667. *The Skraup Reaction with Aminopyrazoles.*

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4-Amino-1-phenylpyrazole has been converted by the Skraup reaction into 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine the structure of which has been proved by synthesis and ultraviolet absorption spectroscopy. Some pyrazolylquinolines have also been prepared from 1-aminophenylpyrazoles by the Skraup reaction.

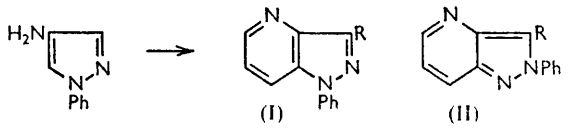
4-Amino-1-phenylpyrazole, previously obtained from glucosazone,[1] was more conveniently prepared by the reduction of 4-nitro-1-phenylpyrazole [2] with hydrazine hydrate and palladised charcoal.[3] Two isomers can theoretically be obtained from this amine in the Skraup reaction, by ring closure in the 5- or the 3-position of the pyrazole ring to give compound (I or II; R = H).

Attempts to cause ring closure with 75% and 85% sulphuric acid [4] and arsenic pentoxide as oxidising agent failed; small amounts of unchanged amine were recovered.

[1] Heubner and Link, *J. Amer. Chem. Soc.*, 1950, **72**, 4812.
[2] Finar and Hurlock, *J.*, 1957, 3024.
[3] Dewar and Mole, *J.*, 1956, 2556.
[4] B.P. 394,416/1933.

Ring closure, however, was achieved with concentrated sulphuric acid, and to give 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine (I; R = H). The yield was only 2%, but a higher yield (19%) was obtained by using nitrobenzene as oxidising agent instead of arsenic pentoxide.

The structure of 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine was established as follows. 3′-Methyl-1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine (I; R = Me) was prepared by the

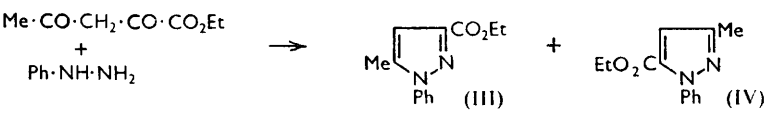


Skraup reaction with 4-amino-3-methyl-1-phenylpyrazole, ring closure being forced into position 5 by the 3-methyl group. The ultraviolet absorption curves of the two products between 210 and 350 mμ (*c* 0·03 in EtOH) were almost identical (R = H: $\lambda_{max.}$ 250 mμ, ε 2·2. R = Me: $\lambda_{max.}$ 271 mμ, ε 2·21). The general shape of the curves corresponds reasonably with published curves for 1-methylindazole derivatives but not with those for 2-methylindazole derivatives.[5] Thus the Skraup product from 4-amino-1-phenylpyrazole is 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine (I; R = H).

4-Amino-3-methyl-1-phenylpyrazole, previously obtained by reduction of 4-amino-5-chloro-3-methyl-1-phenylpyrazole,[6] was prepared as follows: 4 : 4-Dimethoxybutan-2-one [7] was condensed with *p*-nitrophenylhydrazine, to give 3-methyl-1-*p*-nitrophenylpyrazole.[8] This was nitrated with mixed acids at 22° to give 3-methyl-4-nitro-1-*p*-nitrophenylpyrazole, which, on reduction in ethanol with ammonium hydrogen sulphide, gave 1-*p*-aminophenyl-3-methyl-4-nitropyrazole (cf. Finar and Hurlock [2]). This compound was diazotised and treated with hypophosphorous acid, to give 3-methyl-4-nitro-1-phenylpyrazole which, on reduction with hydrazine hydrate and palladised charcoal, gave 4-amino-3-methyl-1-phenylpyrazole.

An attempt was then made to synthesise the homologue of (II; R = Me) from 4-amino-5-methyl-1-phenylpyrazole. This amine was synthesised as follows: According to Claisen,[9] ethyl 2 : 4-dioxopentanoate condenses with phenylhydrazine to give ethyl 5-methyl-1-phenylpyrazole-3-carboxylate (III) as an oil. Claisen did not obtain the other isomer, ethyl 3-methyl-1-phenylpyrazole-5-carboxylate (IV) which theoretically could be obtained by hydrazone formation on the 2-oxo-group, followed by ring closure. We have repeated this reaction and obtained the two isomeric pyrazole esters as low-melting solids. They were orientated by hydrolysis to the pyrazole acids.[9]

5-Methyl-1-phenylpyrazole-3-carboxylic acid was decarboxylated to 5-methyl-1-phenylpyrazole which with mixed nitrating acids at 22° gave 5-methyl-4-nitro-1-*p*-nitrophenylpyrazole. This was reduced in ethanol with ammonium hydrogen sulphide to 1-*p*-aminophenyl-5-methyl-4-nitropyrazole, which was diazotised and treated with



hypophosphorous acid. 5-Methyl-4-nitro-1-phenylpyrazole, thus obtained, was reduced to 4-amino-5-methyl-1-phenylpyrazole. The Skraup reaction with this amine failed.

[5] Rousseau and Lindwall, *J. Amer. Chem. Soc.*, 1950, **72**, 3047.
[6] Michaelis and Schäfer, *Annalen*, 1915, **407**, 238.
[7] Hata, Yamada, Iwao, Kato, Sugimoto, and Inouye, *J. Pharm. Soc. Japan*, 1949, **69**, 477; *Chem. Abs.*, 1950, **44**, 3455.
[8] Burness, *J. Org. Chem.*, 1956, **21**, 97.
[9] Claisen, *Annalen*, 1894, **278**, 269.

Unchanged material was recovered, together with a small amount of quinoline obtained as a by-product from the nitrobenzene present (cf. Das Gupta [10]).

1-*p*-Aminophenylpyrazole, prepared from 1-*p*-nitrophenylpyrazole by reduction with hydrazine hydrate and palladised charcoal, was heated with glycerol, 60% sulphuric acid, and arsenic pentoxide. 6-1′-Pyrazolylquinoline was obtained; 1-*p*-aminophenyl-4-nitropyrazole under the same conditions gave 6-(4-nitro-1-pyrazolyl)quinoline. Both amines were destroyed in the Skraup reaction when concentrated sulphuric acid was used.

Experimental

The light petroleum had a boiling range of 40—60° and the ligroin 90—100°.

4-*Amino*-1-*phenylpyrazole*.—4-Nitro-1-phenylpyrazole (20·0 g.) was refluxed with ethanol (100 c.c.), 60% hydrazine hydrate (40 c.c.), and 5% palladised charcoal (2·0 g.) for 10 min. The catalyst was filtered off, and the filtrate evaporated to small bulk, diluted with water, and set aside. Colourless needles of 4-amino-1-phenylpyrazole separated (14·3 g., 85%), m. p. 103—104°, raised to 104—105° on recrystallisation from ligroin.

1′-*Phenylpyrazolo*(4′ : 5′-2 : 3)*pyridine*.—Sulphuric acid (22·6 g.; *d* 1·84) was slowly added to a mixture of 4-amino-1-phenylpyrazole (17·2 g.), anhydrous glycerol (42·3 g.), nitrobenzene (8·9 g.), and ferrous sulphate (5·3 g.), and the mixture was heated at 180—185° for 4 hr. When cool, the mixture was diluted with water, filtered, and steam-distilled to remove excess of nitrobenzene. It was then made alkaline with 10% aqueous sodium hydroxide and again steam-distilled to remove quinoline. The distillation was continued until a portion of the filtrate no longer gave a precipitate of quinoline picrate when treated with an ethanolic solution of picric acid. The mixture was filtered and the tarry residue and the filtrate were separately extracted with benzene. The residue obtained after the removal of benzene was distilled *in vacuo*, to give material (5·5 g., 26·0%), b. p. 114—116°/0·1 mm., m. p. 58—62°, which was then chromatographed in benzene on alumina. Elution with benzene gave crystals which, on recrystallisation from light petroleum, gave 1′-*phenylpyrazolo*(4′ : 5′-2 : 3)*pyridine* (4·0 g., 19%) as needles, m. p. 72—73° (Found: C, 73·6; H, 4·4; N, 21·5. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6; N, 21·5%).

3-*Methyl*-1-p-*nitrophenylpyrazole*.—4 : 4-Dimethoxy-2-butanone [7] (50·0 g., 1 mol.) and *p*-nitrophenylhydrazine hydrochloride (71·8 g., 1 mol.) were refluxed in 50% ethanol (600 c.c.). After 10 min. the hot solution deposited reddish-brown needles which, recrystallised from ethanol, gave 3-methyl-1-*p*-nitrophenylpyrazole (49·0 g., 64·2%), m. p. 170—170·5° (Burness [8] gives 165·5°; Knorr [11] gives 165°).

3-*Methyl*-4-*nitro*-1-p-*nitrophenylpyrazole*.—A mixture of sulphuric acid (165 c.c.; *d* 1·84) and nitric acid (165 c.c.; *d* 1·42) was added dropwise with stirring during 1 hr. to a cooled solution of 3-methyl-1-*p*-nitrophenylpyrazole (25·0 g.) in sulphuric acid (200 c.c.; *d* 1·84). The solution was kept at 22° for 16 hr., then poured on ice. The yellow solid was washed and dried (29·0 g., 95·0%; m. p. 201—203°). A portion on recrystallisation from benzene gave 3-*methyl*-4-*nitro*-1-p-*nitrophenylpyrazole* as pale yellow needles, m. p. 203—205° (Found: C, 48·1; H, 3·6; N, 22·8. $C_{10}H_8O_4N_4$ requires C, 48·4; H, 3·2; N, 22·6%).

1-p-*Aminophenyl*-3-*methyl*-4-*nitropyrazole*.—3-Methyl-4-nitro-1-*p*-nitrophenylpyrazole (30·0 g.) (m. p. 201—203°) was suspended in ethanol (800 c.c.) containing aqueous ammonia (120 c.c.; *d* 0·880). Hydrogen sulphide was passed in for 15 min., and the mixture was then refluxed for 30 min. and finally cooled. This process was repeated twice. When then set aside, the reaction mixture deposited lemon-yellow needles which were collected and extracted with boiling 0·75N-hydrochloric acid (900 c.c.). The hot extract, when made alkaline with aqueous ammonia (*d* 0·88), gave 1-p-*aminophenyl*-3-*methyl*-4-*nitropyrazole*, lemon-yellow needles (from ethanol) (22·6 g., 86·5%), m. p. 167—168° (Found: C, 55·0; H, 4·7; N, 25·5. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6; N, 25·7%).

3-*Methyl*-4-*nitro*-1-*phenylpyrazole*.—1-*p*-Aminophenyl-3-methyl-4-nitropyrazole (18·2 g.) was dissolved in 70% w/w sulphuric acid (150 c.c.) and diazotised at 40° with sodium nitrite (6·65 g., 10% excess) in sulphuric acid (20 c.c.; *d* 1·84). The solution was kept at 35—40° for 2 hr., then diluted with water (100 c.c.). The diazonium sulphate solution was added dropwise

[10] Das Gupta, *J. Indian Chem. Soc.*, 1952, **29**, 711.
[11] Knorr, *Annalen*, 1894, **279**, 221.

during 1 hr. to a stirred solution of 31% w/w hypophosphorous acid (260 g.) at 20°. The solution was set aside overnight. The product, a yellow solid, was collected, washed, and dried (14·6 g., 87·5%; m. p. 107—109°). The crude deamination product was chromatographed in benzene on alumina which was then eluted with a 1% solution of methanol in benzene. The yellow solid obtained recrystallised from benzene–light petroleum, to give yellow needles of 3-*methyl*-4-*nitro*-1-*phenylpyrazole*, m. p. 109—110·5° (Found: C, 58·8; H, 4·2; N, 20·45. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

4-*Amino*-3-*methyl*-1-*phenylpyrazole*.—A mixture of 3-methyl-4-nitro-1-phenylpyrazole (14·0 g.; m. p. 107—109°), 60% hydrazine hydrate (30 c.c.), 5% palladised charcoal (4·1 g.) and ethanol (400 c.c.) was heated on the steam-bath for 1 hr. Working up as in the preparation of 4-amino-1-phenylpyrazole gave a dark-red impure solid. This was extracted with boiling ligroin which, on cooling, deposited colourless needles of the amine (5·7 g., 48%), m. p. 88—89·5° (Michaelis and Schäfer [6] give 88°).

3′-*Methyl*-1′-*phenylpyrazolo*(4′ : 5′-2 : 3)*pyridine*.—Sulphuric acid (7·4 g.; *d* 1·84) was slowly added to a stirred mixture of 4-amino-3-methyl-1-phenylpyrazole (6·1 g.), glycerol (13·9 g.), nitrobenzene (3·0 g.), and ferrous sulphate (2 g.). The mixture was heated at 180—185° for 4 hr. and worked up as in the preparation of 1′-phenylpyrazolo(4′ : 5′-2 : 3)-pyridine. The benzene extract gave, on evaporation, a brown viscous tar. This was distilled under reduced pressure, to give a product (3·54 g., 48·5%), m. p. 59—63°, which was chromatographed in benzene on alumina. Elution with benzene gave a colourless solid, which, on recrystallisation from light petroleum gave 3′-*methyl*-1′-*phenylpyrazolo*(4′ : 5′-2 : 3)*pyridine*, m. p. 71·5—72·5° (Found: C, 74·5; H, 5·5; N, 19·8. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%).

Ethyl 2 : 4-*Dioxopentanoate*.—This was prepared from acetone and ethyl oxalate in 71% yield (b. p. 110—112°/15 mm.) by the method of Marvel and Dreger [12] (these authors obtained 61—66% of ester, b. p. 132°/37 mm.).

Condensation between Ethyl 2 : 4-*Dioxopentanoate and Phenylhydrazine*.—Phenylhydrazine (119·0 g., 1 mol.) was added during 45 min. to a stirred solution of ethyl 2 : 4-dioxopentanoate (174·0 g., 1 mol.) in glacial acetic acid (400 c.c.). The solution was refluxed for 2 hr., then poured into water (1200 c.c.). The yellow oil which separated was extracted with ether (1 × 500 c.c.; 4 × 250 c.c.), and the combined extracts were washed with 10% sodium carbonate solution (4 × 200 c.c.), then with water (3 × 50 c.c.). The extracts were dried (Na_2SO_4) and on evaporation gave a yellow viscous oil which was distilled *in vacuo*. *Ethyl* 3-*methyl*-1-*phenylpyrazole*-5-*carboxylate* (51·6 g., 20·3%) had b. p. 106—108°/0·1 mm., m. p. 40—41° (Found: C, 68·1; H, 5·8; N, 11·9. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). Ethyl 5-methyl-1-phenylpyrazole-3-carboxylate (153·85 g., 60·6%) had b. p. 128—130°/0·1 mm., m. p. 35—36°. (These two low-melting esters formed an oil when mixed at room temperature.)

Orientation of the Pyrazole Esters.—The higher-boiling ester (178·0 g.) was heated on the steam-bath with ethanol (300 c.c.), water (50 c.c.) and potassium hydroxide (69·5 g.) for 30 min. Most of the ethanol was removed under reduced pressure. Water (150 c.c.) was added and the solution acidified with hydrochloric acid (*d* 1·18). The pyrazole acid was collected and dried *in vacuo* ($CaCl_2$) to give 5-methyl-1-phenylpyrazole-3-carboxylic acid as the monohydrate (165 g., 97%), m. p. 103—104°. A portion on recrystallisation from aqueous ethanol had m. p. 106°. When kept *in vacuo* over calcium chloride for one week, the anhydrous acid was obtained, having m. p. 136°. The lower-boiling ester gave, on hydrolysis, colourless needles of 3-methyl-1-phenylpyrazole-5-carboxylic acid, m. p. 189—190° (from aqueous ethanol).

5-*Methyl*-1-*phenylpyrazole*.—5-Methyl-1-phenylpyrazole-3-carboxylic acid (163·0 g.), m. p. 103—104°, was decarboxylated at 200—210°. The residual dark brown liquid was distilled under reduced pressure to give 5-methyl-1-phenylpyrazole (93·0 g., 78·8%), b. p. 134—136°/13 mm.

5-*Methyl*-4-*nitro*-1-p-*nitrophenylpyrazole*.—5-Methyl-1-phenylpyrazole (70·0 g.) was nitrated with mixed acids as for the 3-methyl isomer. The crude product (108·7 g., 98·5%) was obtained as a pale yellow solid, m. p. 146—150°. Recrystallisation from benzene gave pale yellow needles of 5-*methyl*-4-*nitro*-1-p-*nitrophenylpyrazole*, m. p. 155—157° (Found: C, 48·6; H, 3·1; N, 22·3. $C_{10}H_8O_4N_4$ requires C, 48·4; H, 3·2; N, 22·6%).

1-p-*Aminophenyl*-5-*methyl*-4-*nitropyrazole*.—5-Methyl-4-nitro-1-*p*-nitrophenylpyrazole

[12] Marvel and Dreger, *Org. Synth.*, Coll. Vol. III, 1955, p. 685.

(103·8 g.), m. p. 146—150°, was suspended in ethanol and reduced with ammonium hydrogen sulphide as for the 3-methyl isomer. Lemon-yellow 1-p-*aminophenyl*-5-*methyl*-4-*nitropyrazole* (60·7 g., 66·5%) had m. p. 146—148° (from aqueous ethanol) (Found: C, 55·3; H, 4·3; N, 25·3. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6; N, 25·7%).

5-*Methyl*-4-*nitro*-1-*phenylpyrazole*.—1-*p*-Aminophenyl-4-nitropyrazole (59·0 g.; m. p. 144—148°) was diazotised in 70% sulphuric acid with sodium nitrite (25·0 g., 10% excess) in sulphuric acid (50 c.c.; *d* 1·84) at 35—40°. After 2 hr. at this temperature the solution was cooled, filtered, and added dropwise during 1 hr. to stirred aqueous 31% w/w hypophosphorous acid (260 g.) at 20°. The solution was set aside overnight and the yellow solid was filtered off, washed, and dried (50·0 g., 90·9%). This (30·0 g.) was chromatographed in benzene on alumina. The yellow solid obtained on elution with a 1% solution of methanol in benzene recrystallised from benzene–light petroleum, to give 5-*methyl*-4-*nitro*-1-*phenylpyrazole* (25·4 g., 77·1%) as yellow needles, m. p. 113—114° (Found: C, 59·4; H, 4·7; N, 20·35. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

4-*Amino*-5-*methyl*-1-*phenylpyrazole*.—5-Methyl-4-nitro-1-phenylpyrazole (23·0 g.) was refluxed in ethanol (250 c.c.) with 60% hydrazine hydrate (60 c.c.) and 5% palladised charcoal (6·8 g.) for 1 hr. The catalyst was removed and the filtrate evaporated to dryness. (The last traces of water were removed by azeotropic distillation with benzene.) The residual viscous yellow oil (19·1 g., 97·5%) solidified and was used without purification in the next stage. A portion, distilled *in vacuo*, had b. p. 114—116°/0·08 mm., m. p. 32—33° (Found: C, 69·2; H, 6·1; N, 24·5. $C_{10}H_{11}N_3$ requires C, 69·4; H, 6·35; N, 24·3%).

Skraup Reaction with 4-*Amino*-5-*methyl*-1-*phenylpyrazole*.—Sulphuric acid (18·4 g.; *d* 1·84) was slowly added to a mixture of 4-amino-5-methyl-1-phenylpyrazole (15·0 g.), anhydrous glycerol (32·4 g.), nitrobenzene (7·4 g.), and ferrous sulphate (5·0 g.), and the mixture was then heated at 180—185° for 4 hr. When cool, the mixture was diluted with water, filtered, and steam-distilled to remove excess of nitrobenzene. When the mixture was made alkaline with 30% aqueous sodium hydroxide, a tar separated. This was steam-distilled until no more quinoline (identified as the picrate) was obtained in the aqueous distillate. The mixture was filtered and the residue and the filtrate were separately extracted with benzene. The extracts on evaporation gave a tarry residue which on distillation *in vacuo* gave a pale-yellow oil (0·3 g.), b. p. 114—116°/0·08 mm. The infrared spectrum of the oil was identical with that of authentic 4-amino-5-methyl-1-phenylpyrazole. No other product was obtained when extractions were carried out with ether and chloroform.

6-(1-*Pyrazolyl*)*quinoline*.—60% Sulphuric acid (60 g.) was cautiously added to a mixture of 1-*p*-aminophenylpyrazole (10·0 g.), anhydrous glycerol (11·2 g.), and arsenic pentoxide (10·0 g.). The mixture was slowly heated to the b. p., then refluxed for 3 hr. When cool, the solution was diluted with water, filtered, and made alkaline with 30% aqueous sodium hydroxide. The brown tar that was precipitated was extracted with benzene (4 × 200 c.c.). The extracts were washed with water (3 × 50 c.c.), and the benzene was removed by distillation. The residual brown oil, which solidified, was extracted with boiling ligroin. The latter was filtered free from insoluble material and evaporated. The residue was chromatographed in benzene on alumina. The yellow solid obtained on elution with benzene recrystallised from ether, to give yellow crystals (3·0 g., 23·9%), m. p. 115—116°. Recrystallisation from ligroin gave pale-yellow needle clusters of 6-(1-*pyrazolyl*)*quinoline*, m. p. 116—117° (Found: C, 73·8; H, 4·4; N, 21·7. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6; N, 21·5%).

6-(4-*Nitro*-1-*pyrazolyl*)*quinoline*.—Sulphuric acid was slowly added to a mixture of 1-*p*-aminophenyl-4-nitropyrazole (5·0 g.), anhydrous glycerol (4·5 g.), and arsenic pentoxide (5·0 g.). The mixture was refluxed for 3 hr., and, when cool, diluted with water, filtered, and made alkaline with 30% aqueous sodium hydroxide. The brown tar that was precipitated was collected and extracted with ether. The extracts on evaporation gave a brownish-yellow solid which was chromatographed in benzene on alumina. Elution with benzene gave a yellow solid, m. p. 224—225°. Recrystallisation from benzene–light petroleum gave pale yellow needles of 6-(4-*nitro*-1-*pyrazolyl*)*quinoline*, m. p. 225—226° (Found: C, 59·7; H, 3·3; N, 23·3. $C_{12}H_8O_2N_4$ requires C, 60·0; H, 3·3; N, 23·3%).

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