440. *Cinnolines. Part XXVII.* The Preparation and Nitration of Cinnoline.*

By J. S. Morley.

Nitration of cinnoline in concentrated sulphuric acid gives 8-nitrocinnoline and an isomeric mononitrocinnoline in approximately equal proportion; the latter differs from 6-nitro- and 7-nitro-cinnoline and is regarded as the 5-nitro-compound. Cinnoline is best prepared by decarboxylation of cinnoline-4-carboxylic acid in benzophenone during which 4 : 4′-dicinnolyl is formed as a minor product. Catalytic reduction of 4-chloro- or 4 : 7-dichloro-cinnoline gives only a little cinnoline or 7-chlorocinnoline; in the former case the main product is 4 : 4′-dicinnolyl.

As one extension of the previous work on the comparative chemistry of simple heterocyclic systems (Simpson *et al.*, *J.*, 1948, 360; 1949, 1014, 1354, 1356; 1950, 1104), it is planned to study the qualitative nitration of the bicyclic bases under comparable conditions. In this respect, the nitration of quinoline and *iso*quinoline is well known and that of quinazoline has recently been described (Elderfield *et al.*, *J. Org. Chem.*, 1947, **12**, 405; Schofield and Swain,

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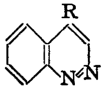
* Part XXVI, *J.*, 1950, 392.

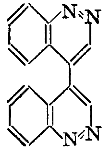
J., 1949, 1367). The present paper describes preliminary work on the preparation and nitration of cinnoline (I; R = H).

Cinnoline was first prepared by reduction of 4-chlorocinnoline (I; R = Cl) with iron and 15% sulphuric acid to 1 : 2-dihydrocinnoline, which gave cinnoline when oxidised with mercuric oxide (Busch and Rast, *Ber.*, 1897, **30**, 521). In contrast, catalytic hydrogenation of (I; R = Cl) with palladium on calcium carbonate, under conditions which convert 4-chloroquinazoline into 3 : 4-dihydroquinazoline in almost quantitative yield (Elderfield *et al.*, *loc. cit.*, and confirmed), gave only a trace of cinnoline, the main product being a compound, m. p. 232°, analysis of which suggested 4 : 4′-dicinnolyl (II) (see below). Likewise, catalytic reduction of 4 : 7-dichlorocinnoline gave only a little 7-chlorocinnoline (III; R = Cl), after ferricyanide oxidation.

An alternative route to cinnoline (Jacobs *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1310) is decarboxylation of cinnoline-4-carboxylic acid (I; R = CO_2H), prepared from 4-methylcinnoline (I; R = Me) *via* 4-styrylcinnoline (I; R = CH:CHPh). The conditions and high yields for these reactions were found to be readily reproducible, and since 4-methylcinnoline itself is now prepared in excellent yield from methyl anthranilate (Jacobs *et al.*, *loc. cit.*, and confirmed), this is to be preferred as a preparative route to cinnoline. The final decarboxylation of (I; R = CO_2H) gives, in addition to cinnoline, a small amount (5·6% average yield) of the compound, m. p. 232°, prepared by catalytic reduction of 4-chlorocinnoline; this can therefore be regarded as 4 : 4′-dicinnolyl (II).



(I.)



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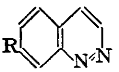

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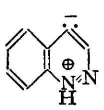

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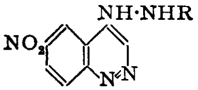

(V.)

The production of (II) by decarboxylation of (I; R = CO_2H) in benzophenone is of interest in that Brown, Hammick, and Thewlis (*Nature*, 1948, **162**, 73) report that, under similar conditions, the related quinoline-4-carboxylic acid gives 7—10% of diphenyl-4-quinolylcarbinol, and Mislow (*J. Amer. Chem. Soc.*, 1947, **69**, 2559) has shown that *iso*nicotinic acid gives 3·5% of diphenyl-4-pyridylcarbinol. If, as seems probable from analogy with the work of Hammick *et al.* (*J.*, 1937, 1724; 1939, 809; 1949, 173, 659; *Nature*, *loc. cit.*), the decarboxylation of (I; R = CO_2H) occurs *via* the protonised cinnolyl anion (IV), then the reason for the formation of (II) in preference to a carbinol such as is formed in the quinoline and pyridine series, may well lie in changes governing the competition of the intermediate anion, on the one hand, and the decarboxylated base or benzophenone on the other, within the three heterocyclic series. The increased reactivity of the 4-position in the cinnoline nucleus towards anionoid reagents in comparison with the quinoline nucleus has already been commented on (Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104).

Nitration of cinnoline in concentrated sulphuric acid gave a mixture of two mononitrocinnolines in good yield, which were readily separated by fractional crystallisation from benzene and sublimation. That least soluble in benzene was identical with a specimen of 8-nitrocinnoline, m. p. 132·5—133·5°, kindly supplied by Dr. K. Schofield (Alford and Schofield, unpublished work). The other nitrocinnoline, m. p. 152—153°, markedly depressed the m. p. of both 6-nitro- (see below) and 7-nitro-cinnoline (III; R = NO_2), m. p. 153—154° (Dr. Schofield); since nitration in the hetero-ring is unlikely in the conditions used, the compound is regarded as 5-nitrocinnoline. Both nitrocinnolines from the nitration were extremely sensitive to warm dilute sodium hydroxide solution, but they were stable to hot 4N-ammonia solution and to mineral acids. 8-Nitrocinnoline was mostly unchanged after being refluxed for a short time with phosphorus pentachloride and oxychloride; reductive acetylation gave 8-acetamidocinnoline in poor yield as the sole identifiable product. 5(?)-Nitrocinnoline gave no useful product on treatment with stannous chloride, iron and acetic acid, hydrogen and palladium or Adams's catalyst, and alkaline sodium dithionite.

4-Chloro-6-nitrocinnoline reacted readily with hydrazine and toluene-*p*-sulphonhydrazide in chloroform giving 4-hydrazino-6-nitrocinnoline (V; R = H) and 6-nitro-4-toluene-*p*-sulphonylhydrazinocinnoline (V; R = *p*-Me·C_6H_4·SO_2). Neither of these hydrazines could be oxidised successfully by aqueous copper sulphate, nor could a crystalline product be obtained by their decomposition with alkalis. However, 4-hydrazino-6-nitrocinnoline gave a hydrazone with acetone, which was readily converted by aqueous copper sulphate oxidation into 6-nitrocinnoline, m. p. 205—206°. This differed from either of the two nitrocinnolines prepared by direct nitration of cinnoline.

Earlier work (Keneford, Morley, Simpson, and Wright, *loc. cit.*) has shown that in reactivity 4-substituted cinnolines occupy a position intermediate between those of quinolines and quinazolines. It is clear, however, that so far as nitration is concerned, cinnoline resembles quinoline, which gives 5- and 8-nitroquinoline in about equal proportions, and is quite distinct from quinazoline, from which only the 6-nitro-compound (56%) has been isolated (Elderfield *et al.*, *loc. cit.*; Schofield and Swain, *loc. cit.*). There are, however, many puzzling features in the nitration of nitrogenous heterocyclic compounds (cf. Schofield, *Quart. Reviews*, 1950, **4**, 382), and the reaction as it applies to benzodiazines cannot be usefully discussed further until more facts are available.

EXPERIMENTAL.

Cinnoline.—The yields of this base and its intermediates in the preparation from methyl anthranilate were in close agreement with those obtained by Jacobs *et al.* (*loc. cit.*) : 2-*o*-aminophenylpropene (86%, methylmagnesium iodide being used); 4-methylcinnoline (90%); 4-styrylcinnoline (theoretical yield on 1-mole scale; m. p. 120—123°; a digestion of the dried, crude hydrochloride with benzene was advantageous); cinnoline-4-carboxylic acid (81% on 0·4-mole scale, an efficient glass stirrer being used); cinnoline (72·5%). Cinnoline hydrochloride monohydrate (long, brittle, pale-green needles from ethanol–ether) melted between 82° and 137° to a clear, pale-green melt, which darkened and decomposed at 205°. Cinnoline, b. p. 114°/0·35 mm., solidified during the distillation; the solid had m. p. 40—41° and slowly liquefied to a green liquid on being set aside in air. There is, however, no appreciable decomposition of the base since cinnoline picrate was formed in quantitative yield from liquid which had been exposed to the atmosphere for two months.

4 : 4′-*Dicinnolyl.*—Cinnoline-4-carboxylic acid was decarboxylated in 5-g. batches by the procedure described by Jacobs *et al.* (*loc. cit.*). The combined reaction mixture from four such runs was dissolved in ether (720 ml.) and extracted with N-hydrochloric acid (400 ml.; in three portions). The acid extracts were then washed once with ether, cooled in an ice-bath, saturated with potassium carbonate, and extracted with ether. 4 : 4′-*Dicinnolyl*, m. p. 233—234°, was obtained by (*a*) evaporation of the ethereal extracts (charcoal) to 300 ml. (0·24 g.; average of two runs), and (*b*) filtration of the remaining aqueous suspension from the extraction, followed by digestion of the residue with water (0·51 g.; average of two runs). After further removal of the ether from the ethereal extracts (corresponding to eight 5-g. decarboxylations), cinnoline (21·7 g.) distilled at 114°/0·35 mm. An additional crop of 4 : 4′-dicinnolyl (0·75 g.; m. p. 204—206°) was obtained by digestion of the residue from this distillation with water (75 ml.); the aqueous digest contained cinnoline, isolated as the picrate (1·22 g.), m. p. 195—196°. Pure 4 : 4′-dicinnolyl (total yield 7·5% based on cinnoline-4-carboxylic acid) formed long, soft, pale-yellow needles, m. p. 237—238°, from aqueous acetic acid (Found : C, 74·2; H, 4·0; N, 21·7. $C_{16}H_{10}N_4$ requires C, 74·4; H, 3·9; N, 21·7%).

Catalytic Reduction of 4-*Chlorocinnoline.*—The chloro-compound (2·0 g.) in methanol (100 ml.) was shaken with palladium hydroxide on calcium carbonate catalyst [10 g., prepared by Busch and Stöve's procedure (*Ber.*, 1916, **49**, 1063)] at room temperature and 4—5 atmospheres' pressure of hydrogen during 15 minutes. Evaporation under reduced pressure of the filtered, deep-red solution gave a sticky, brown solid, which was digested with hot water (40 ml.) and filtered in the cold. The residue (0·46 g.), m. p. 195—197° (decomp.), was insoluble in 2N-sodium hydroxide solution (20 ml.) and gave small, brittle, golden prisms, m. p. 231—232° (mixed m. p. 235—237°), of 4 : 4′-dicinnolyl (0·15 g.) after two recrystallisations from ethanol (7 parts) (Found : C, 73·6; H, 4·2; N, 21·3%). The original aqueous digest, after concentration in a vacuum, was treated with 4N-sodium carbonate solution (15 ml.), the solution filtered from calcium carbonate (0·45 g.), and the filtrate saturated with potassium carbonate. Ether extraction gave a brown oil, which yielded cinnoline picrate (90 mg.), m. p. and mixed m. p. 190—191°, after treatment with alcoholic picric acid.

Catalytic Reduction of 4 : 7-*Dichlorocinnoline.*—The chloro-compound (2·0 g.), hydrogenated exactly as above, gave a residue, after evaporation of the filtered solution, which was dissolved in water (50 ml.). Treatment with 33% potassium hydroxide solution (15 ml.), followed by a solution of potassium ferricyanide (6·5 g.) in hot water (50 ml.) and addition of 33% potassium hydroxide solution (100 ml.) after 10 minutes, gave 7-*chlorocinnoline* (0·29 g.; isolated by ether extraction), which formed fine needles, m. p. 92—93°, from water (in which it was appreciably soluble) (Found : C, 57·9; H, 3·1; N, 17·2. $C_8H_5N_2Cl$ requires C, 58·4; H, 3·05; N, 17·0%).

Nitration of Cinnoline.—Powdered cinnoline (10 g.) was added with stirring during ½ hour to a mixture of concentrated sulphuric acid (50 ml.) and fuming nitric acid (50 ml., *d* 1·50) at −5°. The temperature was then allowed to rise to 20° during 1 hour, the clear, yellow-green solution was then poured on ice (1 kg.), and the mixture partly neutralised with 20% aqueous sodium hydroxide at 0°, and finally made alkaline with solid potassium carbonate. Extraction of the resulting suspension with benzene and concentration of the combined, dried (anhydrous $CuSO_4$) extracts to 50 ml., gave a yellow solid *X* (6·04 g.), m. p. 111—118°, on cooling, and a solid *Y* (4·1 g.), m. p. 117—125°, on further evaporation and addition of light petroleum (b. p. 60—80°).

Recrystallisation of solid *X* from benzene (80 ml.) gave long, yellow needles (3·77 g., 28%), m. p. 135—136°, of 8-*nitrocinnoline* (mother liquors *Z*), which after further recrystallisations melted constantly at 136—138°. There was no depression in m. p. on admixture with genuine 8-nitrocinnoline, m. p. 132·5—133·5°. After adsorption on alumina (Peter Spence, Grade H), and elution with benzene, the nitrocinnoline was recovered almost quantitatively and the m. p. had dropped to 133—134° (m. p. and mixed m. p.), unchanged after recrystallisation (Found: C, 55·1; H, 2·85; N, 23·8. $C_8H_5O_2N_3$ requires C, 54·9; H, 2·9; N, 24·0%).

The mother liquors *Z*, after evaporation to 10 ml., gave a solid (1·84 g.), m. p. 110—114°, which after sublimation at 80°/0·05 mm. and rejection of the first (50 mg.) and later crops, gave a combined sublimate (1·34 g.), m. p. 140—142°, of 5(?)-*nitrocinnoline*. This was likewise obtained from solid *Y* by sublimation at 90°/9·05 mm. (3·06 g.; m. p. of various sublimates, 141—144° to 144—146°). The total yield was 4·4 g. (33%). Repeated sublimation and recrystallisation from absolute ethanol gave mustard-yellow needles of pure 5(?)-nitrocinnoline, m. p. 151—152° (Found: C, 54·9; H, 2·7; N, 24·0%). A mixture with 8-nitrocinnoline had m. p. 111—113°, with 6-nitrocinnoline m. p. 125—126°, and with 7-nitrocinnoline m. p. 113—118°.

Both nitrocinnolines were easily soluble in cold chloroform and acetone, and in hot water, ethanol, benzene and ethyl acetate; 5(?)-nitrocinnoline was, however, very appreciably more soluble in cold benzene and in cold ethyl acetate. 5(?)-Nitrocinnoline, in particular, darkened on storage. Each was recovered unchanged after being refluxed for 1 hour with 2N- or concentrated hydrochloric acid or with 4N-ammonia solution.

Decomposition of the Nitrocinnolines by Sodium Hydroxide Solution.—(*a*) To a solution of 8-nitrocinnoline (100 mg.) in hot water (8 ml.) was added 2N-sodium hydroxide solution (1 ml.); there was an immediate colour change from yellow through deep red to a deep olive-green. Acidification of the cold solution with dilute hydrochloric acid gave a dark amorphous solid (50 mg.), m. p. >300°, soluble in cold alkalis and reprecipitated on acidification, but insoluble in most organic solvents. (*b*) 5(?)-Nitrocinnoline likewise gave an amorphous solid (70 mg.), m. p. >300°.

8-*Acetamidocinnoline.*—8-Nitrocinnoline (1 g.), acetic anhydride (20 ml.), and anhydrous sodium acetate (0·4 g.) were treated at 90—95° with zinc dust (1·5 g.) added during 10 minutes; after a further ½ hour at 90—95°, the suspension was warmed with water (120 ml.), the hot solution filtered (charcoal), and the filtrate neutralised at 0° with 4N-ammonia solution. Extraction with ether (750 ml. in all), and evaporation of the dried (K_2CO_3) extracts, gave a sticky solid residue (0·41 g.), which formed dense prisms, m. p. 174—175°, of 8-*acetamidocinnoline* (0·11 g.) from benzene (5 ml.); after further recrystallisation from benzene–light petroleum (b. p. 60—80°) this melted at 177—178° (Found: C, 64·25; H, 4·5; N, 22·6. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·8; N, 22·45%). The *picrate* formed yellow needles, m. p. 238—239° (decomp.), from aqueous ethanol (Found: C, 45·9; H, 3·15; N, 20·1. $C_{10}H_9ON_3,C_6H_3O_7N_3$ requires C, 46·15; H, 2·9; N, 20·2%). A tan-coloured granular solid (0·29 g.), m. p. 240—242° (decomp.), was obtained from the ammoniacal aqueous phase, from the above ether extraction, by saturation with solid potassium carbonate and extraction with chloroform.

4-*Hydrazino*-6-*nitrocinnoline.*—(*a*) When freshly prepared 4-chloro-6-nitrocinnoline (5 g.), dissolved in cold dry chloroform (100 ml.), was treated with hydrazine hydrate (5 ml.; 90%) and enough absolute ethanol (up to 30 ml.) to give a homogeneous solution, maroon-coloured crystals of the crude hydrazine (5·4 g.), decomposing sharply at 233°, separated after 1 hour, and a further crop (0·3 g.), was obtained by keeping the solution overnight. A solution in N/2-hydrochloric acid was basified with ammonia solution, and a maroon solid, m. p. >330°, was obtained. A suspension of this (0·35 g.) in hot ethanol (50 ml.) was treated with concentrated hydrochloric acid (1—2 ml.) and filtered; golden-coloured needles (0·22 g.) of the *hydrochloride* separated on cooling, which decomposed at 215° (Found: C, 40·3; H, 3·6; N, 27·9; Cl, 14·7. $C_8H_7O_2N_5$,HCl requires C, 39·8; H, 3·35; N, 29·0; Cl, 14·7%).

(*b*) The crude hydrazine (2·2 g.), m. p. >330°, was likewise obtained from the chloro-compound (2 g.), hydrazine hydrate (2 ml.; 90%), and ethanol (100 ml.); the suspension was shaken for 5 minutes, stored overnight, and filtered.

6-*Nitro*-4-iso*propylidenehydrazinocinnoline* (*Acetone* 6-*Nitro*-4-*cinnolylhydrazone*).—The above crude hydrazine (0·5 g.) was refluxed with acetone (50 ml.) for 10 minutes; dilution with water (50 ml.) gave the crude *hydrazone* (0·35 g.), m. p. 176—177°, which formed orange, hair-like needles (or, occasionally, maroon needles), m. p. 179—180°, from aqueous acetone (Found: C, 53·6; H, 4·35; N, 25·65. $C_{11}H_{11}O_2N$ requires C, 53·7; H, 4·55; N, 28·7%).

6-*Nitrocinnoline.*—Acetone 6-nitro-4-cinnolylhydrazone (0·2 g.), water (2 ml.), and 10% aqueous copper sulphate solution (4 ml.) were refluxed for ½ hour; filtration of the hot solution and cooling of the filtrate gave a yellow solid (0·12 g.), which formed yellow needles, m. p. 205—206°, of 6-*nitrocinnoline* after recrystallisation from ethanol (Found: C, 54·7; H, 2·95; N, 24·2, 23·8. $C_8H_5O_2N_3$ requires C, 54·9; H, 2·9; N, 24·0%).

6-*Nitro*-4-*toluene*-p-*sulphonylhydrazinocinnoline.*—Solutions of toluene-*p*-sulphonhydrazide (1·6 g.) and 4-chloro-6-nitrocinnoline (2 g.; freshly prepared) in cold chloroform (each 100 ml.) were mixed and set aside at room temperature for 2 days. After decantation of the supernatant liquid, the dark-red, sticky tar, which had separated, was washed with chloroform and digested with acetone (50 ml.) giving a brown, granular solid (2·02 g.), m. p. 187—189°, which gave the *hydrazine* (1·55 g.) after crystallisation from aqueous acetic acid; the pure compound formed glittering, orange-red needles, m. p. 212—213° (decomp.), from aqueous acetone (Found: C, 49·8; H, 3·4; N, 19·4. $C_{15}H_{13}O_4N_5S$ requires C, 50·1; H, 3·65; N, 19·5%). It had only weak basic properties, formed a deep green solution in dilute sodium hydroxide solution, and was very sparingly soluble in hot ethanol and in hot acetic acid, and insoluble in ether, benzene, and chloroform. When a solution of the hydrazine (0·4 g.) in 0·5N-sodium hydroxide solution (25 ml.) was kept at 90° for 3 hours, nitrogen was evolved but no benzene-soluble material was left; acidification gave a flocculent, dirty-brown, amorphous precipitate, m. p. >300°. The hydrazine was likewise not decomposed smoothly by sodium carbonate–ethylene glycol (cf. Albert and Royer, *J.*, 1949, 1148). It was recovered unchanged after being refluxed for a short period with 3% aqueous copper sulphate solution.

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