Synthesis and Properties of the Analgesic DL-α-1,3-Dimethyl-4-phenyl-4-propionoxyazacycloheptane (Proheptazine)[1]

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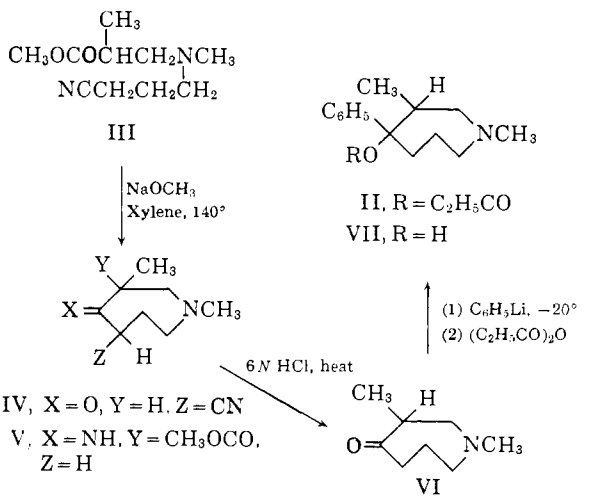
A synthesis and proof of structure of the analgesic proheptazine are described. Evidence supporting a *trans*-Me/Ph configuration for proheptazine is discussed. Studies are presented to show that in the azacycloheptane series, increase in analgesic activity is not necessarily accompanied by a parallel increase in addiction liability.

The synthesis of ethoheptazine,[3-5] a seven-membered ring analog of meperidine, has made available a clinically useful analgesic[6,7] with no demonstrable addiction liability.[8] Reversal of the carbethoxy function and introduction of a 3-methyl group in meperidine markedly increases analgesic activity and results in the formation of the diastereomeric analgesics alphaprodine (Ia) and betaprodine (Ib),[9] which have been assigned the *trans*-Me/Ph and *cis*-Me/Ph configurations, respectively.[10,11] In our study of the effect of ring enlargement on analgesic activity and addiction potential, we synthesized an analogous compound 1,3-dimethyl-4-phenyl-4-propionoxyazacycloheptane (II).[12] Although two diastereomeric racemates are theoretically possible for structure II, we isolated only one racemate, which has been designated the α form, and has been given the generic name proheptazine.

The synthesis of proheptazine was accomplished by the series of reactions outlined in Chart I. N-(2-Carbomethoxypropyl)-N-(3-cyanopropyl)-methylamine (III) was cyclized by sodium methoxide in xylene,[13] and the initial cyclization product (IV and/or V) converted by hydrochloric acid to 1,3-dimethylazacycloheptanone-4 (VI). The ketonitrile structure (IV) is preferred for the initial cyclization product because the substance gave a positive enol test with ferric chloride, and hydrolysis with decarboxylation occurred very slowly. The aminoketone (VI) was converted by phenyl lithium to the lithium salt of 1,3-dimethyl-4-phenylazacycloheptanol-4 (VII), and the latter treated with propionic anhydride to produce proheptazine (II).

The skeletal structure of proheptazine (II) was confirmed by the series of reactions outlined in Chart II. Upon heating a solution of II in mineral oil at 280–300°, propionic acid was eliminated. Catalytic hydrogenation of the pyrolysis product IX produced 1,3-dimethylazacycloheptane (X), identified through its methiodide derivative with material obtained by the decyanation of 1,3-dimethyl-4-phenyl-4-cyanoazacycloheptane (XI).[14]

CHART I



However, although the decyanation of XI led to two diastereomeric racemates of X (α-methiodide, m.p. 199–201; β-methiodide, m.p. 171–173°), catalytic hydrogenation of the pyrolysis product IX from II led only to the β-racemate (methiodide, m.p. 169–171°) of X. A gas chromatogram showed no evidence of another product from the pyrolysis.

The elementary analysis and infrared spectrum of the pyrolysis product supported the structure 1,3-dimethyl-4-phenylazacycloheptene, and the ultraviolet absorption spectrum ($\lambda_{max}^{C_2H_5OH}$ 2425 Å., ϵ_{max} 9789) confirmed the position of the double bond in conjugation with the phenyl group. In order to locate the position of the double bond and to distinguish between the two possible structures, VIII or IX, for the pyrolysis product, its proton magnetic resonance spectrum was examined.[15]

(1) Taken in part from the Ph.D. thesis of J. Diamond, Temple University, 1955.

(2) To whom communications regarding this paper may be sent.

(3) The generic name for *dl*-1-methyl-4-phenyl-4-carboethoxyazacycloheptane, also known as Zactane®.

(4) J. Diamond and W. F. Bruce, U. S. Patent 2,666,050 (1954); J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Org. Chem.*, **22**, 399 (1957).

(5) F. F. Blicke and E. Tsao, *J. Am. Chem. Soc.*, **75**, 5587 (1953).

(6) J. Seifter, D. Eckfeld, I. Letchack, E. Gore, and J. Glassman, *Federation Proc.*, **13**, 403 (1954).

(7) Reviewed in "U. S. Dispensatory," Vol. 2, J. B. Lippincott Co., Philadelphia, Pa., 1960, p. 65, and in "New and Nonofficial Drugs," J. B. Lippincott Co., Philadelphia, Pa., 1961, p. 378.

(8) Minutes of the 17th Meeting of the Committee on Drug Addiction and Narcotics, 1956, Addendum, p. 3.

(9) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947), first synthesized Ia and Ib, the two diastereomeric racemates of 1,3-dimethyl-4-propionoxypiperidine.

(10) A. H. Beckett and J. Walker, *J. Pharm. and Pharmacol.*, **7**, 1039 (1955).

(11) A. F. Casy, *J. Chem. Soc.*, 5057 (1961).

(12) J. Diamond and W. F. Bruce, U. S. Patent 2,775,589 (1956).

(13) N. J. Leonard and E. Barthel [*J. Am. Chem. Soc.*, **71**, 3098 (1948); **72**, 3632 (1950)] employed a similar method for the preparation of 1-methyl-2-alkylazacycloheptan-3-ones from ω,ω,-dicarboxylic esters.

(14) J. Diamond and W. F. Bruce, U. S. Patent 2,740,777 (1956), have described a synthesis of XI. The structure of XI was established by identification of the Hofmann degradation product of its methochloride derivative (ref. 1).

(15) Suggested by a referee.

(16) Determination and interpretation by D. Hollis, Varian Associates, Palo Alto, California.

CHART II

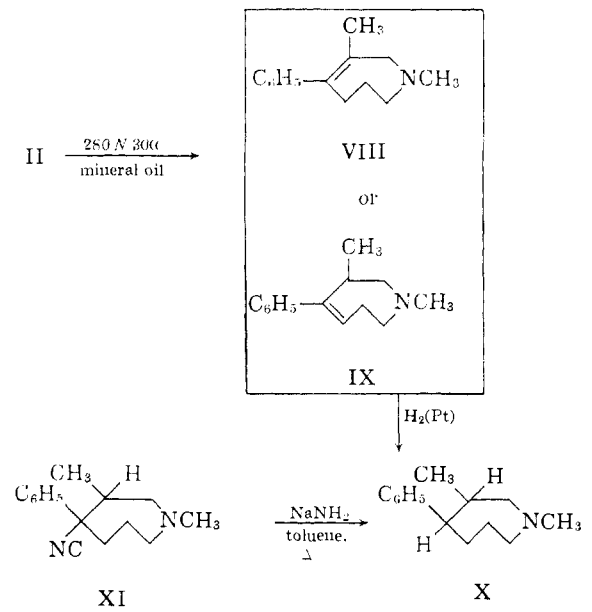
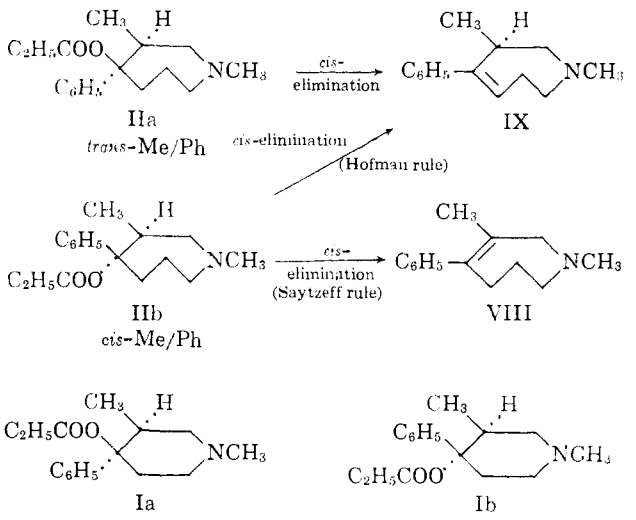


CHART III



The p.m.r. spectrum[16] (Fig. 1) revealed a quadruplet centered at 5.85 p.p.m. which indicated the single vinyl proton which is coupled to the two adjacent ring protons present in IX. A doublet centered at 1.3 p.p.m. was assigned to the C-methyl protons, being split by the proton on the adjacent carbon atom, and a strong peak appearing at 2.35 p.p.m. showed the presence of the N-methyl protons. A band at 2.0–3.0 p.p.m. was due to the ring methylene protons, and a strong peak at 7.25 p.p.m. was assigned to the phenyl protons. Thus, the vinyl hydrogen absorption in the p.m.r. spectrum together with the evidence for C-methyl with a proton on the adjacent carbon clearly indicate structure IX for the pyrolysis product.

The two possible configurations for proheptazine are shown in Chart III, IIa representing the *trans*-Me/Ph isomer and IIb, the *cis*-Me/Ph isomer. It was expected that elucidation of the structure of the pyrolysis product from II would provide insight into the configuration of proheptazine. The formation of an olefin by pyrolysis of a carboxylic ester is known to occur by

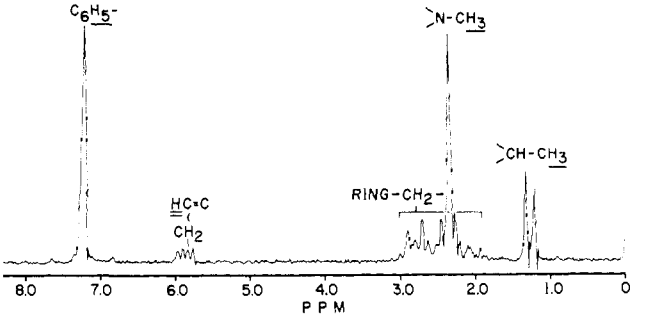


Figure 1.

preferential *cis* elimination without rearrangement.[17] Accordingly, pyrolysis of the *cis* isomer (IIb) could lead to *either* olefin VIII or IX by *cis* elimination of propionic acid, whereas pyrolysis of the *trans* isomer (IIa) could lead *only* to olefin IX in the absence of rearrangement. Since IX was established as the structure of the pyrolysis product, and because IX could result from the pyrolysis of either IIa or IIb, it is not possible to assign unequivocally a configuration to proheptazine from these data.

However, the question arises in the case of the *cis* isomer (IIb) which olefin (VIII or XI) would result preferentially during liquid phase pyrolysis. From an extensive study of carboxylic ester pyrolyses, Bailey and Hale[18] concluded that at lower temperatures the elimination reaction follows the Saytzeff rule, and that liquid phase pyrolyses would be more likely to follow the Saytzeff rule than would vapor phase pyrolyses. Barton[19] also concluded, mostly on the basis of liquid phase pyrolyses, that the Saytzeff rule is followed quite generally, and that the stability of the olefin becomes an increasingly more important factor as the temperature of pyrolysis is lowered.

In view of the work of Bailey and Hale, and of Barton, it is suggested that the liquid phase pyrolysis of the *cis*-Me/Ph isomer IIb would preferentially follow the Saytzeff rule, and that *cis* elimination of propionic acid would lead predominantly to the more highly substituted and more stable olefin VIII. However, *cis* elimination of propionic acid from the *trans*-Me/Ph isomer IIa should lead to olefin IX under *all* conditions of pyrolysis. Since neither the p.m.r. spectrum nor g.l.p.c. of the pyrolysis product from proheptazine revealed the presence of any olefin VIII, the pyrolysis product formed in mineral oil being exclusively olefin IX, we have tentatively assigned the *trans*-Me/Ph configuration IIa to proheptazine, pending isolation of the other possible racemate, if this proves feasible.

Pharmacological examination[20,21] revealed that the analgesic activity of proheptazine in mice is approximately 40 times that of etoheptazine, twice that of alphaprodine or morphine, and 0.7 times that of betaprodine. Therefore, ring enlargement in the case of alphaprodine to the seven-membered analog proheptazine appears to increase analgesic activity.

Prophetazine is reported to be capable of producing physical dependence at relatively high doses. Eddy,

(17) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
(18) W. J. Bailey and W. F. Hale, *J. Am. Chem. Soc.*, **81**, 647, 2126 (1959).
(19) D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949).
(20) J. Glassman and J. Seifter, *J. Pharmacol. Exptl. Therap.*, **116**, 23 (1956).
(21) N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. World Health Org.*, **14**, 353 (1956).

Halbach, and Braenden[21] have ranked numerous analgesics in the order of their addiction potential: morphine ≥betaprodine > alphaprodine ≥ meperidine > proheptazine >ethoheptazine. When compared to their order of analgesic effectiveness: betaprodine > proheptazine > alphaprodine ≥ morphine > meperidine > ethoheptazine, it is significant that in the case of proheptazine there is not a parallel increase in addiction potential with analgesic effectiveness.

Experimental[22]

N-(2-Carbomethoxypropyl)-N-(3-cyanopropyl)-methylamine (III).—A mixture of 1.4 moles (187 g.) of methyl 3-methylamino-2-methylpropionate,[23] 1.4 moles (144 g.) of 4-chlorobutyronitrile, and 1.6 moles (221 g.) of anhydrous potassium carbonate in 350 ml. of di-*n*-butyl ether was heated at 110–115°, while stirring, for 15 hr. After cooling the mixture, the inorganic salts were filtered, and the filtrate was extracted with aqueous hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled.

III was obtained as a colorless liquid, b.p. 100–105° (0.25 mm.), $n^{25}D$ 1.4445; yield 277.5 g. (56.2%).

Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.55; H, 9.09; N, 14.09.

1,3-Dimethylazacycloheptanone-4 (VI).—A mixture of 0.40 mole (79.3 g.) of III and 0.42 mole (22.7 g.) of sodium methoxide in 1.5 l. of dry xylene was stirred under a nitrogen atmosphere while the temperature was gradually raised. A mixture of methanol and xylene was distilled slowly. Within 4 hr., 250 ml. of distillate was collected. This was replaced by an equal volume of dry xylene, and the slow distillation continued. The operation was repeated until the boiling point of pure xylene was attained. The total time required to collect 750 ml. of distillate was 12 hr. At this point an orange solid was suspended in the xylene. This material, the sodio derivative of IV and/or V, was extracted with 750 ml. of 1.75 *N* hydrochloric acid. The acid extract gave a strong positive enol test with ferric chloride solution. An additional 250 ml. of 12 *N* hydrochloric acid was added, and the solution heated at its reflux temperature for 24 hr. The evolution of carbon dioxide gas, vigorous at the beginning, gradually subsided, and was negligible after 24 hr. At this point the enol test with ferric chloride was negative. The cold solution was made basic with 40% sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled. VI was obtained as a very pale yellow liquid, b.p. 110° (35 mm.); $n^{29}D$ 1.4656; yield 18.6 g. (33%).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.70; N, 9.93. Found: C, 68.07; H, 10.45; N, 10.23.

The **picrate,** m.p. 192–193° dec., was formed in hot methanol.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.50; H, 4.90; N, 15.14. Found: C, 45.64; H, 4.92; N, 15.14.

The **hydrochloride** m.p. 158-160°, was formed in ether.

Anal. Calcd. for $C_8H_{16}ClNO$: N, 7.84; Cl, 19.95. Found: N, 7.81; Cl, 19.8.

***dl*-α-1,3-Dimethyl-4-phenyl-4-propionoxyazacycloheptane (II).**—A solution of phenyllithium was prepared, under a nitrogen atmosphere, from 0.667 mole (4.6 g.) of lithium shot and 0.332 mole (52.0 g.) of bromobenzene in 50 ml. of anhydrous ether. The solution was cooled to −20°, and 0.10 mole (14.1 g.) of VI in 100 ml. of ether was added dropwise while stirring. The temperature was maintained at −20° for 0.5 hr. after the addition was completed, then the mixture containing the lithium salt of VII was allowed to warm to room temperature, and to stand overnight under nitrogen. The mixture was cooled to 0°, and 0.35 mole (45 ml.) of propionic anhydride in 100 ml. of dry toluene, containing 5 drops of concentrated sulfuric acid, was added dropwise while stirring. The temperature of the mixture was then gradually raised, and about 75 ml. of ether distilled out as an equal volume of toluene was added dropwise. A temperature of 70–80° was finally maintained for 2 hr. The mixture was cooled to 0°, and 200 ml. of 1:3 48% hydrobromic acid–water solution was added dropwise while stirring to precipitate II·hydrobromide. It was observed that even when hydrochloric acid was used, some II precipitated out as its hydrobromide. The source of bromide ion was apparently lithium bromide, formed during the preparation of phenyllithium. After stirring for 15 min., the mixture was filtered, and the precipitate washed with ether, then cold water, and finally acetone. The crude precipitate was dissolved directly in a methanol–methyl ethyl ketone solvent mixture and the solution concentrated to a small volume.

The **hydrobromide,** m.p. 201–202°, crystallized, was filtered, and washed with ethyl methyl ketone; yield 18.2 g. (63% based on VI). Recrystallization of the hydrobromide from methanol–acetone gave 85% recovery of white crystals, m.p. 207–207.5°. The solubility of the hydrobromide in water at room temperature was 1–2%.

Anal. Calcd. for $C_{17}H_{26}BrNO_2$: C, 57.32; H, 7.36; N, 3.93; Br, 22.41. Found: C, 57.14; H, 7.48; N, 3.80; Br, 22.71.

The **picrate,** m.p. 162–163°, was formed by the addition of aqueous lithium picrate to a solution of the hydrobromide in dilute acetic acid.

Anal. Calcd. for $C_{23}H_{28}N_4O_9$: C, 54.75; H, 5.59; N, 11.10. Found: C, 54.46; H, 5.50; N, 11.04.

The **base,** b.p. 126° (0.3 mm.), $n^{28}D$ 1.5182, $n^{21}D$ 1.5215, was formed by treating an aqueous suspension of the hydrobromide with sodium hydroxide, extracting with ether, drying over potassium carbonate, and vacuum distilling.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.15; H, 9.15; N, 5.09. Found: C, 73.83; H, 9.34; N, 5.17.

The **hydrochloride,** m.p. 207° dec., was formed from the base in a 1:2 ethyl methyl ketone–ether solvent mixture.

Anal. Calcd. for $C_{17}H_{26}ClNO_2$: C, 65.50; H, 8.41; N, 4.49; Cl, 11.37. Found: C, 65.80; H, 8.63; N, 4.57; Cl, 11.1.

The mother liquors from the hydrobromide of II were combined, *i.e.*, the aqueous acid–toluene filtrate, and the methanol–ethyl ketone filtrate. Water and ether were added, and the layers separated. The aqueous layer was washed with ether, made basic with sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and concentrated. Vacuum distillation of the residue gave 2.7 g. of amber liquid, b.p. 124–128° (0.3 mm.), $n^{25}D$ 1.5142; this material may contain the diastereomer of II.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.15; H, 9.15; N, 5.09. Found: C, 73.66; H, 9.09; N, 5.32.

1,3-Dimethyl-4-phenylazacycloheptane (X). (a) From *dl*-α-1,3-Dimethyl-4-phenyl-4-propionoxyazacycloheptane (II) by Pyrolysis and Hydrogenation.—The hydrobromide of II (7.0 g.) was suspended in water and ether. Aqueous sodium hydroxide was added and the layers were separated. The ether layer was dried over anhydrous potassium carbonate, filtered, and all the solvent removed under high vacuum. II was obtained as a colorless liquid, $n^{25}D$ 1.5150, yield 5.0 g. It was dissolved in 300 ml. of heavy mineral oil and the solution heated under a nitrogen atmosphere. Near 280° (inside temperature), propionic acid was detected in the exit vapors. The temperature of the solution was maintained at 280–300° for 25 min. No discoloration was observed. The mixture was cooled, extracted with aqueous hydrochloric acid, and the acid extract washed with ether, made basic with sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled to give 3.0 g. (75%) of colorless liquid IX b.p.; 99–100°, (0.3 mm.), $n^{25}D$ 1.5492, $n^{21}D$ 1.5510.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.25; H, 9.40; N, 6.69.

Its picrate was made by adding aqueous lithium picrate to a neutral solution made from dilute hydrochloric acid and the base. It melted at 126–127° after crystallization from ethyl acetate–hexane. Direct formation from the base and picric acid in methanol gave an uncrystallizable gum.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.70; H, 5.41; N, 12.78.

The base (0.93 g.) was dissolved in 30 ml. of methanol, 0.00025 mole (0.05 g.) of platinum oxide was added, and the mixture was shaken with hydrogen gas at 25° near atmospheric pressure. The absorption of 75 ml. (66% based on II) of hydrogen required 3.5 hr. after which no more hydrogen was used up. (Reduction of the platinum oxide used 12 ml. of hydrogen in the first 5 min.) The catalyst was filtered and the methanol was removed from the

(22) All melting points were determined in an oil bath with a 75-min. immersion calibrated thermometer.

(23) D. R. Howton, *J. Org. Chem.* **10**, 277 (1945).

filtrate under reduced pressure. X remained as a colorless liquid, $n^{20}D$ 1.5210.

A **methiodide,** m.p. 169–171°, of X was formed in isobutyl methyl ketone and recrystallized from acetone–isobutyl methyl ketone. A mixture of this material with the lower melting methiodide prepared by method **b** melted at 170–172°.

(**b**) **From α-1,3-Dimethyl-4-phenyl-4-cyanoazacycloheptane (XI) by Decyanation.**—A mixture of 0.337 mole (76.8 g.) of XI[14] and 0.74 mole (28.9 g.) of sodamide in 500 ml. of toluene was heated at reflux while stirring for 6 hr. The cooled mixture was washed with water, then extracted with dilute hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled. Compound X was obtained as a colorless liquid, b.p. 93–95° (0.2 mm.), $n^{31}D$ 1.5251; yield 55.6 g. (81.1%).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.40; N, 6.88. Found: C, 82.40; H, 10.35; N, 6.60.

The **higher melting methiodide,** m.p. 199–201°, was formed in acetone and purified by digesting with boiling acetone.

Anal. Calcd. for $C_{15}H_{24}IN$: C, 52.20; H, 7.00; I, 36.75; N, 4.06. Found: C, 51.96; H, 6.81; I, 36.6; N, 4.42.

The **lower melting methiodide,** m.p. 171–173°, was obtained by fractional concentration of the mother liquor from the higher melting methiodide.

Anal. Calcd. for $C_{15}H_{24}IN$: C, 52.20; H, 7.00; I, 36.75; N, 4.06. Found: C, 52.17; H, 7.14 I, 36.45; N, 4.38.

Acknowledgment.—We are indebted to Mr. Carl Gochman for excellent technical assistance and to Dr. Gordon Ellis and associates for the microanalyses.

Pyrrolidines. IX. 3-Aryl-3-pyrrolidinols

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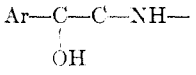
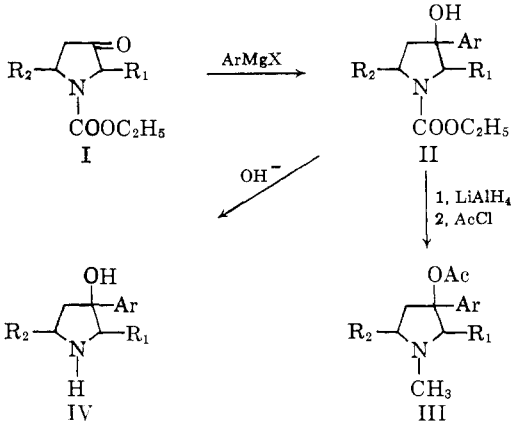
3-Aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters were hydrolyzed and decarboxylated in the presence of a strong base to produce 3-aryl-3-pyrrolidinols. These substances exhibited central nervous system stimulant activity and smooth muscle depressant action variously selective for smooth muscle of the bronchioles, uterus, gut, and the coronary and peripheral vascular system.

In general, useful autonomic drugs of the phenylalkanolamine type meet three criteria: (1) the aromatic nucleus and the nitrogen atom are separated by two carbon atoms; (2) the hydroxyl group is substituted on the carbon atom of the benzyl position; (3) the nitrogen atom is substituted by at least one hydrogen atom.[1,2] During the investigation of the



syntheses of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters (II)[3] and 3-acyloxy-3-aryl-1-methyl pyrrolidines (III),[4] we found that 3-aryl-3-pyrrolidinols (IV) that feature these three structural requirements could be produced.



This report is primarily concerned with the syntheses and pharmacological properties of these 3-aryl-3-pyrrolidinols.[5]

Chemistry.—The preparation of 3-aryl-3-pyrrolidinols (IV) was effected by an alkaline hydrolysis and decarboxylation of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters (II). Hydrolysis under both acidic[6] and basic[7] conditions for the removal of the protective N-alkoxycarbonyl group are known in the literature. In the present work, acid hydrolysis was not attempted because of the unstable nature of these tertiary alcohols under acidic conditions.[8] Kuhn and Osswald[9] prepared D,L-*allo*-hydroxyproline by refluxing diethyl 4-hydroxy-1,2-pyrrolidinedicarboxylate with 10% aqueous barium hydroxide for 3 hr. This procedure was used successfully for the preparation of 3-phenyl-3-pyrrolidinol, 3-(2-thienyl)-3-pyrrolidinol, and 2-methyl-3-phenyl-2-pyrrolidinol. However, for the last compound, a 30-hr. reflux time was required for a satisfactory yield. Evidently substituents in the 2- and 5-positions of the pyrrolidine ring sterically hinder the hydrolysis of the ethoxycarbonyl group. This became more apparent in the hydrolysis of ethyl 2,5-dimethyl-3-phenyl-3-hydroxy-1-pyrrolidinecarboxylate. Using equal volumes of ethanol and 56% aqueous potassium hydroxide and a 6-hr. reflux time, 2,5-di-

(1) R. A. McLean, in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 592.

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," John Wiley & Sons, Inc., New York, N. Y., 1955, p. 231.

(3) Y. H. Wu, W. A. Gould, W. G. Lobeck, Jr., H. R. Roth, and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 752 (1962).

(4) Y. H. Wu, W. G. Lobeck, Jr., and R. F. Feldkamp, *ibid.*, **5**, 762 (1962).

(5) Two reports on synthesis of N-substituted 3-aryl-3-pyrrolidinols have been published. Reference to two N-unsubstituted compounds were made in these publications. These pyrrolidinols were prepared by the hydrogenolysis of the corresponding N-benzyl compounds. (a) C. D. Lunsford, U. S. Patent 2,878,264 (March 17, 1959) (3-phenyl-3-pyrrolidinol); (b) J. F. Cavalla, R. A. Selway, J. Wax, L. Scotti, and C. V. Winder, *J. Med. Pharm. Chem.*, **5**, 441 (1962) (2-methyl-3-phenyl-3-pyrrolidinol).

(6) P. Ruggli, H. Steiger, and P. Schobel, *Helv. Chim. Acta*, **28**, 333 (1945).

(7) W. R. Biggerstaff and A. L. Wilds, *J. Am. Chem. Soc.*, **71**, 2132 (1949).

(8) Acid dehydration of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters was found to occur without significant hydrolysis and decarboxylation of the alkoxycarbonyl group.

(9) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956).