0.95 mm., n_D^{20} 1.5004, and trimethylsilyl 2-trimethylsiloxybenzoate, b.p. 77.5°C. at 1.1 mm., n_D^{20} 1.4788.

Anal. Calcd. for $C_{10}H_{14}O_3Si$: Si, 13.34; sapon. equiv., 210. Found: Si, 13.4; sapon. equiv., 211.

Anal. Calcd. for $C_{13}H_{22}O_3Si_2$: Si, 19.87; sapon. equiv., 282. Found: Si, 19.5; sapon, equiv., 280.

The absorption band at 3.18 μ in the infrared spectrum of the monosubstituted derivative indicated the presence of a free rather than a combined carboxyl group, thus permitting an assignment of the above structure to this derivative.

Trimethylsilyl 4-trimethylsiloxybenzoate. 4-Hydroxybenzoic acid, in contrast to salicylic acid, gave only one derivative, trimethylsilyl 4-trimethylsiloxybenzoate, when it was allowed to react with trimethylchlorosilane under the same conditions used for salicylic acid. The trimethylsilyl 4-trimethylsiloxybenzoate was a water clear liquid, b.p. 82°C. at 0.85 mm., n_D^{20} 1.4838.

Anal. Calcd. for $C_{13}H_{22}O_3Si_2$: Si, 19.87; sapon. equiv., 282. Found: Si, 19.7; sapon. equiv., 274.

Bistrimethylsilyl 4-trimethylsiloxyisophthalate. Bistrimethylsilyl 4-trimethylsiloxyisophthalate was obtained as a viscous water clear liquid by the further distillation of the residue which resulted from the distillation of the trimethylsilylation of the dried carbonation products of phenol in dry pyridine. The preliminary distillation removed the two trimethylsilyl derivatives of salicylic acid. The distillation of the residue gave bistrimethylsilyl 4-trimethylsiloxyisophthalate, b.p. 148–150°C. at 1 mm., n_D^{20} 1.4801.

Anal. Calcd. for $C_{17}H_{30}O_5Si_2$: Si, 21.12; sapon. equiv., 199. Found: Si, 21.0; sapon. equiv., 202.

The structure of this organosilicon derivative was established by hydrolysis giving 4-hydroxyisophthalic acid, m.p. 303°C. (uncorrected), 312° (corrected).

Anal. Calcd. for $C_8H_6O_5$: neutral equiv., 91. Found: neutral equiv., 95.

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RESEARCH LABORATORY
GENERAL ELECTRIC CO.
SCHENECTADY, N. Y.

Structures Related to Morphine. VII.[1] Piperidine Derivatives and Examples of Failure in Knoevenagel Reaction

EVERETTE L. MAY

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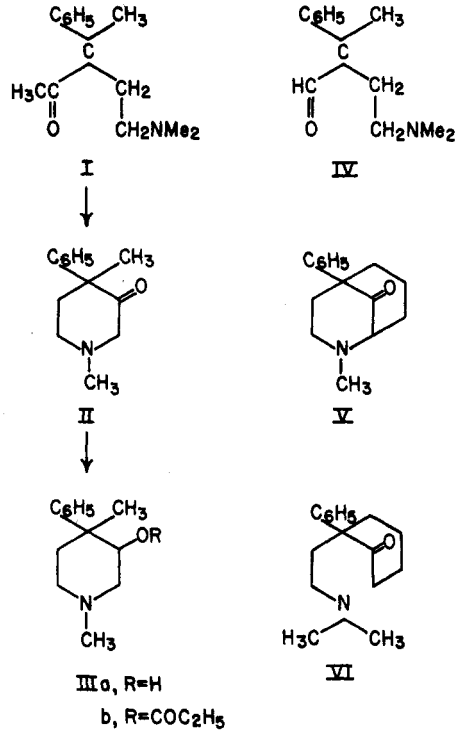
This note deals principally with the synthesis of α- and β-*dl*-1,4-dimethyl-4-phenyl-3-propionoxypiperidine (IIIb), isomers of *alpha-* and *beta*-prodine[2] in which the positions of the C-methyl and propionoxy groups are reversed. The IIIb diastereoisomers were prepared by the hydrogenation (platinum oxide) of 1,4-dimethyl-4-phenyl-3-piperidone (II)[3] followed by treatment of the resultant alcohol hydrochloride mixture (IIIa) with propionic anhydride in pyridine. A satisfactory separation of the acylated mixture into the IIIb α- and β-racemates could be effected by fractional crystallization. Although a practicable separation of the IIIa hydrochloride mixture was not achieved (chromatographic purification was not attempted), the predominant IIIa racemate[4] was readily obtained pure and in good yield, by conversion of the hydrochloride mixture to the free bases in aqueous ammonium hydroxide.



The results reported in this paper are, in fact, a by-product of another project aimed at the synthesis of 2,5,9-trimethyl-6,7-benzomorphan,[5] a compound which was desired for its potential as an analgesic agent. The sequence of reactions planned for the preparation of this substance (which has now been prepared by another method) involved, at an early stage, the Knoevenagel reaction with 5-dimethylamino-3-methyl-3-phenyl-2-pentanone (I). However, neither I nor its hydrochloride (both of which showed strong carbonyl absorption in the infrared) could be induced to react with either methyl cyanoacetate or malononitrile by

(1) Paper VI, E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(2) *Alpha*-prodine and *beta*-prodine are international, nonproprietary names for α-*dl*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine and the β-diastereoisomer, respectively, two potent analgesic agents; *cf.* A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947) and O. J. Braenden, N. B. Eddy, and Halbach, *Bull. World Health Organization*, **13**, 937(1955).

(3) F. F. Blicke and J. Krapcho, *J. Am. Chem. Soc.*, **74**, 4001 (1952).

(4) This predominant form has been designated as the α-alcohol. Although its configuration has not been established, one might expect the hydroxy to form more readily in a position *trans* (equatorial-equatorial) to the bulkiest (phenyl) adjacent group. The lesser isomer is designated as β.

(5) The corresponding *2,5-dimethyl* analog, E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955), was moderately effective.

the Cope[6] procedure or under much more vigorous conditions[7]; the I was usually recovered. This is in sharp contrast to the behavior of the closely related aldehyde IV[5] which quickly gives the normal condensation product with methyl cyanoacetate. Moreover, the 3-piperidone derivative II and the phenylcyclohexanone VI[8] failed to participate in this reaction, giving results similar to those obtained with I. Again in contrast, the bicyclic compound V[8] (somewhat resembling both VI and II in structure) and malononitrile give an excellent yield of the expected product. Concerning the failure of I, II (and the open nitrogen analog of V[8]) to yield Knoevenagel products, it may be pointed out that they contain enolizable carbonyl groups, whereas IV and V, the reactive compounds, cannot enolize. The aldehyde IV would be expected to be markedly more reactive than its methyl ketone counterpart I, although so vast a difference was not foreseen. The bicyclic ketone V, in addition to being nonenolizable (Bredt's rule), also has potentially less hyperconjugative stabilization of the carbonyl than its open nitrogen analog VI and II.

Compound I, structurally similar to methadone, was about 30 times less effective and 5 to 10 times less toxic than methadone when tested in mice. The *α-dl*-IIIa and *α-dl*-IIIb were 30 times less effective than *alpha*-prodine. The *β-dl*-IIIb was twice as active as the *α*-isomer.[2,9]

EXPERIMENTAL[10]

5-Dimethylamino-3-methyl-3-phenyl-2-pentanone (I)[3] *hydrochloride.* γ-Dimethylamino-α-methyl-α-phenylbutyronitrile (20.5 g., from 26.5 g. of nitrate[5]) in 80 ml. of dry xylene was added rapidly to a stirred solution prepared from 5 g. of magnesium, 50 ml. of ether, and 33.1 g. of methyl iodide. The mixture was distilled (stirring) until the vapor temperature reached 60° (*ca.* 15 min.) then refluxed for an additional 10–15 min. When the magma could no longer be stirred 80 ml. of 20% HCl was added at such a rate as to cause gentle refluxing. Stirring was resumed when possible, and after 30 min. the aqueous phase was basified with concentrated NH_4OH; the liberated base was dried in ether. Evaporation of the ether left 17.5 g. of I[3] (λ_{max}^{smear} 5.85μ)[11] which was redissolved in ether and acidified with 18 ml. of 33% HBr-acetic acid to give 24.3 g. (87%) of I hydrobromide,[3] m.p. 156–159°. Treatment of the I above with ethereal hydrogen chloride gave the hydrochloride, m.p. 159–161°, λ_{max}^{nujol} 5.86μ; needles from acetone.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.7; H, 8.7. Found: C, 65.6; H, 8.6.

The *picrate* crystallized from alcohol in yellow prisms, m.p. 109–110.5°.

Anal. Calcd. for $C_{20}H_{24}N_4O_8$: C, 53.6; H, 5.4. Found: C, 53.9; H, 5.6.

α-dl-1,4-Dimethyl-4-phenyl-3-piperidinol (IIIa).[4] Platinum oxide (0.1 g.), 2.0 g. of II,[3] and 10 ml. of methanol absorbed one molecular equivalent of hydrogen during 15 min. The filtered solution was evaporated to dryness *in vacuo* to give a syrup which crystallized from acetone in a yield of 1.8 g.; m.p. 198–203°. This mixture of diastereoisomers[12] was dissolved in water and basified with concentrated NH_4OH to give 1.4 g. of the α-IIIa,[13] m.p. 143–145°; needles from acetone, m.p. 145–146.5°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3. Found: C, 75.8; H, 9.1.

The *hydrochloride*, plates from acetone, melted at 211–213.5°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.4; H, 8.3. Found: C, 64.4; H, 8.3.

α-dl-1,4-Dimethyl-4-phenyl-3-propionoxypiperidine (IIIb) *hydrochloride.* Propionic anhydride (1.5 ml.), 1.0 g. of the mixture (m.p. 198–203°) of IIIa hydrochlorides, and 2.0 ml. of dry pyridine were kept on the steam bath until solution was complete. Dilution with ether and cooling to 0° gave 1.2 g. of hydrochloride mixture, m.p. 235–245°. It was dissolved in *ca.* 150 ml. of boiling acetone. Concentrating the solution to 40–50 ml. gave, after cooling to 0°, 0.8 g. (65%) of the α-IIIb hydrochloride, m.p. 253–256°; fine needles from 2-propanol, m.p. 257–258.5°.

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.5; H, 8.1. Found: C, 64.5; H, 8.0.

Propionylation of 0.2 g. of pure *α-dl*-IIIa hydrochloride gave 80% of *α-dl*-IIIb hydrochloride, m.p. 250–253°.

β-dl-1,4-Dimethyl-4-phenyl-3-propionoxypiperidine (IIIb) *hydrochloride.* The filtrate from the 0.8 g. of *α-dl*-IIIb hydrochloride above was concentrated and diluted with an equal volume of ether to give 0.2 g. of principally plates, m.p. 216–220°. Two recrystallizations from acetone gave 0.1 g. (8%) of pure *β-dl*-IIIb hydrochloride, m.p. 247–250°; oblong plates.

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.5; H, 8.1. Found: C, 64.4; H, 7.8.

The *picrate*, yellow prisms from acetone, melted at 215–216.5° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.9; H, 5.4. Found: C, 54.1; H, 5.2.

NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MD.

(6) A. C. Cope and E. M. Hancock, *Org. Syntheses*, **25**, 46 (1945).

(7) For example boiling xylene as the medium. Sodamide in boiling xylene was also used.

(8) E. L. May and J. G. Murphy, *J. Org. Chem.*, **19**, 618 (1954).

(9) N. B. Eddy, personal communication.

(10) Melting points are corrected (Hershberg apparatus); microanalyses are from the Institutes' service analytical laboratory, under Dr. William C. Alford's direction.

(11) There was also very slight absorption at 2.98 μ perhaps indicating the presence of a small amount of enol tautomer.

(12) By recrystallizing this mixture from 2-propanol-acetone a low yield of fairly pure α-hydrochloride could be obtained, but separation at this stage did not appear practicable.

(13) No attempt was made to recover the apparently water soluble β base.

Carbamates and Ureas Derived from 4-Methyl-*m*-phenylene Diisocyanate

J. A. PARKER, J. J. THOMAS, AND C. L. ZEISE

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The current interest in polyisocyanates, particularly 4-methyl-*m*-phenylene diisocyanate (I), for use in the preparation of useful high molecular weight polymers has presented a need for model compounds with which to study the reactions of this