123. *Cinnolines. Part XXX.** *The Nature of the* $C_{(3)}$-*Position. The Synthesis of 3-Methyl-, 3-Chloro-, and 3-Bromo-cinnoline ; also, of Cinnoline and the* Bz-*Nitrocinnolines.*

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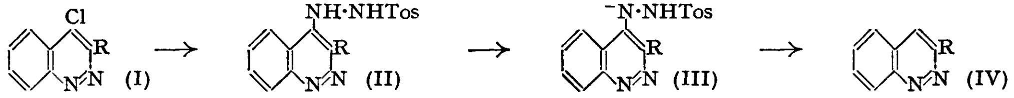
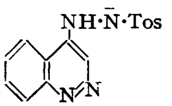
The cinnolines mentioned in the title have been prepared by treating their 4-chloro-derivatives with toluene-*p*-sulphonylhydrazide, and decomposing the resulting 4-toluene-*p*-sulphonylhydrazinocinnolines with aqueous sodium carbonate.

We recently described the synthesis of 3-hydroxycinnoline (*J.*, 1952, 2102) as the beginning of work aimed at establishing the character of the cinnoline $C_{(3)}$-position. Three other compounds necessary for this purpose are now described, and we record the preparation by the same method of cinnoline and the *Bz*-nitrocinnolines.

Since Dewar (*J.*, 1944, 619) first used the method in the quinazoline series, several authors (Albert, Brown, and Duewell, *J.*, 1948, 1284; Albert and Royer, *J.*, 1949, 1148; Clinton, *J. Amer. Chem. Soc.*, 1949, **71**, 755; Badger, Seidler, and Thomson, *J.*, 1951, 3207) have removed reactive halogen atoms from heterocyclic compounds by reaction with toluene-*p*-sulphonylhydrazide and decomposition of the product with alkali. Recently Morley (*J.*, 1951, 1971) attempted to use this method to prepare 6-nitrocinnoline, but, although 4-chloro-6-nitrocinnoline reacted readily with the hydrazide, the resulting 6-nitro-4-toluene-*p*-sulphonylhydrazinocinnoline gave none of the desired product when treated with sodium carbonate. In contrast, the corresponding intermediate from 4-chloro-8-methoxycinnoline gave good yields of 8-methoxycinnoline (Alford, Marsh, Irving, and Schofield, *J.*, 1952, 3009), and the method has been applied satisfactorily to a number of 4-chlorocinnolines (I), as is now described.



(I) (II) (III) (IV)



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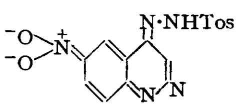

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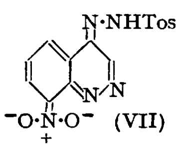

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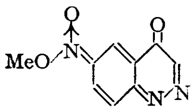

(VIII)

$(\text{Tos} = p\text{-C}_6\text{H}_4\text{Me·SO}_2)$

Cinnoline itself was readily prepared by this procedure. In small-scale experiments the recovery of (II; R = H) as its hydrochloride, after treatment of 4-chlorocinnoline with two equivalents of toluene-*p*-sulphonylhydrazide in chloroform, was almost quantitative, but was reduced on the larger scale, probably because of the instability of 4-chloro-

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* Part XXIX, *J.*, 1952, 3009.

cinnoline. Hot aqueous sodium carbonate converted (II; R = H) into cinnoline in 80% yield. The method represents a practicable synthesis of cinnoline, but is probably not so convenient as that described by Jacobs, Winstein, Henderson, and Spaeth (*J. Amer. Chem. Soc.*, 1946, **68**, 1310; cf. Morley, *loc. cit.*).

Equally satisfactory were the results with 4-chloro-3-methyl-, 3-bromo-4-chloro-, and 3 : 4-dichloro-cinnoline.

Morley (*loc. cit.*) obtained two mononitro-derivatives, m. p. 135—136° and 151—152°, by nitrating cinnoline, and the availability of the 4-chloro-*Bz*-nitrocinnolines (Schofield and Simpson, *J.*, 1945, 512; Schofield and Theobald, *J.*, 1949, 2404) offered a means of orienting these products. The 4-chloro-nitrocinnolines reacted readily with toluene-*p*-sulphonylhydrazide. The crude crystalline products of type (II) underwent characteristic colour changes during crystallisation from acetic acid: the 6-nitro-compound changed from purple to reddish-orange, the 7-nitro-isomer from red to orange, and the 8-nitro-derivative from pink to brownish-red. The pure products proved to be the free bases, and the colour changes may have signified the decomposition of the original crude hydrochlorides. When treated with aqueous ammonia or sodium carbonate the nitro-4-toluene-*p*-sulphonylhydrazinocinnolines produced characteristically coloured solutions (reddish-brown with the 5- and the 7-nitro-compound, purplish-red and intense purple with the 6- and the 8-isomer respectively). The colours are possibly due to anions of the type (III) [which might be tautomeric with (V) (Limpricht, *Ber.*, 1887, **20**, 1238; Albert and Royer, *loc. cit.*)], and the resonance forms (VI) and (VII) would explain the special intensity of those observed with the 6- and the 8-nitro-compound. With warm aqueous sodium carbonate the colours were gradually destroyed, and moderate yields of 7- and 8-nitrocinnoline were obtained. Like Morley (*loc. cit.*) we were unable to isolate even a trace of 6-nitrocinnoline. Although 6-nitrocinnoline is unstable towards hot alkali (Morley, *loc. cit.*), we believe that the complete failure to secure it in the present case was due rather to the nature of the intervening anion (VI). It is striking that the *aci*-derivative (VIII), of similar structure, is rapidly destroyed by alkali (Schofield and Simpson, *J.*, 1945, 512; Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104). Because of the relative inaccessibility of 4-chloro-5-nitrocinnoline, 5-nitrocinnoline was obtained only in very small amount. The nitration products of cinnoline, m. p. 135—136° and 151—152°, proved to be identical (mixed m. p.) with 8- and 5-nitrocinnoline respectively. Thus, in its orientation the nitration resembles that of quinoline (Schofield, *Quart. Reviews*, 1950, **4**, 382).

3-Methylcinnoline, a pale yellow solid, possessed a characteristic somewhat sickly smell, very similar to that of cinnoline. Like cinnoline it liquefied in air, but more slowly. The other cinnolines described in this paper did not do this, and were odourless. Cinnoline and 3-methylcinnoline were readily soluble in water, whilst 3-chloro-, 3-bromo-, and 5-, 7-, and 8-nitro-cinnoline could be crystallised from this solvent.

EXPERIMENTAL

All extracts and the chloroform used were dried over anhydrous sodium sulphate.

Cinnoline.—4-Hydroxycinnoline (10 g.) and phosphorus oxychloride (30 c.c.) were refluxed together until dissolution occurred (cf. Schofield and Swain, *J.*, 1950, 384), and then warmed ½ hour at 95°. The product (isolated in the usual way) in chloroform (50 c.c.) was added to toluene-*p*-sulphonylhydrazide (25 g.) (Albert and Royer, *J.*, 1949, 1148) in the same warm solvent (800 c.c.). The red crystals formed were collected after about 1 week (total yield from 30 g. of 4-hydroxycinnoline : 71·5 g., 59%; m. p. 198—200°). The loss probably occurred in the chlorination stage, for small-scale experiments gave quantitative yields based on the 4-chlorocinnoline used. Several crystallisations from acetic acid gave 4-*toluene*-p-*sulphonylhydrazinocinnoline hydrochloride* as crimson needles, m. p. 224—226° (with darkening) (Found : C, 50·6; H, 4·4; N, 15·0. $C_{15}H_{14}O_2N_4S,HCl$ requires C, 51·35; H, 4·3; N, 16·0%).

The above compound (1 g.) was added in portions to sodium carbonate (2 g.; anhyd.) in water (20 c.c.) at 95°. The clear yellow solution formed soon became brown, and deposited some amorphous matter. After being refluxed for ¼ hour the mixture was filtered, and the filtrate was extracted with ether. Removal of the solvent left a brown oil which solidified when chilled. With picric acid in hot alcohol this formed large amber crystals of cinnoline picrate (0·82 g., 80%), m. p. 191—193°, alone and mixed with an authentic specimen.

3-*Methylcinnoline*.—4-Hydroxy-3-methylcinnoline (10 g.; Keneford and Simpson, *J.*, 1948, 354), treated as above, gave 3-*methyl*-4-*toluene*-p-*sulphonylhydrazinocinnoline hydrochloride* (21 g., 92% calc. on 4-hydroxy-3-methylcinnoline) as pink rosettes, m. p. 186—187° (decomp.) (from acetic acid) (Found: C, 52·4; H, 4·5; N, 14·3. $C_{16}H_{16}O_2N_4S,HCl$ requires C, 52·65; H, 4·7; N, 15·35%). Decomposition of this (1 g.) as above gave a red oil (0·42 g.), and thence 3-*methylcinnoline picrate* (86%, crude), khaki prisms, m. p. 175—176·5° (from dioxan) (Found: C, 48·6; H, 2·9. $C_9H_8N_2,C_6H_3O_7N_3$ requires C, 48·3; H, 2·9%).

The product obtained from 14 g. of the toluenesulphonylhydrazine crystallised when cooled. Distillation gave a pale yellow oil (5·08 g., b. p. 106—111°/0·3—0·4 mm.) which crystallised. 3-*Methylcinnoline* separated from ether–light petroleum (b. p. 40—60°) as pale yellow plates, m. p. 58·5—61° (Found: C, 74·9; H, 5·75. $C_9H_8N_2$ requires C, 75·0; H, 5·6%).

3-*Chlorocinnoline*.—3 : 4-Dichlorocinnoline (3·47 g.; Schofield and Swain, *loc. cit.*) and toluene-*p*-sulphonylhydrazide (6·6 g.) were allowed to react in chloroform (200 c.c.). The product (6·83 g., 98%) was deposited in several crops during a fortnight. Slightly impure 3-*chloro*-4-*toluene*-p-*sulphonylhydrazinocinnoline* formed almost colourless crystals, m. p. 167—169° (Found: C, 50·8; H, 4·2. $C_{15}H_{13}O_2N_4SCl$ requires C, 51·6; H, 3·8%), from acetic acid.

The above compound (5·8 g.) was decomposed in the usual way, except that the solution was finally refluxed for 1½ hours. The solution was then filtered from some purple material. Most of the product crystallised on cooling, and more was obtained by extraction with chloroform (total yield: 1·8 g., 75%). 3-*Chlorocinnoline* formed needles, m. p. 90—91° (Found: C, 58·6; H, 3·0. $C_8H_5N_2Cl$ requires C, 58·35; H, 3·1%), from ligroin (b. p. 80—100°).

3-*Bromocinnoline*.—3-Bromo-4-hydroxycinnoline (0·5 g.) and phosphorus oxychloride (3 c.c.) were refluxed for 3 minutes (Schofield and Swain, *loc. cit.*). 3-*Bromo*-4-*chlorocinnoline* (0·54 g., 100%), isolated in the usual way, crystallised from acetone as lemon-yellow blades, m. p. 153—154° (Found: C, 40·1; H, 1·85. $C_8H_4N_2ClBr$ requires C, 39·5; H, 1·6%). This (8 g.) and toluene-*p*-sulphonylhydrazide (15 g.) in chloroform (600 c.c.) gave after a few days 3-bromo-4-toluene-*p*-sulphonylhydrazinocinnoline as a pink solid [14·32 g., m. p. 187—189° (decomp.)] which was not analysed. This (10·6 g.) was decomposed with aqueous sodium carbonate as in the case of the 3-chloro-compound. Some insoluble reddish-brown material was formed and the solution acquired a faint blue fluorescence. After filtration and cooling the product crystallised. It was isolated in the same way as 3-chlorocinnoline. Crystallisation from ligroin (b. p. 80—100°) gave 3-*bromocinnoline* (4·16 g., (80%), m. p. 92—93° (Found: C, 45·7; H, 2·1. $C_8H_5N_2Br$ requires C, 45·95; H, 2·4%). The *picrate* formed yellow prisms, m. p. 118—120° (Found: C, 39·3; H, 1·9. $C_8H_5N_2Br,C_6H_3O_7N_3$ requires C, 38·4; H, 1·8%). 3-Bromo- and 3-chloro-cinnoline showed a mixed m. p. depression of only 2°.

Nitrocinnolines.—2-Amino-nitroacetophenones were obtained by oxidising the 2 : 3-dimethyl-*Bz*-nitroindoles (Schofield and Theobald, *J.*, 1949, 796). Appreciably better yields of the 2-acetamido-nitroacetophenones were gained by modification of the conditions: 2 : 3-dimethyl-7-nitroindole (55 g.) gave 61% of 2-acetamido-3-nitroacetophenone when the stirred reaction mixture (Schofield and Theobald, *loc. cit.*) was kept at 30—35° during the addition of the chromic acid solution, and then stirred for ½ hour at room temperature before being left overnight. On the same scale the appropriate indole provided 57% of 2-acetamido-5-nitroacetophenone. Similarly, in oxidising 6- and 4-nitro-2 : 3-dimethylindole, by keeping the reaction temperatures at 5—12° and 20—25°, the yields of 2-acetamido-4- and 2-acetamido-6-nitroacetophenone were improved to 39% and 46% respectively.

4-Hydroxy-8-nitrocinnoline was best prepared as follows: 2-amino-3-nitroacetophenone (6 g.) in acetic acid (40 c.c.) was stirred and treated with ice-cold sulphuric acid (10 c.c. of concentrated acid and 2 c.c. of water) at <15°. Powdered sodium nitrite (2·7 g.) was then added at 0—5°, and the mixture was kept at 0° overnight and then 2 days at room temperature, before being heated at 95° for ¾ hour. The product (4·37 g.) was precipitated with water, and crystallised from alcohol, giving yellow needles (3·5 g., 55%), m. p. 183—185°.

The 4-chloro-nitrocinnolines were prepared in the usual way. 4-Chloro-8-nitrocinnoline (2·03 g.) in chloroform (90 c.c.) was treated with toluene-*p*-sulphonylhydrazide (4·0 g.) in the same solvent (160 c.c.), and the product (4·2 g.) was collected after 1 week. Initially pink, 8-*nitro*-4-*toluene*-p-*sulphonylhydrazinocinnoline* gave brown needles, m. p. 195—196° (decomp.) (Found: C, 50·2; H, 3·4. $C_{15}H_{13}O_4N_5S$ requires C, 50·1; H, 3·65%), after several crystallisations from acetic acid.

In the same way 4-chloro-6-nitrocinnoline (0·5 g.), toluene-*p*-sulphonylhydrazide (0·9 g.), and chloroform (25 c.c.) gave at first an oil which slowly crystallised and was collected after 1 week (yield, 0·94 g.). One crystallisation provided red prisms of 6-nitro-4-toluene-*p*-sulphonylhydrazinocinnoline, m. p. 190—192° (decomp.) (Found : C, 49·4; H, 3·9%). Morley (*loc. cit.*) gave m. p. 212—213° (decomp.), and the temperature of decomposition may depend on the rate of heating.

Similarly, 4-chloro-7-nitrocinnoline (0·47 g.) gave a product (0·87 g., 98%) which though initially an oil, soon crystallised. Recrystallisation from acetic acid gave at first small red prisms, and finally clusters of orange crystals of 7-*nitro*-4-*toluene*-p-*sulphonylhydrazine*, m. p. 195—196° (decomp.) (Found : C, 50·35; H, 3·55%).

The 5-nitro-compound was obtained as above, but was not analysed.

8-Nitrotoluenesulphonylhydrazinocinnoline (0·57 g.) was added in portions to sodium carbonate (5·7 g.; anhyd.) in water (57 c.c.) at 95°. Heating was continued for ¼ hour and the mixture was then refluxed for ¾ hour, whereupon the intense purple colour was destroyed. The mixture was extracted with ether, and the product was crystallised from water, giving 0·09 g. (36%) of fairly pure material. 8-Nitrocinnoline formed yellow needles, m. p. 132—132·5° (Found : C, 54·5; H, 3·05; N, 23·2. Calc. for $C_8H_5O_2N_3$: C, 54·85; H, 2·9; N, 24·0%). The m. p. was not depressed by admixture with the lower-melting nitration product of cinnoline (Morley, *loc. cit.*).

Obtained in the same way, 7-*nitrocinnoline* (51% yield) separated from water as light yellow crystals, m. p. 153—154·5° (Found : C, 54·8; H, 2·85%).

5-Nitrocinnoline prepared by this method formed yellow needles, m. p. 147—148·5°, from water. Morley (*loc. cit.*) recorded m. p. 151—152° for the second nitration product of cinnoline. A somewhat darkened specimen (these compounds deteriorate on keeping), kindly supplied by Dr. Morley, melted at 146—148° after crystallisation from water, and a mixture with the authentic 5-nitro-compound at 147—148°.

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