Synthesis of 1-Methylpyrazolidine and Some of Its Derivatives

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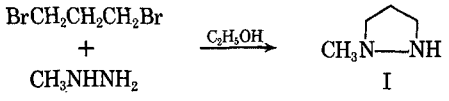
1-Methylpyrazolidine has been prepared *via* a two-step reaction sequence from ethyl acrylate and methylhydrazine, and also directly from trimethylene bromide and methylhydrazine. The *N*-methylpyrazolidino group was substituted for the dialkylamino group in a limited number of clinically effective agents. These derivatives are to be screened for pharmacologic activity.

RECENTLY, a series of esters which has a *N*-alkylated pyrazolidinyl group substituted for a dialkylamino group has been synthesized and found to possess local anesthetic activity (1). One of the compounds, 3-(*N*,*N'*-diethylpyrazolidinyl)methyl *p*-(*n*-butylamino) benzoate was found to be six times as effective as piperocaine[1] when tested on earthworms of genus *Lumbricus*. In view of these encouraging results, it appeared desirable to extend this work and to incorporate the pyrazolidine ring into other types of drug molecules. To this end, the previously unknown 1-methylpyrazolidine has been synthesized, and substituted for the customary dialkylamino group, as a *N*-methylpyrazolidino group, in a number of clinically active agents.

DISCUSSION

1-Methylpyrazolidine (I) was obtained *via* a two-step reaction sequence from methylhydrazine and ethyl acrylate. The intermediate product obtained by distillation was not characterized, but was reduced directly by lithium aluminum hydride and afforded 1-methylpyrazolidine (I) in an over-all yield of 68%. Presumably the intermediate is predominantly 1-methyl-3-pyrazolidinone rather than the 2-methyl isomer. Reduction of either isomer would give 1-methylpyrazolidine. The above structure is proposed for the intermediate because reaction of methylhydrazine with methacrylic acid reportedly gave 1,4-dimethyl-3-pyrazolidinone as the sole product (2). The structure of I is supported by its elemental analysis and infrared spectrum. With excess phenyl isothiocyanate, I forms a monophenylthiourea derivative. Further support for structure I is an alternate one-step synthesis from methylhydrazine and trimethylene bromide. (Scheme I.)



Scheme I

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[1] 3-(2-Methylpiperidino)propyl benzoate.

The infrared spectrum of the product obtained by this pathway was identical to that of the product obtained *via* the methylhydrazine–ethyl acrylate route. Furthermore, no depression was observed when a melting point determination was performed on a mixture of the phenylthiourea derivatives of the two products, and the infrared spectra of these derivatives were identical (see under *Experimental*). Because of a higher yield and purer product, 1-methylpyrazolidine (I) is best prepared *via* the longer two-step route.

The preparation of the *N*-methylpyrazolidino analog of the local anesthetic lidocaine[2] was attempted by reacting *N*-chloroacetyl-2,6-dimethylaniline with excess 1-methylpyrazolidine. A crystalline salt having the correct elemental analysis was obtained in 92% yield. However, the salt is not the desired 2-(2-methylpyrazolidino)-2′,6′-dimethylacetanilide hydrochloride but is instead a hydrazinium chloride, 1-methyl-1-[2-(2′,6′-dimethylanilino)-2-oxoethyl]pyrazolidinium chloride (II). The infrared spectrum of the salt supports structure II since it revealed the absence of absorption in the NH^+ region. Treatment of an aqueous solution of the salt with sodium bicarbonate failed to evolve carbon dioxide, behavior which rules out a hydrochloride salt. Furthermore, an aqueous solution of the salt reacted with silver oxide to precipitate silver chloride and gave a strongly alkaline solution (pH ~ 11, Hydrion E paper) indicating the conversion of a hydrazinium chloride to a hydrazinium hydroxide. This observation is in agreement with the report that hydrazinium hydroxides are slightly less basic than quaternary ammonium hydroxides (3). Studies concerned with the alkylation of alkylhydrazines have shown that substitution occurs at the substituted nitrogen atom to give good yields of the trialkylated quaternary hydrazinium halide unless the alkyl halide contains bulky groups (4, 5). Thus α-bromopropiophenone reacts with 1,1-dimethylhydrazine at the methylated nitrogen atom, resulting in the formation of a quaternary hydrazinium bromide product (6). In view of these earlier findings, it is not surprising that II is the product of the reaction between *N*-methylpyrazolidine and *N*-chloroacetyl-2,6-dimethylaniline.

The *N*-methylpyrazolidino analog of an aminoalkyl ether type of antihistaminic agent, of which chlordiphenhydramine[3] is the prototype, was realized in the following way. Reaction of I with ethyl acrylate proceeded smoothly and afforded the adduct, 1-(2-ethoxycarbonylethyl)-2-methylpyrazolidine (IV) in 85% yield. Lithium aluminum hydride reduction of IV gave an 87% yield of the

[2] 2-(Diethylamino)-2′,6′-acetoxylidide.

[3] 2-(*p*-Chlorobenzhydryloxy)-*N*-dimethylethylamine.

corresponding alcohol (V), which was condensed with *p*-chlorobenzhydryl chloride to give the ether, 1-[3-(*p*-chlorobenzhydryloxy)propyl]-2-methylpyrazolidine (VI). The preparation of a pyrazolidinoethyl ether was abandoned in favor of a pyrazolidinopropyl ether when it was found that I could be converted to 1-(2-hydroxyethyl)-2-methylpyrazolidine (III) in only 9% yield by reaction with ethylene oxide.

Cyanoethylation of 1-methylpyrazolidine proceeded readily and in 77% yield to give the nitrile, 1-(2-cyanoethyl)-2-methylpyrazolidine (VII) which was reduced by lithium aluminum hydride and afforded the propylamine derivative (VIII) in 83% yield. The latter compound, upon reaction with *S*-methylisothiourea sulfate, was converted into the guanidino derivative, 1-(3-guanidinopropyl)-2-methylpyrazolidine sulfate (IX). Compound IX may be regarded as a relative of the hypotensive agent guanethidine.[4]

1-Nicotinoyl-2-methylpyrazolidine (X), related to the respiratory stimulant nikethamide,[5] was prepared from 1-methylpyrazolidine and ethyl nicotinate using sodium methoxide as the catalyst. In addition, I reacted with ethyl chloroformate and gave 1-ethoxycarbonyl-2-methylpyrazolidine (XI). This compound bears structural resemblances to 1-ethoxycarbonyl-4-methylpiperazine, a potent filaricidal agent (7). The above transformations are summarized in Scheme II. The derivatives described in this paper are to be screened for pharmacological activity.

EXPERIMENTAL[6]

1-Methylpyrazolidine (I)—*Method A*—To a solution of 50.6 Gm. (1.10 moles) of methylhydrazine in 25 ml. of absolute ethanol was added dropwise a solution of 100 Gm. (1.00 mole) of ethyl acrylate in 65 ml. of absolute ethanol with stirring (magnetic) and ice-bath cooling. The reaction mixture was stirred and allowed to come to room temperature overnight, and refluxed for 24 hr. The ethanol was distilled *in vacuo* on a water bath, and the residue was distilled and gave 98.6 Gm. of a nearly colorless liquid, b.p. 90–110° (0.7 mm.). The liquid was partially dissolved in 500 ml. of anhydrous ether and the resulting mixture (2-phase) was added dropwise to a suspension of 70.0 Gm. (1.85 moles) of $LiAlH_4$ in 1300 ml. of anhydrous ether with stirring (mechanical). After refluxing for 18 hr. the complex was decomposed with 40% aqueous KOH, with cooling of the reaction mixture by means of a brine and ice cooling mixture. The ether layer was separated and the inorganic sludge was washed twice with 100-ml. portions of ether. The combined ether layers were dried ($MgSO_4$) and the filtered solution was distilled through a Todd column (12 × 90 mm.) packed with glass helices (4 mm. diameter). After removal of the ether fraction and a small fraction of b.p. 78° (probably ethanol), the product distilled and gave 58.9 Gm. (68.5% yield based on ethyl acrylate) of a colorless liquid, b.p. 118° (739 mm.); n_D^{20} 1.4561; $\lambda_{max.}^{film}$ 3.06 μ (NH). In addition, 10 Gm. of a higher boiling residue remained which was not further investigated.

Anal.—Calcd. for $C_4H_{10}N_2$: C, 55.77; H, 11.70; N, 32.52. Found: C, 55.73; H, 11.62; N, 32.58.

A phenylthiourea derivative (8) was prepared and recrystallized from 95% ethanol, m.p. 90–91°.

Anal.—Calcd. for $C_{11}H_{15}N_3S$: C, 59.69; H, 6.83; N, 18.99. Found: C, 59.58; H, 6.72; N, 18.93.

The dihydrobromide was recrystallized from absolute ethanol–ether, m.p. 181–182.5°.

Anal.—Calcd. for $C_4H_{10}N_2 \cdot 2HBr$: C, 19.37; H, 4.88. Found: C, 19.83; H, 5.16.

Method B—To a mechanically-stirred solution of 34.5 Gm. (0.75 mole) of methylhydrazine in 100 ml. of 98% ethanol was added 75.7 Gm. (0.375 mole) of trimethylene bromide in small portions over a period of 30 min. with cooling by means of a cold water bath. The mixture was stirred for 1 hr. at room temperature and refluxed for 17 hr. The clear yellow solution was treated with 45 Gm. (0.8 mole) of KOH pellets with stirring whereupon KBr precipitated. After stirring for 1 hr. the reaction mixture was filtered and the filtrate was distilled through the Todd column described above. The fraction of b.p. 75–84° was collected and discarded. The contents of the still pot was cooled, dissolved in 250 ml. of tetrahydrofuran, and dried over KOH pellets overnight. After filtering, the solution was distilled through the Todd column and afforded 11 Gm. (34%) of a fraction, b.p. 107–115° (735 mm.). Redistillation (without a fractionating column) from KOH pellets gave 8.5 Gm. of liquid, b.p. 110–116° (735 mm.). The infrared spectrum (film) of the product obtained by method *B* was the same as the I.R. spectrum of the product obtained by method *A*, except that the intensity of the NH band was somewhat weaker in the spectrum of the product obtained *via* method *B*. The phenylthiourea derivative was prepared, m.p. 90–91°. A mixed melting point with the phenylthiourea derivative obtained by method *A* was 90–91°, and the infrared spectra of the two derivatives were identical.

1-Methyl-1-[2-(2′,6′-dimethylanilino)-2-oxoethyl]pyrazolidinium chloride (II)—To a solution of 8.25 Gm. (0.096 mole) of 1-methylpyrazolidine (I) in 35 ml. of dry benzene was added 7.90 Gm. (0.040 mole) of *N*-chloroacetyl-2,6-dimethylaniline (9) and the mixture was refluxed for 1.75 hr. The mixture was cooled and filtered to give 10.5 Gm. (92.5%) of a white crystalline salt, m.p. 189–197°. Two recrystallizations from absolute ethanol afforded the analytically pure compound, m.p. 200–201.5°; $\lambda_{max.}^{Nujol}$ 6.0 μ (C=O), 3.2 μ (NH).

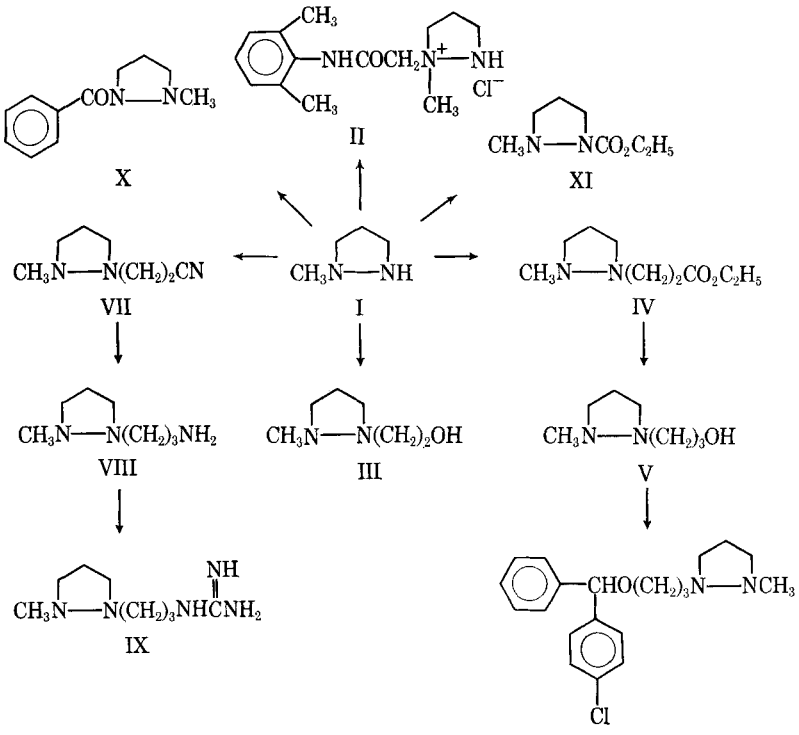
Anal.—Calcd. for $C_{14}H_{22}ClN_3O$: C, 59.25; H, 7.81. Found: C, 59.19; H, 7.83.

1-(2-Hydroxyethyl)-2-methylpyrazolidine (III)—To a solution of 17.2 Gm. (0.2 mole) of 1-methylpyrazolidine (I) in 40 ml. of methanol was added dropwise a solution of 13.3 Gm. (0.30 mole) of ethylene oxide in 65 ml. of anhydrous ether over a period of 30 min. with ice-salt bath cooling. The stoppered reaction mixture was allowed to reach room temperature overnight and was stored for 4 days. An additional 3 ml. of ethylene oxide was added and the reaction mixture was refluxed for 5 hr. using a dry ice–acetone condenser and allowed to stand overnight. The solvents were removed on a water bath *in vacuo* and the residue was fractionally distilled to give 2.4 Gm. (9.2%) of a colorless liquid,

[4] [2-(Octahydro-1-azocinyl)ethyl]guanidine.

[5] *N,N*-Diethylnicotinamide.

[6] Melting points were determined with the Fisher-Johns melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR 8 spectrophotometer using sodium chloride optics. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland.



Scheme II

b.p. 78–83° (28 mm.); n_D^{20} 1.4432. The picrate was prepared and recrystallized from absolute ethanol, m.p. 146.5–148.5°.

Anal.—Calcd. for $C_{12}H_{17}N_5O_8$: N, 19.49. Found: N, 19.31.

1-(2-Ethoxycarbonylethyl)-2-methylpyrazolidine (IV)—A solution of 13.7 Gm. (0.137 mole) of ethyl acrylate in 16 ml. of absolute ethanol was added dropwise to a stirred (magnetic) solution of 11.8 Gm. (0.137 mole) of 1-methylpyrazolidine (I) in 6 ml. of absolute ethanol with ice-bath cooling. After stirring overnight at room temperature the reaction mixture was refluxed on the steam bath for 44 hr. The ethanol was removed (rotary evaporator) and the residue was distilled to give 21.7 Gm. (85%) of a colorless liquid, b.p. 105° (8 mm.); b.p. 60° (0.08 mm.); n_D^{20} 1.4533. In a second experiment with a 20-hr. reflux period the yield was 21.8 Gm. (85.4%).

Anal.—Calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74. Found: C, 58.19; H, 9.77.

A picrate derivative was prepared and recrystallized from absolute ethanol, m.p. 118–119°.

Anal.—Calcd. for $C_{15}H_{21}N_5O_9$: C, 43.37; H, 5.10; N, 16.86. Found: C, 43.52; H, 5.07; N, 17.00.

1-(3-Hydroxypropyl)-2-methylpyrazolidine (V)—A solution of 20.6 Gm. (0.111 mole) of 1-(2-ethoxycarbonylethyl)-2-methylpyrazolidine (IV) in 75 ml. of anhydrous ether was added to a suspension of 4.20 Gm. (0.111 mole) of $LiAlH_4$ and the resulting mixture was refluxed for 17 hr. After decomposing the complex with 40% aqueous KOH (about 50 ml.), the inorganic salts were extracted with ether and the combined ether layers were dried ($MgSO_4$). The spent drying agent was filtered and the filtrate was distilled at atmospheric pressure to remove the ether. The residue was distilled and afforded 13.97 Gm. (87.5%) of a colorless oil, b.p. 112° (11 mm.); n_D^{20} 1.4788; $\lambda_{max.}^{film}$ 2.97 μ (broad H-bonded OH).

Anal.—Calcd. for $C_7H_{16}N_2O$: C, 58.30; H, 11.18. Found: 58.36; H, 11.56.

1-[3-(p-Chlorobenzhydryloxy)propyl]-2-methylpyrazolidine (VI)—A solution of 11.8 Gm. (0.050 mole) of *p*-chlorobenzhydryl chloride in 75 ml. of dry xylene was added dropwise with stirring (mechanical) to a refluxing mixture of 7.2 Gm. (0.05 mole) of 1-(3-hydroxypropyl)-2-methylpyrazolidine (V) and 5.3 Gm. (0.05 mole) of anhydrous sodium carbonate in 30 ml. of dry xylene. The mixture was refluxed for 27 hr. After cooling, the reaction mixture was extracted several times with 10% aqueous HCl and the combined extracts were made alkaline with 40% aqueous NaOH and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and distilled at atmospheric pressure to remove the chloroform. The residue was distilled and gave 2.0 Gm. (11.6%) of a pale yellow oil, b.p. 169° (0.1 mm.); n_D^{20} 1.5615; $\lambda_{max.}^{film}$ 9.2 μ (COC), 13.3, 14.3 μ (monosubstituted benzene).

Anal.—Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.65; H, 7.31; N, 8.12. Found: C, 69.67; H, 7.40; N, 8.13.

1-(2-Cyanoethyl)-2-methylpyrazolidine (VII)—To 12.9 Gm. (0.15 mole) of 1-methylpyrazolidine (I) was added dropwise 7.59 Gm. (0.15 mole) of acrylonitrile with stirring (magnetic) and ice-bath cooling. The resulting mixture was stirred at room temperature overnight and then heated on the steam bath for 2 hr. The yellow mixture was

distilled and afforded 15.96 Gm. (76.6%) of a colorless liquid, b.p. 128–130° (26 mm.); b.p. 64° (0.17 mm.); n_D^{20} 1.4663; $\lambda_{max.}^{film}$ 4.44 μ (C≡N).

Anal.—Calcd. for $C_7H_{13}N_3$: C, 60.40; H, 9.41; N, 30.19. Found: C, 60.38; H, 9.64; N, 29.98.

A picrate derivative was prepared and recrystallized from absolute ethanol, m.p. 151–152.5°.

Anal.—Calcd. for $C_{13}H_{16}N_6O_7$: C, 42.39; H, 4.38. Found: C, 42.31; H, 4.90.

1-(3-Aminopropyl)-2-methylpyrazolidine (VIII)—A solution of 10.0 Gm. (0.0719 mole) of 1-(2-cyanoethyl)-2-methylpyrazolidine (VII) in 50 ml. of anhydrous ether was added dropwise with stirring (mechanical) to a suspension of 5.0 Gm. (0.132 mole) of $LiAlH_4$ in 450 ml. of anhydrous ether. The mixture was refluxed overnight and cooled, and the complex was decomposed with 40% aqueous KOH. The ether layer was decanted, the inorganic sludge was extracted twice with ether, and the combined ether layers were dried ($MgSO_4$). The drying agent was filtered and the ether distilled on a water bath at atmospheric pressure. The residue was distilled to give 8.56 Gm. (83.1%) of a colorless liquid, b.p. 45° (0.25 mm.); n_D^{20} 1.4777; $\lambda_{max.}^{film}$ 3.02 μ (NH).

Anal.—Calcd. for $C_7H_{17}N_3$: C, 58.70; H, 11.96; N, 29.34. Found: C, 58.59; H, 12.28; N, 29.30.

A dipicrate derivative was prepared and recrystallized from 95% ethanol, m.p. 175.5–176.5°.

Anal.—Calcd. for $C_{19}H_{23}N_9O_{14}$: C, 37.94; H, 3.85. Found: C, 38.07; H, 3.96.

1-(3-Guanidinopropyl)-2-methylpyrazolidine Sulfate (IX)—A mixture of 5.0 Gm. (0.035 mole) of 1-(3-aminopropyl)-2-methylpyrazolidine (VIII) and 8.8 Gm. (0.032 mole) of *S*-methylisothiourea sulfate (10) in 35 ml. of 95% ethanol was refluxed with stirring for 6 hr. After cooling, the reaction mixture was filtered and the solid obtained (2.66 Gm.) was identified as *S*-methylisothiourea sulfate. The filtrate was evaporated *in vacuo* and the oily residue was dried (P_2O_5) in an evacuated desiccator for 3 days. Trituration with anhydrous ether gave a hygroscopic crystalline solid which was filtered and redried (P_2O_5). The dried solid weighed 6.0 Gm. (61%) and was recrystallized by dissolving it in water and adding absolute ethanol to the cloud point, m.p. 223.5–224°.

Anal.—Calcd. for $C_8H_{19}N_5 \cdot H_2SO_4$: C, 33.91; H, 7.47; N, 24.72. Found: C, 34.02; H, 7.47; N, 24.70.

1-Nicotinoyl-2-methylpyrazolidine (X)—A solution of 4.3 Gm. (0.05 mole) of 1-methylpyrazolidine (I), 7.55 Gm. (0.05 mole) of ethyl nicotinate (11), and 53 ml. of hexane was dried by azeotropic distillation using a Dean-Stark trap. After 1 hr., 0.3 Gm. of anhydrous sodium methoxide was added and the refluxing was continued for 19 hr. The hexane was distilled *in vacuo* on a water bath. About 10 ml. of water was added, and the mixture was extracted three times with chloroform. The chloroform solution was dried ($MgSO_4$) and the solvent was removed *in vacuo* on a water bath. The residue was distilled and gave 5.1 Gm. (53%) of a colorless oil, b.p. 124° (0.08 mm.). The oil crystallized upon standing, m.p. 50.5–52.5°; $\lambda_{max.}^{Nujol}$ 6.2 μ (C=O).

Anal.—Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.62; H, 6.97; N, 21.90.

A dipicrate was prepared and recrystallized from aqueous ethanol, m.p. 167–168°.

Anal.—Calcd. for $C_{22}H_{19}N_9O_{15}$: C, 40.69; H, 2.95; N, 19.41. Found: C, 40.76; H, 3.29; N, 19.43.

1-Ethoxycarbonyl-2-methylpyrazolidine (XI)—In a 250-ml. three-necked flask provided with a mechanical stirrer and cooled by an ice–salt mixture were placed 25 ml. of ether and 25.8 Gm. (0.1 mole) of a 33% aqueous 1-methylpyrazolidine solution. When the stirred mixture had cooled to 5°, 10.9 Gm. (0.1 mole) of ethyl chloroformate was added without allowing the temperature to rise above 5°. After all of the chloroformate had been added, a solution of 4.0 Gm. (0.1 mole) of NaOH in 6 ml. of water was added dropwise keeping the temperature below 5°. The reaction mixture was stirred for 10 min. longer, the ether layer was separated, and the aqueous solution was extracted with 15 ml. of ether. The combined ether layers were dried ($MgSO_4$) and the ether was distilled using a rotary evaporator. The residue was distilled and afforded 3.03 Gm. (19.2%) of a colorless liquid, b.p. 118° (18 mm.); n_D^{20} 1.4630; $\lambda_{max.}^{film}$ 5.92 μ (C=O).

Anal.—Calcd. for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.24; H, 8.93; N, 17.57.

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