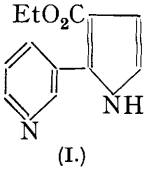
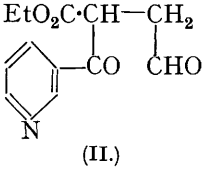
378. *The Synthesis of Pyridylpyrazoles.*

By George R. Clemo and Thomas Holmes.

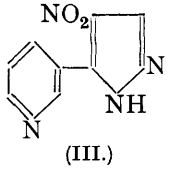
It was expected that application of the pyrrole synthesis of Benary (*Ber.*, 1911, **44**, 495) to ethyl nicotinoylacetate would lead to ethyl 2-(3′-pyridyl)pyrrole-3-carboxylate (I), and thence on reduction of the pyrrole ring to ethyl nornicotine-3-carboxylate. When ethyl nicotinoylacetate was treated with αβ-dichloroethyl ether and ammonia, however, a crystalline compound, $C_{12}H_{13}O_4N$, was obtained. The same compound resulted when methylamine was used in place of ammonia, and, as it reduced ammoniacal silver oxide and restored the colour to Schiff's reagent, it would appear to be *ethyl β-nicotinoylpropaldehyde-β-carboxylate* (II). The compound is unchanged by heating with either alcoholic ammonia or, rather remarkably, alcoholic hydrogen chloride.



(I.)



(II.)

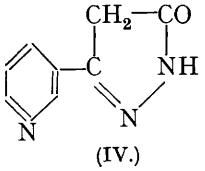


(III.)

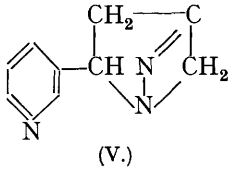
Ethyl nicotinoylacetate and phenylhydrazine gave 3-(3′-*pyridyl*)-1-*phenyl*-5-*pyrazolone*. Gough and King (J., 1931, 2968) isolated, as a by-product in the oxidation of nicotine, a compound which they considered to be 4-nitro-5-(3′-pyridyl)pyrazole (III). Lund, however (J., 1933, 686), suggested that the nitro-group was in the 3-position in the pyrazole ring, and so it was decided to apply the above pyrazole synthesis to settle the question.

4-*Amino*-3(or 5)-(3′-*pyridyl*)*pyrazole* has now been synthesised as follows, and shown to be different from the amino-compound derived by reduction of the nicotine oxidation product. Ethyl nicotinoylacetate was condensed with hydrazine hydrate by heating in methyl-alcoholic solution, giving 3-(3′-*pyridyl*)-5-*pyrazolone* (IV), which with phosphorus oxychloride gave 5-*chloro*-3-(3′-*pyridyl*)*pyrazole*. The latter was nitrated with fuming nitric acid, with formation of 5-*chloro*-4-*nitro*-3-(3′-*pyridyl*)*pyrazole*, and this on reduction with red phosphorus and dilute hydriodic acid gave 4-amino-3(or 5)-(3′-pyridyl)pyrazole.

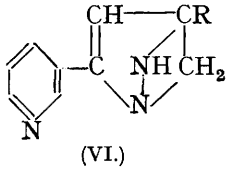
The alternative possibility, the 3-*amino*-5-(3′-*pyridyl*)*pyrazole*, has therefore been synthesised from 5-(3′-pyridyl)pyrazole-3-carboxylic acid (Gough and King, J., 1933, 350). The acid was esterified and converted into the *hydrazide*, which reacted readily with amyl nitrite and hydrochloric acid in aqueous ethyl alcohol, giving a good yield of the *urethane*. This was converted by boiling concentrated hydrochloric acid into 3-*amino*-5-(3′-*pyridyl*)-*pyrazole*, and the latter corresponded in every way with the amino-compound from nicotine. Gough and King's nitro-compound is therefore 3-nitro-5-(3′-pyridyl)pyrazole.



(IV.)



(V.)



(VI.)

This being so, it would appear that the introduction of the nitro-group during the nitric acid oxidation of nicotine takes place before the formation of the final pyrazole ring system, and not subsequently, as supposed by Gough and King. Possibly, after the formation of their claimed nitrogen-bridged intermediate compound (V), a tautomeric change occurs, and gives the compound (VI, R = H), which on subsequent nitration gives (VI, R = NO_2). Finally the residual pyrrole α-carbon atom is eliminated by oxidation as postulated by Gough and King, to give 3-nitro-5-(3′-pyridyl)pyrazole.

Experimental.

Ethyl Nicotinoylacetate.—Sodium ethoxide from sodium (1 g.) and absolute alcohol (15 c.c.) was made in a round-bottomed flask fitted with a dropping-funnel and stirrer through a mercury

seal, and evaporated to dryness. Ethyl nicotinate (6·5 g.) was dropped in with stirring at the ordinary temperature, followed by ethyl acetate (4·5 c.c.), and the mixture was stirred and heated at 77° for 2½ hours. Sufficient water was added to dissolve the product, and the solution made just acid with hydrochloric acid (1 : 1), treated with excess of sodium bicarbonate, and extracted with ether. The extract was dried over sodium sulphate and fractionated, giving ethyl nicotinate (1·8 g.) up to 121°/1 mm., and ethyl nicotinoylacetate (4·1 g.), b. p. 125—35°/1 mm. (Found: C, 62·5; H, 5·5. Calc. for $C_{10}H_{11}O_3N$: C, 62·2; H, 5·7%).

3-Pyridyl Methyl Ketone.—Ethyl nicotinoylacetate (1·7 g.) was refluxed gently for 1 hour with 15 c.c. of sulphuric acid (10%), the solution made alkaline with potassium carbonate and extracted with ether, and the extract dried over sodium sulphate and fractionated, giving 0·8 g. of oil, b. p. 106°/12 mm. (Found: C, 69·0; H, 5·8. Calc. for C_7H_7ON: C, 69·4; H, 5·8%). The *oxime* crystallised from ethyl alcohol in stout prisms, m. p. 130·5° (Found: C, 61·6; H, 6·1. $C_7H_8ON_2$ requires C, 61·8; H, 5·9%).

Ethyl β-Nicotinoylpropaldehyde-β-carboxylate.—Ethyl nicotinoylacetate (2·3 g.) was shaken with aqueous ammonia (4 c.c., *d* 0·88) and water (8 c.c.), and αβ-dichloroethyl ether (2 c.c.) added at once. The mixture was well shaken for about 5 minutes, much heat being evolved, and then left over-night in the refrigerator. The resulting pasty solid was collected, the oil washed out with water, dried on a porous plate, and the *solid* (0·55 g.) crystallised from benzene–ligroin (b. p. 60—80°), giving stout colourless prisms, m. p. 116° (Found: C, 61·5; 61·8; H, 5·65, 5·4; N, 5·9. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 5·9%). A molecular-weight determination by the Rast method could not be done.

3-(3′-Pyridyl)-1-phenyl-5-pyrazolone.—Ethyl nicotinoylacetate (0·3 g.) and phenylhydrazine (0·15 g.) were heated in acetic acid for ½ hour at 100°, water added, and the resulting solid crystallised from a little ethyl alcohol, giving faintly yellow prisms, m. p. 188° (Found: C, 71·0; H, 4·7. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·6%).

3-(3′-Pyridyl)-5-pyrazolone.—Ethyl nicotinoylacetate (3 g.), methyl alcohol (6 c.c.), and hydrazine hydrate (3 c.c., 95%) were refluxed together for 4 hours on the water-bath, filtered from a trace of solid, and evaporated to dryness under reduced pressure. The resulting crystalline solid was ground with water and a slight excess of acetic acid (to neutralise the residual hydrazine), and gave rectangular prisms (2·5 g.), m. p. 268° (Found: C, 59·6; H, 4·2. $C_8H_7ON_3$ requires C, 59·6; H, 4·3%).

5-Chloro-3-(3′-pyridyl)pyrazole.—The above pyrazolone (1 g.) and phosphorus oxychloride (8 c.c.) were heated in a sealed tube for 6 hours at 180°. The residue after evaporation of the excess of phosphorus oxychloride was treated with ice, and the solution neutralised with sodium bicarbonate. The separated solid (0·95 g.) crystallised from ethyl alcohol and water (1 : 1) in long colourless needles, m. p. 190° (Found: C, 53·4; H, 3·6. $C_8H_6N_3Cl$ requires C, 53·5; H, 3·3%).

5-Chloro-4-nitro-3-(3′-pyridyl)pyrazole.—The chloro-pyrazole (1 g.) was heated on the water-bath for ½ hour with fuming nitric acid (6 c.c.) in a loosely stoppered flask. The product was diluted with water, made alkaline with sodium hydroxide solution, and neutralised by carbon dioxide. The *nitro*-compound was filtered off (0·9 g.) and crystallised from alcohol and water (1 : 1) in long colourless needles, m. p. 220·5° (Found: C, 43·2; H, 2·3. $C_8H_5O_2N_4Cl$ requires C, 42·8; H, 2·2%).

4-Amino-5(or 3)-(3′-pyridyl)pyrazole.—The chloronitro-compound (1·5 g.) was heated with red phosphorus (1·5 g.) and hydriodic acid (21 c.c., 20%) in a sealed tube at 170° for 8 hours. The hydriodic acid was then evaporated off, and the residue treated with ammonia, giving *4-amino-5(or 3)-(3′-pyridyl)pyrazole*, which crystallised from alcohol in long colourless needles (1 g.), m. p. 176° (Found: C, 59·8, 60·0; H, 5·1, 5·1. $C_8H_8N_4$ requires C, 60·0; H, 5·0%). The *dipicrate* crystallised in yellow dendritic clusters from water, m. p. 205° (Found: C, 38·9; H, 2·1. $C_8H_8N_4,2C_6H_3O_7N_3$ requires C, 38·8; H, 2·3%). The *monoacetyl* derivative crystallised in white acicular prisms from alcohol, m. p. 183° (Found: C, 58·7; H, 5·4. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 5·0%). The *acetyl-dihydrochloride* crystallised in white needles from alcohol, m. p. 254° (Found: N, 20·7. $C_{10}H_{10}ON_4,2HCl$ requires N, 20·4%).

5-(3′-Pyridyl)pyrazole-3-carboxylic Acid.—This acid was made by the method of Gough and King (*loc. cit.*) with the exception that nicotinoylacetone was made by the following much improved method (yield, 82%). Sodium ethoxide from sodium (4·5 g.) was prepared in a flask as for ethyl nicotinoylacetate above, ethyl nicotinate (29·2 g.) added slowly with stirring, and then acetone (20 c.c.) was run in. The mixture was heated with stirring at 56° for 3 hours and worked up as for ethyl nicotinoylacetate, 26 g. of nicotinoylacetone being obtained, b. p. 154°/12 mm., m. p. 85°.

Ethyl 5-(3′-pyridyl)pyrazole-3-carboxylate.—The above acid (2·7 g.) was suspended in absolute alcohol (25 c.c.) and saturated with hydrogen chloride at 0°. After standing over-night, the mixture was refluxed for 4 hours on the water-bath, the alcohol removed under reduced pressure, and the solid residue neutralised with sodium bicarbonate solution. The resulting *ethyl* ester (2·55 g.) crystallised from alcohol in colourless prisms, m. p. 170° (Found : C, 60·6; H, 5·0. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·1%). The *hydrazide* was formed when the above ester (2 g.) was heated with hydrazine hydrate (3 c.c., 95%) and methyl alcohol (10 c.c.) for 48 hours in a sealed tube in a water-bath, and crystallised on cooling (1·79 g.). It was recrystallised from alcohol, giving long, colourless monoclinic prisms, m. p. 260° (Found : C, 52·9; H, 4·5. $C_9H_9ON_5$ requires C, 53·2; H, 4·4%).

5-(3′-Pyridyl)pyrazole-3-urethane.—Amyl nitrite (3 c.c.) was added with stirring to a suspension of the hydrazide (2·1 g.) in alcohol (20 c.c.) and water (10 c.c.), followed by hydrochloric acid (3·5 c.c.). The pale yellow solution was left over-night and then evaporated to dryness on the water-bath under reduced pressure. The residue was refluxed for ½ hour with alcohol (8 c.c.) and then concentrated. The *urethane dihydrochloride* separated (2·1 g.) and gave white needles from alcohol, losing solvent of crystallisation at 126°, and melting finally at 302° (Found : C, 44·8; H, 5·7. $C_{11}H_{12}O_2N_4,2HCl,C_2H_6O$ requires C, 44·5; H, 5·7%).

3-Amino-5-(3′-pyridyl)pyrazole.—The urethane dihydrochloride (1 g.) was refluxed with hydrochloric acid (5 c.c.) for 16 hours and then evaporated to dryness, giving *3-amino-5-(3′-pyridyl)pyrazole hydrochloride* (0·7 g.), which crystallised from water in fine needles, m. p. 301°. A portion treated with a solution of sodium picrate gave a crystalline *dipicrate*, m. p. 210°, raised to 219° by recrystallisation from water, and not depressed by admixture with the dipicrate of Gough and King's amino-compound (m. p. 219—220°) (Found : C, 38·95; H, 2·5. $C_8H_8N_4,2C_6H_3O_7N_3$ requires C, 38·8; H, 2·3%). The hydrochloride (0·1 g.), warmed with acetic anhydride (1 c.c.), acetic acid (1 c.c.), and sodium acetate (0·1 g.), gave on neutralisation with sodium bicarbonate solution a *monoacetyl* derivative, m. p. 300°, raised to 308—309° by recrystallisation from alcohol. The mixed m. p. with the acetyl derivative of the amino-compound from nicotine (Lund, *loc. cit.*) showed no depression (Found : C, 59·5; H, 5·5. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 5·0%).

One of us (T. H.) is indebted to the Council of Armstrong College and to Durham County Council for Scholarships which have enabled him to take part in this work, and our thanks are also due to the Imperial Chemical Industries, Ltd., for a grant.

THE UNIVERSITY OF DURHAM, ARMSTRONG COLLEGE,
NEWCASTLE-UPON-TYNE.

[*Received, July 31st,* 1934.]