[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, RESEARCH DIVISION, MEAD JOHNSON AND CO.]

Pyrrolidines. IV. The Investigation of the Synthesis of 1-Methyl-2-pyrrolidineethanol

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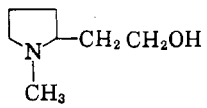
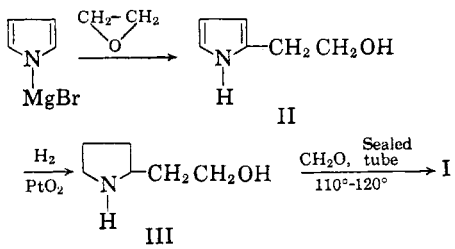
1-Methyl-2-pyrrolidineethanol was synthesized by four methods. Lithium aluminum hydride reduction of ethyl ecgoninate (obtained by the action of methylamine on diethyl β-hydromuconate) was the preferred procedure. The amino alcohol was transformed into its benzilate ester for antispasmodic screening. The corresponding chloride reacted with phenothiazine to give 10-[2-(1-methyl-2-pyrrolidinyl)ethyl]phenothiazine for antihistaminic testing.

In the course of some work in these laboratories, it became desirable to prepare 1-methyl-2-pyrrolidineethanol (I) and certain derivatives for pharmacological comparison with similar derivatives of 1-methyl-3-pyrrolidinemethanol.[1]



I

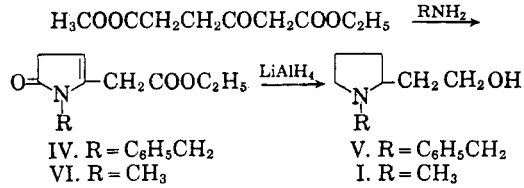
A search of the literature revealed only one report[2,3] on the synthesis of this amino alcohol. The published procedure involved the reaction of *N*-pyrrylmagnesium bromide with ethylene oxide to form 2-pyrroleethanol (II) which was catalytically reduced to 2-pyrrolidineethanol (III) and subsequently *N*-methylated. The preparative route (Method 1) was repeated. Because the reported method gave poor yields and was impractical for large scale preparation, other synthetic approaches were studied.



II

III

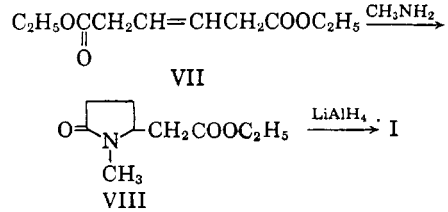
One of the first methods considered was the *N*-methylation of 2-pyrrolidineethanol (III) prepared according to the general scheme of Baker *et al.*[4] This synthetic route (Method 2) comprised the reaction of methyl ethyl β-ketoadipate with benzylamine to produce ethyl 1-benzyl-5-oxo-2-pyrroline-2-acetate (IV) which was reduced with lithium aluminum hydride to 1-benzyl-2-pyrrolidineethanol (V). Hydrogenolysis over palladium gave 2-pyrrolidineethanol (III). *N*-Methylation by the method of Clarke *et al.*,[5] produced the desired 1-methyl-2-pyrrolidineethanol which was identical with the product prepared by Method 1.



IV. R = $C_6H_5CH_2$
VI. R = CH_3
V. R = $C_6H_5CH_2$
I. R = CH_3

A third scheme investigated (Method 3) similar to the above, involved the reaction between methylamine and methyl ethyl β-ketoadipate by Ruggli and Maeder's method[6] to produce ethyl 1-methyl-5-oxo-2-pyrroline-2-acetate (VI), which, with excess lithium aluminum hydride, was reduced to the pyrrolidineethanol. The latter reduction was never 100% complete for infrared spectra[7] of different samples showed the presence of a few per cent of double bond contaminant. The slightly higher indices of refraction also reflected the presence of an unsaturated impurity.

Reduction of ethyl ecgoninate (VIII) with lithium aluminum hydride was the last method studied (Method 4). The required ethyl ecgoninate was obtained by the action of methylamine on diethyl β-hydromuconate (VII). The reaction is



VII

VIII

(1) Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, to be published.

(2) K. Hess, F. Merck, and C. Uibrig, *Ber.*, **48**, 1886 (1915).

(3) Since the completion of our work another report has appeared [F. P. Doyle, M. D. Mehta, G. S. Sach, and J. L. Pearson, *J. Chem. Soc.*, 4458 (1958)] on the preparation of 2-(1-methyl-2-pyrrolidyl)ethanol by the reduction of ethyl α-(1-methyl-2-pyrryl)acetate.

(4) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **17**, 116 (1952).

(5) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(6) P. Ruggli and A. Maeder, *Helv. Chim. Acta*, **25**, 936 (1942).

(7) We are indebted to Mr. John G. Schmidt for infrared spectra.

similar to the synthesis of ecgoninic acid employed by Evans, *et al.*[8]

A comparison of the availabilities of starting materials, the percentage yields, the purities of the final products as indicated by their infrared spectra, and the amounts of work and time required for these four preparative routes showed that Method 4 was the most favorable. Therefore, it was chosen for the synthesis of a larger amount of 1-methyl-2-pyrrolidineethanol.

This amino alcohol was converted to its benzilate ester by transesterification with methyl benzilate in *n*-heptane according to Feldkamp.[9] The ester was tested in comparison with the benzilates of 1-substituted 3-pyrrolidinemethanols.[10]

Reaction of the amino alcohol with thionyl chloride produced the chloride which was condensed with phenothiazine to give 10-[2-(1-methyl-2-pyrrolidinyl)ethyl]phenothiazine. Pharmacological comparison between this derivative and the corresponding 3-pyrrolidinylmethyl[11] compound was also carried out.

EXPERIMENTAL[12]

Method 1: 1-Methyl-2-pyrrolidineethanol. The procedures of Hess *et al.*,[2] were repeated. The yields and physical constants of the intermediates and the product are listed in the following table.

Compound	Yield, %	n_D^{25}	B.P., mm.
2-Pyrroleethanol (II)	6–7	1.5321	101–103 (0.35)
2-Pyrrolidineethanol (III)	51.9	1.4820	63–69 (0.21)
1-Methyl-2-pyrrolidineethanol (I)	41.1	1.4685	114–116 (28)

Anal. Calcd. for $C_7H_{15}NO$: N, 10.84. Found: N, 10.62.

Method 2: β-Carbomethoxypropionyl chloride. The acid chloride was prepared according to Ruggli and Maeder[6] in 88% yield from the starting succinic anhydride, b.p. 98–99° (27 mm.). Cason[13] has described a similar synthesis.

Diethyl 3-carbomethoxypropionylmalonate. The procedure of Baker, *et al.*,[4] was followed. The yield of the product was 66%, b.p. 128–134° (0.5 mm.), n_D^{25} 1.4500.

Methyl ethyl β-ketoadipate. The above malonate ester was hydrolyzed and decarboxylated according to Baker, *et al.*,[4] to give a 52% yield of product, b.p. 86–88° (0.2 mm.), n_D^{25} 1.4398. A simplified procedure for the preparation of a similar ester, dimethyl β-ketoadipate, in 38% overall yield has recently been published.[14]

Ethyl 1-benzyl-5-oxo-2-pyrroline-2-acetate (IV). The condensation of methyl ethyl β-ketoadipate with benzylamine followed by cyclization as described by Baker, *et al.*,[4] gave the desired product in 90% crude yield, m.p. 63–70°.

1-Benzyl-2-pyrrolidineethanol (V). The lithium aluminum hydride reduction of ethyl 1-benzyl-5-oxo-2-pyrroline-2-acetate (IV) produced a 50% yield of the pyrrolidineethanol, b.p. 117–123° (0.55 mm.), n_D^{25} 1.5343.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 6.82. Found: N, 6.65.

1-Methyl-2-pyrrolidineethanol (I). 1-Benzyl-2-pyrrolidineethanol (V) (5.5 g., 0.027 mole) was debenzylated in 75 ml. of acetic acid over 1.5 g. of 10% palladium-on-charcoal with hydrogen at 3 atm. The crude 2-pyrrolidineethanol (III) (2.8 g., 90%) was *N*-methylated by refluxing with 2.8 g. (0.06 mole) of 90% formic acid and 2.3 g. (0.026 mole) of 35% formaldehyde according to Clarke, *et al.*[5] A yield of 0.4 g. (11.5%) of 1-methyl-2-pyrrolidineethanol (I) was obtained upon distillation of the crude product, b.p. 96° (14 mm.), n_D^{25} 1.4680. The infrared spectrum agreed with that of material prepared by Method 1.

Method 3: Ethyl 1-methyl-5-oxo-2-pyrroline-2-acetate (VI). This compound was prepared by a modification of the procedure reported by Ruggli and Maeder.[6] Methyl ethyl β-ketoadipate (102 g., 0.505 mole) was dissolved in 300 ml. of methanol and cooled in an ice bath. Methylamine gas (33 g., 1.06 moles) was introduced over approximately 1 hr. and the resulting solution allowed to warm gradually (1.5 hr.) to room temperature. The crystalline mass which separated was stored overnight at 0° before collecting on a filter. The solid product was washed with a small volume of methanol and dried at 65°; yield, 44 g. (47.5%), m.p. 120–121°. A second crop of product was obtained by concentrating the mother liquor to one-third the original volume and storing at 0°; weight, after collecting and drying, 5 g. (5.5%); m.p. 119–120°.

A recrystallized sample from another run had a melting point of 120–122°. The infrared spectrum showed a strong band at 6.15 μ suggesting that the double bond had shifted into conjugation with the carbonyl group.

Anal. Calcd. for $C_9H_{13}NO_3$: N, 7.65. Found: N, 7.70.

1-Methyl-2-pyrrolidineethanol (I). A solution of 13.2 g. (0.072 mole) of ethyl 1-methyl-5-oxo-2-pyrroline-2-acetate (VI) in 100 ml. of tetrahydrofuran was added dropwise in 25 min. to a slurry of 7 g. (0.18 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The reaction mixture, after being stirred and refluxed for 5 hr., was cooled in an ice bath and treated carefully with 10 ml. of water. The mixture was filtered and the filter cake extracted with 300 ml. of ethanol. The filtrate and extracts were combined and concentrated, leaving an oily residue which was fractionated under reduced pressure to give 5.43 g. (60%) of the product, b.p. 101–104° (21 mm.), n_D^{25} 1.4702.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.84. Found: N, 10.73.

Method 4: Diethyl β-hydromuconate (VII). A mixture of 34.5 g. (0.24 mole) of β-hydromuconic acid prepared according to Evans, *et al.*,[8] 10 ml. of concd. sulfuric acid, and 250 ml. of anhydrous ethanol was refluxed for 24 hr. The residue obtained after removing the ethanol under reduced pressure was dissolved in 100 ml. of chloroform. The resulting solution was washed successively with 50 ml. of saturated brine and 50 ml. of saturated sodium bicarbonate. Fractional distillation gave the diethyl β-hydromuconate (VII) (40.2 g., 84.1%) as a colorless oil, b.p. 144–148° (23 mm.), n_D^{25} 1.4410.

Ethyl ecgoninate (VIII). Methylamine gas (6.8 g., 0.22 mole) was introduced into 40 g. (0.20 mole) of diethyl β-hydromuconate (VII). The mixture was transferred to a steel bomb and heated at 210–230° for 2 hr. The contents were fractionated under reduced pressure to give 23.4 g. (63%) of ethyl ecgoninate (VIII) as a light colored oil, b.p. 164–184° (21 mm.), n_D^{25} 1.4646.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.43; H, 7.68.

1-Methyl-2-pyrrolidineethanol (I). A solution of 18 g. (0.1 mole) of ethyl ecgoninate (VIII) in 30 ml. of tetrahydro-

(8) G. L. Evans, H. W. Gray, and H. W. Jacobson, *J. Am. Chem. Soc.*, **72**, 2727 (1950).

(9) R. F. Feldkamp, *J. Am. Chem. Soc.*, **74**, 3834 (1952).

(10) Y. H. Wu, R. F. Feldkamp, J. R. Corrigan, and H. J. Rhodes, *J. Org. Chem.*, **26**, 1519 (1961).

(11) Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1529 (1961).

(12) Melting points and boiling points are uncorrected. Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill.

(13) J. Cason, *Org. Syntheses*, **Coll. Vol. III**, 169 (1955).

(14) J. Korman, *J. Org. Chem.*, **22**, 848 (1957).

furan was added dropwise over 45 min. to a slurry of 7.6 g. (0.2 mole) of lithium aluminum hydride in 70 ml. of tetrahydrofuran. After being stirred and refluxed for 3.5 hr., the reaction mixture was cooled in an ice bath and treated with 10.8 ml. of water. The resulting slurry was filtered and the filter cake extracted with two 150-ml. portions of ethanol. The combined filtrate and extracts were concentrated and the residue distilled under reduced pressure to yield 8.8 g. (70%) of colorless product, b.p. 101–103.5° (19 mm.), n_D^{25} 1.4691.

2-(1-Methyl-2-pyrrolidinyl)ethyl benzilate. A mixture of methyl benzilate (12.1 g., 0.05 mole), 1-methyl-2-pyrrolidineethanol (I) (6.5 g., 0.05 mole), a small piece of freshly-cut sodium about the size of a pea, and 100 ml. of *n*-heptane was refluxed for 3 hr. in a flask attached to a Dean and Stark apparatus. During the refluxing, 2.55 ml. of methanol separated. The reaction mixture was filtered to remove gelatinous impurities. The filtrate was washed with 50 ml. of water, dried over anhydrous magnesium sulfate, decolorized with activated carbon, and concentrated to give 8.5 g. (72%) of the product, m.p. 78.5–80°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.30; H, 7.42; N, 4.13. Found: C, 74.19; H, 7.20; N, 3.97.

2-(2-Chloroethyl)-1-methylpyrrolidine. A solution of 20 g. (0.168 mole) of thionyl chloride in 25 ml. of chloroform was added over 15–20 min. to a stirred solution of 8.0 g. (0.062 mole) of 1-methyl-2-pyrrolidineethanol in 50 ml. of chloroform. The reaction mixture was refluxed for 2 hr. and then concentrated. Ethanol was added and removed by distillation and the residue dissolved in 40 ml. of water. The aqueous solution was made strongly alkaline with 56% potassium hydroxide and the liberated oil extracted into isopropyl ether. Fractional distillation of the ethereal extract yielded 5.3 g. (57.5%) of a colorless, but cloudy, oil, b.p. 72° (18 mm.), n_D^{25} 1.4631. The same chloride has recently been prepared by Bourquin, *et al.*[15]

10-[2-(1-Methyl-2-pyrrolidinyl)ethyl]phenothiazine. A mixture of phenothiazine (6.8 g., 0.034 mole), sodium amide (1.7 g., 0.042 mole), 2-(2-chloroethyl)-1-methyl-pyrrolidine (5.0 g., 0.034 mole), and 75 ml. of dry toluene was refluxed for 8 hr. The mixture was carefully treated with 50 ml. of water and the toluene layer separated after thorough mixing. The organic phase was washed with water and then extracted with 50 ml. of 3*N* hydrochloric acid in three portions. The combined acid extracts were made strongly basic with 56% potassium hydroxide to liberate the base. The oily product was extracted with ether and the ether solution dried over anhydrous magnesium sulfate. Fractional distillation gave 5.9 g. (56%) of a pale yellow viscous oil as the product, b.p. 168–175° (0.15 mm.).

Anal. Calcd. for $C_{19}H_{22}N_2S$: C, 73.50; H, 7.14; S, 10.33. Found: C, 73.66; H, 6.83; S, 10.36.

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(15) J. P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldiman, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, 41, 1079 (1958).

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Reactions of Amines. VIII. Pyrolysis of Diphenyl *N*-Alkylphosphoramidates[1,2]

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The preparation of four diphenyl *N*-alkylphosphoramidates is described. The pyrolysis of these materials at 350–450° gave high yields of olefin, but the olefins showed evidence of considerable isomerization.

In an earlier paper[3] in this series it was shown that the pyrolysis at 350–400° of dimethyl *N*-alkylphosphoramidates gave in most instances mixtures of olefin and the tertiary amine formed by dimethylation of the alkylamine. Furthermore, the olefin was found to be extensively isomerized during the process. It was suggested that reactions involving the methoxy groups of the phosphoramidate were responsible in large part for both the formation of isomerized olefin and tertiary amine. This communication reports experiments designed to eliminate one or more of these side reactions by replacement of the methoxy by phenoxy groups.

In this work the diphenyl *N*-alkylphosphoramidates were prepared by the reaction of diphenyl phosphite with the appropriate amine in carbon tetrachloride. Other polyhalogen compounds (*e.g.*, bromotrichloromethane) could be used but appeared to have no advantage over carbon tetrachloride. The compounds prepared by this procedure and their infrared spectra are listed in Tables I and II.

$$(C_6H_5O)_2P(O)H + 2\ RNH_2 + CCl_4 \longrightarrow (C_6H_5O)_2P(O)NHR + CHCl_3 + RNH_3Cl$$

The disadvantage of having to use two moles of the amine to one of the secondary phosphite was not compensated for in the present examples by the use of a tertiary amine (*e.g.*, triethylamine) to form the amine hydrochloride, as the separation procedure became more complicated.

A second method employed for the preparation of diphenyl *N*-cyclohexylphosphoramidate involved the reaction of diphenyl phosphorochloridate with cyclohexylamine in carbon tetrachloride solution.

$$(C_6H_5O)_2P(O)Cl + 2\ C_6H_{11}NH_2 \longrightarrow (C_6H_5O)_2P(O)NHC_6H_{11} + C_6H_{11}NH_3Cl$$

The reaction proceeded smoothly, but since comparable yields were obtained with the less

(1) Paper VII. *J. Am. Chem. Soc.*, 83, 399 (1961).

(2) This work was supported in part by grant G-3689 of the National Science Foundation.

(3) H. E. Baumgarten and R. A. Setterquist, *J. Am. Chem. Soc.*, 81, 2132 (1959).