headed "Method of isolation." Methods A, B and C have been described previously.[2]

Method B′ is a modification of B in which steam distillation of the basic material is omitted and the amidine is separated from secondary amine by extraction from ethereal solution by successive portions of dilute hydrochloric acid. This is to be preferred with N-arylamidines since the secondary amine is feebly basic and the amidine base may undergo some decomposition during a prolonged steam distillation.

Method A′ differs from A only in that the amidine base is not itself distilled. The secondary amine is volatilized by heating *in vacuo* to a temperature preferably not over 160°. In some cases more drastic heating (up to 200° at 1 mm.) was employed with no apparent decomposition but it is believed that the yield of pure amidine hydrochloride suffered from such treatment.

The amidine hydrochlorides were purified by crystallization from ethanol–ether mixtures.

Electrometric Titrations.—These were performed at 0.02 molar initial concentration of amidine hydrochloride in 50% methanol, adding 0.1 *N* sodium hydroxide solution. The apparatus was a Beckman *p*H meter, Model G. Determinations of the *p*H range 6–9 were accomplished with a glass electrode 960 standardized at *p*H 4 and *p*H 7 with potassium acid phthalate and phosphate buffers, respectively. Above *p*H 9 a high *p*H glass electrode 960 E standardized at *p*H 9 and *p*H 12 with sodium chloride–glycine[6] buffers was employed.

Direct comparison of titrations in water and in 50% methanol is not possible with most of these amidines. The most accurate but laborious procedure is to perform a series of titrations in diminishing concentrations of methanol so as to permit extrapolation to zero per cent.—as was done by Hall and Sprinkle.[3] From observations on certain quinoline amidines we believe that in the range 9.5–11, the pK_a observed in 50% methanol runs about 0.3 unit above that in water. Compound XXX was titrated both in 50% methanol and in water. The two curves were roughly parallel, that for methanol being above that for water except at high *p*H (at 11.9 the curves cross). The first two pK_a values, at 8.65 in water and 8.80 in 50% methanol, presumably are due to the phenolic hydroxyl group. The higher pK_a values, relating to the amidine portion were at 12.05 in 50% methanol and 12.15 in water.

Summary

1. A number of N,N-disubstituted benzamidines have been prepared.

2. The effect of substitutions upon the basicity of unsymmetrically disubstituted benzamidines is discussed.

(6) Clark, "The Determination of Hydrogen Ions," 3rd Edition, Williams and Wilkins Co., Baltimore, Md., 1928, Chapter IX.

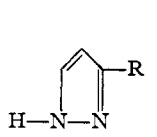
TUCKAHOE 7, N. Y. RECEIVED JUNE 11, 1949

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

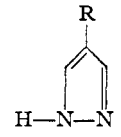
The Synthesis of Some Amines and Amino Acids Containing the Pyrazole Nucleus

BY REUBEN G. JONES

As part of a study concerned with the biological activity of certain amines and amino acids[1] the two isomeric β-aminoethylpyrazoles, I and II, and the two corresponding pyrazolealanines, III and IV, were prepared.



I, R = $CH_2CH_2NH_2$

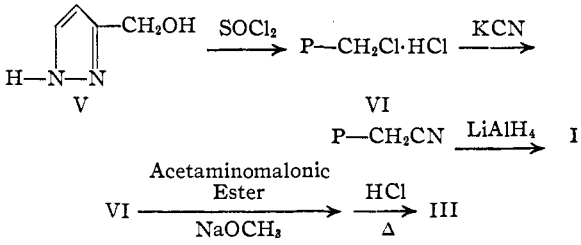


II, R = $CH_2CH_2NH_2$

III, R = $CH_2CHNH_2CO_2H$ IV, R = $CH_2CHNH_2CO_2H$

These pyrazole compounds were of particular interest because of their apparently close structural resemblance to the imidazole derivatives, histamine and histidine.

Compounds I and III were synthesized by straightforward procedures as indicated in the accompanying reactions.



Two methods were developed for the preparation of the starting material, 3-hydroxymethylpyrazole, V. Reduction of ethyl 3-pyrazolecarboxylate[2] with lithium aluminum hydride in ether gave V in 84% yield. Compound V was also prepared by the condensation of diazomethane with propargyl alcohol. It has been observed that substituted acetylenes of the type R—C≡CH undergo reaction with diazomethane to yield predominately 3-substituted pyrazoles,[3]

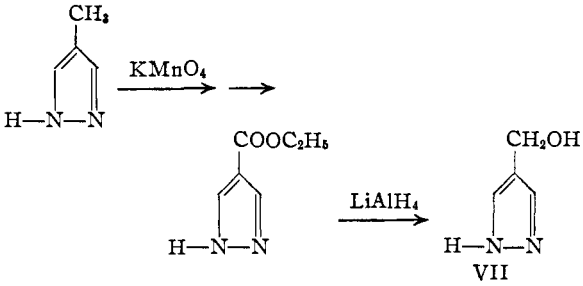
(1) (a) Jones, THIS JOURNAL, **71**, 383 (1949); (b) Jones, *ibid.*, **71**, 644 (1949).

(2) Knorr, *Ber.*, **37**, 3522 (1904).

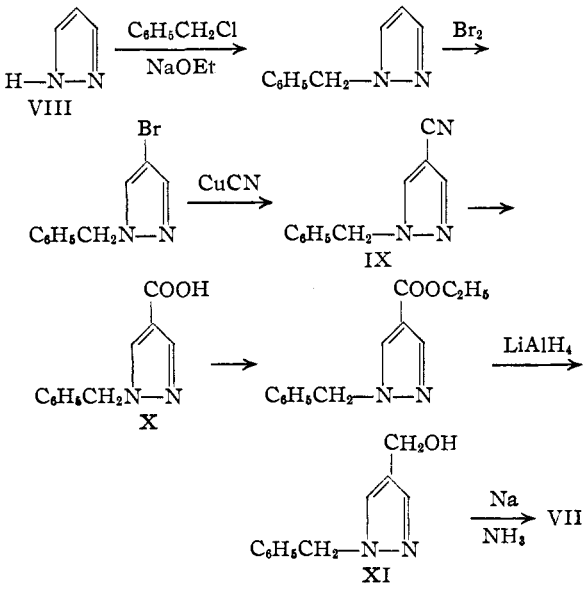
(3) (a) Kuhn and Henkel, *Ann.*, **549**, 279 (1941); (b) Huttel, *Ber.*, **74**, 1680 (1941).

and only insignificant amounts of the alternative 4-substituted isomers. In the present case the yield of 3-hydroxymethylpyrazole was about 50% and that of 4-hydroxymethylpyrazole about 2%.

A number of unforseen difficulties were encountered in the preparation of the 4-substituted pyrazole compounds, II and IV. It was at first supposed that these could be synthesized readily from 4-hydroxymethylpyrazole by the same methods as outlined above for the corresponding 3-isomers. Consequently the preparation of 4-hydroxymethylpyrazole, VII, was undertaken. One series of reactions by which VII was obtained consisted of the permanganate oxidation of 4-methylpyrazole[4] to yield 4-pyrazolecarboxylic acid,[5] which was esterified, and the resulting ester was then reduced with lithium aluminum hydride.



An alternative method of preparing VII is outlined in the following series of reactions.



Pyrazole VIII, the starting material for these latter reactions, was conveniently obtained by the condensation of hydrazine hydrochloride with the recently available 1,1,3,3-tetraethoxypropane.[6]

(4) Auwers and Cauer, *J. prakt. Chem.*, **126**, 146 (1930).

(5) (a) Büchner and Fritsch, *Ann.*, **273**, 253 (1893); (b) Behaghel and Büchner, *Ber.*, **35**, 34 (1902).

(6) Obtained from Carbide and Carbon Chemicals Corporation; see Hultquist, U. S. Patent 2,459,076.

The reaction of 1-benzyl-4-bromopyrazole with cuprous cyanide required a very careful control of experimental conditions in order to obtain satisfactory yields of IX. Several attempts to carry out a similar reaction between 4-bromopyrazole and cuprous cyanide resulted in failure to obtain any of the desired 4-cyanopyrazole. Sodium in liquid ammonia smoothly cleaved the benzyl group from XI to yield VII. Likewise, the acid X underwent facile cleavage to yield 4-pyrazolecarboxylic acid. Thus the 1-benzylpyrazoles behave in the same way as the 1-benzylimidazoles toward sodium in liquid ammonia.[1a]

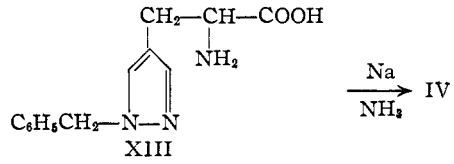
4-Hydroxymethylpyrazole reacted vigorously with thionyl chloride but the resulting 4-chloromethylpyrazole hydrochloride, unlike the isomeric 3-chloromethyl compound, was completely insoluble in thionyl chloride. Furthermore, 4-chloromethylpyrazole proved to be a highly reactive and unstable substance, and no analytically pure sample was isolated. It appeared to react rapidly with ice-water to form 4-hydroxymethylpyrazole. From the reaction of a cold absolute alcohol solution of 4-chloromethylpyrazole hydrochloride with excess potassium cyanide there was obtained a small yield of 4-cyanomethylpyrazole. This was treated with lithium aluminum hydride in ether solution, but none of the expected 4-(β-aminoethyl)-pyrazole (II) could be isolated from the reaction mixture.

In view of these disappointing results, attention was turned to the reactions of 1-benzyl-4-hydroxymethylpyrazole, XI. With thionyl chloride, this yielded 1-benzyl-4-chloromethylpyrazole hydrochloride which could not be induced to crystallize, and an analytically pure sample was not obtained. This chloromethyl compound likewise was highly reactive. An absolute alcohol solution was allowed to react with aqueous potassium cyanide, and there was obtained a liquid product which appeared to consist of a mixture of 1-benzyl-4-cyanomethylpyrazole and 1-benzyl-4-ethoxymethylpyrazole. These could not be separated by distillation, and so the mixture was subjected to the action of lithium aluminum hydride. From this reaction there was isolated a liquid mixture of 1-benzyl-4-(β-aminoethyl)-pyrazole and the unchanged 1-benzyl-4-ethoxymethylpyrazole. When this mixture in dry ether solution was treated with carbon dioxide the β-aminoethyl compound was precipitated as a white crystalline solid which was apparently the ammonium carbamate salt.[7] The dihydrochloride of 1-benzyl-4-(β-aminoethyl)-pyrazole was obtained by treating the carbamate salt with hydrogen chloride in absolute alcohol. The benzyl group was removed from 1-benzyl-4-(β-aminoethyl)-pyrazole carbamate salt by sodium in liquid ammonia to yield compound II.

The condensation of 1-benzyl-4-chloromethyl-

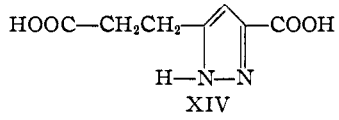
(7) For a recent discussion of ammonium carbamate salts of this type see Wright and Moore, THIS JOURNAL, **70**, 3865 (1948).

pyrazole hydrochloride with sodium acetaminomalonic ester led to the preparation of 1-benzyl-4-pyrazolealanine, XIII. This was converted through the agency of sodium in liquid ammonia to IV, which was purified by precipitation as an insoluble mercuric chloride complex.



XIII

In the early part of this work, another possible approach to the synthesis of the 3-substituted pyrazole compounds was considered. Diethyl α,γ-diketopimelate[8] was allowed to react with hydrazine to yield 5-(β-carbethoxyethyl)-3-pyrazolecarboxylate which was saponified to form the acid XIV.



XIV

When XIV was heated to about 200° in vacuum it sublimed unchanged. No method was discovered by which XIV could be decarboxylated to yield β-(3-pyrazole)-propionic acid which would have been a suitable intermediate for the synthesis of other 3-substituted pyrazoles.

Neither 3- nor 4-(β-aminoethyl)-pyrazole possessed any histamine-like action[9] or other observable pharmacological activity. 3-Pyrazolealanine was not inhibitory to *E. coli, L. arabinosis, Leuconostoc mesenteroides, Strep. viridans, Influenza virus or E. coli phages* T_2 and T_7.

Experimental[10]

3-Hydroxymethylpyrazole. (a) **Reaction of Diazomethane with Propargyl Alcohol.**—The diazomethane solution prepared in 1500 ml. of ether from 103 g. (1 mole) of nitrosomethylurea[11] was dried over potassium hydroxide pellets for three hours and then decanted into a dry two-liter flask. To the solution was added 56 g. (1.0 mole) of freshly distilled propargyl alcohol (b. p. 110–111°). The solution was allowed to stand at room temperature, and after sixty hours it had become colorless. The ether was evaporated, and the sirupy residue was distilled *in vacuo*. After a forerun of 31 g. (55%) of unreacted propargyl alcohol there was obtained 30 g. of viscous liquid, b. p. 120–150° (0.5 mm.), and about 2 g. of higher boiling material which partially crystallized upon cooling. After several recrystallizations from acetone–petroleum ether mixtures the crystalline substance melted at 121–122° and was identified by mixed melting point as 4-hydroxymethylpyrazole (see below).

The 30 g. of viscous liquid was dissolved in 50 ml. of water and added to a boiling-hot solution of 80 g. of picric acid in 1200 ml. of water. The resulting solution was boiled with 5 g. of decolorizing carbon, filtered and cooled to 40°. The yellow, crystalline precipitate of 3-hydroxymethylpyrazole picrate was collected, washed with a little absolute alcohol and air-dried, The yield was 78 g. (53% based upon unrecovered propargyl alcohol). It melted at 183.5–184.5°, and the melting point remained unchanged after recrystallization from water.

Anal. Calcd. for $C_{10}H_9N_5O_8$: N, 21.41. Found: N, 21.43.

The picrate, 75 g., was suspended in 200 ml. of nitrobenzene, and the mixture was vigorously shaken with 50 ml. of 12 *N* hydrochloric acid (6 *N* hydrochloric acid did not decompose the picrate). The hydrochloric acid layer was washed with three 50-ml. portions of chloroform, and then the nitrobenzene and chloroform solutions were extracted with a fresh 50-ml. portion of 12 *N* hydrochloric acid. After the total acid solution had been filtered, it was evaporated in vacuum to dryness. The residual solid was taken up in absolute alcohol, and the solution was evaporated to dryness in vacuum, leaving the 3-hydroxymethylpyrazole hydrochloride as a very hygroscopic, white, crystalline solid. It was dried in vacuum over potassium hydroxide, and the yield was 30 g. (97%); m. p. 113–115°. A sample recrystallized from absolute alcohol–ether and dried in vacuum melted at 117–118°.

To 0.5 g. (0.005 mole) of the crude 3-hydroxymethylpyrazole in 30 ml. of distilled water was added 1.05 g. (0.0067 mole) of potassium permanganate. The mixture was shaken and heated for one-half hour and then filtered. The colorless filtrate together with about 30 ml. of water used to wash the manganese dioxide was evaporated to a volume of about 5 ml. This solution was brought to *p*H 2 with hydrochloric acid and, after scratching, 0.35 g. of white crystalline precipitate separated, m. p. 216–217°. The product was identified as 3-pyrazolecarboxylic acid by a mixed melting point with an authentic sample,[12] m. p. 216–217°.

Anal. Calcd. for $C_4H_4N_2O_2$: C, 41.98; H, 3.60. Found: C, 42.16; H, 3.92.

(b) **Reduction of Ethyl 3-Pyrazolecarboxylate with Lithium Aluminum Hydride.**—3-Pyrazolecarboxylic acid[12] was esterified with ethanol and hydrogen chloride. The ethyl ester, obtained in 89% yield, melted[2] at 158°. In a Soxhlet thimble above a refluxing solution of 15 g. of lithium aluminum hydride[13] in 1 l. of ether was placed 28 g. (0.20 mole) of ethyl 3-pyrazolecarboxylate. After fifteen hours all of the ester had been dissolved and carried down into the lithium aluminum hydride solution. Very cautiously and with stirring, 50 ml. of water was added dropwise to the reaction mixture, and then the ether was almost all removed by evaporation. The residual, white, granular solid was treated with 300 ml. of methanol, and the mixture was thoroughly saturated with carbon dioxide. After the mixture had been heated to boiling it was filtered, and the solid was extracted with two more 300-ml. portions of boiling methanol. The total filtrate was evaporated in vacuum, and the residual sirup containing some solid was extracted with 50 ml. of dry methanol. This methanol solution was again filtered and evaporated, and the residual sirup was distilled in vacuum to yield 16.5 g. (84%) of pure 3-hydroxymethylpyrazole; b. p. 137–140° (0.5 mm.), $n^{25}D$ 1.5340, d^{25}_{25} 1.225.

Anal. Calcd. for $C_4H_6N_2O$: N, 28.56. Found: N, 28.42.

The 3-hydroxymethylpyrazole was a colorless, very viscous liquid which could not be induced to crystallize. It was highly soluble in water or alcohol, moderately soluble in ether, and it could not be extracted from its water solution with organic solvents. The picrate melted at 184–185°, and the melting point was not depressed when mixed with the picrate described above under (a).

3-Chloromethylpyrazole Hydrochloride.—To 40 ml. of thionyl chloride was added in small portions 30 g. (0.22 mole) of 3-hydroxymethylpyrazole hydrochloride. Reaction took place immediately, and a clear solution was formed. After the solution had been warmed on the steam-bath for fifteen minutes, the excess thionyl chloride

(8) Wislicenus, *Ber.*, **21**, 2583 (1888).

(9) Lee and Jones, *J. Pharmacol.*, **95**, 71 (1949).

(10) All melting points are corrected.

(11) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(12) Knorr, *Ann.*, **279**, 231 (1894).

(13) Obtained from Metal Hydrides Inc., Beverly, Mass.

was removed by evaporation in vacuum. The white, crystalline 3-chloromethylpyrazole hydrochloride was washed with anhydrous ether and stored in a vacuum desiccator over potassium hydroxide. The yield was 34 g. (100%), m. p. 155–156° dec. It was deliquescent.

Anal. Calcd. for $C_4H_5N_2Cl \cdot HCl$: N, 18.31. Found: N, 18.20.

3-Cyanomethylpyrazole.—To a well-stirred solution of 60 g. of potassium cyanide in 65 ml. of water cooled in an ice-bath was added a solution of 15.3 g. (0.10 mole) of 3-chloromethylpyrazole hydrochloride in 200 ml. of absolute alcohol over a period of one hour. The reaction mixture was removed from the cooling bath and stirred at room temperature for four hours. It was then filtered, the salts were washed with two 200-ml. portions of 95% alcohol and the total filtrate was evaporated in vacuum to a volume of about 100 ml. After the addition of a little water to bring some precipitated salts into solution, the mixture was extracted with four 100-ml. portions of chloroform. The chloroform extract was evaporated in vacuum leaving 9.5 g. of liquid residue. This was distilled in vacuum. It all came over at 117–120° (0.4 mm.) as a colorless liquid. The yield was 8.5 g. (80%) of 3-cyanomethylpyrazole; $n^{25}D$ 1.5138.

Anal. Calcd. for $C_5H_5N_3$: N, 39.23. Found: N, 38.94.

The picrate, m. p. 63–64°, was appreciably water soluble.

3-(β-Aminoethyl)-pyrazole.—A solution of 7.5 g. (0.07 mole) of 3-cyanomethylpyrazole in 50 ml. of dry ether was added dropwise to a solution of 5 g. of lithium aluminum hydride in 150 ml. of ether. After the mixture had stood for about one-half hour, 25 ml. of water was added dropwise through the condenser. The ether was then evaporated and 200 ml. of methanol was added. The mixture was saturated with carbon dioxide, heated to boiling and filtered. The solid was extracted with four additional 300-ml. portions of hot methanol, and the total methanol filtrate was evaporated in vacuum to dryness. The residue was dissolved in 200 ml. of warm methanol and the solution filtered and evaporated. The solid residue which appeared to be a 3-(β-aminoethyl)-pyrazole salt with carbon dioxide was dissolved in 50 ml. of water and the solution added to a hot solution of 35 g. of picric acid in 600 ml. of water. After cooling to 10° the crystalline solid was collected and recrystallized from 250 ml. of water to yield 21 g. (53%) of 3-(β-aminoethyl)-pyrazole dipicrate; m. p. 195–197°.

Anal. Calcd. for $C_{17}H_{15}N_9O_{14}$: N, 22.20. Found: N, 22.90.

The dipicrate, 20 g., was treated with concentrated hydrochloric acid in nitrobenzene and the mixture worked up as described above to yield 6.2 g. (96%) of 3-(β-aminoethyl)-pyrazole dihydrochloride; m. p. 223–224°. It was deliquescent, but only sparingly soluble in hot absolute alcohol.

Anal. Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83; Cl, 38.52. Found: N, 23.21; Cl, 38.16.

3-Pyrazolealanine.—In a 500-ml. three-necked flask provided with a stirrer and dropping funnel was placed 150 ml. of absolute alcohol. In the alcohol was dissolved 6.9 g. (0.3 g. atom) of sodium. To the solution was added 43 g. (0.2 mole) of acetaminomalonic ester, and then the flask was surrounded with an ice-bath. With stirring a solution of 15.3 g. (0.1 mole) of 3-chloromethylpyrazole hydrochloride in 100 ml. of absolute alcohol was added. The ice-bath was removed, and the mixture was stirred at room temperature for one hour after which most of the alcohol was removed by evaporation in vacuum on the steam-bath. The residue was taken into 400 ml. of 2 *N* hydrochloric acid, the solution was extracted with ethyl acetate to remove unreacted acetaminomalonic ester, and then the aqueous solution was made basic with sodium carbonate and extracted with ether. Evaporation of the dried ether solution left a glass which did not crystallize. It was heated on the steam-bath for five hours with 100 ml. of concentrated hydrochloric acid. The solution was evaporated, the residual glass was taken up in water, and the solution was freed of chloride ion with silver carbonate and hydrogen sulfide in the usual way. The resulting aqueous solution was evaporated to small volume and alcohol was added to precipitate 13 g. (84% yield) of 3-pyrazolealanine as a white crystalline powder, m. p. 226–228° dec.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.50; H, 6.38; N, 27.00.

Pyrazole.—A mixture of 220 g. (1 mole) of 1,1,3,3-tetraethoxypropane,[6] 105 g. (1 mole) of hydrazine dihydrochloride, 150 ml. of water and 100 ml. of alcohol was heated on the steam-bath for two hours. The solution was evaporated in vacuum to remove the alcohol. The brown residual sirup was taken up in 200 ml. of water, and 200 g. of sodium carbonate was added. The mixture was filtered and the salts were thoroughly washed with two 200-ml. portions of ether which were then used to extract the filtrate. The dried ether solution was evaporated and the residue was distilled in vacuum to yield 59–63 g. (87–93%) of very pure pyrazole; b. p. 95–97° (20 mm.); m. p. 70°.

1-Benzylpyrazole.—To a solution prepared by dissolving 14 g. (0.6 g. atom) of sodium in 500 ml. of absolute alcohol was added 34 g. (0.5 mole) of pyrazole. The solution was heated to gentle boiling under reflux and 150 g. (1.2 moles) of benzyl chloride was added slowly from a dropping funnel. After a few minutes the mixture had become neutral. It was filtered, and the filtrate was evaporated in vacuum to remove the alcohol. The residual liquid was poured into 100 ml. of 6 *N* hydrochloric acid. The aqueous layer was separated, washed with ether and then made basic with excess sodium hydroxide, cooled, and extracted with two 100-ml. portions of ether. After evaporation of the ether the residual 1-benzylpyrazole was distilled; b. p. 255–257° (750 mm.), 134–136° (15 mm.); $n^{25}D$ 1.5558; d^{25}_{25} 1.078. The yield was 62–68 g. (79–86%).

Anal. Calcd. for $C_{10}H_{10}N_2$: N, 17.71. Found: N, 17.59.

1-Benzylpyrazole failed to react with excess formalin. After heating the two together in a sealed tube at 120° for nine hours 95% of the 1-benzylpyrazole was recovered unchanged.

1-Benzyl-4-bromopyrazole.—A solution of 104 g. (0.65 mole) of 1-benzylpyrazole in 200 ml. of chloroform was cooled in an ice-bath and stirred well while 104 g. (0.65 mole) of bromine in 100 ml. of chloroform was slowly poured in. The chloroform solution was then shaken with excess aqueous sodium carbonate solution, dried over anhydrous sodium carbonate, and, after removal of the chloroform, the 1-benzyl-4-bromopyrazole was distilled in vacuum. It all came over at 169–170° (20 mm.) as a colorless liquid, which crystallized after cooling, m. p. 44–45°. The yield was 148–154 g. (94–98%).

Anal. Calcd. for $C_{10}H_9N_2Br$: N, 11.82. Found: N, 11.45.

1-Benzyl-4-cyanopyrazole.—A 200-ml. round-bottom flask was provided with a short Claisen head and wide-bore condenser set for distillation with a receiver attached to a vacuum line in such a way that the system could be immediately evacuated. In the flask was placed 23.7 g. (0.1 mole) of 1-benzyl-4-bromopyrazole and 13.4 g. (0.15 mole) of cuprous cyanide. The mixture was slowly and carefully heated with a soft flame and occasionally swirled until it had all melted. Local heating was avoided. As soon as the contents had become homogeneous the heating was stopped and the liquid was closely watched. Usually, at this point a slight bubbling of the liquid became evident indicating that an exothermic reaction had begun. If there was no evidence within about thirty seconds that the exothermic reaction was starting a little more heat was applied. At the first sign of spontaneous bubbling the vacuum of about 20 mm. was *immediately* applied being careful not to cause the material to bump over into the condenser. The mixture was then distilled as rapidly as possible at about 20 mm. using a flame until no more liquid

came over. The distillate of crude 1-benzyl-4-cyanopyrazole solidified upon cooling. The product was triturated with a little warm petroleum ether and then filtered and air-dried. The yield was 11–14 g. (60–76%). It was soluble in ether, alcohol, benzene or ethyl acetate, sparingly soluble in petroleum ether and insoluble in water. A sample for analysis was recrystallized from petroleum ether, m. p. 63–64°.

Anal. Calcd. for $C_{11}H_9N_3$: N, 22.21. Found: N, 22.33.

This experiment was carried out many times and it was possible to get satisfactory yields consistently. With larger-sized runs the yields were lower. If the distillation was begun as soon as the mixture had melted and before the exothermic reaction started then the distillate consisted mostly of unchanged 1-benzyl-4-bromopyrazole. However, it was essential to start the vacuum distillation just as soon as the exothermic reaction had become evident. On one or two occasions, a delay of only five or ten seconds resulted in the reaction getting out of control and leaving only charred decomposition products.

1-Benzyl-4-cyanopyrazole did not form a hydrochloride. A solution in ether was saturated with dry hydrogen chloride, but nothing precipitated. When the solution was evaporated pure, unchanged 1-benzyl-4-cyanopyrazole, m. p. 63–64°, remained.

1-Benzyl-4-pyrazolecarboxylic Acid.—1-Benzyl-4-cyanopyrazole was boiled with aqueous sodium hydroxide and alcohol until no more ammonia was evolved. The alcohol was removed by evaporation and the aqueous solution was acidified with hydrochloric acid to precipitate 1-benzyl-4-pyrazolecarboxylic acid in 94% yield. A sample was recrystallized from water containing a little alcohol, m. p. 151–152°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.88.

Ethyl 1-Benzyl-4-pyrazolecarboxylate.—A solution of 1-benzyl-4-pyrazolecarboxylic acid in ten parts of absolute alcohol was saturated with hydrogen chloride, refluxed for eighteen hours and then worked up in the usual way to give the ethyl ester in 94% yield. A sample recrystallized from petroleum ether melted at 62–63°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: N, 12.27.

1-Benzyl-4-aminomethylpyrazole Hydrochloride.—A solution of 5 g. of 1-benzyl-4-cyanopyrazole in 50 ml. of dry ether was added to a stirred solution of 1.5 g. of lithium aluminum hydride in 100 ml. of ether. After one-half hour, 10 ml. of water was added dropwise. The mixture was filtered, and the solid was washed by suspension in another 50 ml. of ether. The combined ether filtrate was dried and saturated with dry hydrogen chloride. Recrystallization of the resulting precipitate from absolute alcohol–ether gave 5.0 g. (72% yield) of the monohydrochloride, m. p. 232–233°.

Anal. Calcd. for $C_{11}H_{13}N_3 \cdot HCl$: N, 18.78; Cl, 15.85. Found: N, 18.94; Cl, 16.28.

4-Pyrazolecarboxylic Acid. (a) **Cleavage of 1-Benzyl-4-pyrazolecarboxylic Acid with Sodium in Liquid Ammonia.**—A suspension of 2.02 g. (0.01 mole) of 1-benzyl-4-pyrazolecarboxylic acid in 30 ml. of liquid ammonia was treated with sodium in small pieces until a permanent blue color was formed (0.5 g. of sodium). The ammonia was allowed to evaporate, and then the residue was taken up in 20 ml. of water. After the aqueous solution had been washed with ether it was acidified to *p*H 2 with hydrochloric acid to precipitate 0.89 g. (80% yield) of 4-pyrazolecarboxylic acid. A sample was recrystallized from water; m. p. 279–280° dec. (lit.[5] 275 dec.).

Anal. Calcd. for $C_4H_4N_2O_2$: N, 25.00. Found: N, 25.20.

(b) **Oxidation of 4-Methylpyrazole.**—4-Methyl-3-pyrazolecarboxylic acid was prepared in a yield of about 50% by the condensation of methyl crotonate with diazomethane, followed by oxidation of the intermediate pyrazoline with bromine and saponification of the ester according to the method of v. Pechmann and Burkard.[14] The acid was decarboxylated by heating, to give a 70% yield of 4-methylpyrazole,[4] b. p. 202–203° (730 mm.).

4-Methylpyrazole was oxidized with potassium permanganate in the same way as has been described for the oxidation of the corresponding 3-isomer.[12] The yield of 4-pyrazolecarboxylic acid was 50–53%, m. p. 278–279° dec.

Ethyl 4-Pyrazolecarboxylate.—4-Pyrazolecarboxylic acid was esterified with ethanol and sulfuric acid, and the yield of ethyl ester was 70%; b. p. 138–140° (3 mm.), m. p. 78–79° from petroleum ether–ethyl acetate mixture.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 19.99. Found: N, 20.18.

Methyl 4-Pyrazolecarboxylate.—This was prepared from the acid and diazomethane in methanol, m. p. 136–137°.

Anal. Calcd. for $C_5H_6N_2O_2$: N, 22.22. Found: N, 21.69.

1-Benzyl-4-hydroxymethylpyrazole.—A solution of 58 g. (0.25 mole) of ethyl 1-benzyl-4-pyrazolecarboxylate in 600 ml. of anhydrous ether was added dropwise to a solution of 15 g. of lithium aluminum hydride in 300 ml. of ether. After a few hours 50 ml. of water was added dropwise. The resulting mixture was filtered and the solid was extracted with three 400-ml. portions of hot methanol. The methanol and ether filtrates were evaporated in vacuum, the residue was extracted with three 200-ml. portions of dry ether, and the filtered ether solution was evaporated. Distillation of the residual liquid gave 43.5–45.3 g. (92–96% yield) of 1-benzyl-4-hydroxymethylpyrazole as a colorless, viscous liquid; b. p. 146–148° (0.2 mm.), $n^{25}D$ 1.5742, d^{25}_{25} 1.155.

Anal. Calcd. for $C_{11}H_{12}N_2O$: N, 14.89. Found: N, 14.60.

4-Hydroxymethylpyrazole. (a) **Reduction of Ethyl 4-Pyrazolecarboxylate with Lithium Aluminum Hydride.**—Ethyl 4-pyrazolecarboxylate was reduced with lithium aluminum hydride in ether and the mixture worked up in the manner described above for the corresponding ethyl 3-pyrazolecarboxylate. The 4-hydroxymethylpyrazole obtained in a yield of 86% was a solid, It was purified by dissolving in absolute alcohol, filtering and evaporating the solution, m. p. 120–122°. A sample was recrystallized from a mixture of absolute alcohol and chloroform, m. p. 126.5–127°. It was very soluble in water or alcohol, very sparingly soluble in chloroform and insoluble in ether.

Anal. Calcd. for $C_4H_6N_2O$: N, 28.56. Found: N, 28.25.

(b) **Cleavage of 1-Benzyl-4-hydroxymethylpyrazole with Sodium in Liquid Ammonia.**—To a solution of 9.4 g. (0.05 mole) of 1-benzyl-4-hydroxymethylpyrazole in 75 ml. of liquid ammonia was added small pieces of sodium (2.3 g.) until a permanent blue color was formed. Ammonium chloride, 6 g., was then added and the ammonia was allowed to evaporate. The residue was extracted with 300 ml. of hot acetone. The solution was filtered, evaporated to small volume, and 100 ml. of petroleum ether was added. There was thus obtained 4.5 g. (92% yield) of 4-hydroxymethylpyrazole; m. p. 125–126° and mixed with a sample prepared as described under (a), m. p. 126–127°. The picrate, recrystallized from water, melted at 149–150° dec.

1-Benzyl-4-(β-aminoethyl)-pyrazole.—Dry hydrogen chloride was passed into a mixture of 9.4 g. (0.05 mole) of 1-benzyl-4-hydroxymethylpyrazole and 75 ml. of anhydrous ether. The resulting oily hydrochloride could not be induced to crystallize. Therefore, the ether was removed by evaporation and 25 ml. of thionyl chloride was added. Reaction took place immediately. The resulting clear solution was warmed on the steam-bath for a short time, and then the excess thionyl chloride was evaporated in vacuum. The residual oily product, presumably 1-benzyl-4-chloromethylpyrazole hydrochloride, would not crystallize. It was readily soluble in absolute alcohol and was precipitated as an oil by the addition of dry ether.

(14) v. Pechmann and Burkard, *Ber.*, **33**, 3590 (1900).

A solution of the crude 1-benzyl-4-chloromethylpyrazole hydrochloride in 100 ml. of cold absolute alcohol was added to aqueous potassium cyanide and the mixture worked up as described above for the preparation of 3-cyanomethylpyrazole. The liquid reaction product distilled at 130–150° (0.2 mm.), and it proved to be a mixture containing the desired 1-benzyl-4-cyanomethylpyrazole together with 1-benzyl-4-ethoxymethylpyrazole (see below) which resulted from the reaction of the chloro compound with alcohol.

The liquid, 8.5 g., in 50 ml. of ether was added to a solution of 3 g. of lithium aluminum hydride in 200 ml. of ether. After this reaction mixture had been decomposed with 10 ml. of water it was filtered and the solid was extracted with three 200-ml. portions of ether. The liquid obtained after evaporation of the dried ether extract was distilled in vacuum, b. p. 110–140° (0.1 mm.). It weighed 6.2 g. This liquid was dissolved in 100 ml. of dry ether and the solution was saturated with carbon dioxide to precipitate a white, non-hygroscopic, crystalline solid. The product appeared to be the carbamate[7] formed by the reaction of one molecule of carbon dioxide with two molecules of 1-benzyl-4-(β-aminoethyl)-pyrazole. It melted with decomposition over the range 100–115°. The yield was 2.7 g. (24% based on 1-benzyl-4-hydroxymethylpyrazole).

Anal. Calcd. for $C_{25}H_{30}N_6O_2$: N, 18.83. Found: N, 18.65.

A solution of 2.0 g. of the carbamate in 20 ml. of absolute alcohol was saturated with dry hydrogen chloride; and after the addition of 30 ml. of dry ether, 2.3 g. (94% yield) of white, crystalline 1-benzyl-4-(β-aminoethyl)-pyrazole dihydrochloride separated, m. p. 177–179°. It was not hygroscopic. A sample was recrystallized from absolute alcohol, m. p. 179–180°.

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot 2HCl$: C, 52.56; H, 6.25; N, 15.33. Found: C, 52.45; H, 6.51; N, 15.42.

The ether filtrate from the above carbamate was evaporated and the residual liquid was distilled in vacuum. After a small forerun 2 g. of colorless liquid was obtained, b. p. 115–117° (0.1 mm.). This was believed to be 1-benzyl-4-ethoxymethylpyrazole.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96. Found: C, 71.94; H, 7.52; N, 13.31.

4-(β-Aminoethyl)-pyrazole.—To a suspension of 4.0 g. of the above carbamate of 1-benzyl-4-(β-aminoethyl)-pyrazole in 150 ml. of liquid ammonia was added small pieces of sodium until a permanent blue color was formed. This required 1.1 g. of sodium, and the reaction was very slow toward the end. After evaporation of the ammonia the residue was treated with 100 ml. of warm absolute alcohol, and the mixture was saturated with carbon dioxide and filtered. The filtrate was boiled for a few minutes, again filtered, then evaporated to dryness in vacuum. The residue, dissolved in 20 ml. of water, was added to a hot solution of 9 g. of picric acid in 150 ml. of water. The product which separated after cooling was recrystallized from 100 ml. of water to yield 8.1 g. (83%) of 4-(β-aminoethyl)-pyrazole dipicrate, m. p. 190–191°.

Anal. Calcd. for $C_{17}H_{15}N_9O_{14}$: N, 22.14. Found: N, 22.03.

The dipicrate, 7.0 g., was decomposed with hydrochloric acid and the reaction worked up as described above for the preparation of 3-(β-aminoethyl)-pyrazole dihydrochloride. There was thus obtained 1.72 g. (76% yield) of 4-(β-aminoethyl)-pyrazole dihydrochloride, m. p. 227–228°.

Anal. Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83. Found: N, 22.82.

It was only sparingly soluble in hot absolute alcohol and was not deliquescent.

1-Benzyl-4-pyrazolealanine.—An absolute alcohol solution of crude 1-benzyl-4-chloromethylpyrazole hydrochloride (prepared from 0.1 mole of 1-benzyl-4-hydroxymethylpyrazole) was caused to react with sodium acetaminomalonic ester. The reaction was carried out and worked up as described above for the preparation of 3-pyrazolealanine except that the evaporated mixture was treated with 6 *N* instead of 2 *N* hydrochloric acid. The 1-benzyl-4-pyrazolealanine was rather sparingly soluble in water and, therefore, the precipitate formed by the addition of silver carbonate to the hydrochloride solution was washed several times with hot water before the treatment of the filtrate with hydrogen sulfide. There was obtained 5.4 g. (22%) of 1-benzyl-4-pyrazolealanine, m. p. 243–244° dec.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: N, 17.13. Found: N, 16.93.

4-Pyrazolealanine.—1-Benzyl-4-pyrazolealanine, 1.0 g. (0.004 mole), in 50 ml. of liquid ammonia was treated with small pieces of sodium until a permanent blue color was formed (0.30 g. sodium). Then 0.70 g. (0.013 mole) of ammonium chloride was added. After the ammonia had evaporated the residue was taken up in 25 ml. of hot water and to the solution was added 5 g. of mercuric acetate dissolved in 25 ml. of water. The resulting white precipitate was thoroughly washed by suspension in two 50-ml. portions of fresh water, and then it was suspended in 100 ml. of water and hydrogen sulfide was bubbled in until the mixture was saturated. The precipitate of mercuric sulfide was separated by filtration, and the filtrate was evaporated in vacuum to a sirup. This was taken up in 50 ml. of absolute alcohol and 100 ml. of dry ether was added, whereupon a white crystalline precipitate separated which proved to be a mixture of the mono- and dihydrochlorides of 4-pyrazolealanine, m. p. 235–236° dec. The yield was 0.60 g. (72%).

Anal. Calcd. for $C_6H_9N_3O_2 \cdot 1.44HCl$: C, 34.6; H, 5.1; N, 20.4; Cl, 24.7. Found: C, 34.2; H, 5.2; N, 21.0; Cl, 24.0.

The above hydrochloride, 0.40 g. (0.0019 mole) was dissolved in 25 ml. of water and 0.40 g. (one equivalent) of silver carbonate was added. The mixture was digested on the steam-bath for one hour, filtered, and the filtrate was saturated with hydrogen sulfide. The solution was clarified with carbon, filtered and evaporated to dryness in vacuum leaving 0.25 g. (80% yield) of white crystalline 4-pyrazolealanine. It was insoluble in alcohol and only sparingly soluble in water. A solution of the product in 4 ml. of hot water was filtered and the filtrate diluted with 8 ml. of alcohol to precipitate 0.15 g. of pure 4-pyrazolealanine, m. p. 304–306° dec.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.23; H, 6.17; N, 26.81.

4-Cyanomethylpyrazole.—To 50 ml. of thionyl chloride was added 13 g. of powdered 4-hydroxymethylpyrazole. A vigorous reaction took place, but the resulting product, presumably 4-chloromethylpyrazole hydrochloride, was insoluble in the thionyl chloride. The excess thionyl chloride was evaporated in vacuum and the solid was washed with dry ether. It was extremely hygroscopic and no satisfactory analysis was obtained. A sample, dissolved in ice-water, appeared to be quickly hydrolyzed to form 4-hydroxymethylpyrazole which was obtained after evaporation of the water solution and identified by melting point and mixed melting point.

A cold absolute alcohol solution of the crude 4-chloromethylpyrazole hydrochloride was allowed to react with potassium cyanide and the reaction was worked up as described for the preparation of 3-cyanomethylpyrazole. There was obtained 4.0 g. (28% yield) of crude 4-cyanomethylpyrazole, b. p. 125–130° (0.2 mm.) which crystallized after cooling, m. p. 73–77°. A sample was recrystallized from a mixture of chloroform–petroleum ether and then from benzene–petroleum ether, m. p. 83–84°.

Anal. Calcd. for $C_6H_5N_3$: N, 39.23. Found: N, 38.68.

5-(β-Carboxyethyl)-3-pyrazolecarboxylic Acid and its Diethyl Ester.—Diethyl α,γ-diketopimelate, b. p. 183–185° (14 mm.), was prepared in 27% yield from ethyl levulinate and diethyl oxalate according to the procedure of Wislicenus.[8]

To a solution of 61 g. (0.25 mole) of the above diketo ester in 200 ml. of methanol was added 12.5 g. (0.25 mole) of 100% hydrazine hydrate. Heat was evolved, and the solution boiled spontaneously. After removal of the methanol the ethyl 5-(β-carbethoxyethyl)-3-pyrazolecarboxylate was distilled in vacuum to yield 56 g. (93.5%) of viscous colorless liquid which soon crystallized; b. p. 180° (0.5 mm.), m. p. 70–72°. A sample was recrystallized from petroleum ether, m. p. 72–73°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: N, 11.66. Found: N, 12.17.

The above ester, 55 g., was saponified with sodium hydroxide solution and the 5-(β-carboxyethyl)-3-pyrazolecarboxylic acid was precipitated with hydrochloric acid. The yield was 42.5 g. (100%). A sample, recrystallized from water, melted at 243–244° dec.

Anal. Calcd. for $C_7H_8N_2O_4$: N, 15.23. Found: N, 15.15.

A sample of the acid was sublimed twice in vacuum at a temperature of about 200–230°. It remained unchanged, m. p. 243–244° dec.

Anal. Calcd. for $C_7H_8N_2O_4$: neut. equiv., 92.08. Found: neut. equiv., 93.57.

A sample of the acid was boiled for several hours in quinoline and another sample was boiled in glacial acetic acid. In neither case was there any evidence of decarboxylation.

Acknowledgment.—The author is indebted to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here, and to Frank Streightoff and Dr. H. M. Lee for the biological tests.

Summary

3-Pyrazolealanine, 3-β-aminoethylpyrazole, 4-pyrazolealanine and 4-β-aminoethylpyrazole have been synthesized.

These pyrazole compounds appear to have no significant biological activity.

INDIANAPOLIS, INDIANA RECEIVED JUNE 2, 1949

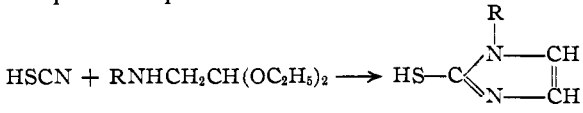
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazoles. IV.[1] The Synthesis and Antithyroid Activity of Some 1-Substituted-2-mercaptoimidazoles

BY REUBEN G. JONES, EDMUND C. KORNFELD, KEITH C. MCLAUGHLIN AND ROBERT C. ANDERSON

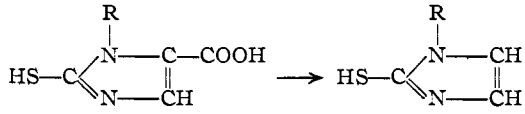
A large amount of synthetic work on antithyroid drugs appears to have been directed toward the preparation of 2-thiouracil types.[2] However, in 1945, Astwood[3] showed that 2-mercaptoimidazole had antithyroid activity about one and one-half times that of thiouracil when tested in rats. In connection with other work a number of 1-substituted-2-mercaptoimidazoles became available, and it appeared to be worthwhile to prepare others of this series and submit them to pharmacological testing.

Easson and Pyman have described a general method of preparing 1-substituted-2-mercaptoimidazoles by the reaction of primary amines with acetalylisothiocyanate.[4] Earlier, Marckwald and others had synthesized compounds of this type from isothiocyanates and aminoacetal.[5] The reaction of thiocyanic acid with N-substituted aminoacetals has proved to be a most useful method for obtaining the greater number of the compounds reported in Table I.



This is designated as method A in the table. The requisite N-substituted aminoacetals were readily prepared by heating chloro- or bromoacetal with primary amines.

Another satisfactory method (B) of synthesizing some of the compounds of Table I consisted of the decarboxylation of 1-substituted 2-mercapto-5-imidazolecarboxylic acids.



The acids were heated to about 250° at which temperature the decarboxylation was rapid, and the yields of the desired products were practically quantitative. Surprisingly the resulting 2-mercaptoimidazoles, in the absence of air, appeared to be quite stable at these elevated temperatures.

The antithyroid activities of a number of the compounds of Table I as determined by the rat test[6] are recorded in the last column. Although 2-mercaptoimidazole appears to be somewhat less active in rats than is propylthiouracil, Astwood has recently found[7] that in man 2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole are much more active.

In addition to the compounds of Table I, three related members were synthesized (see Experimental) and tested. These together with their activities were: 4(or 5)-methyl-2-mercaptoimidazole,[8] 0.05; 4(or 5)-ethyl-2-mercaptoimidazole, 0.1; and 1-methyl-5-ethyl-2-mercaptoimidazole, 0.5. After the completion of this work

(1) For the preceding paper of this series see THIS JOURNAL, **71**, 2444 (1949).

(2) (a) Anderson, Halverstadt, Miller and Roblin, *ibid.*, **67**, 2197 (1945); (b) Jackman, Bergman and Archer, *ibid.*, **70**, 497 (1948); (c) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948).

(3) Astwood, Bissell and Hughes, *Endocrinology*, **37**, 456 (1945).

(4) Easson and Pyman, *J. Chem. Soc.*, 1806 (1932).

(5) (a) Marckwald, *Ber.*, **25**, 2354 (1892); (b) Wohl and Marckwald, *ibid.*, **22**, 568, 1353 (1889).

(6) Astwood, *J. Pharmacol.*, **78**, 79 (1943).

(7) Stanley and Astwood, *Endocrinology*, **44**, 588 (1949).

(8) Gabriel and Pinkus, *Ber.*, **26**, 2203 (1893).