers, both geometric and tautomeric, which are possible for compounds of such structure, should, partly because of the basic nitrogen atom and partly because of their presumably similar stabilities, be readily interconvertible; and the failure of this representative to exhibit either reproducible or sharply defined physical properties is therefore not surprising. Anhydrous 2,4-dicarbomethoxytropinone seems to exist only as a liquid, but two possibly distinct modifications of a solid hemihydrate, $C_{12}H_{17}NO_5 \cdot 1/2H_2O$, one white (m.p. 82.5–84°) and the other tan (m.p. 88–91°), were obtained. These forms, which precipitated slowly and appeared to be only partly crystalline, have nearly indistinguishable infrared spectra in Nujol. The binoxalate salt seems to exist in two modifications also, one being obtainable directly from the hemihydrate and melting about 146°, the other from the newly liberated anhydrous base and melting about

(10) The strength of the indicated bonds, NaO—H and NaO—R, being different, one need not expect sodium alkoxides or enolates to effect acid cleavage of β-keto esters. While no ester of acetoacetic acid itself has seemingly been observed to yield a dialkyl carbonate, malonic ester and sodium ethoxide do give under certain conditions about 10% of diethyl carbonate which may be a decomposition product of the carboethoxyphloroglucinols, the chief products of this reaction. H. Leuchs and A. Geserick, *Ber.*, **41**, 4171 (1908); H. Leuchs and F. Simion, *Ber.*, **44**, 1874 (1911).

According to V. H. Wallingford, A. H. Homeyer, and D. M. Jones [*J. Am. Chem. Soc.*, **63**, 2252 (1941)] excess methanol lowers the yield in such reactions.

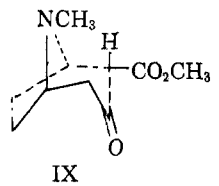
(11) (a) E. Ormerod, *Proc. Chem. Soc. London*, **22**, 205 (1906); (b) H. Cornelius and H. v. Pechmann, *Ber.*, **19**, 1446 (1886); (c) L. F. Fieser and M. M. Pechet, *J. Am. Chem. Soc.*, **68**, 5277 (1946).

(12) R. Kaushall, *J. Indian Chem. Soc.*, **17**, 138 (1940).

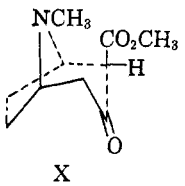
(13) R. Robinson, *J. Chem. Soc.*, **111**, 762 (1917).

155°. In aqueous sodium sulfate or in aqueous acetone equivalent amounts of 2,4-dicarbomethoxytropinone and sodium hydroxide react slowly to give a yellow precipitate which may be the sodium salt of the half ester and which is decomposed by mineral acids to carbon dioxide and racemic 2-carbomethoxytropinone.

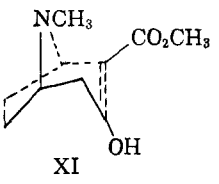
Although 2-carbomethoxytropinone (I) has three asymmetric carbon atoms and hence, theoretically, four racemic forms, the formation of only two of these (IX and X and their antipodes) is, of course, to be expected. Another kind of racemate, that of the enol form (XI and its antipode), is also possible and the benzoyl derivative thereof has indeed been prepared.[2] According to Willstätter,[2] racemic 2-carbomethoxytropinone melts at 111° and its monohydrate at 100°; but whether these two forms have the same molecular constitution has not been established before. Neither he nor Preobrashenski[7] looked for or found more than one racemic form.



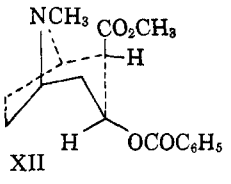
IX



X



XI



XII

None of the numerous batches of anhydrous racemic 2-carbomethoxytropinone prepared in this investigation melted sharply or as high as 111°. An analytically pure sample, generated from the pure picrate and then sublimed, melted at 103.5–104.6°; and chromatography of a somewhat less pure sample furnished material which melted no higher. In one instance needles melting at 104–107.4° were obtained. Furthermore, no monohydrate melting at or near 100° could be isolated. Indeed the only analytically pure hydrated form obtained in this work crystallized from aqueous acetone or from aqueous methyl acetate as colorless needles melting at 93–96° and having the composition of a dihydrate. Another form (m.p. 81.5–86°), which appeared to be largely a monohydrate, was also obtained from aqueous acetone; and from aqueous methanol a granular modification slowly separated which melted at 97.5–98° and had a composition approximating that of a trihydrate. From all of these forms the anhydrous base can be obtained by sublimation or distillation in high vacuum. It is noteworthy that Preobrashenski[7] reported the hydrate to melt at 96–98°.

These indications that racemic 2-carbomethoxytropinone, as usually obtained, is a somewhat variable mixture of easily interconvertible epimers or tautomers were supported by the isolation of two picrate salts. One, which is granular or powdery and melts about 167°, is got from acetone solution; the other, which crystallizes well and melts at 176°, separates from solutions in methyl alcohol. One form may be converted to the other merely by recrystallization from the other solvent. Two binoxalate salts were also found. One crystallizes from water as a sesquihydrate, is readily dehydrated, and melts about 135° with decomposition. The other crystallizes from water as a dihydrate, is less readily dehydrated, and melts at 145° with little or no decomposition. Both binoxalates regenerate one and the same form of racemic 2-carbomethoxytropinone.

The inhomogeneity of anhydrous 2-carbomethoxytropinone was confirmed by infrared measurements. In chloroform solution the base absorbs in regions characteristic of both keto and enol structures. On the other hand the dihydrate in Nujol gives no evidence of the presence of the keto form; and, similarly, 2,4-dicarbomethoxytropinone hemihydrate appears to exist exclusively as the enol. The ultraviolet spectra of the two esters in absolute alcohol demonstrate the predominance of the enol form of such compounds in polar solvents, and a molecular model of 2-carbomethoxytropinone suggests that the bridged-ring structure characteristic of the tropane alkaloids contributes to the stability of this tautomer. One concludes that, although this β-keto ester in the anhydrous state is usually obtained as a mixture of ketone (IX and/or X and their optical antipodes) and enol (XI and its antipode), it exists largely or entirely as the enol when hydrated or dissolved in a hydroxylic solvent. Since Willstätter employed methanol which favors the enol form to recrystallize the base, the high and sharp melting point reported by him may represent that of the pure anhydrous enol.

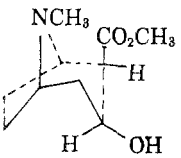
2-Carbomethoxytropinone was readily resolved by recrystallizing its L- and D-bitartrates from water. The L-bitartrate dihydrate has a specific rotation in water of +15.4° ($[M]_D^{20}$ + 5898 ±40). Recovered from the L-bitartrate, *d*-(2-carbomethoxytropinone) has a specific rotation in methanol of +18.3°. Like the racemic modification it crystallizes in the presence of water as a dihydrate and gives, seemingly, two picrate salts. It melts higher and more distinctly at 108.5–109.5° (Table I).

TABLE I

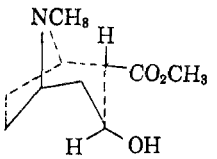
MELTING POINTS OF 2-CARBOMETHOXYTROPINONES AND SOME OF THEIR SALTS

	Racemic	*d*- or *l*-
Anhydrous Base	103.5–104.6° (111°[2])	108.5°–109.5°
Dihydrate	93–96° (100°[2])	98.5–101.5°
Picrate	167–168° and 176° (164°[7])	174 and 176.5°
Binoxalate	137° and 145°	142°

To ascertain its configurational relation to the naturally occurring, parent alkaloid, *l*-cocaine, the oxidation of *l*-ecgonine methyl ester (XIII) and its C_2-epimer,[14] *d*-pseudoecgonine methyl ester (XIV), was undertaken.



XIII



XIV

Although catalytic dehydrogenation, dehydrobromination, and photochemical oxidation experiments were unsuccessful, a small yield of the keto ester as the *d*-antipode was at length obtained by oxidizing either epimer in acetone with Kiliani's chromic acid solution.[15,16] Accordingly, *d*-(2-carbomethoxytropinone) is derived configurationally from *l*-cocaine (XII)[17] and must therefore have the structures, IX-XI, rather than their mirror images.[12] The low yield of the β-keto ester may be owing both to the resistance of equatorial hydroxyl groups[14,18] to oxidation and to the ease with which this product is further oxidized.[2]

Inasmuch as racemic 2-carbomethoxytropinone has been reduced both with sodium amalgam[2] and with catalytic hydrogen[3] to the two possible configurations of the C_3-hydroxyl group, which have been converted in turn to the four possible racemic cocaines,[2,3] the resolution of racemic 2-carbomethoxytropinone just described is tantamount to the direct synthesis of all the optically active cocaine isomers, known and unknown. Indeed, catalytic reduction of the *d* antipode in aqueous acetic acid furnished what is presumably alloecgonine methyl ester[3] which was isolated as the optically active hydroacetate.

The results here set forth are in essential agreement with the long and excellent memoir of Mannich concerning the preparation and properties of the analogous 1,2,6-trialkyl-3,5-dicarboalkoxy-4-piperidones from which were obtained "open" tropine, cocaine, and their derivatives.[19] A few of the similarities of and the differences between these two similar classes of compounds are noteworthy. Mannich likewise obtained better yields of keto diesters by using methylamine as the hydrochloride rather than as the free base, noted the instability of such compounds and their salts in hydroxylic solvents, and resolved 1,2,6-trimethyl-4-keto-3-carbomethoxypiperidine by means of the bitartrate salts. On the other hand, he was unable to obtain this last compound in good yield by partial saponification and found that catalytic hydrogenation of its hydrochloride resulted in the formation of racemic β-hydroxy esters.[20]

Miscellaneous Observations. Tropinone, prepared approximately according to the procedure of Keagle and Hartung,[9] was contaminated by a small quantity of a high-boiling, liquid by-product, which is presumably the other possible form of 2,5-diacetonyl-1-methylpyrrolidine.[8] It was characterized as its picrate and *bis*-*p*-nitrophenylhydrazone.

Reduced with ethereal lithium aluminum hydride, racemic 2-carbomethoxytropinone gave a mixture which could not be readily purified. One of the products, isolated as the picrate, appeared to be racemic anhydroecgonine methyl ester.

Dimethyl β-ketoglutarate was prepared in 65% yield by adding dry methanol to the mixture resulting from the reaction of anhydrous citric acid and fuming sulfuric acid.[21] Distillation had the expected effect on the keto-enol equilibrium. The action of fuming sulfuric acid on dimethyl citrate produces this ester directly in small yield.

Exploratory experiments to determine whether racemic 2-carbomethoxytropinone can be got from 2,5-diethoxytetrahydrofuran or succindialdehyde, methylamine, and the readily available methyl acetoacetate resulted, according to the conditions, in two seemingly new compounds, $C_{11}H_{18}N_2O_2$ (m.p. 166°) and $C_{15}H_{21}NO_5$ (m.p. 119–124°), which were rather laboriously separated from large quantities of viscous by-products. The former is basic and gives a well-defined binoxalate; the latter is neutral.

EXPERIMENTAL[22]

Materials. Carbide and Carbon 2,5-diethoxytetrahydrofuran (n_D^{20} 1.4208; reported:[23] n_D^{25} 1.4164), Charles Pfizer

(14) S. P. Findlay, *J. Am. Chem. Soc.*, **76**, 2855 (1954).

(15) H. Kiliani, *Ber.*, **46**, 676 (1913), footnote 1. I am indebted to Dr. Walter A. Jacobs of The Rockefeller Institute for supplying this reference.

(16) Dr. Yoshio Sato of this Institute kindly called this method to my attention and conducted the first oxidation experiment.

(17) The structure, XII, also represents the absolute configuration of *l*-cocaine [E. Hardegger and H. Ott, *Helv. Chim. Acta*, **38**, 312 (1955)].

As will be set forth in more detail elsewhere, *l*-cocaine and its derivatives are more dextrorotatory than the corresponding salts. In the seven examples so far examined only one exception to this rule has been found. By using the value of the molecular rotation for ammonium bitartrate [H. Landolt, *Ber.*, 6, 1073 (1873); J. H. Long, *J. Am. Chem. Soc.*, 23, 815 (1901)] or that of bitartrate calculated from the rotations of the L- and D-bitartrates of *d*-(2-carbomethoxytropinone) (see Experimental), one finds that the molecular rotation of *d*-(2-carbomethoxytropinone) is more dextrorotatory, *i.e.*, more positive, than the calculated molecular rotation of the corresponding ammonium ion.

(18) W. Klyne, *Progress in Stereochemistry*, Vol. 1, The Academic Press, New York, 1954, pp. 60 and 63.

(19) C. Mannich, *Arch. Pharm.*, **272**, 323 (1934).

(20) 2-Carbomethoxytropinone hydrochloride is under similar conditions nearly inert (unpublished observations of the author).

(21) *Cf.*, B. R. Baker, R. E. Schaub, M. V. Querry, and J. H. Williams, *J. Org. Chem.*, **17**, 97 (1952).

(22) All melting points recorded herein are corrected and were observed in Pyrex glass capillaries.

(23) J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.*, **72**, 869 (1950).

β-ketoglutaric acid (m.p. 133°), Fisher sodium methoxide, and Fisher methylamine hydrochloride (C.P.) were used without further purification. Eastman Kodak dimethyl carbonate was dried over potassium carbonate and distilled from silver carbonate: b.p. 88°/760 mm., n_D^{20} 1.3684 (reported:[24] n_D^{20} 1.3687). L-Tartaric acid (the naturally occurring, dextrorotatory tartaric acid, also known as L-threaric acid) was a Mallinckrodt Chemical Works product; D-tartaric acid was obtained from Aldrich Chemical Company, Milwaukee, Wis.

Tropionone. 2,5-Diethoxytetrahydrofuran (32 g., 0.200 mole) was stirred 15 min. under nitrogen with 0.2*N* sulfuric acid (160 ml.) and kept 4–5 hr. under nitrogen with occasional agitation.[25] The homogeneous solution was then stirred with $BaCO_3$ (8 g.) until nearly neutral and the barium salts collected and washed. The filtrate (~200 ml.) was added to a solution of disodium phosphate (142 g., 1.00 mole), β-ketoglutaric acid (36.5 g., 0.250 mole), and methylamine hydrochloride (16.9 g., 0.250 mole) in water (1800 ml.) at 10° and the whole kept 3 days at room temperature. The initial and final *p*H's were about 6.8. The pale yellowish-green solution was worked up according to the directions of Keagle and Hartung. From two such preparations was obtained after two distillations tropinone (40 g., 72%), m.p. 39–43.8°, b.p. 107–110°/23 mm. The base, initially colorless, acquires a brown coloration in a matter of hours. Inasmuch as the base is scarcely darker after a month than after the first day, the discoloration is no doubt caused by a small quantity of unstable impurity.

Evaporative distillation (80°/1 mm.) of the high-boiling residue from the first distillation (above) gave a small amount (~0.6 g.) of colorless, basic oil which became red on keeping. Prepared in and purified from methanol, its *bis*-*p*-nitrophenylhydrazone was obtained as small, yellowish-orange, stout prisms having hexagonal faces, m.p. 112–114° (softening at 102°).

Anal. Calcd. for $C_{23}H_{29}N_7O_4 + 2CH_3OH$: C, 56.48; H, 7.02; N, 18.45. Found: C, 56.91; H, 6.59; N, 18.40.

Its picrate, which is extremely soluble in acetone but sparingly so in methanol and alcohol, was purified from the last solvent: slender prisms, m.p. 167.6–168.6°.

Anal. Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.88; H, 5.20; N, 13.14. Found: C, 47.83; H, 4.84; N, 13.02.

The reaction of tropinone with dimethyl carbonate. (*a*) *Using sodium in xylene.*[7] To a warm solution of tropinone (3.6 g.) and dimethyl carbonate (6.1 ml.) in dry xylene (7.0 ml.) was added sodium (0.70 g.) in small pieces; and the reaction mixture, protected against moisture and carbon dioxide, heated quickly to boiling. The initially nearly colorless solution, which gradually darkened during the subsequent heating, was refluxed 20 min., the sodium dissolving with effervescence within about 13 min. After cooling to 0°, the mixture was extracted with cold water (2 × 10 ml.), the aqueous extracts mixed with ammonium chloride (2.0 g.) and extracted with chloroform (5 × 50 ml.), and the dried extracts concentrated *in vacuo* to a brown oil (5.8 g.). Mixed with water (1.5 ml.) at 0° this gave the crude hydrate (3.2 g.) which was collected after several hours and which darkened on keeping overnight. It was recrystallized by dissolving in hot acetone, cooling, adding a little water, and rubbing to induce crystallization. The yellowish-brown crystals were then freed of remaining gummy by-products by sublimation *in vacuo alto:* 1.8 g. (36%) of yellowish deposit, m.p. 97–102° (reported:[2] 111°). Unlike pure 2-carbomethoxytropinone this material soon darkened.

(*b*) *Using sodium methoxide.* Sodium methoxide (1.35 g., 0.025 mole) was added to a solution of tropinone (3.48 g., 0.025 mole) and dimethyl carbonate (4.0 ml.) in dry methanol (5.0 ml.) and the mixture heated at reflux temperature 1 hr. The mixture gradually thickened and became dark red. It was mixed at 0° with water (15 ml.) containing ammonium chloride (2.5 g.) and extracted with chloroform (4 × 50 ml.). The dried extracts were concentrated to an oil which was taken up in ether (100 ml.) and washed twice with a mixture of saturated aqueous potassium carbonate (6 ml.) and 3*N* potassium hydroxide (3.0 ml.). The oil which separated at the interface was taken up in saturated aqueous ammonium chloride, extracted into chloroform, and purified as described above: 0.05 g. of 2-carbomethoxytropinone. From the ether solution was recovered tropinone (3.0 g.).

Another experiment, conducted the same way except by using less methanol (2 ml.) and 10 min. of refluxing, gave 0.7 g. of 2-carbomethoxytropinone. A third experiment, conducted like the first except that toluene (10 ml.) and 30 min. of refluxing were used, gave 1.5 g. of nearly pure 2-carbomethoxytropinone and unreacted tropinone recovered as picrate (2.7 g.), m.p. 200°.

Dimethyl β-ketoglutarate. Powdered, anhydrous citric acid[26] (192 g., 1.00 mole), m.p. 153°, was added in 32-g. portions to fuming sulfuric acid (383 g., 202 ml., 21%) with stirring, the first two cautiously at 0° and the other four at 15–20° during 1.5 hrs. The mixture was stirred 1 hr. at 25°, 3 at 35°, and 17 at 25°.

To the stirred, yellow mixture absolute methanol (500 ml.) was added dropwise at −5 to 0° (3 hrs.). The mixture was kept 13–20 hrs. at 25° and added to a stirred mixture of sodium bicarbonate (700 g.), ice (500 g.), and water (200 g.). The precipitated salts were immediately filtered off and washed with 50% aqueous methanol (150 ml.). The slightly alkaline yellow filtrates were extracted with ether (7 × 400 ml.), the extracts dried (Na_2SO_4), and the solvent removed on the water bath and then *in vacuo*. The residual oil, which contained some water, was distilled *in vacuo:* after two distillations 112 g. (64%, b.p. 85°/1 mm., n_D^{20} 1.4452 (after several days), d_4^{20} 1.202). A small fore-run (5 g.) and a residue of trimethyl citrate (3.5 g.) were obtained from the first distillation. Distillation of nearly pure dimethyl β-ketoglutarate (100 g.) (n_D^{20} 1.4463) afforded two fractions:

Fraction	B.P.	Wt.	n_D^{21} (Immediately After distillation)
1	77–77.7°/0.65–0.60 mm.	50 g.	1.4539
2	77.7–78°/0.65–0.7 mm.	40 g.	1.4538

After a week Fraction 1 had n_D^{20} 1.4466.[27]

When 31% fuming sulfuric acid (265 g.) was substituted in the foregoing procedure, the yield was 10% lower. At 0° the reaction between anhydrous citric acid and fuming sulfuric acid is slow even after half of the citric acid has been added. At the height of the reaction the foaming mixture fills a 2-l. flask. The evolution of carbon monoxide is not complete even after 24 hr. The amount of fuming sulfuric acid employed is that calculated to convert all the water theoretically formed to sulfuric acid.

β-Ketoglutaric acid itself is perhaps obtainable in better yield than reported. The procedure in Organic Syntheses[28] prescribes U.S.P. citric acid, which is a monohydrate;[29] but

(24) P. N. Kogerman and J. Kranig, *Chem. Zentr.*, 1928 II, 2551.

(25) *Cf.*, J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Am. Chem. Soc.*, **77**, 4401 (1955).

(26) Citric acid, which is efflorescent (*Merck Index*, 6th Ed., p. 252), loses its moisture by exposure to air in dry weather, more readily by heating *in vacuo* at 60°.

(27) The refractive index of the freshly distilled ester changed much more rapidly between the prisms of the refractometer than in the container. That of the equilibrated ester does not change between the prisms.

(28) *Org. Syntheses*, **Coll. Vol. I**, 10 (1946).

(29) *The Pharmacopeia of the United States of America*, 14th Revision, The Mack Printing Company, Easton, Pa., 1950, p. 143.

the yield reported there (85–90%) is calculated on the assumption that the anhydrous acid was used.

Under similar conditions dimethyl citrate[30,31] and fuming sulfuric acid gave dimethyl β-ketoglutarate directly in about 10% yield.

Monomethyl β-ketoglutarate, dipotassium salt. A solution of potassium hydroxide (33.6 g., 0.600 mole) in absolute methanol (150 ml.) was added dropwise at 0° during 35 min. to a mixture of dimethyl β-ketoglutarate (43.5 ml., 0.300 mole) and methanol (10 ml.). When about one fifth of the alkali had been added a granular precipitate began to separate, and a yellow color appeared when the addition was about half complete.[1] The mixture was kept 3 hours at room temperature during which period it became thicker. After storing overnight in the refrigerator, the salt was collected and washed with cold methanol (15 ml.): 56.5 g.

Anal. Calcd. for $C_6H_6O_5K_2$: K, 33.09. Found: K, 27.41.

Another experiment differing only in that the alkali was admitted at room temperature during 1 hr. afforded the same yield of salt of the same potassium content. Kept in a closed jar the salt slowly turned orange and after a year contained 2% more potassium.

2,4-Dicarbomethoxytropinone (VI). Powdered succindialdoxime[32] (23.2 g., 0.200 mole), m.p. 172–173°, was suspended in 1*N* sulfuric acid (410 ml.), and a solution of sodium nitrite (27.6 g., 0.400 mole) in water (250 ml.) was added dropwise at 2–3° with mechanical stirring during 3–3.5 hr. The stirred, pale yellow mixture, protected from air, was kept 2 hr. at room temperature,[33] stirred with $BaCO_3$ (5.0 g.) and Super-cel, filtered through Super-cel, and diluted to 1.00 l. (*By treating an aliquot with a slight excess of aqueous p-nitrophenylhydrazine hydrochloride and recovering the p-nitrophenylhydrazone,[8,32] the yield of succindialdehyde was estimated to be 96–97%.*) The dialdehyde solution was mixed successively with methylamine hydrochloride (15.0 g., 0.222 mole), methanol (100 ml.), and dimethyl β-ketoglutarate (34.8 g., 0.200 mole) in methanol (50 ml.) [a small sample removed at the beginning had a pH of ~4.30 at the beginning, 4.20 after 10 min., 4.12 after 30, 4.09 after 40, 4.06 after 60, 3.90 after 12 hr.; no change occurred on longer keeping], and allowed to warm slowly.

After 20 hr. the solution, which had become yellowish orange, was mixed with potassium bicarbonate (30.0 g., 0.300 mole), and extracted with chloroform (5 × 200 ml.). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to a reddish orange oil (49.8 g.). This was dissolved in methanol (50 ml.) and mixed at room temperature with powdered oxalic acid dihydrate (24.5 g.). The crystalline binoxalate which slowly separated was stored overnight at 0°, collected, and washed with cold methanol: 52.1 g., m.p. 150.5–151° (dec.). By diluting the mother liquor and washings with an equal volume of ether and storing a day at 0°, a second crop was obtained: 3.1 g., m.p. 150.5–151° (*total yield: 55.2 g. or 80%*).

The powdered binoxalate (55.2 g., 0.160 mole) was stirred with chloroform (100 ml.) and water (150 ml.), potassium bicarbonate (35.0 g.) added cautiously, and the mixture shaken. The aqueous phase was extracted with more chloroform (3 × 100 ml.), and the base recovered approximately as before: 45.4 g. of light orange oil. It was dissolved in ether (100 ml.), water (2.5 ml.) added, and the mixture seeded and stirred 8 hr. at room temperature. The light tan, voluminous precipitate, which was augmented by storing 2 days at 0°, was collected and washed with ether: 39.6 g. (75%), m.p. 85–88.5°.

In later experiments succindialdehyde generated from 2,5-diethoxytetrahydrofuran as described above and appropriately diluted was employed. The ethanol necessarily present did not seem to contaminate the product appreciably through ester exchange. Conduct of the reaction at room temperature indicated that the condensation is fairly rapid, very mildly exothermic, and not notably favored by low temperatures. The intermediate binoxalate salt usually melted about 152° (sometimes at 155°), acquired a superficial pink coloration during drying, and was probably a mixture of at least two isomeric binoxalates.

Anal. Calcd. for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55. Found: C, 48.60; H, 5.51.

The base generated as described above melted as low as 85–88° and as high as 88–91° and was obtained in over-all yields of 69–79%.

Anal. Calcd. for $C_{12}H_{17}NO_5 \cdot 1/2H_2O$: C, 54.54; H, 6.87. Found: C, 54.29; H, 6.88.

In the first experiments, methylamine hydrochloride was always neutralized by adding potassium bicarbonate. The yield of 2,4-dicarbomethoxytropinone in these experiments was comparatively low owing to the formation of large quantities of brown, polymeric by-products. By using lower temperatures and greater dilutions in the experiments with free methylamine the tendency to by-product formation was somewhat reduced; but the isolation became correspondingly more laborious, and in alkaline solution at any dilution some ester appeared always to be lost by hydrolysis. In the foregoing procedure, neutralization of only 10% of the methylamine hydrochloride with potassium hydroxide lowered the yield about 10%.

Properties of 2,4-dicarbomethoxytropinone. Anhydrous 2,4-dicarbomethoxytropinone was obtained only as an oil which was at least moderately soluble in all common solvents, polar and non-polar. Isolated as described above the hemihydrate has usually a tan coloration, is relatively high melting, seems to be largely amorphous, and is partially (but not completely) liquefied by storing *in vacuo* over potassium hydroxide. Crystallized by dissolving in the minimum quantity of warm acetone, adding about 10% of water, seeding, and storing in the cold, the anhydrous oil afforded a white product melting at 82.5–84° and giving some extinction under the polarizing microscope.

Anal. Calcd. for $C_{12}H_{17}NO_5 \cdot 1/2H_2O$: C, 54.54; H, 6.87; CH_3O, 23.5. Found: C, 54.50; H, 6.75; CH_3O, 23.2.

A solution composed of equal parts of the hemihydrate and methanol was mixed with the theoretical amount of powdered oxalic acid dihydrate. On cooling the solution and scratching the *binoxalate* crystallized out: aggregates of minute, colorless prisms melting at 143–145° or at 146° and remaining colorless. The higher-melting binoxalate described above could not be thus obtained.

Anal. Calcd. for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55; CH_3O, 17.96. Found: C, 48.43; H, 5.58; CH_3O, 17.54.

The *nitrate* was prepared from 3*N* nitric acid at 0° and purified from methanol-ether and from acetone: minute, stout prisms, m.p. 146–146.5°.

Anal. Calcd. for $C_{12}H_{17}NO_5 \cdot HNO_3$: C, 45.28; H, 5.70. Found: C, 45.34; H, 5.66.

The *picrate* was prepared in aqueous acetone and purified from acetone: needles, m.p. 167–167.5°.

Anal. Calcd. for $C_{18}H_{20}N_4O_{12} \cdot 1/2H_2O$: C, 43.82; H, 4.29. Found: C, 43.84; H, 4.26.

Racemic 2-carbomethoxytropinone (I). (*a*) *From 2,4-dicar-*

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(30) G. Schroeter and L. Schmitz, *Ber.*, **35**, 2085 (1902).

(31) C. A. Naw, E. B. Brown, and J. R. Bailey, *J. Am. Chem. Soc.*, **47**, 2596 (1925).

(32) S. P. Findlay, *J. Org. Chem.*, **21**, 644 (1956).

(33) The equation for this reaction appears to be as follows:

$$\text{-(-CH}_2\text{—CH=NOH)}_2 + 2\text{NaNO}_2 + \text{H}_2\text{SO}_4 \longrightarrow \text{-(-CH}_2\text{—CHO)}_2 + \text{NaSO}_4 + 2\text{H}_2\text{N}_2\text{O}_2$$

Hyponitrous acid, which is known to result from the reaction of nitrous acid and hydroxylamine, slowly decomposes liberating nitrous oxide; and the evolution of gas for at least 24 hr. from another dialdehyde solution, similarly prepared, indicates its presence in this reaction too. It appears not to interfere appreciably with the subsequent condensation reaction.

bomethoxytropinone. Finely divided 2,4-dicarbomethoxytropinone hemihydrate (21.1 g., 0.0800 mole) was dissolved at room temperature with stirring in a solution (41 ml.) made by diluting sodium hydroxide (8.0 g.) and saturated aqueous sodium sulfate (25 ml.) to 100 ml. of aqueous solution. During the stirring (5 hr.) the light orange mixture became turbid. After keeping 48 hr. at room temperature, this mixture, which had become a yellowish white semi-solid, was suspended in water (50 ml.) and 6*N* aqueous sulfuric acid (~27.5 ml.) added cautiously (effervescence!) to *p*H 4.0. The mixture was made basic with potassium bicarbonate (12 g.) and extracted with chloroform (5 × 50 ml.). After removing about 75% of the solvent from the dried (Na_2SO_4) extracts on the steam bath, the solution was concentrated *in vacuo* to a yellow oil which slowly solidified when seeded: ~16 g. of crude product.

This was purified by dissolving it in hot methyl acetate (30 ml.), adding to the cold solution water (4 ml.) and acetone (4 ml.), and keeping several hours at 0°. The yellowish product was collected and washed with cold methyl acetate: 10.3 g., m.p. 97–101°. From the mother liquors additional material was recovered. By evaporative distillation about 100°/1 mm. a solid, partly yellow and partly white, was obtained: 10.2 g. (64%), m.p. 102.5–105°, of anhydrous base. No tropinone was isolated unless excess base was used in the saponification.

One part of diester dissolved in two parts of acetone and the stoichiometric amount of 4*N* aqueous sodium hydroxide gave a lower yield of the keto ester.

(*b*) *From the dipotassium salt of dimethyl β-ketoglutarate.* The potassium salt and succindialdehyde, prepared as described above, were combined with methylamine approximately according to the directions of Willstätter.[2] Based either on succindialdeyhde or on the dipotassium salt, the yield of 2-carbomethoxytropinone was 45%.

(*c*) *From β-ketoglutaric anhydride.*[12] β-Ketoglutaric acid (40 g.) was suspended in a mixture of glacial acetic acid (60 ml.) and acetic anhydride (43 ml.) at *ca.* 10° and stirred 3 hrs. at 8–15°. Usually the acid dissolved in about an hour, and almost at once the anhydride began to crystallize. The crude product was collected, washed with benzene, and dried *in vacuo* over potassium hydroxide 2–3 hr.: 30 g. (86%), m.p. 137.5–138.5° (reported:[4] 138–140°).

Crude β-ketoglutaric anhydride (13.5 g., 0.105 mole) was dissolved in cold methanol (50 ml.) and the solution kept 1 hr. at room temperature. It was added to a solution of methylamine hydrochloride (10.0 g., 0.148 mole) and sodium hydroxide (4.0 g., 0.100 mole) in water (850 ml.) and aqueous succindialdehyde (125 ml. of *ca.* 0.8*N*) stirred in. The mixture warmed almost imperceptibly, turned slowly yellow, and evolved carbon dioxide slowly. After keeping 24 hr. at room temperature the yellow solution was brought to *p*H 4.00 with 6*N* mineral acid (effervescence), washed with chloroform (35 ml.) to remove neutral and colored by-products, basified with sodium hydroxide (20 ml. of 4*N*) and potassium bicarbonate (4 g.), and extracted with chloroform (9 × 100 ml.). Recovered as above described racemic 2-carbomethoxytropinone was obtained as a yellowish brown oil which, when seeded, slowly crystallized as yellowish brown warts: 16.9 g. (86%), m.p. 92–93°. This material was recrystallized from acetone-water as described above: 12.1 g., m.p. 96–98.5°, of granular, pale yellow product. By sublimation *in vacuo* this and the material from the mother liquors were freed of water and small amounts of resinous impurities: 11.6 g. (59%), m.p. 93–100°.

When the reactants were combined near 0° and the mixture kept in the refrigerator 24 hr., the yield was somewhat lower: 10.3 g. (52%), m.p. 99.5–104.4°. When no sodium hydroxide was used to generate free methylamine, the yield of the keto ester was much smaller, and a proportionately greater quantity of resinous by-products was obtained.

Properties of racemic 2-carbomethoxytropinone. The analytically pure base was obtained by mixing the picrate (6.1 g., m.p. 167–168°), described below, with potassium carbonate (2.0 g.) in water (50 ml.) at 0°, filtering off the potassium picrate, and isolating the base as described above: 2.4 g. which, after two sublimations, was colorless and melted at 103.5–104.6°.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67. Found: C, 61.15; H, 7.51.

Anhydrous racemic 2-carbomethoxytropinone (3.0 g.) was dissolved in hot acetone (10 ml.) and water (1 ml.) added to the cooled solution. A crust of rosettes of colorless, small prisms slowly formed. After 24 hr. at room temperature the crystals were washed with acetone and dried: 2.3 g., which melted at 93–96° and at 101–104° after cooling and reheating.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot 2H_2O$: C, 51.49; H, 8.21. Found: C, 51.56; H, 8.13.

Another sample from aqueous acetone having the same composition melted at 96–98°. From the mother liquors rosettes of needles melting at 81.5–86° separated.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot 1H_2O$: C, 55.80; H, 7.96. Found: C, 54.47; H, 8.11.

Similarly recrystallized from methyl acetate the dihydrate was obtained as colorless prisms melting at 93–97°.

Anhydrous racemic 2-carbomethoxytropinone (4.0 g.) was dissolved in hot absolute methanol (4.0 ml.) and the cooled solution poured into water (8.0 ml.). Small mounds or warts separated slowly from the cold solution. After several hours these (~1 g.) were collected. From the filtrate a more finely divided precipitate separated: 3 g., m.p. 97.5–98°.

Anal. Calcd. for $C_{10}H_{16}NO_3 \cdot 3H_2O$: C, 47.80; H, 8.42. Found: C, 48.18; H, 8.52.

The yellow crude product from the partial saponification was chromatographed on alumina. Elution with benzene gave about one third which was colorless and, after sublimation, melted at 90–98°. Further elution afforded approximately the same amount melting, after sublimation, at 101–103°. Secondary butyl alcohol and methanol removed gummy material and a trace of benzene-insoluble substance. The color and about one fifth of the sample were retained by the adsorbent.

The initially obtained crude anhydrous base did not always solidify readily when seeded or scratched. Furthermore, the high-vacuum sublimation of the crude base gave frequently a mixture of solid and liquid, the latter crystallizing only when scratched. The particular phenomena observed appeared to be related to the history of the preparation: whether ammonia or potassium bicarbonate had been used to liberate the base and whether the chloroform extracts had been concentrated *in vacuo* or not.

The anhydrous base dissolves in all the common solvents, polar and non-polar, and is especially soluble in hot methanol, methyl acetate, and acetone. Sublimed about 90°/1 mm. the anhydrous base collects as white flakes and warts which electrify readily. It was also obtained as prisms melting at 104–107.4° from the upper walls of flasks containing the anhydrous base previously generated as noted above from pure salts.

The base gives an intense color with ferric chloride, dissolves in aqueous alkali, and is precipitated therefrom by either carbon dioxide or ammonium chloride. It is unstable in hot water.

The *binoxalate* was prepared in and purified from water in which it is quite soluble even at room temperature. By evaporation of an aqueous solution at room temperature the salt was obtained in two forms: porous mushroom-like growths and colorless prisms. From concentrated aqueous solutions either form could be obtained by seeding, the former separating as a voluminous precipitate. The former melted about 87°. Dried to constant weight *in vacuo* at 40°, the salt lost 8.50% of its weight (theory for $1^1/_2$ H_2O: 8.60%) and melted about 137° (bubbling and discoloration).

Anal. Calcd. for $C_{12}H_{17}NO_7$: C, 50.17; H, 5.97. Found: C, 49.93; H, 6.29.

The prisms melted about 98° and, when partially dehydrated, again at 145° (bubbling, but little or no discoloration). They are not completely dehydrated by heating *in vacuo* first at 57° and then 12 hr. at 80°.

Anal. Calcd. for $C_{12}H_{17}NO_7 \cdot 2H_2O$: C, 44.58; H, 6.55. Found: C, 44.67: H, 5.80.

Regenerated in the customary manner, the base from one salt was indistinguishable from that from the other.

The anhydrous base (0.43 g.) was dissolved in butanone (5 ml.) and a solution of picric acid (0.46 g.) in butanone (5 ml.) added. Rather large polyhedra (0.8 g.) of the *picrate* melting at 175–176° separated overnight. Recrystallized from methanol the salt was obtained either as rhombohedra or as small, transparent, yellow prisms melting at 176–177°.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25; N, 13.14. Found: C, 45.11; H, 3.95; N, 12.99.

A hydrated form (0.43 g.) was dissolved in methanol (5 ml.) and a solution of picric acid (0.46 g.) in warm methanol (5 ml.) added. Seeded with impure picrate recovered from another experiment, a light yellow granular precipitate was obtained: 0.7 g., m.p. 165–167°. Recrystallized to constant melting point from acetone, the salt was obtained as a yellow powder melting at 167.5–168°.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25. Found: C, 44.79; H, 4.46.

It was necessary to dry both salts several hours *in vacuo alto* about 125° before analysis. Dried at room temperature both appeared to retain tenaciously a third of a mole of water per mole of salt. The high-melting picrate, which is rather insoluble in hot methanol, gives with this solvent supersaturated solutions from which both varieties of the picrate can be obtained. Recrystallized from acetone in which it dissolves rather easily, it is converted to the low-melting, powdery picrate. A solution of this form (0.5 g.) in methanol (50 ml.), after refluxing 4 hr. and keeping 2 days at 5°, gave the high-melting form (0.4 g.). The lower-melting modification may be the same as that reported by Preobrashenski to melt at 163–164°.[7]

The *hydrochloride* was prepared in methanol and purified from methanol-ether: m.p. 180° (reported:[8] 180°).

Lithium aluminum hydride reduction. To a solution of lithium aluminum hydride (0.6 g.) in dry ether (200 ml.) was added dropwise during 2 hr. a solution of anhydrous racemic 2-carbomethoxytropinone (2.0 g.) in ether (100 ml.). Near the end of the addition a precipitate was obtained. After refluxing the mixture 1 hr., it was kept 2 days, decomposed with ethereal acetone, and extracted with 6*N* sulfuric acid (25 ml.). The aqueous extract was diluted with water (25 ml.), filtered, mixed with Rochelle's salt (10 g.), and basified with sodium hydroxide (6 g.). Continuous extraction with chloroform removed an orange oil (1.8 g.) which could be distilled *in vacuo alto*. It did not give a crystalline hydrochloride, oxalate, or binoxalate. Neutralized with methanolic picric acid it was converted to an orange gum which, after the evaporation of the solvent, slowly and only partially solidified. By repeated recrystallization from methanol the solid portion was obtained as a rather deep yellow substance which dissolved in methanol with difficulty but readily gave supersaturated solutions therein. Under the polarizing microscope it appeared either to be amorphous or to consist of aggregates of minute crystals. It melted at 206–207° and had a composition approximating that of the picrate of racemic *anhydroecgonine methyl ester*.

Anal. Calcd. for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42; N, 13.65. Found: C, 47.14; H, 4.79; N, 13.57.

d-(2-Carbomethoxytropinone). A mixture of anhydrous racemic 2-carbomethoxytropinone (19.7 g., 0.100 mole), m.p. 100–104°, and L-tartaric acid (15.0 g., 0.100 mole) was finely ground and dissolved in warm water (80–100 ml.). On keeping at room temperature or on seeding a large quantity, augmented by cooling to 0°, of feathery needles of the L-bitartrate separated: m.p. 86–91°. These were recrystallized to constant rotation from water: 4.0 g., m.p. 91–94° (bubbling); $[\alpha]_D^{20}$ +15.4° (*c*, 2, water). Dried at 57° in high vacuum to constant weight (5 hr.), the weight loss was 9.89% (theoretical loss for converting the dihydrate to the anhydrous bitartrate: 9.40%). The dried sample was analyzed.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot C_4H_6O_6$: C, 48.41; H, 6.10; CH_3O, 8.93. Found: C, 48.29; H, 6.08: CH_3O, 9.00.

Evidence of the transitory existence of a more dextrorotatory L-bitartrate was obtained.

The *d*-base was obtained by mixing the salt with a slight excess of potassium bicarbonate, extracting with chloroform, removing the solvent, and subliming the residue: colorless, minute prisms, m.p. 108.5–109.5°, which electrify readily; $[\alpha]_D^{20}$ +18.3° (*c*, 1, methanol).

The D-*bitartrate* prepared in water from stoichiometric amounts of the *d*-base and D-tartaric acid was obtained as colorless, rather stout prisms by evaporation at room temperature. These were converted to the anhydrous salt by dissolving in methanol and removing the solvent at room temperature. This form was recrystallized from absolute methanol in which it is noticeably less soluble than the hydrate: rosettes of prisms (which were dried over $CaCl_2$), m.p. 145–146° (dec.), $[\alpha]_D^{20}$ −7.0° (*c*, 2.5, water).

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot C_4H_6O_6$: C, 48.41; H, 6.10. Found: C, 48.32; H, 6.08.

l-(2-Carbomethoxytropinone). The mother liquors from the L-bitartrate were evaporated to dryness, and the base was regenerated in the usual manner. This was combined with an equivalent amount of D-tartaric acid, and the resulting D-bitartrate purified as above noted for the L-bitartrate: white slender prisms; $[\alpha]_D^{20}$ −15.4° (*c*, 2, water). Recrystallized from methanol the pure dihydrate was converted to stout prisms of the anhydrous D-bitartrate: m.p. 159.5° (dec.); $[\alpha]_D^{20}$ −16.9° (*c*, 2, water).

The base was generated in the manner already described: m.p. 108.6–109.6°, $[\alpha]_D^{20}$ −18.3° (*c*, 1, methanol); $[\alpha]_D^{20}$ −36.7° (*c*, 1.7, H_2O).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67. Found: C, 60.98; H, 7.73.

The hydrated form was obtained by mixing with a slight excess of distilled water and drying *in vacuo* over anhydrous sodium sulfate: m.p. 98.5–101.5°.

Anal. Calcd. for $C_{10}H_{15}NO_3 + 2H_2O$: C, 51.49; H, 8.21. Found: C, 51.16, 51.16; H, 7.85, 8.22.

To a solution of the hydrate (0.60 g.) in methanol (~1 ml.) was added picric acid (0.64 g.) dissolved in methanol (1 ml.). The *picrate* of the *l*-base separated suddenly from the supersaturated solution as balls of prisms: m.p. 176–177° (bubbling). These were recrystallized from methanol: minute, slender prisms, m.p. 176–176.5° (bubbling). The sample was dried to constant weight at 125° *in vacuo alto* for analysis (weight loss: 1.49%).

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25. Found: C, 45.16; H, 4.23.

Recrystallized to constant melting point from acetone this form gives another modification melting at 174° (bubbling) which seems, however, to be indistinguishable from the first in crystalline form. It was similarly dried for analysis.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25. Found: C, 44.95; H, 4.43.

The *binoxalate* was prepared in methanol and crystallized therefrom by adding ether: m.p. 142–143°.

Dehydrogenation experiments. Efforts to dehydrogenate ecgonine, ecgonine methyl ester, and pseudoecgonine methyl ester in alcoholic solution with freshly prepared Raney nickel[34] did not succeed. Silver carbonate in boiling benzene had no effect on either of the foregoing esters. No 2-carbomethoxytropinone was obtained from pseudoecgonine methyl ester by the action of N-bromosuccinimide in chloro-

(34) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

form, by the action of N-bromoacetamide,[35] or by the Oppenauer oxidation. The irradiation of a fused mixture of pseudoecgonine methyl ester and benzophenone containing a small amount of glacial acetic acid with a G.E. Sunlamp produced no 2-carbomethoxytropinone as indicated by a negative ferric chloride test.

d-(2-Carbomethoxytropinone) from pseudoecgonine methyl ester. Kiliani's chromic acid solution[15] (4.0 ml.) was added dropwise during 1 hr. to a stirred solution of pseudoecgonine methyl ester (1.0 g.) dissolved in Fisher Reagent acetone (250 ml.). The first third of the reagent produced an orange turbidity. The remainder caused a color change to greenish orange and the separation of a granular, greenish deposit. After stirring another hour the acetone solution was filtered, made just alkaline with ammonia, and concentrated *in vacuo* to a brown oil. This was taken up in aqueous potassium carbonate, excess ammonium chloride added, and the mixture extracted with chloroform (3 × 50 ml.). The green salts were mixed with aqueous sodium sulfate, made slightly alkaline with potassium bicarbonate, and extracted with chloroform (3 × 50 ml.), emulsions being broken by centrifuging. The dried (Na_2SO_4) extracts were combined, and the residue recovered in the customary manner: ~0.6 g. of crystalline material consisting mainly of unchanged ester. An ether solution of this mixture was extracted twice with a mixture of saturated aqueous potassium carbonate (3 ml.) and 3*N* potassium hydroxide (1.0 ml.). Crude *d*-(2-carbomethoxytropinone) was thus obtained as a yellow, concentrated aqueous solution of its potassium salt. It was washed with ether (10 ml.), treated with excess saturated ammonium chloride, and extracted with chloroform (3 × 50 ml.). Drying and removal of the solvent in the usual manner afforded crude *d*-(2-carbomethoxytropinone): 0.105 g. It was sublimed *in vacuo alto* for analysis: m.p. 103.5–106.7°, $[\alpha]_D^{20}$ + 17° (*c*, 1, methanol).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.11. Found: C, 60.80; H, 7.58; N, 6.82.

Like the synthetic base, it gives an intense red color when treated with ferric chloride.[2] From the ether solution 0.5 g. of pseudoecgonine methyl ester was recovered.

Ecgonine methyl ester, similarly oxidized, gave a much lower yield of the keto ester.

Alloecgonine methyl ester. The keto ester (0.125 g.) from natural sources was dissolved in Mallinckrodt A.R. glacial acetic acid (45 ml.), water was added (9.0 ml.), and the mixture was shaken 12 hr. with platinum oxide (0.17 g.) and hydrogen (at approximately atmospheric pressure). The catalyst-free solution was concentrated *in vacuo* to a yellowish gum. The base was recovered by adding aqueous potassium carbonate, extracting with ether (4 × 30 ml.), and concentrating the dried extracts on the water bath and then *in vacuo*. Inasmuch as the base did not crystallize, it was dissolved in ether (1 ml.) and treated with an acetone-ether solution (1 ml.) containing the stoichiometric amount of acetic acid. The hydroacetate which separated was recrystallized from acetone to constant melting point: 0.07 g., m.p. 111.5–1113.5°, $[\alpha]_D^{20}$ −3.6° (*c*, 2, methanol). The dibenzoyl-L-bitartrate was prepared in methanol and thrice recrystallized therefrom, but not to constant melting point: small crystals having hexagonal faces, m.p. 159.5–160°. This melting point was not depressed by admixture with the dibenzoyl-L-bitartrate (m.p. 160°) similarly obtained from the synthetic *d*-base.

Anal. Calcd. for $C_{28}H_{31}NO_{11}$: C, 60.31; H, 5.60. Found: C, 60.54; H, 5.64.

Experiments with methyl acetoacetate. (a) Methylamine hydrochloride (20.3 g.), potassium acetate (29.4 g.), and water (25 ml.) were warmed and agitated until the mixture was homogeneous. It was diluted with glacial acetic acid (200 ml.), 2,5-diethoxytetrahydrofuran (16.0 g.) added, and then methyl acetoacetate (10.7 ml.). The mixture, initially yellow, had become brown within 24 hr. After 2 weeks it was filtered, concentrated *in vacuo* to a dark syrup, treated with excess aqueous potassium carbonate, and extracted with chloroform (3 × 100 ml.). Removal of the solvent from the dried (Na_2SO_4) extracts on the steam bath and then *in vacuo*, gave a dark thick oil which was leached with hot ligroin (4 × 100 ml.), b.p. 60–70°. Removal of the ligroin afforded an orange brown oil (11 g.) which partially crystallized. The solid material was filtered off and purified from methanol: ~2 g., m.p. 166.5–167°. This material, which retains some methanol, was sublimed for analysis. In chloroform solution it had strong bands at 3.03 μ, 6.09 μ, and 6.27 μ but none for saturated ketone or unconjugated ester groupings. The Rast method indicated the molecular weight of the unsublimed material to be 191. For the same material the methoxyl content was 15.7%.

Anal. Calcd. for $C_{11}H_{18}N_2O_{27}O_2$: C, 62.83; H, 8.63; N, 13.33. Found: C, 63.05; H, 8.59; N, 13.20.

The binoxalate was prepared in and purified from methanol: irregularly shaped crystals, m.p. 193–194°.

Anal. Calcd. for $C_{13}H_{20}N_2O_6$: C, 51.99; H, 6.71; N, 9.33. Found: C, 51.78; H, 6.80; N, 9.22.

(b) Succindialdehyde, prepared from 2,5-diethoxytetrahydrofuran (16 g.) as described under "Tropinone," was diluted to 125 ml., mixed with methylamine hydrochloride (6.75 g.), then with potassium bicarbonate (10.0 g.), and finally with methyl acetoacetate (10.7 ml.) in methanol (350 ml.). The initially pale green solution had become brown within a few hours. During the next two weeks the solution did not become noticeably darker. It was filtered and concentrated *in vacuo* to a mixture of water and oil which partially crystallized on keeping. Purified from methanol it was obtained as minute, stout prisms: 5.9 g. (20%), m.p. 119–124°.

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.09; H, 7.14; N, 4.69.

It is neutral and gives no ferric chloride test. After sublimation it melted at 118–119°. In chloroform solution the sublimed material exhibited pronounced absorption at 5.76 μ, 5.85 μ, 6.02 μ, and 6.45 μ.

Spectral measurements. In chloroform solution racemic 2-carbomethoxytropinone (m.p. ~104°) showed noticeable absorption in the 3.0 μ region and gave two medium bands at 5.74 μ[36] and 5.83 μ and two strong bands at 6.04 μ[36] and 6.18 μ characteristic of unconjugated ester, ketone, conjugated ester, and ethylenic groupings, respectively.

In Nujol the dihydrate gave strong bands at 2.95 μ, and at 6.0 μ. The absence of any bands for unconjugated ester and keto groupings indicates strongly that these two bands are for the hydroxyl and the conjugated ester groups of the enol form.

In Nujol samples of 2,4-dicarbomethoxytropinone hemihydrate melting at 82.5–84° and at 88–91° had strong bands at 2.95 μ, 5.74 μ,[36] and 5.97 μ characteristic of hydroxyl, unconjugated ester, and conjugated ester groupings, respectively. There was little or no evidence of ketone absorption near 5.80 μ.

In absolute alcohol anhydrous racemic 2-carbomethoxytropinone had λ_{max} 255 μ (ε 6190) and 2,4-dicarbomethoxytropinone λ_{max} 255 mμ (ε 7882). In the same solvent methyl acetoacetate had λ_{max} 240 mμ (ε 1513 after 5 min.; 1667 after 1 or more hr.).

The infrared measurements were made with a Perkin-Elmer Recording Spectrophotometer (Model 21) having a sodium chloride prism and the ultraviolet adsorption spectra with a Cary Recording Spectrophotometer (Model 11).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Keto Grignard Reagents. Intramolecular Reduction*[1]

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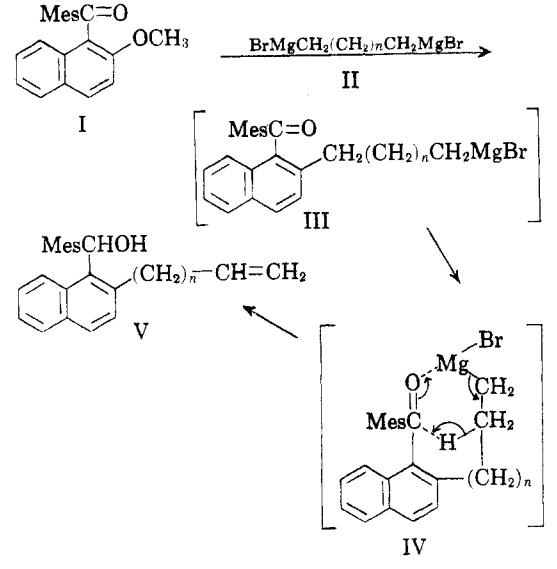
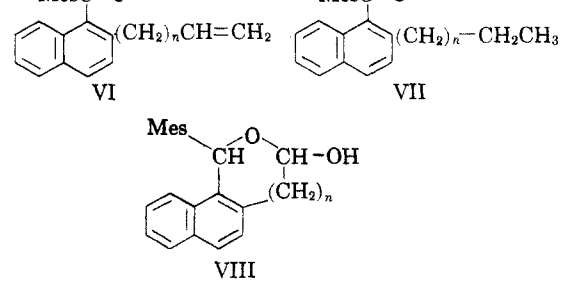
1-Mesitoyl-2-methoxynaphthalene (I) reacts with the dimagnesium derivatives (II) of 1,4-dibromobutane, 1,5-dibromopentane, and 1,6-dibromohexane to yield products that could be derived from intermediate keto Grignard reagents (III). With 1,4-butanedimagnesium dibromide, for example, the principal product is 2-(γ-butenyl)naphthyl-1-mesitylcarbinol (V, $n = 2$). The amount of reduction product decreases progressively as the chain of the Grignard reagent is lengthened. Similarly, duryl 2-methoxyphenyl ketone (X) and the Grignard reagent from 1,4-dibromobutane gave 2-(γ-butenylphenyl)durylcarbinol (XII).

The condensation of esters with certain aliphatic bifunctional Grignard reagents to give cyclic carbinols[3] appears to involve the formation of keto Grignard reagents as transient intermediates. The object of the present study was to determine whether such a keto Grignard reagent could be produced by the action of a dibromomagnesium compound on a hindered *o*-methoxyaryl ketone, a vinylog of an ester.

1-Mesitoyl-2-methoxynaphthalene (I) has been found to react with the Grignard reagent from 1,4-dibromobutane (II, $n = 2$) to give the olefinic carbinol V ($n = 2$) in a yield of 65%. This unexpected product was formed presumably by way of the keto Grignard reagent III ($n = 2$), which may undergo intramolecular reduction by way of a transition state resembling the *quasi*-cyclic system IV ($n = 2$).[4] Since *n*-butylmagnesium bromide displaces the methoxyl group of the methoxy ketone I in 55% yield,[5] the intramolecular reduction of the keto Grignard reagent III ($n = 2$) probably occurs rapidly and quantitatively.

Oxidation with dichromate in glacial acetic acid, by preferential attack of the carbinol function, produced the olefinic ketone VI ($n = 2$), which was hydrogenated catalytically to give 2-*n*-butyl-1-mesitoylnaphthalene (VII, $n = 2$).





The terminal position of the double bond in the side chain of the carbinol was established by ozonization. In addition to formaldehyde, a larger frag-

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(2) Allied Chemical and Dye Corporation Fellow, 1956–1957.

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