

The melting point of a mixture of the above product and tricarbobenzoxy-L-arginine was depressed to 110–115°.

*Tricarbobenzoxy-L-arginyl-L-glutamic acid dibenzyl ester.* The condensation of tricarbobenzoxy-L-arginine with the hydrochloride or *p*-toluenesulfonate salt of L-glutamic acid dibenzyl ester was carried out in chloroform solution as above. Isolation of the condensation product was achieved in comparable manner, with the exception that the crystalline residue, obtained upon evaporation of the reaction mixture, was first triturated with *cold* methanol containing triethylamine, then filtered over suction and recrystallized twice from ethyl acetate; yield, 75%; m.p. 120–121°.

*Anal.* Calcd. for  $C_{49}H_{51}O_{11}N_5$ : C, 66.4; H, 5.8; N, 7.9. Found: C, 66.1; H, 6.0; N, 7.8.

*L-Arginyl-L-glutamic acid.* Hydrogenolysis of tricarbobenzoxy-L-arginyl-L-glutamic acid dibenzyl ester in 95% acetic acid was effected in the presence of palladium black catalyst.<sup>16</sup> Upon completion of the reaction, the catalyst was filtered off, washed first with methanol, then with water, and the combined filtrates finally evaporated to dryness. The residue was dissolved in a small amount of hot water and crystallized as plates upon the addition of hot ethanol; yield, 90% of theory. Recrystallization from water yielded the crystalline tetrahydrate with a recovery of 90%.

*Anal.* Calcd. for  $C_{11}H_{21}O_5N_5 \cdot 4H_2O$ : C, 35.2; H, 7.8; N, 18.7. Found: C, 35.2; H, 7.9; N, 18.4.

The dipeptide tetrahydrate lost 19.1% of its weight upon drying for 2 hr. *in vacuo* at 78° (calcd. for  $4H_2O$ , 19.2%) and melted at 210–214° prior to, and after its conversion to the anhydrous material;  $[\alpha]_D^{25} +21.4^\circ$  for a 1% solution in water, calculated as the anhydrous material.<sup>29</sup>

(29) These values are in agreement with those reported by Gish and Carpenter<sup>7</sup>; m.p. 205–210° for the dihydrate;  $[\alpha]_D +22^\circ$ , calcd. for the anhydrous material in water. Berse and Piche<sup>11</sup> and Hofmann, Peckham, and Rheiner<sup>9</sup> reported melting point values for the anhydrous material as 202–205° and 251–252° dec., respectively, but made no

*Anal.* Calcd. for  $C_{11}H_{21}O_5N_5$ : C, 43.6; H, 7.0; N, 23.1. Found: C, 43.5; H, 7.1; N, 23.2.

A sample of the above dipeptide was hydrolyzed with acid to the corresponding free amino acids with 5*N* HCl and the excess acid was removed *in vacuo*. The hydrolysate was taken up in water and the aqueous solution "spotted," together with a sample of the parent dipeptide and reference standards of glutamic acid and arginine-HCl, on Whatman No. 1 paper. Prior to chromatography, the paper was briefly exposed to ammonia vapors. Four different solvent systems were employed, with the dipeptide revealing only a single ninhydrin positive spot with  $R_f$  values as follows: formic acid-water-*tert*-butyl alcohol (3:3:14), 0.26; methanol-water-pyridine (20:5:1), 0.28; 70% aqueous ethanol, 0.29; 88% phenol with 10% sodium acetate, 0.53. The hydrolyzate, on the other hand, revealed only two spots which corresponded to glutamic acid and arginine, respectively.

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mention of the possibility of hydrate formation. In our experience, the free dipeptide invariably deposits as the tetrahydrate upon crystallization from hot water. However, when precipitation is achieved by the addition of methanol or ethanol to the aqueous solution, a mixture of hydrates is obtained with values found which approach those of either the dihydrate or the tetrahydrate, depending upon the temperature employed. Isolation of the material as the monohydrate has been reported.<sup>10</sup>

[CONTRIBUTION No. 464 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

## Piperidine Derivatives. IV. 1,3-Disubstituted-4-aryl-4-acyloxy Piperidines\*<sup>1</sup>

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On the basis of the infrared spectra of  $\alpha$ -1,3-dimethyl-4-phenyl-4-hydroxypiperidine and  $\beta$ -1,3-dimethyl-4-phenyl-4-hydroxypiperidine, the  $\alpha$ -form was tentatively designated *cis* and the  $\beta$ -form *trans* with respect to H and OH. It was also shown that the  $\alpha$  and  $\beta$  forms of 1-methyl-3-R-4-phenyl-4-propionoxypiperidine (R = ethyl, allyl, crotyl) can be distinguished by several bands in the infrared. Other esters have been prepared where R is butyl, propyl, hexyl, and benzyl. All of the esters have been examined for their analgesic activity.

In a previous paper,<sup>2</sup> we have described the diastereomeric forms of the low melting ( $\beta$ ) [Fig. 1 (1b), R=CH<sub>3</sub>] and the high melting ( $\alpha$ ) [Fig. 1 (1a), R=CH<sub>3</sub>] forms of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride.<sup>3</sup> The infrared spectra of the two forms are shown in Fig. 2.

We have now prepared homologous compounds

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

(1) Presented in part before the Meeting-in-Miniature of the North Jersey Section of the A.C.S., January 28, 1957.

(2) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

(3) The higher melting isomer is also known as alphaprodine [Nisentil®] and the lower melting form as betaprodine (World Health Organization designations).

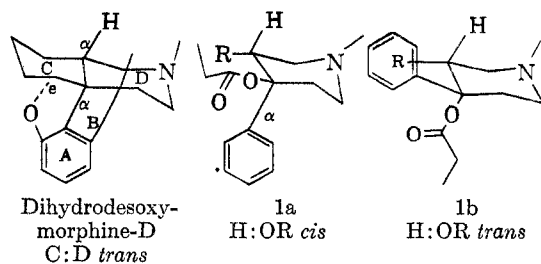


FIGURE 1.

where R is allyl, crotyl, ethyl, propyl, butyl, hexyl, and benzyl. In the case of the first three mentioned, diastereomeric pairs,  $\alpha$  and  $\beta$  forms were encoun-

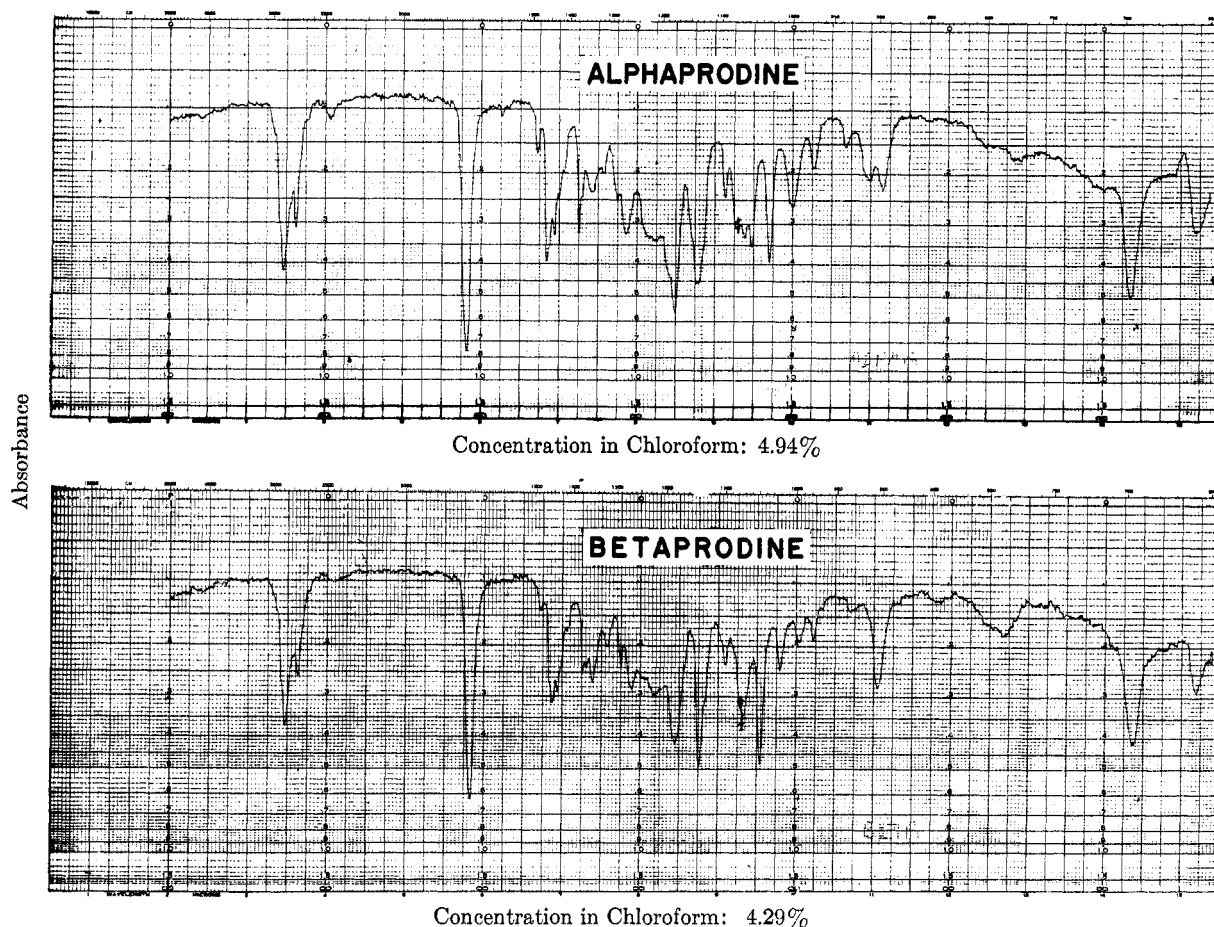


FIG. 2. INFRARED SPECTRA OF DIASTEREOMERIC FORMS OF 1,3-DIMETHYL-4-PHENYL-4-PROPIONOXYPIPERIDINE.

tered but with the last three no attempt was made to isolate the small amounts of the  $\beta$  form that were probably present. Since the compounds are of some pharmacological importance,<sup>4,5</sup> it seemed of interest to assign the diastereomers to the  $\alpha$  and  $\beta$  series and to establish, if possible, the absolute configurations.

In the previous paper, we had assigned the structure 1b (*cis* CH<sub>3</sub>:OR) to the more active  $\beta$ -diastereomer (betaprodine) since that structure simulated the decahydroisoquinoline ring of dihydrodesoxymorphine-D which, at that time, was assumed to have rings C and D in *cis* conformation. Since then, however, it has been established that rings C and D have a *trans* conformation.<sup>6</sup> Thus, one would expect that the more active isomer (betaprodine) probably would have structure 1a Fig. 1 (*trans* CH<sub>3</sub>:OR) on the basis of its similarity to rings C and D of dihydrodesoxymorphine-D and on the basis of the similarity of the analgesic ac-

tivity of the more active isomer to that of dihydrodesoxymorphine-D in rats.

Beckett and co-workers,<sup>7</sup> on the basis of conformational analysis and hydrolysis rates of 1a and 1b, have arrived at the same conclusion; that betaprodine should be represented by 1a and alphaprodine by 1b.

However, examination of the infrared spectra of the alcohols derived from 1a and 1b permits the tentative deduction that the structure assignments remain as originally postulated, *i.e.*, alphaprodine is 1a and betaprodine is 1b.

The relative position of the phenyl, hydroxyl, and methyl groups was determined using the spectra of the  $\alpha$  and  $\beta$  forms of 1,3-dimethyl-4-phenyl-4-hydroxypiperidine, in particular in the region of OH absorption near 3600 cm.<sup>-1</sup>. It is well known that a free OH group will have an absorption band near 3600 cm.<sup>-1</sup>; when association by H-bonding occurs, this absorption band becomes weaker and an absorption band appears at lower frequencies, its intensity depending on the degree of association. Intermolecular H-bonding, which would account for the low OH absorption in both com-

(4) W. M. Benson, D. V. Cunningham, D. L. Hane, and S. VanWinkle, *Arch. intern. pharmacodynamie*, **109**, 171 (1957).

(5) J. Lee, W. M. Benson, and F. F. Foldes, *Can. Anaes. Soc. J.*, **3**, 363 (1956).

(6) H. L. Holmes and R. H. F. Manske, *The Alkaloids*, Academic Press, New York, 1952, Vol. 2, 162, 175; Ajay K. Bose, *Chemistry & Industry*, 130 (1954).

(7) A. H. Beckett and J. Walker, *J. Pharm. and Pharmacol.*, **7**, 1039 (1955); A. H. Beckett and A. F. Casy, *J. Pharm. and Pharmacol.*, **6**, 986 (1954).

pounds, depends on the free access to the hydroxyl from the outside. This, in turn, depends on the arrangement of groups surrounding OH within the molecule.

In the case of a *cis* configuration of OH and CH<sub>3</sub>, corresponding to the form 1b (Fig. 1), the Court-auld scale model shows that the CH<sub>3</sub> is close to the OH to the extent of causing steric interference which restricts the free rotation around the CO bond. This is not the case for the form 1a.

It has been shown by Smith and Creitz<sup>8</sup> in a study of the OH absorption at 3600–3200 cm<sup>-1</sup>, that the substitution of a single methyl in the 2-position of 3-pentanol, where free rotation is still possible, restricts notably the intermolecular H-bond formation. A similar effect can be expected in the present case.

A distinct difference between the two substances,  $\alpha$  and  $\beta$ , is seen in Fig. 3. The molecular extinction

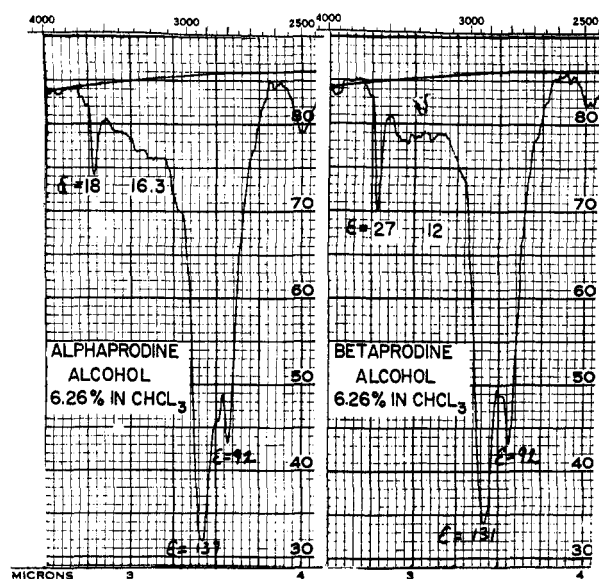


FIG. 3. INFRARED ABSORPTION BANDS (OH AND CH STRETCHING) OF DIASTEREOMERS OF 1,3-DIMETHYL-4-PHENYL-4-HYDROXYPIPERIDINE.

coefficient of the OH stretching band at 3600 cm<sup>-1</sup> is 18 for the  $\alpha$  form and 27 for the  $\beta$  form. These values are about in the same proportion as the values of the area under the free OH peak (between 3700 and 3510 cm<sup>-1</sup>), which are respectively, 15 and 21 percent of the total area under the curve measured from 3700 to 3070 cm<sup>-1</sup>. This total area, representing roughly the total OH absorption (free and bonded), agrees, in the two curves, within 10 percent.

That the difference between the free OH peaks is real and significant follows from the comparison of the OH with the CH absorption at 2900 to 2800 cm<sup>-1</sup> used as an internal standard; this absorption should be equal in the  $\alpha$  and  $\beta$  forms. Actually, at

2800 cm<sup>-1</sup>, the absorption is exactly the same in both forms ( $\epsilon = 92$ ). At 2930 cm<sup>-1</sup>, where it is nearly the same, the discrepancy is even in the opposite direction from the OH band difference. This is seen to be due to the additional absorption in the region of 3200–3300 cm<sup>-1</sup> in the  $\alpha$  compound ( $\epsilon = 16$  for  $\alpha$  as against 12 for  $\beta$ ), which obviously reaches also to lower frequencies and points to the presence of a bonded OH precisely where the absorption of the free OH, at 3600 cm<sup>-1</sup>, is lower.

The conclusion appears justified that in the  $\alpha$  form the OH is more easily accessible from the outside and consequently less crowded by neighboring groups: the CH<sub>3</sub> group would then be *trans* to OH, *i.e.*, the  $\alpha$  compound would have the structure 1a (Fig. 1), or the corresponding inverted structure. The  $\beta$  form would be 1b, or again the corresponding inverted form (*cis* CH<sub>3</sub>:OH) and the higher absorption of the free OH the consequence of a *cis* configuration with respect to the methyl. The absorption in the condensed phase (mull) was essentially in the agreement with this assignment: there was no free OH absorption, but the broad band corresponding to variously bonded OH was displaced farther to lower frequencies in the  $\alpha$  compound than in the  $\beta$ , *i.e.*, there was more bonding in  $\alpha$  than in  $\beta$ .

A more detailed assignment of frequencies is not certain in the absence of data on dilution effects, which are being explored. Nevertheless, it might be justified to mention here the weak doublet 1323 cm<sup>-1</sup>, 1337 cm<sup>-1</sup> in the  $\beta$  form which is absent in  $\alpha$ , whereas the  $\alpha$  form shows an indication of a band at 1428 cm<sup>-1</sup>, which is absent in  $\beta$  (Fig. 4). This relationship corresponds rather closely to the one observed by Smith and Creitz<sup>8</sup> with CH<sub>3</sub>OH: 1330 cm<sup>-1</sup>, 1337 cm<sup>-1</sup> (free), vs. 1420 cm<sup>-1</sup> (associated) for the (OH) bending motion, and would agree with the above assignment based on the behavior of the (OH) stretching band. The excess absorption obtained by subtracting one curve from another around 1330 cm<sup>-1</sup> and 1420 cm<sup>-1</sup>, shown in the figure as shaded areas, corresponds closely to the bands in question.

An attempt has been made to explore the possibility of assigning an absolute configuration. Use could be made of the known difference in the position of the C(3)-OH band in steroids, where the equatorial OH band is shifted by about 30 cm<sup>-1</sup> with respect to the band of an axial OH.<sup>9</sup>

No such shift appears to be present in any of the bands in the region of 1050 cm<sup>-1</sup>, which may suggest that there is no difference in the conformation of the OH in the  $\alpha$  and  $\beta$  compounds.

Such displacement is considered to be the result of interaction between a substituent group and the ring, and a similar effect should be possible with groups other than OH, as well. The absorption of

(8) F. A. Smith and E. C. Creitz, *J. Research Nat. Bur. Standards*, **46**, 145 (1951).

(9) A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 5571 (1952).

the methyl group near  $1380\text{ cm}^{-1}$  showed a characteristic asymmetry of the band in opposite directions in the case of alpha and beta compounds, the band having an inflection on opposite sides (Fig. 4):

	Alpha		Beta	
Position ( $\text{cm}^{-1}$ )	1383	1374	1383	1374
Absorption ( $\text{cm}^2/\text{mol}$ )	94	(25)	(20)	73

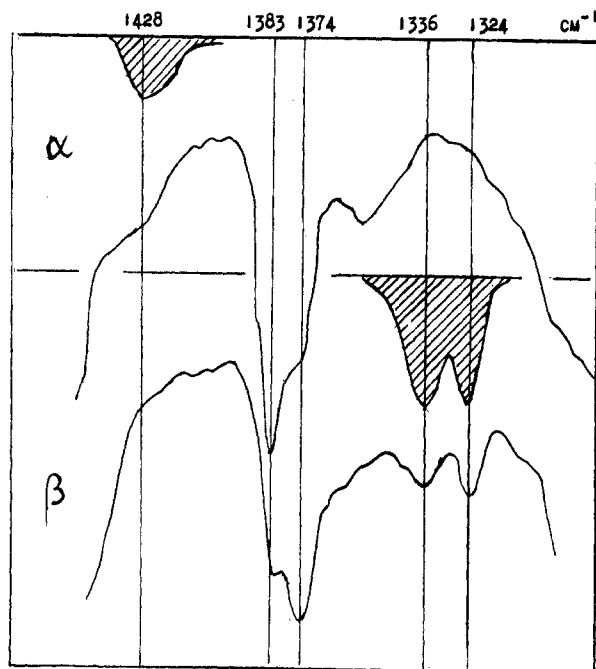


FIG. 4. 1,3-DIMETHYL-4-PHENYL-4-HYDROXYPIPERIDINES. The shaded bands represent differences between the two spectra: ( $\beta - \alpha$ ) at  $1330\text{ cm}^{-1}$  and ( $\alpha - \beta$ ) at  $1428\text{ cm}^{-1}$ .

When compared to the one found with the steroid OH, the observed shift of only  $9\text{ cm}^{-1}$  seems small. On the other hand, a similar shift between tropine and pseudotropine,<sup>10</sup> involving again an OH group, was only  $17\text{ cm}^{-1}$ , *i.e.*, considerably smaller than in the case of steroid OH. With different bonds involved here the interaction could be expected to produce an effect of different magnitude.

It seems reasonable to conclude that the interaction with the ring results in an increase in the force constant of the bending (CH) symmetric vibration of the  $\text{CH}_3$  group. The observed direction of the shift would make the  $\text{CH}_3$  equatorial in the  $\alpha$  form, and consequently, following our previous demonstration, the hydroxyl equatorial also, and the phenyl axial, *i.e.*, the  $\alpha$  compounds would have the form 1a (Fig. 1) and the  $\beta$ -form would be the structure 1b inverted.

The different 3-alkyl derivatives can be distinguished, in the esters, by the frequencies at  $950\text{--}1050\text{ cm}^{-1}$  (Fig. 5).

The 3-methyl compounds showed a sequence of three bands of decreasing intensity:

(10) S. Archer and T. R. Lewis, *Chemistry & Industry*, 853 (1954).

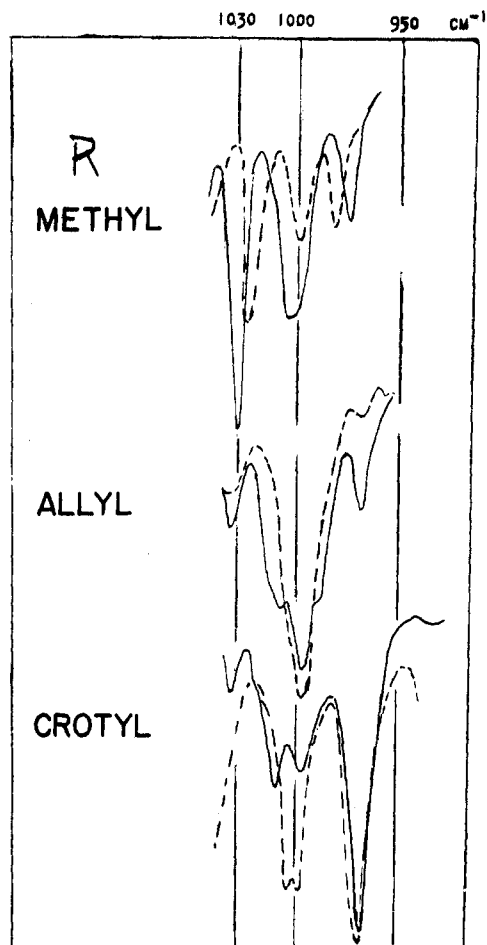


FIG. 5. INFRARED SPECTRA OF THE DIASTEREOMERIC FORMS OF 1-METHYL-3-R-4-PHENYL-4-PROPIONOXYPIPERIDINE.

	$\text{cm}^{-1}$			$\epsilon$		
$\alpha$	1033	1004	975	182	84	48
$\beta$	1024	997	981	84	58	26

The 3-allyl compounds had one prominent complex band and two satellites:

	$\text{cm}^{-1}$			$\epsilon$		
$\alpha$	1034	997	968	56	113	50
$\beta$	(1034)	998	970	(41)	118	13

The 3-crotyl compounds had the sequence of intensity reversed with respect to the 3-methyl and the middle band was a doublet.

	$\text{cm}^{-1}$			$\epsilon$		
$\alpha$	1033	1009, 997	967	55	85	188
$\beta$	(1035)	1004, 997	969	(85)	128	150

The  $\alpha$  and  $\beta$  forms, in the esters, can be distinguished by several bands. Two are shown as examples:

	Band $1350\text{ cm}^{-1}$		Band $1060\text{ cm}^{-1}$	
	$\alpha$	$\beta$	$\alpha$	$\beta$
3-Methyl	1350	1359	1057	1050
3-Allyl	1349	1357	1063	1051
3-Crotyl	1348	1358	1062	1063
			(1052)	1047

TABLE I

Found	R =	$R_f$ Values				Analgesic Activity (Morphine = 1)
		pH 6.3	pH 4.9	pH 3.6	pH 2.2	
$\alpha$	CH <sub>3</sub>	0.65	0.58	0.46	0.27	1.0
$\beta$	CH <sub>3</sub>	0.64	0.48	0.37	0.19	7.0
$\alpha$	C <sub>2</sub> H <sub>5</sub>	0.73	0.70	0.52	0.33	1.1
$\beta$	C <sub>2</sub> H <sub>5</sub>	0.64	0.57	0.45	0.28	1.25
$\alpha$	-CH <sub>2</sub> CH=CH <sub>2</sub>	0.79	0.77	0.56	0.39	11.0
$\beta$	-CH <sub>2</sub> CH=CH <sub>2</sub>	0.82	0.75	0.51	0.31	3.0
$\alpha$	CH <sub>2</sub> CH=CH-CH <sub>3</sub>	0.83	0.84	0.61	0.46	0.03
$\beta$	CH <sub>2</sub> CH=CH-CH <sub>3</sub>	0.85	0.80	0.58	0.37	0.04

The band near 1060 cm<sup>-1</sup> shows that the 3-crotyl compounds were not pure, particularly the  $\beta$  form which contained a large amount of the  $\alpha$  form.

The assignment of equatorial acyloxy groups to both  $\alpha$  and  $\beta$  isomers would explain the findings of the relative ease of hydrolysis of alphaprodine and betaprodine found by Beckett<sup>7</sup> and indeed account for the not too great difference of the hydrolytic rate.

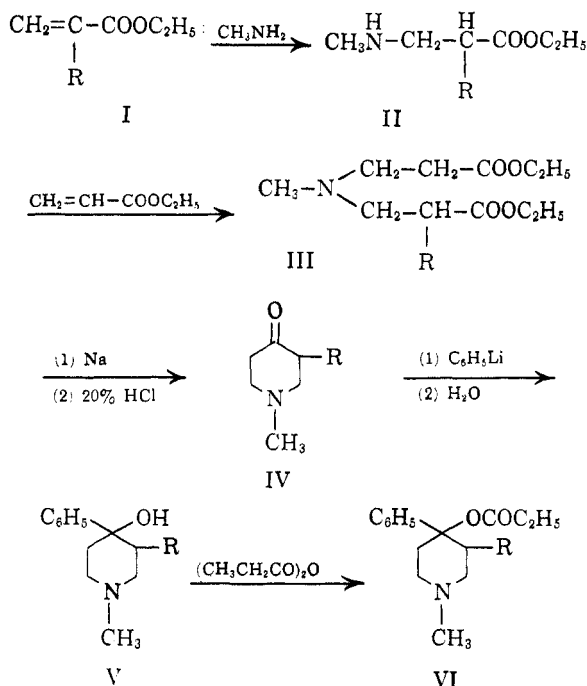
The assignment of the 3-substituted compounds to the  $\alpha$  or  $\beta$  series by this method is also supported by the behavior of the compounds when chromatographed on buffered paper. The solvent used was a mixture of *t*-amyl alcohol, 80 parts; di-*n*-butyl ether, 7 parts; and water, 13 parts, and the results are shown in Table I.

Separations at pH 6.3 and higher were less satisfactory than at the lower pH values. The results given show that at pH 4.9 and below, the  $\alpha$  form has invariably a higher  $R_f$  value than the  $\beta$  form and the series align with the infrared data.

A further observation also places the compounds in either the  $\alpha$  or  $\beta$  series. The  $\alpha$  compound invariably forms in the higher yield under the standardized conditions of the organo-metallic reactions used. In fact, with the higher 3-substituents, *e.g.*, butyl, hexyl, benzyl, the  $\beta$  form was not isolated and was probably formed in very small amounts if at all.

The synthesis of the 1-methyl-3-alkyl-4-phenyl-4-propionoxypiperidines was carried out according to the accompanying scheme.

**Pharmacological results.** In Table I are also given approximate activities of the compounds with respect to morphine. It would appear that there is little relationship between steric configuration and analgesic activity. When there are one or two carbon atoms in the 3-substituent, the  $\beta$ -series (*cis* 3-R: 4-OR) shows the highest activity. However, when the 3-substituent is allyl, the activity is greatest in the  $\alpha$ -series and moreover is greater than



that of any of the  $\beta$ -compounds. Hence, it might be assumed that close simulation of the decahydroisoquinoline ring of dihydrodesoxymorphine-D in these structures is not a necessary condition for high activity.

#### EXPERIMENTAL<sup>11</sup>

$\alpha$ -1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (V, R=CH<sub>3</sub>). This compound was prepared according to the procedure of Ziering and Lee.<sup>12</sup> It can also be prepared in a very pure state by hydrolyzing 2.97 g. of  $\alpha$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 220–221° with 1.4 g. of 85% potassium hydroxide in 50 ml. of ethyl alcohol.

(11) All melting points are corrected; boiling points are uncorrected. The infrared spectra were made with a Perkin-Elmer Model 21 spectrophotometer. The cells were 0.1 mm. Molecular weights were determined by titration with perchloric acid in glacial acetic acid.

(12) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

After the mixture had refluxed for 15 hr., it was filtered and the alcohol distilled off in vacuum. The residue was treated with 30 ml. of water and the oil extracted with ether. The ether extract was dried over anhydrous potassium carbonate and the residue remaining after filtering and distilling off the ether was crystallized from Skellysolve B. The yield of  $\alpha$ -1,3-dimethyl-4-phenyl-4-hydroxypiperidine was 1 g., m.p. 100–101°.

$\alpha$ -1,3-Dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R=CH<sub>3</sub>). To 6 g. of  $\alpha$ -1,3-dimethyl-4-phenyl-4-hydroxypiperidine, m.p. 100–101°, was added 20 ml. of propionic anhydride. After the solution was heated on a steam bath for 12 hr., the excess reagent was distilled off in vacuum. The residue was made alkaline with 10% sodium carbonate solution and the oil extracted with ether. The ether solution, after drying over anhydrous potassium carbonate, was filtered and hydrogen chloride bubbled in to precipitate the hydrochloride. The yield of  $\alpha$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride,<sup>12</sup> after crystallizing from acetone-methanol, was 4.7 g., m.p. 220–221°.

$\beta$ -1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (V, R=CH<sub>3</sub>). After separation of the bulk of the  $\alpha$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride from the diastereoisomeric mixture, the residue containing a diastereoisomeric mixture of the  $\alpha$  and  $\beta$  forms was converted to the free bases. This mixture (88 g.) was added to a solution of 45 g. of *dl*-malic acid in 200 ml. of acetone, and after standing overnight, 71 g. of crude  $\alpha$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine *dl*-malate, m.p. 139–143° was filtered off. The filtrate was distilled to dryness and the residue crystallized from a mixture of ethyl acetate and methyl ethyl ketone to yield the  $\beta$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine *dl*-malate, m.p. 118–121°; yield 40 g. This salt was converted to the free base with 10% sodium carbonate solution. Twenty-eight grams of this base was dissolved in 150 ml. of ethyl alcohol containing 7 g. of 85% potassium hydroxide and the solution was refluxed for 20 hr. The alcohol was distilled off in vacuum and 100 ml. of water added. The separated oil was extracted with ether and dried over anhydrous potassium carbonate. The ether was distilled off and the residue crystallized from hot Skellysolve B. The  $\beta$ -1,3-dimethyl-4-phenyl-4-hydroxypiperidine melts at 116–118°; yield 13 g.

$\beta$ -1,3-Dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride. The  $\beta$ -1,3-dimethyl-4-phenyl-4-hydroxypiperidine (2 g.) was dissolved in 10 ml. of propionic anhydride. After heating 10 hr. on the steam bath, the excess reagent was distilled off in vacuum and the residue made alkaline with 10% sodium carbonate solution. The oil was extracted with ether and the solution dried over anhydrous potassium carbonate. The ether solution was filtered and treated with hydrogen chloride gas. The precipitated  $\beta$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride was filtered off and crystallized from acetone-methanol, m.p. 199–200°; yield 1.7 g.

Ethyl 2-ethyl-3-methylaminopropionate (II, R=C<sub>2</sub>H<sub>5</sub>). Ethyl  $\alpha$ -ethylacrylate<sup>13</sup> (85 g.) was added to a solution of 20 g. of methylamine in 180 ml. of ethyl alcohol. The solution was kept at room temperature for 7 days. The alcohol was distilled off and the product, ethyl 2-ethyl-3-methylaminopropionate (II, R=C<sub>2</sub>H<sub>5</sub>) distilled at 97°/29 mm.; yield 78 g.

Anal. Calcd. for C<sub>8</sub>H<sub>17</sub>NO<sub>2</sub>: Mol. wt., 159. Found: Mol. wt., 157.

Diethyl  $\alpha$ -ethyl- $\beta$ , $\beta'$ -(methylimino)dipropionate (III, R=C<sub>2</sub>H<sub>5</sub>). Ethyl acrylate (100 g.) was added to 78 g. of II, (R=C<sub>2</sub>H<sub>5</sub>) and the solution kept at room temperature for 4 days. The yield of product III, (R=C<sub>2</sub>H<sub>5</sub>) boiling at 126°/2 mm. was 115 g.

Anal. Calcd. for C<sub>13</sub>H<sub>25</sub>NO<sub>4</sub>: C, 60.23; H, 9.65. Found: C, 59.59; H, 9.57.

1-Methyl-3-ethyl-4-piperidone (IV, R=C<sub>2</sub>H<sub>5</sub>). III, R=C<sub>2</sub>H<sub>5</sub> (115 g.) was cyclized according to the procedure described by Lee and coworkers.<sup>14</sup> The yield of 1-methyl-3-ethyl-4-piperidone was 38 g., b.p. 102°/33 mm.

Anal. Calcd. for C<sub>8</sub>H<sub>15</sub>NO: Mol. wt., 141. Found: mol. wt., 140.

1-Methyl-3-ethyl-4-phenyl-4-hydroxypiperidine (V, R=C<sub>2</sub>H<sub>5</sub>). 1-Methyl-3-ethyl-4-piperidone (10.6 g.) was reacted in the usual way<sup>12</sup> with phenyl lithium prepared from 15.7 g. of bromobenzene and 1.5 g. of lithium wire. The yield of  $\alpha$ -1-methyl-3-ethyl-4-phenyl-4-hydroxypiperidine (V, R=C<sub>2</sub>H<sub>5</sub>) after crystallization from Skellysolve B was 10 g., m.p. 96–97°.

Anal. Calcd. for C<sub>14</sub>H<sub>21</sub>NO: mol. wt., 219. Found: mol. wt., 218. The filtrate on concentration yielded 2 g. of the diastereoisomeric mixture ( $\alpha$  and  $\beta$  forms), m.p. 72–82°.

$\alpha$ -1-Methyl-3-ethyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R=C<sub>2</sub>H<sub>5</sub>). The  $\alpha$ -1-methyl-3-ethyl-4-phenyl-4-hydroxypiperidine (10 g.) was reacted with 35 ml. of propionic anhydride on a steam bath for 10 hr. The product,  $\alpha$ -1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine (VI, R=C<sub>2</sub>H<sub>5</sub>) was isolated in the usual way. It was converted to the hydrochloride and crystallized from acetone-methanol; yield 8 g., m.p. 229–230°.

Anal. Calcd. for C<sub>17</sub>H<sub>25</sub>NO<sub>2</sub>·HCl: C, 65.48; H, 8.34. Found: C, 65.44; H, 8.28.

In a similar manner, the diastereoisomeric mixture of alcohols yielded a mixture of propionates from which was isolated the  $\beta$ -1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 201–203°.

Anal. Calcd. for C<sub>17</sub>H<sub>25</sub>NO<sub>2</sub>·HCl: C, 65.48; H, 8.34. Found: C, 65.01; H, 8.24.

Ethyl 1-allyl-2-methylaminopropionate (II, R=allyl). Ethyl  $\alpha$ -allylacrylate<sup>13</sup> (397 g.) was added to a solution of 95 g. of methylamine in 1 l. of ethyl alcohol and the resulting solution heated in an autoclave at 105° for 5 hr. under nitrogen at a pressure of 600 lbs./sq. in. The product (II, R=allyl) distilled at 105–110°/30 mm. and the yield obtained was 315 g.

Anal. Calcd. for C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub>: Mol. wt., 171. Found: Mol. wt., 168.

Diethyl  $\alpha$ -allyl- $\beta$ , $\beta'$ -(methylimino)dipropionate (III, R=allyl). Ethyl acrylate (555 g.) was added to 838 g. of II, (R=allyl) and the solution heated in an autoclave at 100° for 6 hr. under 600 lbs. of nitrogen. The product III, (R=allyl) was distilled at 141–144°/4 mm. and the yield obtained was 1009 g.

Anal. Calcd. for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: Mol. wt., 271. Found: Mol. wt., 274.

1-Methyl-3-allyl-4-piperidone (IV, R=allyl). The diester III, (R=allyl) 1009 g. was cyclized in the usual way<sup>14</sup> to 1-methyl-3-allyl-4-piperidone. The yield of product distilling at 117–122°/31 mm. was 242 g.

Anal. Calcd. for C<sub>9</sub>H<sub>15</sub>NO: Mol. wt., 153. Found: Mol. wt., 150.

1-Methyl-3-allyl-4-phenyl-4-hydroxypiperidine (V, R=allyl). 1-Methyl-3-allyl-4-piperidone (242 g.) was reacted in the usual way with phenyl lithium prepared from 29.4 g. of lithium wire and 331 g. of bromobenzene. The yield of the main product,  $\alpha$ -1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine (V, R=allyl) was 230 g. after crystallization from Skellysolve B, m.p. 110–111°.

Anal. Calcd. for C<sub>15</sub>H<sub>21</sub>NO. Mol. wt., 231. Found: Mol. wt., 230. The filtrate, on concentration yielded 20 g. of a diastereoisomeric mixture of the  $\alpha$  and  $\beta$  forms, m.p. 70–85°.

$\alpha$ -1-Methyl-3-allyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R=allyl). The  $\alpha$ -1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine (162 g.) was reacted with 500 ml. of propionic anhydride on a steam bath for 10 hr. The product,  $\alpha$ -1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine was iso-

(14) A. Ziering, L. Berger, S. D. Heineman, and J. Lee, *J. Org. Chem.*, 12, 894 (1947).

lated in the usual way. It was converted to the hydrochloride and crystallized from acetone, m.p. 185–186°; yield 180 g.

*Anal.* Calcd. for  $C_{18}H_{25}NO_2 \cdot HCl$ : C, 66.77; H, 8.04. Found: C, 66.91; H, 8.29.

In a similar manner, the diastereoisomeric mixture of alcohols on treatment with propionic anhydride yielded a mixture of the  $\alpha$  and  $\beta$  forms of VI, (R=allyl), which was converted to the hydrochlorides. After repeated crystallizations from acetone, the  $\beta$ -1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine hydrochloride was isolated, m.p. 205–206°. To check the purity of the  $\beta$  ester, it was hydrolyzed back to the  $\beta$ -1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine, m.p. 85–86° (hexane).

*Anal.* Calcd. for  $C_{18}H_{21}NO$ : C, 77.91; H, 9.10. Found: C, 78.21; H, 8.72.

Treatment of this  $\beta$ -alcohol with propionic anhydride yielded again the  $\beta$ -1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine which was converted to the hydrochloride (VI, R=allyl), m.p. 205–206°, after crystallization from acetone.

*Anal.* Calcd. for  $C_{18}H_{25}NO_2 \cdot HCl$ : C, 66.77; H, 8.04. Found: C, 66.83; H, 8.18.

*$\alpha$ -1-Methyl-3-propyl-4-phenyl-4-propionoxypiperidine hydrochloride.* The  $\alpha$ -1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine (3 g.) was catalytically reduced in 150 ml. of ethyl alcohol with Raney nickel at 50 lbs. hydrogen pressure and room temperature. The catalyst was filtered off and the filtrate distilled to dryness. The residue was heated on a steam bath for 8 hr. with 20 ml. of propionic anhydride. By working up in the usual way,  $\alpha$ -1-methyl-3-propyl-4-phenyl-4-propionoxypiperidine hydrochloride was isolated. It was crystallized from ethyl acetate-methanol and had a m.p. of 203–205°.

*Anal.* Calcd. for  $C_{18}H_{27}NO_2 \cdot HCl$ : Mol. wt. 325.5. Found: Mol. wt. 325.

*Ethyl  $\alpha$ -crotylacrylate* (I, R=allyl). Diethyl crotylmalonate<sup>15</sup> (738 g.) was dissolved in 600 ml. of ethyl alcohol and added to a solution of 214 g. of 90% potassium hydroxide in 1300 ml. of ethyl alcohol in the cold. After the solution had stood overnight at room temperature, the monopotassium salt was filtered off and the filtrate distilled down in vacuum. The residue and the monopotassium salt were dissolved in water and the solution acidified with 18% hydrochloric acid. The oil was extracted with ether and the solution dried over anhydrous magnesium sulfate. The ether was distilled off and the crude residue, ethyl hydrogen crotylmalonate (642 g.) was converted according to Mannich's procedure<sup>13</sup> to the ethyl  $\alpha$ -crotylacrylate in a yield of 70%, b.p. 104–106°/45 mm.,  $n_D^{25}$  1.4434.

*Ethyl 1-crotyl-2-methylaminopropionate* (II, R=crotyl). Ethyl  $\alpha$ -crotylacrylate (370 g.) was added to a solution of 80 g. of methyl amine in 500 ml. of ethyl alcohol and the solution heated at 100° for 4 hr. under 600 lbs. of nitrogen. II, (R=crotyl) distilled at 128–133°/34 mm.; yield 73%.

*Diethyl  $\alpha$ -crotyl- $\beta,\beta'$ -(methylimino)dipropionate* (III, R=crotyl). Ethyl acrylate (212 g.) was added to 323 g. of II, (R=crotyl) and the solution heated for 4 hr. at 100° under 600 lbs. of nitrogen. The product, III, (R=crotyl), distilled at 150–153°/2 mm.; yield 224 g.

*Anal.* Calcd. for  $C_{18}H_{27}NO_4$ : Mol. wt., 285. Found: Mol. wt., 284.

*1-Methyl-3-crotyl-4-piperidone.* The diester III, (R=crotyl) 459 g. was cyclized in the usual way<sup>14</sup> to the 1-methyl-3-crotyl-4-piperidone, b.p. 123–124°/23 mm.,  $n_D^{25}$  1.4747; yield 116 g.

*1-Methyl-3-crotyl-4-phenyl-4-hydroxypiperidine* (V, R=crotyl). 1-Methyl-3-crotyl-4-piperidone (33.4 g.) was reacted in the usual way with phenyllithium. The yield of the main product,  $\alpha$ -1-methyl-3-crotyl-4-hydroxypiperidine (V, R=crotyl), b.p. 180°/7 mm., after crystallization from Skellysolve B was 30 g., m.p. 98–100°.

*Anal.* Calcd. for  $C_{16}H_{23}NO$ : Mol. wt., 245. Found: Mol. wt., 246. The filtrate contained the diastereoisomeric mixture of the  $\alpha$  and  $\beta$ -alcohols.

*$\alpha$ -1-Methyl-3-crotyl-4-phenyl-4-propionoxypiperidine d-tartrate* (VI, R=crotyl).  $\alpha$ -1-Methyl-3-crotyl-4-phenyl-4-hydroxypiperidine (10 g.) was reacted with propionic anhydride (50 ml.) in the usual way. The ester distilled in vacuo at 152°/1 mm.; yield 9 g.

*Anal.* Calcd. for  $C_{19}H_{27}NO_2$ : Mol. wt., 301. Found: Mol. wt. 302. The  $\alpha$ -ester (3 g.) was converted to the tartrate salt by adding it to a solution of 1.5 g. of *d*-tartaric acid in 20 ml. of acetone and concentrating to dryness. The residue was dissolved in ethyl acetate to which two drops of water were added. The tartrate salt was filtered off and crystallized from methyl ethyl ketone, m.p. 95–97° after drying overnight in an oven at 63°.

*Anal.* Calcd. for  $C_{19}H_{27}NO_2 \cdot C_4H_6O_6 \cdot 1.5H_2O$ : Mol. wt., 478. Found: Mol. wt., 478.

The diastereoisomeric mixture of  $\alpha$  and  $\beta$ -alcohols (V, R=crotyl) was converted to the esters in a similar manner. By repeated crystallization of the maleate salt from ethyl acetate, the  $\beta$ -1-methyl-3-crotyl-4-phenyl-4-propionoxypiperidine maleate was obtained, m.p. 126–130°. Infrared spectra showed, however, that this salt was contaminated with the  $\alpha$  form.

*Anal.* Calcd. for  $C_{19}H_{27}NO_2 \cdot C_4H_4O_4$ : Mol. wt., 417. Found: Mol. wt., 418.

*Ethyl  $\alpha$ -butylacrylate* (I, R =  $C_4H_9$ ). By Mannich's procedure,<sup>13</sup> ethyl hydrogen butylmalonate was converted to ethyl  $\alpha$ -butylacrylate in 60% yield; b.p. 88°/31 mm.

*Ethyl 1-butyl-2-methylaminopropionate* (II, R =  $C_4H_9$ ). To a solution of 51 g. of methylamine in 250 ml. of ethyl alcohol was added 259 g. of ethyl  $\alpha$ -butylacrylate. After standing overnight at room temperature, the solution was refluxed for 1 hr. The alcohol was distilled off and the residue distilled in vacuum. The first fraction (105 g.) b.p. 80–84°/30 mm. was ethyl  $\alpha$ -butylacrylate. The product (II, R =  $C_4H_9$ ) distilled at 118–120°/30 mm.; yield 133 g. The recovered starting material (105 g.) was added to a solution of 21 g. of methylamine in 125 ml. of ethyl alcohol and the solution heated in an autoclave under 600 lbs. of nitrogen at 75° for 4 hr. The yield of product (II, R =  $C_4H_9$ ) was 98 g. The total yield was 231 g. (75% yield).

*Anal.* Calcd. for  $C_{16}H_{21}NO_2$ : Mol. wt., 187. Found: Mol. wt., 191.

*Diethyl  $\alpha$ -butyl- $\beta,\beta'$ -(methylimino)dipropionate* (III, R =  $C_4H_9$ ). Ethyl acrylate (143 g.) was added to 231 g. of ethyl 1-butyl-2-methylaminopropionate and the solution heated overnight on a steam bath. The product (III, R =  $C_4H_9$ ) distilled at 130–133°/1 mm.,  $n_D^{25}$  1.4400; yield, 268 g. The fore-run was treated again with ethyl acrylate in a similar manner and an additional 34 g. of product was obtained. The total yield was 302 g. (85% yield).

*1-Methyl-3-butyl-4-piperidone* (IV, R =  $C_4H_9$ ). The above diester (III, R =  $C_4H_9$ ) 302 g. was cyclized in the usual way<sup>14</sup> to yield 114 g. of 1-methyl-3-butyl-4-piperidone (65% yield);  $n_D^{25}$  1.4595; b.p. 130–131°/32 mm.

*1-Methyl-3-butyl-4-phenyl-4-hydroxypiperidine* (V, R =  $C_4H_9$ ). The reaction of phenyllithium prepared from 3.7 g. of lithium wire and 42 g. of bromobenzene with 33.8 g. of 1-methyl-3-butyl-4-piperidone yielded 33 g. of 1-methyl-3-butyl-4-phenyl-4-hydroxypiperidine, b.p. 166–168°/5 mm. The product is mainly the  $\alpha$  form contaminated perhaps with some of the  $\beta$  form.

*Anal.* Calcd. for  $C_{16}H_{23}NO$ : Mol. wt., 247. Found: Mol. wt., 247.

*$\alpha$ -1-Methyl-3-butyl-4-phenyl-4-propionoxypiperidine d-tartrate* (VI, R =  $C_4H_9$ ). The 1-methyl-3-butyl-4-phenyl-4-hydroxypiperidine was converted to the propionoxy derivative in the usual way. This base (7.3 g.) was then added to a solution of 3.6 g. of *d*-tartaric acid in 50 ml. of acetone containing 2 drops of water. The solution was distilled to dryness and the residue crystallized from acetone, m.p. 140–143°.

(15) D. Barnard and L. Bateman, *J. Chem. Soc.*, 926 (1950).

*Anal.* Calcd. for  $C_{19}H_{29}NO_2 \cdot C_4H_8O_6 \cdot 1.5H_2O$ : Mol. wt., 480. Found: Mol. wt., 480.

*Ethyl  $\alpha$ -hexylacrylate* (I,  $R = C_6H_{13}$ ). Ethyl hydrogen hexylmalonate (490 g.) by Mannich's procedure<sup>13</sup> was converted to ethyl  $\alpha$ -hexylacrylate in 76% yield; b.p. 100–102°/15 mm.

*Ethyl 2-hexyl-3-methylaminopropionate* (II,  $R = C_6H_{13}$ ). Ethyl  $\alpha$ -hexylacrylate (316 g.) was added to a solution of 60 g. of methylamine in 250 ml. of ethyl alcohol and the solution heated at 100° for 4 hr. under 600 lbs. of nitrogen. The product distilled at 130–135°/15 mm.; yield 314 g.

*Diethyl  $\alpha$ -hexyl- $\beta,\beta'$ -(methylimino)dipropionate* (III,  $R = C_6H_{13}$ ). Ethyl 2-hexyl-3-methylaminopropionate (315 g.) was added to 150 g. of ethyl acrylate and the solution heated for 4 hr. at 100° in an autoclave under 600 lbs. of nitrogen. The product distilled at 152–158°/1 mm.; yield 345 g. (77%).

*Anal.* Calcd. for  $C_{17}H_{33}NO_4$ : Mol. wt., 315. Found: Mol. wt., 316.

*1-Methyl-3-hexyl-4-piperidone* (IV,  $R = C_6H_{13}$ ). The above diester (III,  $R = C_6H_{13}$ ), 345 g. was cyclized in the usual way<sup>14</sup> to 1-methyl-3-hexyl-4-piperidone. The product distilled at 153–155°/25 mm.; yield 153 g. (71%).

*1-Methyl-3-hexyl-4-phenyl-4-hydroxypiperidine* (V,  $R = C_6H_{13}$ ). In the usual manner, 40 g. of the ketone (IV,  $R = C_6H_{13}$ ) was reacted with phenyllithium prepared from 43 g. of bromobenzene and 3.8 g. of lithium wire. The product (V,  $R = C_6H_{13}$ ) distilled at 170–173°/2 mm.; yield 47 g. (86%). The product is mainly the  $\alpha$  form contaminated perhaps with some of the  $\beta$  form.

*Anal.* Calcd. for  $C_{18}H_{33}NO$ : Mol. wt., 275. Found: Mol. wt., 275.

*$\alpha$ -1-Methyl-3-hexyl-4-phenyl-4-propionoxypiperidine dl-malate* (VI,  $R = C_6H_{13}$ ). 1-Methyl-3-hexyl-4-phenyl-4-hydroxypiperidine was converted to the 4-propionoxy derivative in the usual way; b.p. 191–193°/4 mm. The dl-malate was prepared by adding 1.1 g. of the 1-methyl-3-hexyl-4-phenyl-4-propionoxypiperidine to a solution of 0.45 g. of dl-malic acid in 10 ml. of acetone. The solution was distilled to dryness and the residue crystallized from ethyl acetate, m.p. 98–100°.

*Anal.* Calcd. for  $C_{21}H_{33}NO_2 \cdot C_4H_8O_6$ : Mol. wt., 465. Found: Mol. wt., 463.

The citrate was prepared in a similar manner, m.p. 125–127°.

*Ethyl  $\alpha$ -benzylacrylate*. By Mannich's procedure<sup>13</sup>, ethyl hydrogen benzylmalonate was converted to ethyl  $\alpha$ -benzylacrylate, b.p. 106–107°/3 mm.; yield 78%.

*Ethyl 1-benzyl-2-methylaminopropionate* (II,  $R = CH_2C_6H_5$ ). Ethyl  $\alpha$ -benzylacrylate (170 g.) was added to a solution of 30 g. of methylamine in 200 ml. of ethyl alcohol and the solution heated in an autoclave at 100° for 4 hr. under

600 lbs. of nitrogen. The product distilled at 115–117°/3 mm.; yield 153 g. (80%).

*Diethyl  $\alpha$ -benzyl- $\beta,\beta'$ -(methylimino)dipropionate* (III,  $R = CH_2C_6H_5$ ). Ethyl acrylate (140 g.) was added to 158 g. of ethyl 1-benzyl-2-methylaminopropionate and the solution heated in an autoclave at 110° for 4 hr. The product distilled at 160–162°/1 mm.; yield 210 g. (92%).

*1-Methyl-3-benzyl-4-piperidone* (IV,  $R = CH_2C_6H_5$ ). The diester (III,  $R = CH_2C_6H_5$ ) 210 g. was cyclized in the usual manner<sup>14</sup> to yield the 1-methyl-3-benzyl-4-piperidone,<sup>15</sup> b.p. 142–143°/4 mm.; yield 97 g. (73%).

*Anal.* Calcd. for  $C_{13}H_{17}NO$ : Mol. wt., 203. Found: Mol. wt., 203.

*1-Methyl-3-benzyl-4-phenyl-4-hydroxypiperidine* (V,  $R = CH_2C_6H_5$ ). In the usual way, 1-methyl-3-benzyl-4-piperidone (40.6 g.) was reacted with phenyllithium prepared from 47.1 g. of bromobenzene and 4.2 g. of lithium in ether. Water (100 ml.) was added to decompose the complex, the ether separated and dried over anhydrous potassium carbonate. The ether was distilled off and the  $\alpha$ -1-methyl-3-benzyl-4-phenyl-4-hydroxypiperidine crystallized from Skellysolve B, m.p. 126–127°; yield 38 g. The filtrate was examined for the presence of the  $\beta$  form but none could be isolated.

*$\alpha$ -1-Methyl-3-benzyl-4-phenyl-4-propionoxypiperidine hydrochloride* (VI,  $R = CH_2C_6H_5$ ). Five g. of V, ( $R = CH_2C_6H_5$ ) was added to 15 ml. of propionic anhydride and the solution heated for 4 hr. on a steam bath. The excess propionic anhydride was distilled off in vacuum and the residue made alkaline with 10% sodium carbonate solution. The oil was extracted with ether and the solution dried, filtered and treated with hydrogen chloride gas. The salt formed was filtered off and crystallized from ethyl acetate-methanol, m.p. 207–208°; yield 4 g.

*Anal.* Calcd. for  $C_{22}H_{27}NO_2 \cdot HCl$ : Mol. wt., 373.5. Found: Mol. wt., 368.

For pharmacological testing, the free base was converted to the dl-malate (light yellow sirup) which is more soluble in water than the hydrochloride.

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(16) S. M. McElvain and Gilbert Stork, *J. Am. Chem. Soc.*, **68**, 1049 (1946).

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## The Structure of Tri-*O*-methylenevolemitol\*

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From the condensation of volemitol with formaldehyde we have obtained a 43% yield of a crystalline tri-*O*-methylene derivative that was converted by acetolysis to a di-*O*-methylene derivative. By combining with our experimental results the well-established empirical rule that in the methylenation of polyhydric alcohols the first preference is for a  $\beta$ C-ring we have established that the tri-*O*-methylenevolemitol is 1,3:2,5:4,6-tri-*O*-methylene-*D*-glycero-*D*-manno-heptitol. Some conformational aspects of this acetal and of the alternative 1,3:4,6:5,7-triacetal are discussed.

In a series of papers from this laboratory, Dr. Raymond M. Hann and Dr. C. S. Hudson, with

\* To Lyndon F. Small, colleague and friend for thirty-five years. N.K.R.

their collaborators, attempted to correlate the configurations of certain polyhydric alcohols (alditols) with the structures of the cyclic methylene acetals derived from them. They were successful in