*Cinnolines. Part XXXIV.** 5-, 6-, *and* 7-*Hydroxy- and* 5-, 6-, *and* 7-*Amino-cinnolines.*

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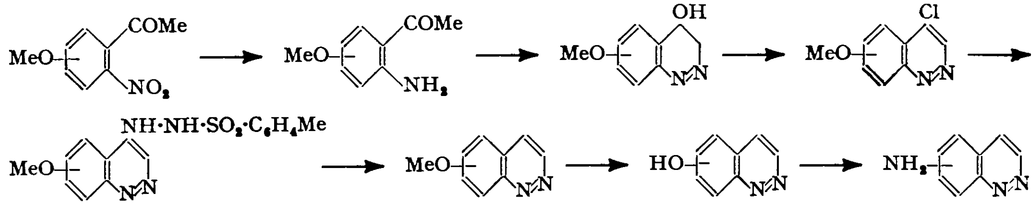
4-Hydroxy-5-, -6-, and -7-methoxycinnoline have been synthesised, and converted, through the 4-chloro-compounds into 5-, 6-, and 7-methoxycinnoline. These were demethylated to the hydroxy-compounds, which by the Bucherer reaction provided 5-, 6-, and 7-aminocinnoline.

For physical studies to be described shortly all the monohydroxy- and monoaminocinnolines were required. The 3-, 4-, and 8-isomers of both series were already known, and we have now obtained the remaining members by the method used for 8-hydroxy- and 8-amino-cinnoline (Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009). The sequence of reactions involved is illustrated below, and the problem is essentially that of obtaining appropriate methoxynitroacetophenones.



The synthesis of the 5-substituted cinnolines thus required the previously unknown 2-methoxy-6-nitroacetophenone. We were unable to hydrolyse the readily available 2-methoxy-6-nitrobenzonitrile (Cartwright, Jones, and Marmion, *J.*, 1952, 3499) to the acid by the method used by Berger and Olivier (*Rec. Trav. chim.*, 1927, **46**, 600) in similarly difficult cases. However, 6-nitrosalicylic acid was obtained by Goldberg and Walker's method (*J.*, 1953, 2049) and methylation readily provided 2-methoxy-6-nitrobenzoic acid which was characterised as its methyl and ethyl esters and converted in good yield into 2-methoxy-6-nitroacetophenone by Walker and Hauser's method (*J. Amer. Chem. Soc.*, 1946, **68**, 1386).

5-Methoxy-2-nitroacetophenone was previously obtained by an inconvenient procedure by Ashley, Perkin, and Robinson (*J.*, 1930, 382) who did not record its physical properties. Whilst the nitration of *m*-hydroxybenzaldehyde gives mainly 3-hydroxy-2-nitrobenzaldehyde, *m*-hydroxybenzaldehyde " carbonate " gives 5-hydroxy-2-nitrobenzaldehyde (Mason, *J.*, 1925, 1196). *m*-Hydroxyacetophenone readily formed a " carbonate " when treated with carbonyl chloride, but nitration gave a gum from which only a small amount of 5-hydroxy-2-nitroacetophenone could be isolated. Methylation gave 5-methoxy-2-nitroacetophenone which was more practicably prepared from 5-methoxy-2-nitrobenzoic acid (Chapman, Gibson, and Mann, *J.*, 1947, 894) by the method used for the 6-isomer. Similarly, 4-methoxy-2-nitroacetophenone was obtained from 4-methoxy-2-nitrobenzoic acid (Chapman *et al.*, *loc. cit.*)

Neither 2-amino-4- nor -6-methoxybenzonitrile could be induced to react with methylmagnesium iodide or methyl-lithium, but the nitro-ketones described above were reduced to the amines, by iron and acetic acid, in good yield. The amines were converted into the 4-hydroxymethoxycinnolines by standard methods (Schofield and Simpson, *J.*, 1948, 1170). 4-Hydroxy-6-methoxycinnoline so prepared was identical with a specimen obtained earlier by the Richter reaction (Schofield and Simpson, *J.*, 1945, 512). 4-Chloro-5-, -6-, and -7-methoxycinnoline, obtained in the usual way, reacted with toluene-*p*-sulphonylhydrazide in chloroform solution to give orange-red or red products which were converted by aqueous sodium carbonate into 5-, 6-, and 7-methoxycinnoline. These were

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stable crystalline solids, in contrast to 8-methoxycinnoline which quickly liquefies and becomes green in the atmosphere (Alford *et al.*, *loc. cit.*).

Demethylation of the methoxycinnolines with hydrobromic acid gave 5-, 6-, and 7-hydroxycinnoline as crystalline solids, melting considerably higher than 8-hydroxycinnoline. Like the 8-isomer, 5-hydroxycinnoline gave a red dye with benzenediazonium chloride, but coupling was not observed with the 6- and the 7-compound. None of the hydroxy-compounds gave a noticeable colour with ferric chloride. The Bucherer reaction converted the hydroxy-compounds into the yellow, crystalline amines. 5- and 8-Aminocinnoline gave violet-red solutions in acid, 6- and 7-aminocinnoline formed yellow solutions, and all four amines formed colourless diazonium solutions which produced red dyes with alkaline β-naphthol.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 40—60° unless otherwise stated.

6-Methoxy-2-nitrobenzoic Acid.—6-Nitrosalicylic acid (32·2 g.; Goldberg and Walker, *loc. cit.*), sodium hydroxide (14·1 g.), and water (90 c.c.) were stirred at 95° and treated dropwise during 1 hr. with methyl sulphate (114 g.), more 50% aqueous sodium hydroxide being added as necessary to maintain alkalinity. After 1½ hours' further heating, the mixture was cooled and acidified, and the precipitate was collected. The filtrate was extracted with chloroform, and the combined products were crystallised from water or benzene (charcoal), affording pale cream plates of 6-methoxy-2-nitrobenzoic acid (85%), m. p. 180° (Found: C, 48·7; H, 3·6. Calc. for $C_8H_7O_5N$: C, 48·7; H, 3·6%). Simonsen and Rau (*J.*, 1917, 220) gave m. p. 179—180°.

From preliminary methylations some of the *methyl ester* of the acid was isolated. It formed small colourless crystals, m. p. 62—64° (Found: C, 51·5; H, 4·0. $C_9H_9O_5N$ requires C, 51·2; H, 4·3%), from light petroleum. The *ethyl ester*, formed from the acid chloride, gave prisms, m. p. 82—83° (Found: C, 53·8; H, 5·0. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9%), from the same solvent.

6-Methoxy-2-nitroacetophenone.—The acid chloride [prepared in benzene from the above acid (39·4 g.) and thionyl chloride in the usual way] in the minimum amount of ether was added dropwise to a stirred ethereal solution of ethoxymagnesiomalonic ester (from 35·2 g. of ethyl malonate; Walker and Hauser, *loc. cit.*), and after being refluxed for ½ hr. the mixture was decomposed with 4N-sulphuric acid. Extraction with ether, drying ($CaSO_4$), and removal of the solvent gave an oil which was refluxed with acetic acid (60 c.c.), concentrated sulphuric acid (7·5 c.c.), and water (40 c.c.) for 4 hr. Cooling, basification, and extraction with ether yielded a sticky solid which on trituration with light petroleum provided the ketone (83%), m. p. 88°. *6-Methoxy-2-nitroacetophenone* formed cream needles, m. p. 91—92°, from light petroleum (b. p. 60—80°) (Found: C, 55·9; H, 4·8. $C_9H_9O_4N$ requires C, 55·4; H, 4·65%).

2-Amino-6-methoxyacetophenone.—The nitro-compound (32 g.) was added during 1 hr. to a stirred mixture of iron dust (46 g.), acetic acid, and water (172 c.c. of each). After being refluxed for a further hr. the mixture was cooled and extracted with ether. Evaporation and distillation gave an oil (22·43 g.), b. p. 130—160°/1·5 mm., which crystallised. *2-Amino-6-methoxyacetophenone* formed yellow cubes, m. p. 89° (Found: C, 56·1; H, 4·9. $C_9H_{11}O_2N,1{\cdot}5H_2O$ requires C, 56·2; H, 7·3%) (the poor analysis is probably connected with the fact that the amine darkens quickly when kept), from ether–light petroleum. The *acetyl derivative* formed colourless needles, m. p. 124—125° (Found: C, 64·4; H, 6·4. $C_{11}H_{13}O_3N$ requires C, 63·75; H, 6·3%), from light petroleum.

4-Hydroxy-5-methoxycinnoline.—The above amine (9·9 g.) in concentrated hydrochloric acid (250 c.c.) was diazotised at 0° with sodium nitrite (5 g.) in water (10 c.c.). Concentrated hydrochloric acid (250 c.c.) was added and after four days at room temperature the solution was rapidly (15 min.) evaporated to dryness. The residue in boiling water was treated with excess of hot aqueous sodium acetate, and the precipitate was recrystallised (charcoal) from boiling water. *4-Hydroxy-5-methoxycinnoline* (5·80 g.) gave pale cream needles, m. p. 275° (decomp.) (Found: C, 60·9; H, 4·5. $C_9H_8O_2N_2$ requires C, 61·35; H, 4·6%), from water. A polymorphic form, m. p. 245° (decomp.) (Found: C, 61·2; H, 5·0%), was observed in early experiments. It changed, on standing, into the higher-melting variety.

4-Chloro-5-methoxycinnoline.—The pure hydroxycinnoline (3·4 g.) and phosphorus oxychloride (50 c.c.) were heated on the steam-bath until dissolution occurred and then for a further 3 hr. (the solution changed from green, through yellow and orange, to deep red). The cooled solution, when decomposed with ice and 4N-potassium hydroxide, yielded to ether the white product which was used directly in the next stage. 4-*Chloro*-5-*methoxycinnoline* gave needles, m. p. 141—142° (Found: C, 55·65; H, 3·6. $C_9H_7ON_2Cl$ requires C, 55·55; H, 3·6%), from light petroleum.

5-*Methoxy*-4-*toluene*-p-*sulphonylhydrazinocinnoline Hydrochloride*.—The chloro-compound, from the above preparation, in pure dry chloroform (50 c.c.) was mixed with a warm solution of toluene-*p*-sulphonylhydrazide (7 g.) in the same solvent (50 c.c.), and the whole was refluxed for 5 hr. The solvent was removed by evaporation and the orange residue used directly in the next stage. Recrystallisation from ethanol gave yellow prisms of 5-*methoxy*-4-*toluene*-p-*sulphonylhydrazinocinnoline hydrochloride*, m. p. 221° (decomp.) (Found: C, 50·6; H, 4·9. $C_{16}H_{17}O_3N_4ClS$ requires C, 50·5; H, 4·5%).

5-*Methoxycinnoline*.—The powdered crude product above, when added during 10 min. to sodium carbonate (70 g.; anhydrous) in water (700 c.c.) at 95°, gave an orange-red solution which was refluxed for 1 hr., cooled, and extracted with ether. Evaporation of the dried (Na_2SO_4) extract afforded the discoloured product. Three recrystallisations from light petroleum (charcoal) gave cream blades of 5-*methoxycinnoline*, m. p. 92—93·5° (Found: C, 67·4; H, 5·0. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%). The overall yield from 4-hydroxy-5-methoxycinnoline was 34%.

5-*Hydroxycinnoline*.—The pure methoxycinnoline (0·79 g.) and hydrobromic acid (50 c.c.; *d* 1·5) were refluxed for 4 hr. The acid was removed under reduced pressure, and the yellow residue in water (25 c.c.) was brought to pH 6 with aqueous ammonia. The greenish-yellow precipitate (0·6 g.) was collected. 5-*Hydroxycinnoline* gave brownish-yellow cubes, m. p. 285° (decomp.) (Found: C, 65·8; H, 4·2. $C_8H_6ON_2$ requires C, 65·75; H, 4·1%), from ethanol.

5-*Aminocinnoline*.—5-Hydroxycinnoline (0·26 g.), aqueous ammonia (12 c.c.; *d* 0·88) and ammonium hydrogen sulphite (4 c.c. of a solution prepared by saturating concentrated aqueous ammonia with sulphur dioxide) were heated at 100° for 72 hr. in a sealed tube. The cooled mixture when basified with 50% aqueous potassium hydroxide yielded to chloroform a bright yellow solid (0·128 g.). 5-*Aminocinnoline* formed small bright yellow prisms, m. p. 160—161° (Found: C, 65·9; H, 4·9. $C_8H_7N_3$ requires C, 66·2; H, 4·9%), after sublimation at 120°/0·1 mm. and crystallisation from benzene–*cyclo*hexane.

m-*Hydroxyacetophenone Carbonate*.—A solution of *m*-hydroxyacetophenone (13·6 g.), sodium hydroxide (4 g.), water (120 c.c.), and saturated aqueous sodium carbonate (50 c.c.) was saturated with sodium chloride. The carbonate (12·7 g.; m. p. 75—92°) was then formed by Mason's method (*loc. cit.*), collected, washed with water, acetic acid, and again with water, and dried at 60°. The *carbonate* formed colourless plates, m. p. 98—100° (Found: C, 68·7; H, 4·7. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%), from ethanol.

5-*Hydroxy*-2-*nitroacetophenone*.—The carbonate (9·3 g.) and concentrated sulphuric acid (50 c.c.) were stirred at −5° and nitric acid (3·2 c.c.; *d* 1·53) in concentrated sulphuric acid (15·5 c.c.) was added dropwise during 20 min. The deep-orange solution was stirred for a further 1 hr. at −5° and poured on ice. The orange precipitate quickly changed into a plastic solid which was washed with water and dried *in vacuo*, giving 10·9 g. of crude material. A portion of this was triturated with ethyl acetate; the resultant brown powder, on crystallisation from this solvent, gave pale fawn needles of 5-*hydroxy*-2-*nitroacetophenone*, m. p. 146—147° (Found: C, 54·1; H, 4·0. $C_8H_7O_4N$ requires C, 53·1; H, 3·9%).

5-*Methoxy*-2-*nitroacetophenone*.—(i) The above phenol (0·4 g.) and sodium hydroxide (0·15 g.) in water (2 c.c.) were treated at 40° with methyl sulphate (0·5 c.c.). Basification and extraction with chloroform secured the product (0·21 g.). 5-*Methoxy*-2-*nitroacetophenone* gave colourless crystals, m. p. 69—70° (Found: C, 55·4; H, 4·6%), from benzene–light petroleum (b. p. 60—80°).

(ii) 5-Methoxy-2-nitrobenzoic acid (20 g.) was converted into the ketone (11 g.) as described for the 6-isomer, except that 1·1 equivs. of ethoxymagnesiomalonic ester were used.

2-*Amino*-5-*methoxyacetophenone*.—The above (29 g.), reduced similarly to the 6-isomer, gave a bright yellow oil (22·25 g.), b. p. *ca.* 170°/18 mm., which solidified. Recrystallised from ether–light petroleum, the *amine* formed yellow cubes, m. p. 55—55·5° (Found: C, 65·4; H, 6·5. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7%).

4-*Hydroxy*-6-*methoxycinnoline*.—Prepared from the amine (10 g.), as described for the 5-isomer, the cinnoline (5·7 g.) formed from water colourless needles, m. p. 252° (Found: C, 61·9; H, 4·8. Calc. for $C_9H_8O_2N_2$: C, 61·4; H, 4·6%), alone and with a specimen prepared by the method of Schofield and Simpson (*loc. cit.*).

6-*Methoxy*-4-*toluene*-p-*sulphonylhydrazinocinnoline*.—4-Chloro-6-methoxycinnoline (5·9 g.; Keneford and Simpson, *J.*, 1947, 917), dry chloroform (200 c.c.) and toluene-*p*-sulphonylhydrazide (12 g.) were refluxed for 24 hr. and kept 1 week at room temperature. After evaporation of the mixture to half volume the red product (10·1 g.) (probably the hydrochloride) was collected. Recrystallisation from ethanol gave cream flocks of 6-*methoxy*-4-*toluene*-p-*sulphonylhydrazinocinnoline hydrate*, m. p. 199—201° (decomp.) (Found: C, 52·7; H, 4·7. $C_{16}H_{16}O_3N_4S,H_2O$ requires C, 53·0; H, 5·0%).

6-*Methoxycinnoline*.—The above compound (5·2 g.) was added during 10 min. to potassium carbonate (50 g.) in water (500 c.c.) at 95° and the solution was refluxed for 4 hr. Ether extracted a reddish solid which was passed in benzene over a short alumina column. The pale pink solid (1·4 g.) recovered from the eluate gave colourless needles of 6-*methoxycinnoline*, m. p. 87—88° (Found: C, 59·9; H, 5·7. $C_9H_8ON_2,H_2O$ requires C, 60·7; H, 5·7%), from light petroleum.

6-*Hydroxycinnoline*.—Prepared from the methoxy-compound (0·20 g.) as in the 5-series, 6-*hydroxycinnoline* (0·148 g.) formed cream, fluffy needles, m. p. >300° (blue-black at *ca.* 195°) (Found: C, 65·3; H, 4·2%), from water.

6-*Aminocinnoline*.—The hydroxy-compound (from 0·2 g. of 6-methoxycinnoline), ammonium hydrogen sulphite solution (3 c.c., prepared as before) and aqueous ammonia (10 c.c., *d* 0·88) were heated at 100° for 60 hr. in a sealed tube. Orange crystals (0·100 g.) were removed from the cooled mixture, and the filtrate was basified with 10N-potassium hydroxide and extracted with chloroform. The extract provided a solid (35 mg.) which formed bright yellow needles, m. p. 204°, when sublimed at 160°/0·5 mm. The products (0·135 g.) were combined and crystallised from benzene, giving deep yellow prisms of the *amine*, m. p. 203—204° (Found: C, 66·2; H, 5·05%).

4-*Methoxy*-2-*nitroacetophenone*.—4-Methoxy-2-nitrobenzoic acid (40 g.), by the method used for the 6-isomer, gave the *ketone* (27 g.), which formed pale yellow crystals, m. p. 49—50° (Found: C, 56·0; H, 4·6%), from ether–light petroleum.

2-*Amino*-4-*methoxyacetophenone*.—The nitro-compound (24 g.) gave in the usual way the *amine* (17·1 g.), which formed pale yellow, chunky crystals, m. p. 120—121° (Found: C, 65·6; H, 6·6%), from benzene–light petroleum (b. p. 60—80°).

4-*Hydroxy*-7-*methoxycinnoline*.—Prepared from the amine (7·9 g.) by the procedure described for the 8-isomer (Alford *et al.*, *loc. cit.*), 4-*hydroxy*-7-*methoxycinnoline* (5·3 g.) formed needles, 255—257° (Found: C, 61·4; H, 4·6%), from water.

4-*Chloro*-7-*methoxycinnoline*.—The hydroxycinnoline (5 g.) and phosphorus oxychloride (30 c.c.) were refluxed for 2 hr. Decomposition with ice and sodium hydroxide gave a precipitate which was collected, washed with water, dried, and extracted (Soxhlet) with light petroleum. 4-Chloro-7-methoxycinnoline (5·0 g., 90%) seperated as needles, m. p. 178—179° (Found: C. 55·2; H, 3·9. $C_9H_7ON_2Cl$ requires C, 55·55; H, 3·6%).

7-*Methoxy*-4-*toluene*-p-*sulphonylhydrazinocinnoline Hydrochloride*.—Formed from the chlorocinnoline (13 g.) and toluene-*p*-sulphonylhydrazide (26 g.) in chloroform (1200 c.c.) after refluxing for 12 hr. and being kept for 1 week at room temperature, this *compound* (24 g.) formed small bright red crystals, m. p. 169—172° (decomp.) (Found: C, 48·2; H, 5·0. $C_{16}H_{17}O_3N_4ClS,H_2O$ requires C, 48·2; H, 4·8%), from ethanol–ether.

7-*Methoxycinnoline*.—The above compound (24 g.), decomposed as described for the 5-isomer, the solution being refluxed for 3 hr., yielded upon continuous ether-extraction a red solid, which was extracted (Sohxlet) with boiling light petroleum. Evaporation afforded 7-*methoxycinnoline* (6·95 g.), which formed needles, m. p. 109—110° (decomp.) (Found: C, 60·4; H, 5·9; N, 16·3. $C_9H_8ON_2,H_2O$ requires C, 60·7; H, 5·7; N, 15·7%), from this solvent. Another experiment gave a product, m. p. 61—63° (decomp.) (Found: C, 62·8; H, 5·6. $C_9H_8ON_2,\frac{2}{3}H_2O$ requires C, 62·8; H, 5·5%), apparently differing in the degree of hydration.

7-*Hydroxycinnoline*.—The methoxy-compound (6·8 g.), demethylated as before, gave 7-*hydroxycinnoline* (3·7 g.), which after crystallisation from water and then ethanol gave needles, m. p. >300° (turning blue-black at *ca.* 200°) (Found: C, 64·3; H, 4·3%).

7-*Aminocinnoline*.—The hydroxy-compound (0·2 g.) gave in the usual way a yellow solid (142 mg.). After sublimation (130°/0·4 mm.) and crystallisation from ethyl acetate the *amine* formed yellow needles, m. p. 191—192° (Found: C, 66·2; H, 4·9; N, 28·9. $C_8H_7N_3$ requires C, 66·1; H, 4·8; N, 29·0%).

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