141. *The Synthesis of Phenyl- and Pyridyl-glyoxalines.*

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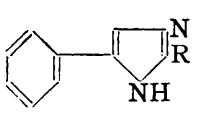
In view of the great physiological interest attached to histidine and histamine, and in continuation of the work done here on pyridylpyrazoles, it was decided to synthesise 5(4)-3′-*pyridylglyoxaline* (III, R = H), which incorporates the structure of histamine, and the isomeric 5(4)-2′-*pyridylglyoxaline* (II, R = H). They were obtained from ethyl nicotinate and picolinate respectively, by preparing the 3- and the 2-ω-aminoacetylpyridine, which were then condensed with potassium thiocyanate to give the glyoxaline thiols. The latter were oxidised by nitric acid to give (III) and (II) respectively.

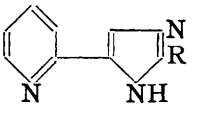
THE physiological importance of the glyoxaline nucleus, as exemplified by the purines, histidine, histamine, the closely related ergothionine, and the pilocarpine alkaloids, has led in the past to considerable work in this field.

In view of the fact that 5(4)-3′-pyridylglyoxaline (III, R = H) incorporates the structure of histidine and histamine (IV), and furthermore also contains the skeleton of the very important nicotinic acid amide, it was decided to continue the work on pyridylpyrazoles (J., 1934, 1739) by preparing it from 3-acetylpyridine.

Syntheses of this type have been much facilitated by the use of the new method of making ω-aminoacetophenone and related compounds (Neber and Huh, *Annalen*, 1935, **515**, 283). The various reactions were tested with acetophenone, which was first converted into ω-aminoacetophenone hydrochloride, and thence into 5(4)-*phenylglyoxaline*-2-*thiol* (I, R = SH) by treatment with potassium thiocyanate. The thiol group was removed by oxidation with dilute nitric acid, 5(4)-phenylglyoxaline (I, R = H), identical with that described by Pinner (*Ber.*, 1902, **35**, 4135), being obtained.

A similar treatment of 2- and 3-acetylpyridines gave 5(4)-2′-*pyridylglyoxaline* and 5(4)-3′-*pyridylglyoxaline* respectively.


(I.)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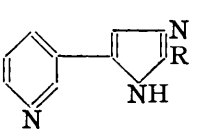
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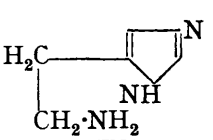
(IV.)

Experimental.

5(4)-*Phenylglyoxaline-2-thiol.*—ω-Aminoacetophenone hydrochloride (2 g.) (Neber and Huh, *loc. cit.*) was dissolved in water (10 c.c.) and treated with potassium thiocyanate (2 g.). The solution was heated on the water-bath for ½ hour, and treated, after cooling, with an excess of sodium bicarbonate. The precipitated *thiol* crystallised from benzene–alcohol (4 : 1) in colourless plates, m. p. 267·5° (Found : C, 61·1; H, 4·9. $C_9H_8N_2S$ requires C, 61·4; H, 4·5%). The *picrate* separated from alcohol in yellow plates, m. p. 177° (Found : C, 45·6; H, 3·9; N, 15·4. $C_9H_8N_2S,C_6H_3O_7N_3,C_2H_5{\cdot}OH$ requires C, 45·2; H, 3·8; N, 15·5%).

Phenacylthiourea (1·25 g.), obtained on concentration of the above bicarbonate solution, crystallised from benzene–alcohol (1 : 1) in colourless needles, m. p. 136° (Found : C, 56·3; H, 5·4. $C_9H_{10}ON_2S$ requires C, 55·7; H, 5·2%). On treatment with an alcoholic solution of picric acid it gave a picrate identical with that obtained from 5(4)-phenylglyoxaline-2-thiol, this treatment being sufficient to complete the condensation. M. p. (alone, and mixed with authentic picrate from the glyoxaline) 177°.

5(4)-*Phenylglyoxaline.*—The thiol (0·4 g.) was added slowly to 22 c.c. of 10% nitric acid on the water-bath, and the whole was heated under reflux for 1 hour. On cooling, the glyoxaline nitrate, m. p. 168°, separated. On treatment of the nitrate with an excess of sodium bicarbonate solution, phenylglyoxaline, m. p. 127°, identical with that already described (*loc. cit.*) was obtained.

Ethyl Picolinoylacetate.—Finely divided potassium (5 g.), suspended in benzene (150 c.c.), was treated with dry ethyl alcohol (7·5 c.c.) and, after cooling, with ethyl picolinate (10 g.), followed by ethyl acetate (20 c.c.). The mixture was heated on the water-bath under reflux for 6 hours, and diluted with water; hydrochloric acid (1 : 1) was added, and the ethyl picolinoylacetate liberated by the addition of excess of sodium bicarbonate. The benzene layer, containing the ester, was separated, and the aqueous layer extracted several times with benzene. The benzene extract was dried over sodium sulphate and fractionated under reduced pressure, giving ethyl picolinoylacetate (6 g.), b. p. 150°/2 mm. (decomp.).

5-2′-*Pyridylpyrazolone.*—Ethyl picolinoylacetate (1·5 g.) was refluxed for 5 hours on the water-bath with hydrazine hydrate (2 c.c.) in methyl alcohol (8 c.c.). The solution was evaporated to dryness under reduced pressure, and the residue dissolved in water and a slight excess of acetic acid, giving 5-2′-*pyridylpyrazolone* (0·9 g.), m. p. 219° after recrystallisation from alcohol (Found : C, 59·7; H, 4·7. $C_8H_7ON_3$ requires C, 59·6; H, 4·4%).

2-*Acetylpyridine.*—In subsequent preparations of ethyl picolinoylacetate, on completion of the condensation, the benzene was removed under reduced pressure, and dilute hydrochloric acid (130 c.c.; 1 : 1) added. The resulting solution was refluxed for 4 hours and cooled, excess of solid sodium bicarbonate added, and the liquid extracted with benzene. The extract was dried over sodium sulphate and fractionated under reduced pressure, giving 2-acetylpyridine (4 g.), b. p. 78°/12 mm. The oxime melted at 120°, as described in the literature.

O-p-*Toluenesulphonyl-2-acetylpyridineoxime.*—The oxime (7·4 g.) in pyridine (15 c.c.) was cooled in a freezing mixture and treated with finely powdered *p*-toluenesulphonyl chloride (11·3 g.). The mixture was kept overnight and then poured into a mixture of ice and water. The O-p-*toluenesulphonyl* ester, which separated, was filtered off, dried in a vacuum (15·8 g.), and crystallised from alcohol by dilution with water; m. p. 81—82° (Found : C, 58·2; H, 4·9. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·8%).

2-(ω-*Aminoacetyl*)*pyridine Hydrochloride.*—Potassium (2·45 g.) was dissolved in dry alcohol (60 c.c.), and the *p*-toluenesulphonyl ester (15·8 g.), in dry alcohol (40 c.c.), added. The mixture was shaken for 1 hour, and the precipitate of potassium *p*-toluenesulphonate removed. The filtrate was diluted with dry ether (800 c.c.), and a further precipitate of the potassium salt filtered off. The filtrate was extracted three times with 2N-hydrochloric acid (200 c.c.), and the combined extracts evaporated to dryness at 30—40° under reduced pressure, giving 2-(ω-

aminoacetyl)pyridine hydrochloride (11 g.), which crystallised from alcohol in colourless, stout prisms, m. p. 171—172° (decomp.) (Found : C, 48·7; H, 5·2. $C_7H_8ON_2$,HCl requires C, 48·7; H, 5·2%).

5(4)-2′-*Pyridylglyoxaline-2-thiol* (II, R = SH).—2-(ω-Aminoacetyl)pyridine hydrochloride (2·5 g.) in water (10 c.c.) was treated with potassium thiocyanate, the solution then being heated for 3 minutes on the water-bath. On cooling, 5(4)-2′-*pyridylglyoxaline-2-thiol hydrochloride* separated (1·9 g.); it crystallised from dilute alcohol (4 : 1), containing a trace of hydrochloric acid, in yellow prisms, m. p. 303° (decomp.) (Found : C, 45·3; H, 4·0. $C_8H_7N_3S$,HCl requires C, 45·0; H, 3·8%). The thiol hydrochloride (1·9 g.) on treatment with excess of sodium bicarbonate solution gave the free *thiol* (1·4 g.), which crystallised from alcohol in colourless prisms, m. p. 247—248° (Found : C, 54·5; H, 4·5; N, 23·5. $C_8H_7N_3S$ requires C, 54·2; H, 4·0; N, 23·7%). The *picrate* crystallised from alcohol in long yellow needles, m. p. 194—195° (Found : C, 43·1; H, 4·1; N, 16·9. $C_8H_7N_3S,C_6H_3O_7N_3,2C_2H_5{\cdot}OH$ requires C, 43·4; H, 4·4; N, 16·9%).

5(4)-2′-*Pyridylglyoxaline* (II, R = H).—The thiol (0·2 g.) was added in small portions to hot nitric acid (1·5 c.c.) in water (10 c.c.), and the solution heated on the water-bath for 1 hour. After cooling, excess of sodium bicarbonate was added, the solution evaporated to dryness, and the residue extracted with dry ether. On concentration of the extract and addition of light petroleum until the solution was cloudy, irregular prisms were obtained, m. p. 112° (Found : C, 66·05; H, 4·8; N, 29·3. $C_8H_7N_3$ requires C, 66·2; H, 4·8; N, 29·0%). The compound was easily soluble in cold water, giving a solution alkaline to litmus. The *picrate* of 5(4)-2′-*pyridylglyoxaline* was formed in alcohol and crystallised from acetone; m. p. 207—208° (Found : C, 40·1; H, 2·2; N, 20·4. $C_8H_7N_3,2C_6H_3O_7N_3$ requires C, 39·8; H, 2·15; N, 20·9%).

O-p-*Toluenesulphonyl-3-acetylpyridineoxime*.—This *ester* (10·3 g.), obtained from 3-acetylpyridineoxime (5 g.) (J., 1934, 1739), pyridine (15 c.c.), and *p*-toluenesulphonyl chloride (7·5 g.) (see the corresponding 2-acetyl compound), crystallised from alcohol, on dilution with water, in colourless plates, m. p. 78° (Found : C, 57·8; H, 4·8; S, 11·2. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·9; S, 11·0%).

3-(ω-*Aminoacetyl)pyridine Hydrochloride*.—Potassium (0·3 g.) was dissolved in dry alcohol (5 c.c.), and the preceding ester (2 g.) added. The mixture was shaken for 1 hour, the precipitate of potassium *p*-toluenesulphonate filtered off, both before and after addition of dry ether (120 c.c.), and the ethereal solution extracted three times with 2N-hydrochloric acid (13 c.c.). The combined extract was evaporated to dryness at 30—40° under reduced pressure, giving 3-(ω-*aminoacetyl)pyridine dihydrochloride* (1·1 g.), which crystallised from alcohol–acetone in colourless needles, m. p. 172° (decomp.) (Found : C, 40·7; H, 4·9; Cl, 33·0. $C_7H_8ON_2$,2HCl requires C, 40·2; H, 4·8; Cl, 34·0%).

5(4)-3′-*Pyridylglyoxaline-2-thiol* (III, R = SH).—3-(ω-Aminoacetyl)pyridine hydrochloride (1·1 g.) in water (6 c.c.) was treated with potassium thiocyanate (0·7 g.), and the resulting solution heated on the water-bath for ½ hour. On cooling, 5(4)-3′-*pyridylglyoxaline-2-thiol hydrochloride* separated (0·4 g.); it crystallised from dilute alcohol in long lemon-yellow prisms, m. p. 241—242° (Found : C, 45·8; H, 4·2. $C_8H_7N_3S$,HCl requires C, 45·0; H, 3·8%). The free *base*, liberated by treatment with sodium bicarbonate solution (1·1 g. of hydrochloride gave 0·85 g. of free base), crystallised from alcohol in clusters of stout prisms, m. p. 291—292° (Found : C, 54·3; H, 4·4. $C_8H_7N_3S$ requires C, 54·2; H, 4·0%).

5(4)-3′-*Pyridylglyoxaline* (III, R = H).—The thiol (0·5 g.) was added in small portions to hot nitric acid (3·75 c.c.) in water (25 c.c.), and the solution heated on the water-bath for 1 hour. On cooling, 0·61 g. of the *dinitrate* of (III, R = H) separated, m. p. 200° (decomp.) after crystallisation from alcohol (Found : C, 35·6; H, 3·0. $C_8H_7N_3,2HNO_3$ requires C, 35·4; H, 3·3%). On treatment of this with sodium bicarbonate solution, followed by evaporation to dryness and extraction of the residue with ether, 5(4)-3′-*pyridylglyoxaline* was obtained as a colourless solid, m. p. 117—118°, after recrystallisation from ether and light petroleum (Found : C, 66·1; H, 4·7; N, 28·5. $C_8H_7N_3$ requires C, 66·2; H, 4·8; N, 29·0%). The compound was easily soluble in cold water, giving a solution alkaline to litmus.

The *picrate* was formed in alcohol and recrystallised from glacial acetic acid, in which it was sparingly soluble, separating in warts, decomp. 285° (Found : C, 44·65; H, 2·55. $C_8H_7N_3,C_6H_3O_7N_3$ requires C, 44·9; H, 2·7%).

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