[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

SUBSTITUTED β-AMINOETHYLPYRAZOLES

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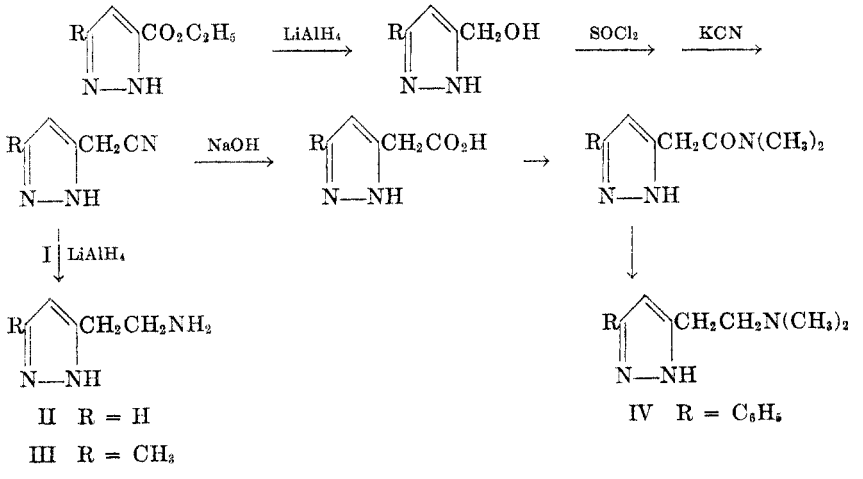
Among a number of aminoalkyl derivatives of heterocyclic nitrogen bases, 3-β-aminoethylpyrazole (II) was found to possess unusually high activity as a stimulator of gastric secretion (1). In order to explore possible relationships of chemical structure to physiological activity, a series of closely related aminoethylpyrazoles was synthesized. This paper describes some 1- and 3-β-aminoethyl derivatives with substituents on the pyrazole ring and on the side-chain nitrogen.

3-Methyl-5-β-aminoethylpyrazole (III) was obtained in good yield by the method indicated in the accompanying series of reactions.

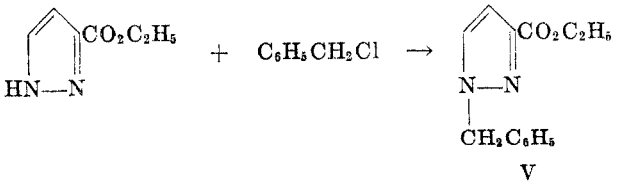


II R = H

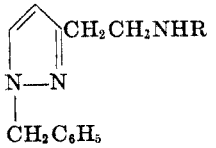
III R = CH_3

IV R = C_6H_5

Attempts to reduce 3-phenyl-5-cyanomethylpyrazole (I, R = C_6H_5) with lithium aluminum hydride gave no recognizable products. 3-Phenyl-5-β-dimethylethylpyrazole (IV), however, was readily obtained by lithium aluminum hydride reduction of N,N-dimethyl-3-phenyl-5-pyrazoleacetamide.



V

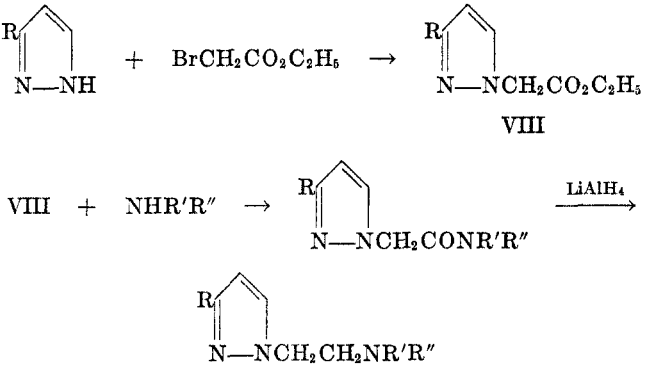


VI R = H

VII R = CH_3

The synthesis of 1-benzyl-3-β-aminoethylpyrazole (VI) and the methylamino analog, VII, involved, first, benzylation of ethyl 3-pyrazolecarboxylate to give ethyl 1-benzyl-3-pyrazolecarboxylate (V). The reason for assigning structure V instead of the alternative ethyl 1-benzyl-5-pyrazolecarboxylate structure is discussed below. Compound V was carried through a sequence of reactions similar to that shown above for the preparation of the 3-substituted-5-aminoethylpyrazoles. Reduction of 1-benzyl-5-cyanomethylpyrazole gave a very poor yield of VI for some unknown reason. Preparation of VII involved reduction of the N-methylamide.

The 1-β-aminoethylpyrazoles, IX through XV, were prepared as indicated by the following reactions.



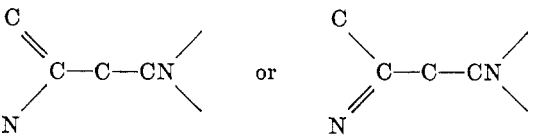
IX R = R′ = R″ = H
X R = R′ = H, R″ = CH_3
XI R = H, R′ = R″ = CH_3
XII R = C_6H_5, R′ = R″ = H
XIII R = C_6H_5, R′ = H, R″ = $CH_2C_6H_5$
XIV R = C_6H_5, NR′R″ = piperidine
XV R = C_6H_5, R′ = R″ = CH_3

Compounds V and VIII, obtained by alkylation of a pyrazole ring nitrogen, are represented as 1,3-substituted derivatives instead of the alternative 1,5-substituted compounds. The reason for assigning the 1,3-structures follows from the work of von Auwers and co-workers (2) who found that alkylation of 3-methyl- and 3-phenyl-pyrazoles gave largely if not exclusively 1,3-disubstituted pyrazoles.

Of the eleven new β-aminoethylpyrazoles, none had any appreciable effect on gastric secretion when tested in dogs (3). Surprisingly, the stimulatory effect of compound II was completely abolished by such a small change as substitution of a methyl group into the ring (compound III).

When tested on guinea pig ileum strips (4), compounds VI, VII, IX, X, and XI were about one five-hundredth as active as histamine. The others were inactive. In depressing the blood pressure of an anesthetized cat (4), the compounds were all less than one one-thousandth as active as histamine with the exception of X. This had quite significant activity, about one one-hundredth that of histamine.

A hypothesis has been advanced (4) that in order to possess histamine-like activity a compound must contain the structural fragment XVI.



XVI

Recently it was reported (5) that 4-β-aminoethylpyrazole, which does not contain fragment XVI, stimulates gastric secretion. The finding that compounds of structures IX, X, and XI possess typical histamine-like activity on smooth muscle and on blood pressure now means that this hypothesis must be abandoned, and that fragment XVI does not represent the minimum structural requirement for histamine activity. As more compounds have been synthesized and tested, the structure-activity relationships in the histamine-analog series have become more and more difficult to define. About all that can be said is that compounds possessing appreciable histamine-like activity are small nitrogen heterocyclic aromatic rings carrying a β-aminoethyl side-chain.

Acknowledgment. The authors are grateful to W. L. Brown, H. L. Hunter, and G. M. Maciak for the microanalyses. Most of the pharmacological tests were conducted by Dr. H. M. Lee and associates.

EXPERIMENTAL

3-Methyl-5-hydroxymethylpyrazole. 3-Methyl-5-hydroxymethylpyrazole was prepared in 75% yield by reduction of ethyl 3-methyl-5-pyrazolecarboxylate (6) with lithium aluminum hydride following the procedure used for the preparation of 3-hydroxymethylpyrazole (7). It was obtained as a white solid which was recrystallized from ethyl acetate; m.p. 86–87°.

Anal. Calc'd for $C_5H_8N_2O$: N, 25.00. Found: N, 24.64.

3-Methyl-5-cyanomethylpyrazole. 3-Methyl-5-hydroxymethylpyrazole was converted in 93% yield to 3-methyl-5-chloromethylpyrazole hydrochloride (m.p. 139–142°) by treatment with thionyl chloride.

The crude chloromethyl hydrochloride was allowed to react with potassium cyanide, following a previously described procedure (7), to give 3-methyl-5-cyanomethylpyrazole; b.p. 140–150° (0.8 mm.); m.p. 41–43° (from ether-petroleum ether).

Anal. Calc'd for $C_6H_7N_3$: N, 34.71. Found: N, 35.01.

3-Methyl-5-β-aminoethylpyrazole dihydrochloride. 3-Methyl-5-cyanomethylpyrazole was reduced with lithium aluminum hydride, and the resulting amine was isolated as the picrate which was finally converted to the dihydrochloride. The procedure has been described previously for the preparation of 3-β-aminoethylpyrazole (7).

The *dipicrate*, obtained in 46% yield, was recrystallized from ethanol; m.p. 178–180°.

Anal. Calc'd for $C_{18}H_{17}N_9O_{14}$: N, 21.62. Found: N, 21.80.

The dipicrate was converted to the *dihydrochloride* in a yield of 80%. It was recrystallized from alcohol-ether; m.p. 186–188° dec.

Anal. Calc'd for $C_6H_{11}N_3 \cdot 2HCl$: N, 21.20. Found: N, 21.20.

3-Phenyl-5-hydroxymethylpyrazole was prepared in 83% yield by reduction of ethyl 3-phenyl-5-pyrazolecarboxylate with lithium aluminum hydride (7). It was a white crystalline solid; m.p. 154–155°.

Anal. Calc'd for $C_{10}H_{10}N_2O$: N, 16.09. Found: N, 15.98.

3-Phenyl-5-chloromethylpyrazole hydrochloride was obtained quantitatively by treating the hydroxymethyl compound with thionyl chloride. It melted over the range 130–150°.

Anal. Calc'd for $C_{10}H_9ClN_2 \cdot HCl$: N, 12.22. Found: N, 12.22.

3-Phenyl-5-cyanomethylpyrazole was obtained in 52% yield from 3-phenyl-5-chloromethylpyrazole hydrochloride and potassium cyanide (7). It melted at 119–120° after recrystallization from ether.

Anal. Calc'd for $C_{11}H_9N_3$: N, 22.95. Found: N, 23.09.

3-Phenyl-5-cyanomethylpyrazole was reduced with lithium aluminum hydride in ether, but no recognizable product could be isolated from the mixture.

3-Phenyl-5-pyrazoleacetic acid. This was prepared in 90% yield by hydrolysis of 3-phenyl-5-cyanomethylpyrazole with sodium hydroxide in alcohol-water solution. It was recrystallized from water; m.p. 168–170°.

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.55.

Ethyl 3-phenyl-5-pyrazoleacetate was prepared by esterification of the acid with ethanol and hydrogen chloride; m.p. 62–63°, from ether-petroleum ether; yield, 88%.

Anal. Calc'd for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.09.
Found: C, 67.52; H, 6.21.

3-Phenyl-5-pyrazole-N,N-dimethylacetamide. The above ester, 17 g., in 100 ml. of methanol saturated with anhydrous dimethylamine was allowed to stand for 24 hours. The solution was evaporated until a solid separated. Recrystallization of the product from methanol-ether and then from chloroform-ether gave 12 g. (70%) of the dimethylamide; m.p. 139–140°.

Anal. Calc'd for $C_{13}H_{15}N_3O$: N, 18.35. Found: N, 18.60.

3-Phenyl-5-β-dimethylaminoethylpyrazole. Reduction of 3-phenyl-5-pyrazole-N,N-dimethylacetamide with lithium aluminum hydride, isolation of the amine as the dipicrate, and conversion of this to the dihydrochloride was carried out by a procedure previously described for the preparation of 3-β-aminoethylpyrazole (7). The *dipicrate* melted at 158–160°. The *dihydrochloride* was obtained as white needles after recrystallization from alcohol; m.p. 165–170°.

Anal. Calc'd for $C_{13}H_{17}N_3 \cdot 2HCl$: N, 14.60. Found: N, 14.40, 14.51.

Ethyl 1-benzyl-3-pyrazolecarboxylate. Ethyl 3-pyrazolecarboxylate was treated, in alcoholic sodium ethoxide solution, with benzyl chloride by a procedure previously described for the preparation of 1-benzylpyrazole (7). The ethyl 1-benzyl-3-pyrazolecarboxylate was obtained in 80% yield; b.p. 150–160° (0.6 mm.); m.p. 75–76° after recrystallization from petroleum ether.

Anal. Calc'd for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: N, 12.42.

1-Benzyl-3-hydroxymethylpyrazole, obtained in 89% yield by reduction of the above ester with lithium aluminum hydride, was a liquid; b.p. 150–153° (1.2 mm.); n_D^{25} 1.5730.

Anal. Calc'd for $C_{11}H_{12}N_2O$: N, 14.91. Found: N, 15.10.

1-Benzyl-3-β-aminoethylpyrazole. 1-Benzyl-3-hydroxymethylpyrazole, 54 g., was added to 100 ml. of thionyl chloride. After the reaction had subsided the excess thionyl chloride was removed by warming under reduced pressure, and a viscous residue remained which did not crystallize. This crude 1-benzyl-3-chloromethylpyrazole hydrochloride was allowed to react with potassium cyanide and the product was isolated by the procedure previously described in the preparation of 1-benzyl-4-β-aminoethylpyrazole (7). The crude material, 40 g., b.p. 160° (2 mm.) appeared to consist of about 40% 1-benzyl-3-ethoxymethylpyrazole (see below) and 60% 1-benzyl-3-cyanomethylpyrazole.

A 13-g. portion of the crude 1-benzyl-3-cyanomethylpyrazole was reduced with lithium aluminum hydride, and the mixture worked up as usual (7) to give 2 g. of *1-benzyl-3-β-aminoethylpyrazole dipicrate*; m.p. 136–138°. The picrate was converted to the *dihydrochloride*, which after recrystallization from alcohol-ether was obtained as white needles in a yield of 0.7 g. (6%); m.p. 183–185°.

Anal. Calc'd for $C_{12}H_{15}N_3 \cdot 2HCl$: N, 15.32. Found: N, 15.44.

1-Benzyl-3-pyrazoleacetic acid. The reaction product of crude 1-benzyl-3-chloromethylpyrazole with aqueous-alcoholic potassium cyanide (see above), 25 g., was heated under reflux for 12 hours with a mixture of 60 ml. of 12 *N* sodium hydroxide solution and 60 ml. of alcohol. The mixture was heated under reduced pressure to remove the alcohol, and the

residue was extracted with two 100-ml. portions of ether. From the ether extract there was obtained by distillation 10 g. (40% yield) of a liquid thought to be *1-benzyl-3-ethoxymethylpyrazole;* b.p. 160–165° (1.5 mm.).

Anal. Calc'd for $C_{13}H_{16}N_2O$: N, 12.95. Found: N, 12.74.

The aqueous basic solution from the above reaction was acidified to *p*H 2 with hydrochloric acid. An oil separated which soon crystallized. This crude 1-benzyl-3-pyrazoleacetic acid, 14.2 g., was recrystallized from ethyl acetate to yield 11.3 g. of pure product; m.p. 125–127°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: N, 12.95. Found: N, 13.20.

Ethyl 1-benzyl-3-pyrazoleacetate. The acid was esterified with ethanol and hydrogen chloride in the usual way to give the ester in 82% yield; b.p. 158° (1.2 mm.).

Anal. Calc'd for $C_{14}H_{16}N_2O_2$: N, 11.47. Found: N, 11.65.

1-Benzyl-3-pyrazole-N-methylacetamide was obtained in 90% yield from ethyl 1-benzyl-3-pyrazoleacetate and methylamine in alcohol; m.p. 70–71° (from ether).

Anal. Calc'd for $C_{13}H_{15}N_3O$: N, 18.34. Found: N, 18.60.

1-Benzyl-3-(β-methylaminoethyl)pyrazole. 1-Benzyl-3-pyrazole-N-methylacetamide was reduced with lithium aluminum hydride, and the amine was isolated in 24% yield as the *dipicrate;* m.p. 166–168°.

Anal. Calc'd for $C_{25}H_{23}N_9O_{14}$: N, 18.72. Found: N, 18.53.

For pharmacological testing the picrate was converted to the *hydrochloride*, which after recrystallization from alcohol-ether was obtained as fine white needles; m.p. 146–148°.

Ethyl 1-pyrazoleacetate. To a solution made by dissolving 23 g. (1.0 g.-atom) of sodium in 900 ml. of absolute ethanol was added 60 g. (0.88 mole) of pyrazole (7). This solution was stirred and 300 g. (1.76 moles) of ethyl bromoacetate was added dropwise. Heat was evolved and sodium bromide was precipitated. The mixture was allowed to stand at room temperature for two days and then evaporated on the steam-bath under reduced pressure. The residue was taken up in 300 ml. of cold 6 *N* hydrochloric acid solution. This was washed with two 200 -ml. portions of ether, and the ether was discarded. The acid solution was made basic with excess solid sodium carbonate and extracted with three 100-ml. portions of chloroform. After drying with magnesium sulfate the chloroform solution was evaporated and the residual liquid was distilled under reduced pressure to yield 84 g. (62%) of ethyl 1-pyrazoleacetate; b.p. 130° (20 mm.).

Anal. Calc'd for $C_7H_{10}N_2O_2$: N, 18.18. Found: N, 18.09.

1-Pyrazoleacetic acid. A sample of ethyl 1-pyrazoleacetate was saponified with hot sodium hydroxide solution. The cooled solution was neutralized to *p*H 7 with hydrochloric acid, evaporated to dryness, and the residue was extracted with hot ethanol. Evaporation of the ethanol left an oil which soon crystallized. The product was recrystallized twice from ethyl acetate and then was sublimed under reduced pressure. It melted at 164–166°.

Anal. Calc'd for $C_5H_6N_2O_2$: N, 22.22. Found: N, 22.65.

1-Pyrazoleacetamide. A solution of 11 g. of ethyl 1-pyrazoleacetate in 150 ml. of absolute ethanol saturated with ammonia was allowed to stand at room temperature for four days. During this time a white crystalline solid separated. The whole mixture was evaporated on the steam-bath under reduced pressure. The solid was washed by suspension in ether and air-dried; wt. 7.5 g. (80% yield); m.p. 151–153°.

Anal. Calc'd for $C_5H_7N_3O$: N, 33.58. Found: N, 33.58.

1-Pyrazole-N-methylacetamide. This was obtained in 89% yield by the action of methylamine on ethyl 1-pyrazoleacetate; m.p. 110–111°.

Anal. Calc'd for $C_6H_9N_3O$: N, 30.21. Found: N, 29.98.

1-Pyrazole-N,N-dimethylacetamide. This was obtained in 97% yield from dimethylamine and ethyl 1-pyrazoleacetate in ethanol; m.p. 112–113°.

Anal. Calc'd for $C_7H_{11}N_3O$: N, 27.45. Found: N, 27.72.

1-β-Aminoethylpyrazole dihydrochloride. 1-Pyrazoleacetamide, 10 g. (0.09 mole), was added *via* a Sohxlet extractor during 48 hours to a solution of 3.4 g. of lithium aluminum hydride in 250 ml. of dry ether. After addition of the amide was complete the mixture was treated with 10 ml. of ethanol added dropwise followed by 10 ml. of water. The ether was

evaporated, and the residual solid was suspended in 200 ml. of methanol. The mixture was saturated with carbon dioxide, heated to boiling, and filtered. After two more extractions with 200-ml. portions of hot methanol the solid was discarded and the combined methanol extracts were evaporated. The residue was taken up in 60 ml. of water and the solution added to a hot solution of 46 g. of picric acid in 750 ml. of water. Upon cooling, 22 g. (44% yield) of *1-β-aminoethylpyrazole dipicrate* was obtained which, after recrystallization from water, melted at 176–178°.

Anal. Calc'd for $C_{17}H_{15}N_9O_{14}$: N, 22.15. Found: N, 21.98.

The picrate was converted to the *hydrochloride* in the customary manner (7) and the resulting 1-β-aminoethylpyrazole dihydrochloride was recrystallized by dissolving in hot absolute ethanol and diluting with dry ether. The white crystals did not melt sharply even after several recrystallizations; m.p. 120–130°.

Anal. Calc'd for $C_5H_9N_3 \cdot 2HCl$: C, 32.61; H, 5.98; N, 22.83.
Found: C, 32.45; H, 5.63; N, 23.30.

1-β-Methylaminoethylpyrazole dihydrochloride. 1-Pyrazole-N-methylacetamide was reduced with lithium aluminum hydride as described above and *1-β-methylaminoethylpyrazole dipicrate* was isolated in 33% yield; m.p. 162–164°.

Anal. Calc'd for $C_{18}H_{17}N_9O_{14}$: N, 21.61. Found: N, 21.95.

The *dihydrochloride* obtained in 75% yield from the picrate did not have a sharp melting point but melted over the range 120–130°.

Anal. Calc'd for $C_6H_{11}N_3 \cdot 2HCl$: N, 21.11. Found: N, 20.77.

1-β-Dimethylaminoethylpyrazole dihydrochloride. Reduction of 1-pyrazole-N,N-dimethylacetamide with lithium aluminum hydride gave 1-β-dimethylaminoethylpyrazole which was isolated in 58% yield as the *dipicrate*; m.p. 175–177°.

Anal. Calc'd for $C_{19}H_{19}N_9O_{14}$: N, 21.11. Found: N, 21.04.

The *dihydrochloride* obtained in 76% yield from the picrate did not melt sharply; m.p. 130–140°.

Anal. Calc'd for $C_7H_{13}N_3 \cdot 2HCl$: N, 19.81. Found: N, 19.54.

Ethyl 3-phenyl-1-pyrazoleacetate. This was prepared from 3-phenylpyrazole (8), sodium ethoxide, and ethyl bromoacetate in the manner described above for the preparation of ethyl 1-pyrazoleacetate. It was obtained as a colorless liquid in a yield of 84%; b.p. 144–146° (0.3 mm.).

Anal. Calc'd for $C_{13}H_{14}N_2O_2$: N, 12.18. Found: N, 12.36.

3-Phenyl-1-β-hydroxyethylpyrazole. The above ester was reduced with lithium aluminum hydride in the usual way to give the alcohol in 88% yield. It was a white solid, soluble in alcohol or benzene, moderately soluble in ether, sparingly so in petroleum ether, and insoluble in water. After recrystallization from petroleum ether it melted at 93–94°.

Anal. Calc'd for $C_{11}H_{12}N_2O$: N, 14.88. Found: N, 14.75.

3-Phenyl-1-pyrazoleacetic acid. A sample of the ethyl ester was saponified with sodium hydroxide in aqueous alcohol. Neutralization of the solution with hydrochloric acid caused precipitation of the 3-phenyl-1-pyrazoleacetic acid as a white crystalline solid. It was recrystallized from alcohol-water; m.p. 166–168°.

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.83.

3-Phenyl-1-pyrazoleacetamide. This was obtained in 84% yield from crude ethyl 3-phenyl-1-pyrazoleacetate and alcoholic ammonia. It was recrystallized from ethyl acetate; m.p. 152–153°.

Anal. Calc'd for $C_{11}H_{11}N_3O$: N, 20.88. Found: N, 20.54.

3-Phenyl-1-pyrazole-N-benzylacetamide. This was prepared in 69% yield from ethyl 3-phenyl-1-pyrazoleacetate and benzylamine in alcohol. It was recrystallized from ethyl acetate; m.p. 146–148°.

Anal. Calc'd for $C_{18}H_{17}N_3O$: N, 14.42. Found: N, 14.30.

3-Phenyl-1-pyrazoleacetylpiperidine was prepared in 62% yield from ethyl 3-phenyl-1-pyrazoleacetate and piperidine in alcohol. After recrystallization from alcohol-ether and twice from chloroform-ether it melted at 184–186°.

Anal. Calc'd for $C_{16}H_{19}N_3O$: N, 15.60. Found: N, 15.59.

3-Phenyl-1-pyrazole-N,N-dimethylacetamide was obtained in 80% yield from dimethylamine and the ester. It was recrystallized from ethyl acetate-petroleum ether. A sample for analysis was sublimed; m.p. 164–166°.

Anal. Calc'd for $C_{13}H_{15}N_3O$: N, 18.35. Found: N, 17.81.

3-Phenyl-1-β-aminoethylpyrazole dihydrochloride. 3-Phenyl-1-pyrazoleacetamide, 8.4 g. (0.04 mole), was added in portions during 15 minutes to a solution of 4.5 g. of lithium aluminum hydride in 250 ml. of dry ether. The mixture was heated at reflux for three hours, and then 40 ml. of water was added, dropwise at first. The ether layer was decanted, and the solid was extracted with two 100-ml. portions of chloroform. After drying the combined ether and chloroform solutions, dry hydrogen chloride was passed in, and the 3-phenyl-1-β-aminoethylpyrazole dihydrochloride precipitated as a white crystalline solid; yield 6.5 g. (63%). A sample was recrystallized from absolute ethanol-ether; m.p. 182–185°.

Anal. Calc'd for $C_{11}H_{13}N_3 \cdot 2HCl$: N, 16.15. Found: N, 16.13.

3-Phenyl-1-β-benzylaminoethylpyrazole and dihydrochloride. 3-Phenyl-1-pyrazole-N-benzylacetamide was reduced with lithium aluminum hydride in the manner described above for the preparation of 3-phenyl-1-β-aminoethylpyrazole. The dried ether-chloroform solution, instead of being treated with dry hydrogen chloride, was evaporated and the residue was distilled under reduced pressure to give a 75% yield of 3-phenyl-1-β-benzylaminoethylpyrazole; b.p. 200–202° (1 mm.); m.p. 63–64°. The *dihydrochloride* was obtained by treating an ether solution of the base with dry hydrogen chloride; m.p. 198–200°.

Anal. Calc'd for $C_{18}H_{19}N_3 \cdot 2HCl$: N, 12.00; Cl, 20.24.
Found: N, 12.04; Cl, 20.13.

3-Phenyl-1-β-N-piperidinoethylpyrazole and monohydrochloride. Reduction of 3-phenyl-1-pyrazoleacetylpiperidine with lithium aluminum hydride gave 3-phenyl-1-β-N-piperidinoethylpyrazole in 55% yield; b.p. 168–171° (1 mm.). The *monohydrochloride* precipitated when an ether solution of the base was treated with dry hydrogen chloride; m.p. 216–218°.

Anal. Calc'd for $C_{16}H_{21}N_3 \cdot HCl$: N, 14.42; Cl, 12.20.
Found: N, 14.47; Cl, 12.25.

3-Phenyl-1-β-dimethylaminoethylpyrazole and dihydrochloride. The base was obtained in 70% yield by reduction of 3-phenyl-1-pyrazole-N,N-dimethylactamide; b.p. 133–135° (1 mm.). The *dihydrochloride*, precipitated from an ether solution of the base with dry hydrogen chloride and recrystallized from alcohol-ether, melted at 185–187°.

Anal. Calc'd for $C_{13}H_{17}N_3 \cdot 2HCl$: N, 14.68. Found: N, 14.82.

SUMMARY

Eleven new β-aminoethylpyrazole compounds variously substituted on the ring and on the side-chain nitrogen atom have been prepared. A number of these compounds with the side chain attached to the 1-position of pyrazole have typical histamine-like activity.

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