The extension of these improvements to aliphatic ketoximes is in progress.

Experimental

The preparation of the alicyclic ketoximes has been described.[2] Eastman practical quality N-bromosuccinimide was used. Sodium borohydride was procured from Metal Hydrides, Inc. The preparation of 1-bromo-1-nitrocyclohexane and nitrocyclohexane are representative of the methods used. Physical constants and analyses of the compounds prepared have been tabulated previously.[2]

Preparation of 1-Bromo-1-nitrocyclohexane by the NBS Procedure.—A solution was prepared by mixing 11.3 g. (0.1 mole) of cyclohexanone oxime[9] with 25.3 g. (0.3 mole) of sodium bicarbonate in 150 ml. of water. This solution was added as rapidly as possible to a vigorously stirred suspension of 54.5 g. (0.30 mole) of N-bromosuccinimide in 150 ml. of water cooled to 10° with an ice-bath. The addition required *ca.* 15 min. and the temperature remained about 10°. Stirring was continued an additional 15 min. The reaction product was extracted by stirring with four 50-ml. portions of 35–37° petroleum ether and each decanted from the aqueous solution and suspended solids. The combined extracts (lachrymatory) were concentrated by distillation until about 30–50 ml. of blue solution remained.[10] This solution was shaken with *ca.* 100 ml. of nitric acid (sp. gr. 1.42) until free of the blue color. After dilution with about 100 ml. of water the organic material was extracted with 35–37° petroleum ether. The extract was washed successively with water, 5% aqueous sodium hydroxide and water. After drying over anhydrous sodium sulfate and concentration of the extract, the 1-bromo-1-nitrocyclohexane was distilled, 7.9 g., b.p. 116–117° at 20 mm.

Preparation of Nitrocyclohexane. A. Methanol–Potassium Hydroxide Procedure.—A solution was prepared from 9.0 g. (0.043 mole) of 1-bromo-1-nitrocyclohexane and 30 ml. of methanol. This was mixed with 21.6 g. (0.13 mole) of potassium iodide and refluxed for 24 hours. The reaction mixture was cooled and the iodine formed was reduced with concentrated sodium bisulfite solution. The solution was made distinctly alkaline by adding dilute potassium hydroxide[11] and was then carefully extracted with petroleum ether. The aqueous portion was acidified with 15% aqueous hydroxylamine hydrochloride and after the nitro compound separated it was collected with the aid of petroleum ether. The petroleum ether solution was washed with 85% phosphoric acid and water. After drying over anhydrous sodium sulfate and concentration, the nitrocyclohexane was distilled, 2.7 g., b.p. 108–110° at 40 mm.

B. Sodium Borohydride Procedure.—A solution of 5.20 g. (0.135 mole) of sodium borohydride was prepared in 100 ml. of 75% (volume) aqueous methanol. This solution was contained in a 500-ml. three-neck flask equipped with a high speed Hershberg stirrer with a mercury seal, a reflux condenser and an addition funnel containing 6.24 g. (0.03 mole) of 1-bromo-1-nitrocyclohexane. A few drops of the bromonitro compound were added to the sodium borohydride solution. The reaction started slowly and occasionally required external heating. Only after the reaction had started (rapid evolution of gas) and the solvent was at reflux temperature, the remainder of the bromonitro compound was added as rapidly as possible. After completion of the reduction, aqueous potassium hydroxide was added if the mixture was not already strongly alkaline and the methanol was then separated by steam distillation. The nitrocycloalkane was isolated from the remaining aqueous solution by acidification with 15% aqueous hydroxylamine hydrochloride and extracted with petroleum ether. The extract was treated as in part A to yield 3.1 g. of nitrocyclohexane, b.p. 109–110° at 40 mm.

(9) Whenever solution was not complete the resulting suspension was used or as in the case of the methylcyclohexanone oximes and cycloheptanone oxime, dioxane was added to increase the solubility.

(10) At this point *ca.* 1.5 g. of white bromonitroso dimer separated in the preparation of bromonitrocyclobutane. This solid decomposed when heated to 80° and dissolved in dioxane, methanol or chloroform yielding intensely blue solutions.

(11) It should be emphasized that adequate time must be allowed for the reaction of the nitro compound with base and the regeneration of the nitro compound from the salt. The reaction of 2-nitro-1-methylcyclohexane was particularly slow even when considerable excess base was used. On the other hand nitrocyclobutane, while insoluble in water, very interestingly dissolves rapidly in dilute aqueous alkali to form the non-extractable salt.

MORGANTOWN, W. VA.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

New Methods of Synthesis of β-Aminoethylpyrazoles

BY REUBEN G. JONES AND MARJORIE J. MANN

RECEIVED APRIL 13, 1953

Some new methods of synthesis and some improvements in the known methods of preparation of the powerful gastric secretory stimulants, 3-β-aminoethylpyrazole (I) and 4-β-aminoethylpyrazole (II), are described. A key intermediate, 3-hydroxymethylpyrazole, has been made by lithium aluminum hydride reduction of *n*-butyl 3-pyrazolecarboxylate and also by condensation, under acidic conditions, of hydrazine with the acetylene compounds, 4,4-diethoxy-2-butyne-1-ol and 2-(4′,4′-diethoxy-2′-butynyl)-oxytetrahydropyrane. 3-β-Aminoethylpyrazole was prepared by catalytic hydrogenation of 3-pyrazoleacetaldehyde hydrazone which, in turn, was obtained quantitatively by the reaction of hydrazine with γ-pyrone. 4-β-Aminoethylpyrazole was prepared from 4-β-hydroxyethylpyrazole which was obtained by the reaction of hydrazine with 2-ethoxy-3-tetrahydrofuranaldehyde diethyl acetal. A new method of preparation of ethyl 4-pyrazolecarboxylate and a number of related new pyrazole derivatives are described.

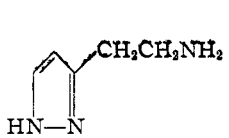
A preceding paper from this Laboratory described the preparation of 3-β-aminoethylpyrazole (I) and 4-β-aminoethylpyrazole (II).[1] These analogs of histamine were tested for their physiological activity and were found to have practically no effect on guinea pig ileum strips or on cat's blood pressure,[2] and were stated to have no other observable physiological activities.[1] Subsequently, they were tested for their effect on gastric secretion and surprisingly were found to possess high stimulatory activity on acid secretion in animals and man.[3] 3-β-Aminoethylpyrazole (I) is particularly interesting in that on a weight basis it is about one-seventieth as active as histamine in stimulating gastric acid secretion[3a] but only very slightly active in causing smooth muscle contractions, and it has no inflammatory action on the skin.[4] Thus, in effect, it possesses only one of the actions of histamine (*i.e.*, stimulation of gastric secretion) and none of the others.

(1) R. G. Jones, THIS JOURNAL, **71**, 3994 (1949).

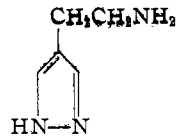
(2) H. M. Lee and R. G. Jones, *J. Pharmacol.*, **95**, 71 (1949).

(3) (a) C. E. Rosiere and M. I. Grossman, *Science*, **113**, 651 (1951); (b) private communication from Dr. M. I. Grossman.

(4) 3-β-Aminoethylpyrazole is relatively non-toxic (LD_{50} in mice is about 800 mg./kg. i.v.), and it has been used clinically.

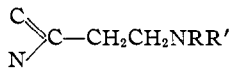


I

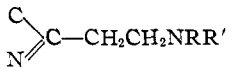


II

4-β-Aminoethylpyrazole (II) also stimulates gastric acid secretion but to a lesser degree than I. It is about one-half as active as I in this respect.[3b] The hypothesis has been advanced that one of the minimum requirements for histamine-like activity of an organic compound is the presence of the structure III or IV within the molecule.[2] This hypothesis must now be modified, since II does not contain either of these structures.



III

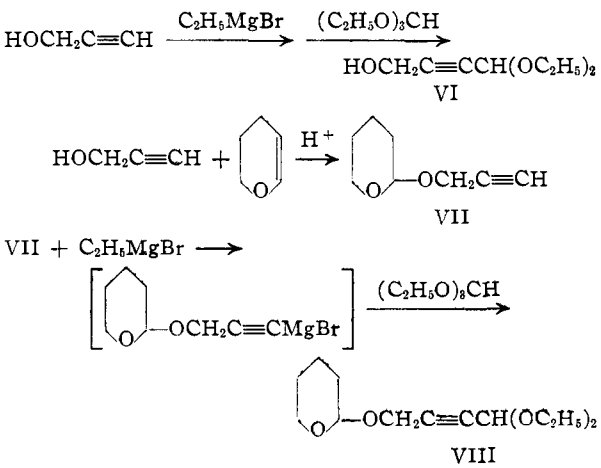


IV

In view of the interesting physiological activities of I and II, it has become of importance to investigate more fully methods for their preparation. This paper describes some new methods of preparing I and II and some improvements and alternative steps in the previously described synthesis.

One of the key intermediates in the reported method of preparation of I was 3-hydroxymethylpyrazole (V).[1] This was obtained by reaction of diazomethane with propargyl alcohol and more conveniently, by reduction of ethyl 3-pyrazolecarboxylate with lithium aluminum hydride. Further experience has shown that *n*-butyl 3-pyrazolecarboxylate, because of its high solubility in ether, is better suited than the ethyl ester for reduction with lithium aluminum hydride.

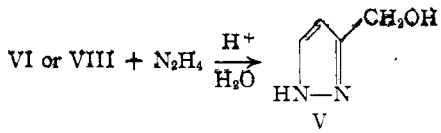
Another synthetic route to V was developed wherein propargyl alcohol was converted *via* the magnesium derivative to 4,4-diethoxy-2-butyne-1-ol (VI). Condensation of VI with hydrazine hydrochloride gave V. The yields in this sequence, however, were low, and it was found that better results could be obtained by first covering the hydroxyl function of propargyl alcohol by reaction with dihydropyrane. Thus, 2-propargyloxytetrahydropyrane (VII) was prepared in yields of over 90%. Reaction of VII with ethylmagnesium bromide followed by ethyl orthoformate gave 2-(4′,4′-diethoxy-2′-butynyl)-oxytetrahydropyrane (VIII) in 70% yield.



VI

VII

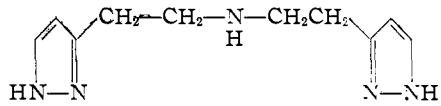
VIII



V

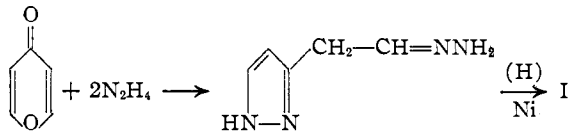
The condensation of VIII with hydrazine hydrochloride in aqueous alcohol gave V in a yield of 57%.

Reduction of 3-cyanomethylpyrazole[1] by hydrogenation under high pressure with Raney nickel catalyst has given I in moderate yields together with an appreciable quantity of the secondary amine, bis-β-(3-pyrazolyl)-ethylamine (IX). Compound IX in relatively large doses has a prolonged stimulatory effect on gastric acid secretion.[3b]



IX

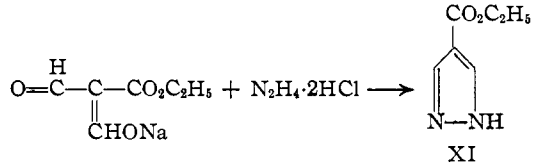
A more direct synthesis of 3-β-aminoethylpyrazole (I) was devised which involved only two steps. The first reaction was between hydrazine and γ-pyrone. This took place readily when the reagents were mixed in alcohol solution, and 3-pyrazoleacetaldehyde hydrazone (X) was formed in practically quantitative yields. Catalytic hydrogenation of X led to I in 80% yield.



X

Reactions of this type between hydrazines and γ-pyrones to yield pyrazoles appear to be quite general and will be discussed in detail in a subsequent paper.

One of the chief problems in the synthesis of 4-β-aminoethylpyrazole (II)[1] was in obtaining simple starting compounds such as 4-pyrazolecarboxylic acid. It has now been found that ethyl 4-pyrazolecarboxylate (XI) can be prepared readily by the condensation of hydrazine hydrochloride with the sodium salt of ethyl diformylacetate. The latter was obtained by a Claisen condensation of ethyl formate with ethyl β,β-diethoxypropionate.[5]



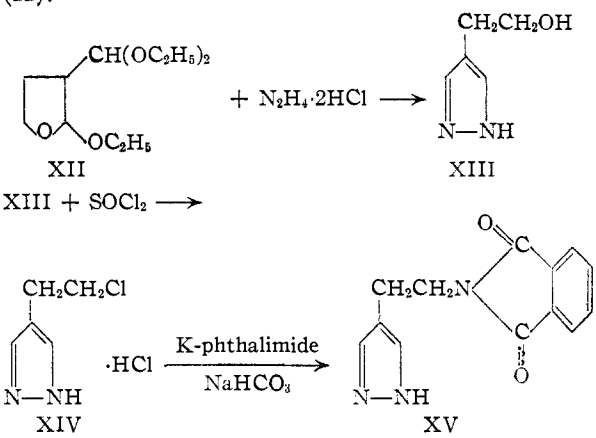
XI

A new synthetic route to II also has been worked out. The starting material for this series of reactions was 2-ethoxy-3-tetrahydrofuranaldehyde diethyl acetal (XII).[6] Condensation of XII with hydrazine hydrochloride gave 4-β-hydroxyethylpyrazole (XIII) in excellent yields. Reaction of XIII with thionyl chloride readily gave the β-chloroethyl compound, XIV, which was allowed to

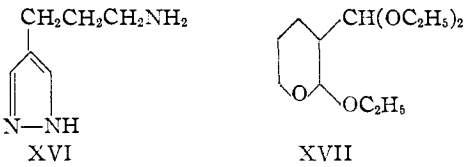
(5) E. Dyer and T. B. Johnson, THIS JOURNAL, **56**, 222 (1934).

(6) (a) J. W. Copenhaver, U. S. Patent 2,517,543 [*C. A.*, **45**, 1166 (1951)]; (b) this sample was kindly supplied by the Organic Research Laboratory of General Aniline and Film Corporation.

react with potassium phthalimide in hot dimethylformamide solution to form 4-β-phthalimidoethylpyrazole (XV). Hydrolysis of XV with hydrochloric acid gave the desired 4-β-aminoethylpyrazole (II).



The next higher homolog of II, 4-γ-aminopropylpyrazole (XVI), was prepared by a series of reactions similar to the above, starting from the easily available 2-ethoxy-3-tetrahydropyranealdehyde diethyl acetal[6a] (XVII).



During the course of the present work 3- and 4-pyrazoleacetic acids, and a number of their derivatives were synthesized.

Experimental

n-Butyl 3-Pyrazolecarboxylate.—A mixture of 500 g. of crude air-dried 3-pyrazolecarboxylic acid,[7] 1500 ml. of butanol and 100 ml. of concentrated sulfuric acid was heated on the steam-bath for six hours. Most of the butanol was removed by evaporation under reduced pressure on the steam-bath. The residual liquid was treated with 2 l. of ice-water and an excess of sodium carbonate was added. The oil which separated quickly crystallized. It was taken into ether, the solution was separated, dried with magnesium sulfate and the ether evaporated leaving 530 g. (70% yield) of ester; m.p. 67.5–68°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: N, 16.67. Found: N, 16.35.

Reduction of *n*-butyl 3-pyrazolecarboxylate with lithium aluminum hydride in ether gave 3-hydroxymethylpyrazole[1] in 84% yield.

4,4-Diethoxy-2-butyne-1-ol (VI).—A Grignard solution was prepared in the usual way from 96 g. (4 g. atoms) of magnesium and 475 g. of ethyl bromide in 1 l. of ether. To this solution was added dropwise with stirring 100 g. (1.75 moles) of propargyl alcohol. The addition required several hours. To the resulting viscous solution was added in one portion, 300 g. (2.0 moles) of freshly distilled ethyl orthoformate. The mixture was stirred, but it soon became very viscous and set to a white crystalline mass with gentle heat evolution. Over a period of two days at room temperature this changed to a dark resinous mass with a supernatant ether layer. The whole was heated on the steam-bath for 20 hours during which time the ether evaporated leaving a spongy glass-like solid. This was broken up with a long spatula, removed from the flask, and added to 2 l. of ice-water containing 500 g. of ammonium acetate. The mixture was well stirred and shaken with 1 l. of ether. An emulsion was formed which was broken by filtering through a pad of Filter-cel on a large buchner funnel. The filtrate and solid on the funnel were extracted with four 500-ml. portions of ether. After drying over magnesium sulfate, the ether was evaporated and the residual liquid distilled under reduced pressure. Following a forerun of ethanol propargyl alcohol and ethyl orthoformate, about 75 g. of liquid was collected at 130–150° (14 mm.). Upon redistillation this yielded 63 g. (23%) of 4,4-diethoxy-2-butyne-1-ol, b.p. 118–122° (9 mm.). A sample for analysis was redistilled; b.p. 88° (0.5 mm.), $n^{25}D$ 1.4495, d^{25}_{25} 1.004.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.73; H, 8.92. Found: C, 60.48; H, 9.02.

3-Hydroxymethylpyrazole from 4,4-Diethoxy-2-butyne-1-ol.—To a solution of 28 g. (0.177 mole) of 4,4-diethoxy-2-butyne-1-ol in 100 ml. of water was added 25 g. (0.24 mole) of hydrazine dihydrochloride. An exothermic reaction took place, and the solution turned very dark brown. After standing overnight, the solution was treated with 35 g. of sodium carbonate, added in small portions, and evaporated to dryness under reduced pressure on the steam-bath. The residue was extracted with three 50-ml. portions of absolute ethanol. Evaporation of this extract left a brown sirup which was distilled under reduced pressure to yield 7 g. (40%) of 3-hydroxymethylpyrazole as a colorless viscous liquid, b.p. 130–150° (0.5 mm.). Decomposition occurred throughout the distillation, and a large quantity of black resin remained in the flask. The crude 3-hydroxymethylpyrazole was converted to the picrate,[1] which was obtained in a yield of 18 g. (30%); m.p. 181–182°. The melting point was not depressed when mixed with an authentic sample.

2-Propargyloxytetrahydropyrane (VII).—To 268 g. (3.2 moles) of freshly distilled dihydropyrane in a 500-ml. flask, provided with a stirrer, was added 0.5 ml. of concentrated hydrochloric acid. With stirring 168 g. (3 moles) of propargyl alcohol was added in small portions during one-half hour. Heat was evolved and the temperature went up to 60° where it was held by occasionally cooling in an ice-bath. After two hours the solution was placed in a separatory funnel, washed with saturated sodium carbonate solution, dried over sodium carbonate and distilled under reduced pressure to yield 390 g. (93%) of 2-propargyloxytetrahydropyrane; b.p. 63–65° (9 mm.), $n^{25}D$ 1.4523, d^{25}_{25} 0.9965.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.80.

The 2-(4′,4′-Diethoxy-2′-butynyl)-oxytetrahydropyrane (VIII).—A Grignard solution was prepared from 72 g. (3 g. atoms) of magnesium and 350 g. of ethyl bromide in 1500 ml. of ether. To it was added with stirring over a period of two hours 350 g. (2.5 moles) of 2-propargyloxytetrahydropyrane. During this addition the reflux condenser was removed and the ether was allowed to distil. To the resulting very viscous gray mass was added 500 ml. of dry benzene, and the mixture was occasionally stirred and allowed to stand for two hours. With stirring 450 g. (3 moles) of ethyl orthoformate was added in one portion. The mixture was agitated for one hour and then heated on the steam-bath. As soon as there was evidence of an exothermic reaction, the flask was removed from the steam-bath, and the mixture was stirred. It became less viscous and turned dark brown as the reaction proceeded. Once it was necessary to cool the reaction to keep the benzene from boiling. When the exothermic reaction was over, after about one hour, the mixture was heated for 15 minutes, cooled, and poured into 2 l. of ice-water. Another 500 ml. of water was used to rinse the flask. To the mixture was added 500 g. of ammonium acetate. After standing overnight in a large separatory funnel, the mixture had separated into a water layer with an emulsion on top. The emulsion was filtered through a thick pad of Filter-cel. The non-aqueous layer of the filtrate was separated, washed with sodium carbonate solution, dried with magnesium sulfate and distilled under reduced pressure. After the benzene and lower boiling fraction had been removed, 415 g. (70% yield) of 2-(4′,4′-diethoxy-2′-butynyl)-oxytetrahydropyrane was collected at 120–130° (0.5 mm.). A portion was redistilled and a fraction boiling at 115° (0.1 mm.) was taken for analysis; $n^{25}D$ 1.4570, d^{25}_{25} 1.025.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15. Found: C, 64.20; H, 9.26.

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

3-Hydroxymethylpyrazole from 2-(4′,4′-Diethoxy-2′-butynyl)-oxytetrahydropyrane.—To a solution of 200 g. (1.9 moles) of hydrazine dihydrochloride in 1 l. of water was added 1 l. of alcohol. With shaking, 415 g. (1.7 moles) of 2-(4′,4′-diethoxy-2′-butynyl)-oxytetrahydropyrane was added in portions during one-half hour. A little heat was evolved and the mixture was cooled briefly to keep the temperature below 40°. After standing overnight, the dark brown solution was treated with 150 g. of sodium carbonate, and evaporated under reduced pressure on the steam-bath. The residue was extracted with three 500-ml. portions of absolute alcohol. The alcohol solution was evaporated and the residual brown sirup was divided into four equal portions. Each portion was distilled under reduced pressure (about 1 mm.) until nothing more would distil over. The combined distillates were redistilled to yield 95 g. (57%) of 3-hydroxymethylpyrazole, b.p. 135–140° (0.5 mm.). A sample was converted to the picrate which melted at 182–183° and did not depress the melting point of authentic 3-hydroxymethylpyrazole picrate.[1]

Catalytic Hydrogenation of 3-Cyanomethylpyrazole.—In a one-liter hydrogenation bomb was placed 400 ml. of methanol containing 60 g. of ammonia, 20 g. of Raney nickel catalyst and 50 g. of 3-cyanomethylpyrazole.[1] The bomb was charged with hydrogen to 2000 lb. pressure and agitated at room temperature. Hydrogen uptake was very slow. After three hours the bomb was heated to 75°. The absorption of hydrogen was more rapid, and the reduction appeared to be complete within three hours. The bomb was opened, and after removal of the catalyst and evaporation of the solvent, the residual liquid was distilled under reduced pressure. There was obtained 30 g. (60% yield) of 3-β-aminoethylpyrazole as a viscous, colorless liquid; b.p. 120–130° (0.5 mm.). It was converted to the dihydrochloride,[1] m.p. 224–227°, by solution in absolute ethanol and treatment with dry hydrogen chloride.

Bis-β-(3-pyrazolyl)-ethylamine (IX).—After the 3-β-aminoethylpyrazole fraction in the above described distillation had passed over, the temperature went up rapidly to 220° and an extremely viscous liquid came over at 220–230° (0.5 mm.). This compound, bis-β-(3-pyrazolyl)-ethylamine, had the appearance and consistency of stiff honey. The yield was 13 g. (26%). It was readily soluble in water and formed a sparingly soluble tripicrate; m.p. 112–114°.

Anal. Calcd. for $C_{28}H_{24}N_{14}O_{21}$: C, 37.70; H, 2.69; N, 21.95. Found: C, 37.77; H, 3.09; N, 21.89.

The picrate was converted[1] to the trihydrochloride which was obtained as white crystalline powder, soluble in water but insoluble in hot absolute alcohol; m.p. 213–214° dec.

Anal. Calcd. for $C_{10}H_{15}N_5 \cdot 3HCl$: N, 22.20. Found: N, 21.68.

3-Pyrazoleacetaldehyde Hydrazone (X).—A solution of 4.8 g. (0.05 mole) of γ-pyrone[8] in 10 ml. of methanol was added in portions with shaking to a cold solution of 10 g. (0.2 mole) of hydrazine hydrate in 10 ml. of methanol. An exothermic reaction took place. The resulting solution was warmed on the steam-bath for 10 minutes and then evaporated under reduced pressure. The viscous residue crystallized after standing for several days at room temperature; yield, quantitative. The white solid was readily soluble in water. It could not be successfully recrystallized from alcohol. Eventually it was found that the compound could be recrystallized well from anhydrous hydrazine[9] from which it separated as a white powder. It was washed with a little absolute ethanol followed by dry ether; m.p. 122–123°.

Anal. Calcd. for $C_5H_8N_4$: C, 48.38; H, 6.45; N, 45.20. Found: C, 48.41; H, 6.74; N, 45.00.

A 0.25-g. sample of the compound was oxidized with 1.26 g. of potassium permanganate in 20 ml. of water. The manganese dioxide was removed by filtration and the filtrate acidified to *p*H 2 with hydrochloric acid. The solution was evaporated to dryness and the residue extracted with acetone. Evaporation of the acetone left 3-pyrazolecarboxylic acid; m.p. 216–217° dec. The melting point was not depressed when mixed with an authentic sample.[7]

3-β-Aminoethylpyrazole.—The 3-pyrazoleacetaldehyde hydrazone in alcohol solution was hydrogenated under 40 lb. pressure with a platinum catalyst, and 3-β-aminoethylpyrazole was isolated in 40% yield as the dihydrochloride. A better preparative procedure, however, was as follows:

To a solution of 55 g. (1.1 moles) of hydrazine hydrate in 100 ml. of methanol was added dropwise with stirring a solution of 48 g. (0.5 mole) of γ-pyrone in 100 ml. of methanol. The temperature was maintained at about 25° by cooling. After the exothermic reaction was over, the solution was warmed on the steam-bath for a few minutes. It was then cooled and 25 ml. of liquid ammonia was added cautiously, with stirring. Immediately the solution was placed in a hydrogenation autoclave together with a liberal quantity (about 20 g.) of Raney nickel catalyst, and hydrogenated under 1500 lb. pressure at 90°. The hydrogenation was complete after one or two hours. After removal of the catalyst and evaporation of the methanol, the amine was distilled under reduced pressure and obtained as a colorless viscous liquid, b.p. 118–123° (0.5 mm.). The yield was 44.5 g. (81%). It was converted to the dihydrochloride with dry hydrogen chloride in ethanol. This melted at 224–226° and the melting point was not depressed when mixed with an authentic sample.

Anal. Calcd. for $C_5H_9N_3$: N, 22.82. Found: N, 22.66.

4-β-Hydroxyethylpyrazole (XIII).—To a solution of 20 g. (0.19 mole) of hydrazine dihydrochloride in 50 ml. of water was added 25 ml. of alcohol and 32 g. (0.15 mole) of 2-ethoxy-3-tetrahydrofuranaldehyde diethyl acetal.[6] Heat was evolved and the mixture was cooled in an ice-bath. After a few minutes the reaction was complete. The solution was treated with 30 g. of sodium carbonate added in small portions. The mixture was evaporated under reduced pressure to dryness, and the residue was extracted with three 50-ml. portions of absolute ethanol. Evaporation of the ethanol extracts left a liquid residue which was distilled; b.p. 140–145° (0.3 mm.). After standing it crystallized; m.p. 54–55°. The yield was 15.2 g. (92%).

Anal. Calcd. for $C_5H_8N_2O$: C, 53.55; H, 7.19. Found: C, 53.29; H, 7.21.

4-β-Chloroethylpyrazole Hydrochloride (XIV).—To 25 ml. of thionyl chloride in a small round-bottom flask was added in portions 10.1 g. (0.09 mole) of 4-β-hydroxyethylpyrazole. The resulting solution was heated on the steam-bath for a few minutes after which the excess thionyl chloride was evaporated under reduced pressure. The crystalline residue was dissolved in 50 ml. of hot absolute ethanol, and this solution was diluted with 200 ml. of dry ether. The white crystalline precipitate was collected and air dried. It weighed 14.3 g. which is a 95% yield; m.p. 129–130°.

Anal. Calcd. for $C_5H_7N_2Cl \cdot HCl$: N, 16.70. Found: N, 16.27.

4-β-Phthalimidoethylpyrazole (XV).—A mixture of 14.0 g. (0.084 mole) of 4-β-chloroethylpyrazole hydrochloride and 15.7 g. (0.085 mole) of powdered potassium phthalimide in 100 ml. of dimethylformamide was treated with 7.2 g. (0.085 mole) of sodium bicarbonate. After the evolution of carbon dioxide subsided, the mixture was heated under reflux for one-half hour. The mixture was allowed to cool, the salt was removed by filtration on a buchner funnel, and the filtrate was concentrated to a volume of about 50 ml. by heating on the steam-bath under reduced pressure. To the residual liquid was added 300 ml. of water. A white crystalline precipitate quickly separated. It was collected on a filter, washed well with water and air dried. The yield was 17.4 g. (86%); m.p. 168–170°. A sample for analysis was recrystallized from water; m.p. 175–176°.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: N, 17.40. Found: N, 17.15.

4-β-Aminoethylpyrazole Dihydrochloride.—A suspension of 17 g. (0.071 mole) of 4-β-phthalimidoethylpyrazole in 200 ml. of 6 *N* hydrochloric acid was heated under reflux for 12 hours. The resulting solution was cooled, the precipitate of phthalic acid was removed by filtration and the filtrate was evaporated to dryness on the steam-bath under reduced pressure. To the residue was added 50 ml. of absolute ethanol, the mixture was warmed, diluted with 100 ml. of dry ether, and the white, crystalline product was collected and air dried. The yield was 11.2 g. (90%). It melted at

(8) R. Cornubert, R. Delmas, S. Montiel and J. Viriot, *Bull. soc. chim.*, 36 (1950); R. Willstatter and R. Pummerer, *Ber.*, **37**, 3740 (1904). The intermdiate dioxalacetone is best prepared by the method of B. Puetzer, C. H. Niedl and R. H. Barry, THIS JOURNAL, **67**, 836 (1945).

(9) *Org. Syntheses*, **24**, 53 (1944).

216–218° and did not depress the melting point of authentic 4-β-aminoethylpyrazole dihydrochloride.[1]

Anal. Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83. Found: N, 22.77.

4-γ-Hydroxypropylpyrazole.—2-Ethoxy-3-tetrahydropyranealdehyde diethyl acetal was prepared in 92% yield from 2,3-dihydropyrane and ethyl orthoformiate using boron trifluoride as a catalyst according to the method of Copenhaver.[6a]

The acetal was allowed to react with hydrazine dihydrochloride, and the reaction was worked up in the manner described above for the preparation of 4-β-hydroxyethylpyrazole. On a one-mole scale there was obtained a 91% yield of 4-γ-hydroxypropylpyrazole as a viscous, colorless liquid; b.p. 170° (3 mm.), $n^{25}D$ 1.5190, d^{25}_{25} 1.124. After standing the liquid crystallized. A sample recrystallized from ethyl acetate–petroleum ether mixture melted at 50–52°. The hydrochloride, recrystallized from alcohol–ether, melted at 104–105°.

Anal. Calcd. for $C_6H_{10}N_2O \cdot HCl$: N, 17.25. Found: N, 16.98.

4-γ-Chloropropylpyrazole Hydrochloride.—This was prepared in quantitative yield from 4-γ-hydroxypropylpyrazole and thionyl chloride. A sample recrystallized from absolute ethanol–ether melted at 115–116°.

Anal. Calcd. for $C_6H_9N_2Cl \cdot HCl$: N, 15.49. Found: N, 15.66.

4-γ-Phthalimidopropylpyrazole.—This was prepared in 88% yield from 4-γ-chloropropylpyrazole hydrochloride and potassium phthalimide in the same way as described above for 4-β-phthalimidoethylpyrazole. The crude product melted at 127–130° and after recrystallization from a large volume of water it melted at 136–137°.

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: N, 16.47. Found: N, 16.46.

4-γ-Aminopropylpyrazole Dihydrochloride.—This was obtained in 92% yield by hydrolysis of 4-γ-phthalimidopropylpyrazole with hydrochloric acid in the manner described above for the preparation of 4-β-aminoethylpyrazole dihydrochloride. The melting point was 188–190°.

Anal. Calcd. for $C_6H_{11}N_3 \cdot 2HCl$: N, 21.21. Found: N, 21.19.

Ethyl 4-Pyrazolecarboxylate (XI).—In a 2-l. round-bottom flask were placed 350 ml. of anhydrous ether and 23 g. (1 g. atom) of clean sodium metal cut up in small pieces. To this was added in one portion a mixture of 74 g. (1 mole) of ethyl formate and 143 g. (0.75 mole) of ethyl β,β-diethoxypropionate.[10] The flask was provided with a reflux condenser. After about one-half hour the reaction became exothermic; refluxing of the ether began and continued for about one hour. The reaction was allowed to stand overnight, and then 1 l. of ice-water was added. The mixture was well shaken, and the aqueous solution of the sodium salt of ethyl diformylacetate[5] was separated. It was added immediately to a solution made by mixing 32.5 g. (0.65 mole) of 100% hydrazine hydrate with 60 g. (1 mole) of acetic acid and 100 g. of ice. A little heat was evolved and a non-aqueous layer separated. After standing for one hour, this mixture was extracted with two 300-ml. portions of ether. The ether solution was dried, the ether evaporated, and the residual liquid distilled under reduced pressure to yield 50 g. (47%) of ethyl 4-pyrazolecarboxylate,[1] b.p. 120–130° (0.6 mm.); m.p. 76–78°.

4-Pyrazoleacetic Acid.—A solution of 16 g. of 4-cyanomethylpyrazole[1] in 50 ml. of alcohol was treated with 50 ml. of 12 *N* sodium hydroxide solution. The mixture was heated under reflux for two hours, and then the alcohol was removed by evaporation under reduced pressure. Water, 50 ml., was added followed by 50 ml. of 12 *N* hydrochloric acid. The 4-pyrazoleacetic acid separated as a white solid which was collected, after cooling, washed with a little cold water and air dried. The yield was 18 g. (96%). A sample recrystallized from water melted at 208–210°.

Anal. Calcd. for $C_5H_6N_2O_2$: N, 22.20. Found: N, 22.30.

When a solution of the acid in absolute ethanol saturated with hydrogen chloride was allowed to stand for four days, no ester was formed. The acid was recovered unchanged.

4-Pyrazole-N-benzylacetamide.—4-Pyrazoleacetyl chloride, prepared by warming 4-pyrazoleacetic acid with thionyl chloride, was obtained as a white solid. This added to excess benzylamine in dry ether, followed by evaporation of the ether and washing of the residue with water gave the N-benzylamide as a white crystalline solid; m.p. 170–172° from water or absolute alcohol.

Anal. Calcd. for $C_{12}H_{13}N_3O$: N, 19.55. Found: N, 19.08.

3-Pyrazoleacetic Acid.—A mixture of 5 g. of 3-cyanomethylpyrazole[1] and 25 ml. of 12 *N* sodium hydroxide solution was heated on the steam-bath for 16 hours. The resulting solution was cooled, acidified with concentrated hydrochloric acid to about *p*H 2 and evaporated to dryness under reduced pressure on the steam-bath. The residue was extracted with acetone, which on evaporation left 3-pyrazoleacetic acid hydrochloride as a crystalline solid; m.p. 137–140°.

Anal. Calcd. for $C_5H_6N_2O_2 \cdot HCl$: C, 36.95; H, 4.31; N, 17.25. Found: C, 36.93; H, 4.80; N, 16.89.

Ethyl 3-Pyrazoleacetate.—3-Pyrazoleacetic acid was dissolved in absolute ethanol, and the solution was saturated with dry hydrogen chloride. After standing overnight, the solution was evaporated to dryness under reduced pressure. The residue was taken into water, and the solution treated with excess sodium bicarbonate and extracted with ether. Evaporation of the ether left a liquid which was distilled under reduced pressure; b.p. 106° (0.4 mm.), $n^{25}D$ 1.4870.

Anal. Calcd. for $C_7H_{10}N_2O_2$: N, 18.18. Found: N, 18.20.

The hydrochloride precipitated fron ether as white crystals; m.p. 107–109°.

Anal. Calcd. for $C_7H_{10}N_2O_2 \cdot HCl$: N, 14.73. Found: N, 14.65.

3-Pyrazoleacetamide.—A solution of ethyl 3-pyrazoleacetate in methanol saturated with dry ammonia was allowed to stand for 72 hours. Addition of ether caused precipitation of the amide as colorless needles; m.p. 148–149°.

Anal. Calcd. for $C_5H_7N_3O$: N, 33.60. Found: N, 33.75.

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(10) N. C. Deno, THIS JOURNAL, **69**, 2233 (1947); S. M. McElvain and R. L. Clark, *ibid.*, **69**, 2657 (1947).