328. *Cinnolines. Part XIV. N-Oxides of 4-Arylcinnolines. Conversion of 4-Substituted Cinnolines into Indoles.*

By C. M. Atkinson and J. C. E. Simpson.

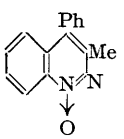
Treatment of 4-arylcinnolines with hydrogen peroxide in acetic acid gives the corresponding *N*-oxides. In contrast to 3 : 4-benzocinnoline *N*-oxide (III) (King and King, *J.*, 1945, 824), *4-phenyl-3-methylcinoline* N-*oxide* (I) is not nitrated selectively, four isomeric mono-nitro-derivatives being obtained.

Alkaline reduction of 4-substituted cinnolines leads to formation of the corresponding indoles; with 6- and 7-chloro-3-methylcinnoline reductive dehalogenation also occurs, and skatole is produced.

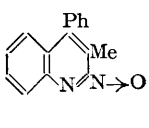
Although formally comparable cinnolines, quinolines, and quinazolines have certain reactions in common, this is not always so (cf. Schofield and Simpson, *J.*, 1946, 472; Simpson, J. 1946, 1035; and unpublished work), and in attempting to account for the properties of certain types of cinnoline derivatives, the following * experiments were carried out to examine the possibility that this heterocyclic group might retain some of the characteristics of azo-compounds.

In the first place, we have found that 4-arylcinnolines are readily converted into *N*-oxides on treatment with hydrogen peroxide in acetic acid. This reaction was tried with 4-phenyl-3-methyl-, 4-phenyl-3-benzyl-, 3-phenyl-4-*p*-anisyl-, 4-*p*-anisyl-3-methyl, and 3 : 4-diphenylcinnoline, and in each case the corresponding N-*oxide* was isolated in good yield. This result was not of direct diagnostic value, for although the oxidation of azo- to azoxy-compounds can be effected under somewhat similar conditions (*Chem. Reviews*, 1931, **9**, 126), the formation of *N*-oxides is likewise characteristic of many heterocyclic types, *e.g.*, pyridines and quinolines (Meisenheimer, *Ber.*, 1926, **59**, 1848), phenanthrolines (Linsker and Evans, *J. Amer. Chem. Soc.*, 1946, **68**, 403), and quinoxalines (McIlwain, *J.*, 1943, 322; Linsker and Evans, *loc. cit.*, and p. 874), although the cinnoline *N*-oxides, in contrast to the quinoxaline derivatives (McIlwain, *loc. cit.*), showed complete absence of peroxidic properties.

Our experiments with 4-methylcinnolines (this vol., p. 808) and with certain *N*-alkylcinnolinium salts (following paper) have indicated that the cinnoline *N*-oxides should be formulated as (I) and not as (II). If (I) is properly regarded as a vinylogue of an azoxy-compound, it should undergo preferential substitution in the 4-phenyl group. The nitration of (I) was therefore examined, but proved to be unexpectedly complex, and gave rise to four isomers, designated α-, β-, γ-, and δ-*nitro-4-phenyl-3-methylcinnoline* N-*oxide*; there was no evidence of the formation of dinitro-compounds.



(I.)



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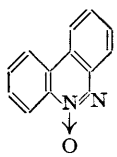


(III.)

No definite conclusion regarding the azoxy-compound-like nature of 4-arylcinnoline *N*-oxides can be drawn from these results, but the complete lack of any selective attack on the molecule was unexpected, and is in marked contrast to the results of King and King (*J.*, 1945, 824) which appeared after the present work had been discontinued. These workers investigated the nitration of 3 : 4-benzocinnoline *N*-oxide (III), and, arguing from essentially the same premises as ourselves, anticipated and encountered nitration almost exclusively in one position, which was assumed to be in the ring remote from the *N*-oxide linkage.

As an alternative approach to the discovery of azo-compound characteristics in 4-substituted cinnolines, we turned our attention to the reduction of such compounds with sodium and alcohol. 4-Phenyl-3-methylcinnoline gave a mixture of unchanged material (1 part) and 3-phenyl-2-methylindole (2·5 parts), and when the reaction was extended to other compounds it was evident that indole formation, accompanied by evolution of ammonia, is the predominating reaction. The results are summarised in the following table, in which the figures (representing ammonia values expressed as percentages of the amounts corresponding to complete conversion into indole) indicate the extent of the reaction. Examination of the products of reduction gave the following results. From (i) only the indole was isolated. In experiments (ii) and (vi) both the indole and unchanged material were identified. Experiment (v) gave an oil,

* It has been necessary temporarily to discontinue our study of 4-arylcinnolines, and the experiments with such compounds recorded in this and the following paper are therefore incomplete.

(iii) gave an unidentified mixture, and (iv) gave an oil together with unchanged cinnoline. Skatole and 4-methylcinnoline were obtained from (vii) and also from (ix), and (viii) yielded skatole and (as picrate) a substance which was not identical with the picrate of 4-methylcinnoline or of its 6- and 7-chloro-derivatives.

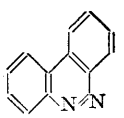
Cinnoline.	NH_3 evolved, %.	Cinnoline.	NH_3 evolved, %.
(i) 4-*p*-Anisyl-3-methyl-	58	(vi) 4-*p*-Hydroxyphenyl-	53
(ii) 4-*p*-Hydroxyphenyl-3-methyl- ...	55	(vii) 4-Methyl-	65
(iii) 3-Phenyl-4-*p*-anisyl-	3	(viii) 6-Chloro-4-methyl-	57
(iv) 3-Phenyl-4-*p*-hydroxyphenyl- ...	1	(ix) 7-Chloro-4-methyl-	60
(v) 4-*p*-Anisyl-	15		

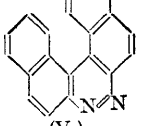
The production of 3-methylindole from each of the 4-methylcinnolines is noteworthy. It is possible that the chloro-indole may be formed and may then undergo further reduction, but the results of (ix) indicate that, in this case at least, dehalogenation of the cinnoline occurs more readily than ring-contraction. The unidentified picrate from (viii) might well be that of 5-chloro-3-methylindole, but owing to interruption of the work it has not been possible to investigate this point.

The *indoles* obtained from (i), (ii), and (vi) are apparently new compounds, and their orientation is based on the assumption (which appears to be justified by the formation of skatole and 3-phenyl-2-methylindole) that the ring-contraction is not accompanied by any form of molecular rearrangement.

A comparison of (i) with (v) and of (v) with (vi) suggests that a 3-methyl group and a *p*-hydroxyl group (in the 4-phenyl substituent) both favour the reaction as compared with hydrogen and a methoxyl group respectively; a 3-phenyl group, on the other hand, has a strongly inhibitory effect in conjunction with a 4-aryl group. The contrast between (v) and (vi—ix) seems to indicate that the normal electromeric effect of the 4-substituent is not the sole controlling influence, and it is possible that chemical and spatial factors are both involved. This conclusion is supported by the following evidence from the literature, which, taken in conjuction with our own results, indicates that the tendency of cinnolines to pass into indoles is markedly dependent on the nature and degree of substitution in the pyridazine ring.

(*a*) Neber, Knöller, Herbst, and Trissler (*Annalen*, 1929, **471**, 113), working with various acid reducing media, found that 4-phenylcinnoline yielded 3-phenylindole *via* 4-phenyl-1 : 2-dihydrocinnoline, and that oxindole was formed from 3-hydroxycinnoline; no indoxyl or indigo derivative resulted, however, from 4-hydroxycinnoline, which (with hydriodic acid and red phosphorus) gave 4-hydroxytetrahydrocinnoline hydriodide. (*b*) 3 : 4-Benzocinnolines of type (IV) are more stable, as they are themselves produced from 2 : 2′-dinitrodiaryls by reduction in alkaline or acid media or electrolytically (Täuber, *Ber.*, 1891, **24**, 3081; Meyer, *ibid.*, 1893, **26**, 2238; Ullmann and Dieterle, *ibid.*, 1904, **37**, 23), and 5 : 6-benzo-1′ : 2′ : 4 : 3-naphthocinnoline (V) is also formed in an alkaline reducing medium (from β-nitronaphthalene; Meisenheimer and Witte, *Ber.*, 1903, **36**, 4153). (*c*) If it is assumed that the ammonia evolved in the cinnoline→indole reaction is formed by ring-closure of an intermediate diamine, then


(IV.)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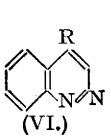

(VI.)

a comparable variation in stability may also be discerned among the diamines corresponding to types (VI), (IV), and (V). Thus the diamines derived from a 4-substituted cinnoline (VI; R = Ar or Me) do not survive the reaction conditions used (sodium and alcohol), but they have been isolated from compounds of type (IV) (King and King, *loc. cit.*) and from (V) (Meisenheimer and Witte, *loc. cit.*). (*d*) Formation of the pyridazine ring [regeneration of type (IV)] from 2 : 2′-diaminodiaryls occurs at least as readily (Täuber, *Ber.*, 1893, **26**, 1703; 1896, **29**, 2270; Dobbie, Fox, and Gauge, *J.*, 1911, 1615; Sandin and Cairns, *J. Amer. Chem. Soc.*, 1936, **58**, 2016) as does the conversion of such compounds into carbazoles (formation of the pyrrole ring) (Täuber, *locc. cit.*; Meisenheimer and Witte, *loc. cit.*; Dobbie, Fox, and Gauge, *loc. cit.*; King and King, *loc. cit.*). Such variations in stability of the diamines are presumably an indication of the greater degree of ring-strain involved in the carbazole, as compared with the indole, nucleus.

Experimental.

(Melting points are uncorrected.)

4-p-*Hydroxyphenyl*-3-*methylcinnoline*.—4-*p*-Anisyl-3-methylcinnoline (5 g.; *J.*, 1946, 673) was refluxed with hydrobromic acid (37 c.c., *d* 1·5) for 1 hour. The cold mixture was basified (ammonia), the supernatant liquid decanted, and the solid dissolved in aqueous sodium hydroxide, and the combined alkaline solutions were made acid with acetic acid. 4-p-*Hydroxyphenyl*-3-*methylcinnoline* (yield of almost pure compound, 4·4 g.) separated from alcohol in small yellow prisms, m. p. 241—242° (Found: N, 12·2. $C_{15}H_{12}ON_2$ requires N, 11·9%); its solution in warm 2N-sodium hydroxide deposited silky needles of the sodium salt on cooling.

4-p-*Hydroxyphenylcinnoline*.—4-*p*-Anisylcinnoline was prepared by the method of Stoermer and Gaus (*Ber.*, 1912, **45**, 3104), but as a result of its poor crystallising properties was difficult to purify and was most conveniently handled as the hydrochloride, which crystallised well from acetic acid or 2N-hydrochloric acid in bright yellow needles, m. p. 215—217° (decomp.) after shrinking at 195°. The salt (15 g.) was refluxed for 1 hour with hydrobromic acid (105 c.c., *d* 1·45) and the crude hydroxyphenylcinnoline isolated as described above. It was best purified by way of the *acetoxy*-compound [obtained by refluxing the crude base with acetic anhydride (5 parts) for ½ hour], which separated from aqueous alcohol in pale yellow rectangles, m. p. 127·5—128° (Found: C, 72·35; H, 4·8; N, 11·35. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·6; N, 10·6%), and when boiled with 5N-hydrochloric acid was rapidly hydrolysed with quantitative separation of 4-*p*-hydroxyphenylcinnoline hydrochloride, m. p. 270—273° (decomp.); this when boiled with water gave the free base as yellow prisms (from alcohol), m. p. 234—235° (Stoermer and Gaus, *loc. cit.*, give m. p. 230°).

3-*Phenyl*-4-p-*hydroxyphenylcinnoline*.—3-Phenyl-4-*p*-anisylcinnoline (5·5 g.; *J.*, 1946, 673) was refluxed with hydrobromic acid (55 c.c., *d* 1·5) and acetic acid (27·5 c.c.) for 2½ hours; the mixture was cooled, basified with ammonia, and the base recrystallised from acetic acid. 3-*Phenyl*-4-p-*hydroxyphenylcinnoline* (yield of almost pure compound, 4·9 g.) formed almost colourless needles (occasionally thin parallelepipeds), m. p. 283—286° (Found: C, 80·3; H, 4·9. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7%).

Preparation of Cinnoline N-*Oxides*.—The cinnolines (1 part) were dissolved in glacial acetic acid (8—10 parts), hydrogen peroxide (5—8 parts, 30%) added, and the clear solutions heated at 90—95° for 2 hours; the products separated on cooling and, if necessary, dilution with water (yields, 80—90%). 4-*Phenyl*-3-*methylcinnoline* N-*oxide* formed long straw-coloured needles, m. p. 124—125°, from aqueous alcohol or aqueous acetic acid (Found: C, 75·85; H, 5·2; N, 12·0. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·1; N, 11·9%). 4-*Phenyl*-3-*benzylcinnoline* N-*oxide*, colourless needles from aqueous alcohol, had m. p. 110—111° to a turbid melt which cleared at 130° (Found: C, 80·4; H, 4·8; N, 9·4. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·2; N, 9·0%). 3:4-*Diphenylcinnoline* N-*oxide* formed radial clusters of stout yellow prismatic needles, m. p. 196—198° (clear at 202°), from ethyl acetate or acetic acid, and was very sparingly soluble in alcohol (Found: C, 80·4; H, 4·65; N, 9·5. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7; N, 9·4%). 4-p-*Anisyl*-3-*methylcinnoline* N-*oxide* separated from aqueous acetic acid in colourless blades, m. p. 161° (Found: C, 71·9; H, 5·0. $C_{16}H_{14}O_2N_2$ requires C, 72·1; H, 5·3%). 3-*Phenyl*-4-p-*anisylcinnoline* N-*oxide*, light brown blades from aqueous alcohol, had m. p. 176—177° (Found: C, 77·1; H, 4·85. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9%).

Nitration of 4-*Phenyl*-3-*methylcinnoline* N-*Oxide*.—The substance (1·5 g.) was added during 35 minutes to 9 c.c. of a mixture of nitric acid (10·5 c.c., *d* 1·48) and sulphuric acid (3 c.c., *d*. 1·84). After a total of 1½ hours (reaction temperature —13° to —10° throughout the experiment) the solution was poured into water and the precipitated solid filtered off, washed, and digested with alcohol (1·55 g., m. p. *ca.* 160—175°). Material so obtained, representing 2·5 g. of cinnoline oxide, was digested with acetone, and the insoluble fraction repeatedly crystallised from a large volume of this solvent; *α-nitro*-4-*phenyl*-3-*methylcinnoline* N-*oxide* was thus obtained in faintly yellow, microcrystalline nodules, m. p. 256—257° (Found: C, 64·0; H, 3·95; N, 15·2. $C_{15}H_{11}O_3N_3$ requires C, 64·0; H, 3·95; N, 14·9%). This compound was very much less soluble in acetone than the isomers described below; it was insoluble in hot aqueous sodium hydroxide and in 2N-hydrochloric acid, and sparingly soluble in hot 6N-hydrochloric acid.

Attempted fractional crystallisation (from benzene and acetone) of the material in the acetone filtrates from the α-compound gave only a little impure β-compound. A benzene solution (200 c.c.) of the combined fractions was drawn through a 26 cm. column of Merck's alumina (50 g.) prepared with benzene (80 c.c.). The filtrate and successive washings (50 c.c. portions of benzene) were separately evaporated, yielding respectively (*a*) 80 mg., (*b*) 530 mg., (*c*) 530 mg., (*d*) 290 mg., (*e*) 140 mg., and (*f*) 80 mg. Fractions (*a*) and (*b*) were solid, (*c*) and (*d*) semi-crystalline, and (*e*) and (*f*) were brown resins.

A solution of fraction (*b*) in acetone, after removal of a little impure α-compound, gave a product which, after repeated crystallisation from acetone and finally from ethyl acetate, yielded the *β-isomer* as pale yellow, brittle, hexagonal plates, m. p. 235—238° after previous shrinking (Found: C, 63·7; H, 3·75; N, 15·05%).

Fraction (*c*) was similarly freed from a little α-compound; recrystallisation (finally from slightly aqueous acetone) furnished small, soft, lemon-yellow prismatic needles, m. p. 218—219° (clear at 222°) of the *γ-isomer*; a mixture with the β-compound had m. p. 200—220° (Found: C, 63·95; H, 3·95; N, 15·0%). From the filtrates a small amount of the β-compound was isolated by means of ethyl acetate.

Fraction (*d*) (extremely soluble in acetone) was combined with the material remaining in the mother-liquors of fractions (*b*) and (*c*), and the whole fractionated from ethyl acetate; some β-isomer was first removed, and the filtrates then deposited *δ-nitro*-4-*phenyl*-3-*methylcinnoline* N-*oxide*, which separated in rosettes of small colourless needles, m. p. 198—199° (180—188° when mixed with the γ-compound) (Found: C, 64·0; H, 3·8; N, 15·25%).

Owing to the difficulty of separation, it was not possible to assess the relative proportions in which the isomers were present in the crude nitration product.

Reduction of 4-*Substituted Cinnolines*.—(*a*) A solution of 4-phenyl-3-methylcinnoline (2·5 g.) in

alcohol (100 c.c.) was reduced, and the product isolated, as described in (*b*). The oil obtained by evaporation of the washed and dried extract was treated (in alcohol; 20 c.c.) with picric acid (2·5 g.), and the mixture of picrates (3·75 g.) fractionated from alcohol. The least soluble fraction was *4-phenyl-3-methylcinnoline picrate* (1 g.), which formed small brown leaflets or prismatic needles, m. p. 179—181° alone and mixed with an authentic specimen (m. p. 180—181°) (Found: C, 55·85; H, 3·4; N, 15·6. $C_{15}H_{12}N_2,C_6H_3O_7N_3$ requires C, 56·1; H, 3·35; N, 15·6%). The filtrates yielded 3-phenyl-2-methylindole picrate (2·5 g.) as purple needles with a green reflex, m. p. 139—141° (Found: C, 58·0; H, 3·85; N, 13·15. Calc. for $C_{15}H_{13}N,C_6H_3O_7N_3$: C, 57·8; H, 3·7; N, 12·8%) (Trenkler, *Annalen*, 1888, **248**, 106, gives m. p. 141—142°).

(*b*) 4-*p*-Anisyl-3-methylcinnoline (0·01 mol.) in alcohol (150 c.c.) was refluxed and treated with sodium (10 g., *ca.* 20 pieces) during ¾ hour, added through a trap to avoid loss of the evolved gases, which were led *via* the reflux condenser into two flasks containing N/5-hydrochloric acid. After the sodium had dissolved the system was swept out with a slow stream of nitrogen for ½ hour; the mixture was then poured into water (400 c.c.) and extracted with ether. [This procedure was followed in all the experiments described below, and in general at least two runs were carried out for each compound; individual results, of which the ammonia figures on p. 1650 are mean values, agreed within 5—6%. In experiments with cinnolines containing a *p*-hydroxyphenyl group, the alkaline solution from the ether-extraction was acidified to pH 8 with acetic acid and again extracted (such extracts are referred to as "pH 8 fractions"). Separation of the reaction products was only qualitative.] The extract yielded 3-p-*anisyl-2-methylindole* as sole crystalline product, separating from benzene–ligroin (b. p. 40—60°) or from aqueous alcohol in colourless needles, m. p. 127—128° (Found: C, 80·8; H, 6·25. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3%). The *picrate*, prepared in benzene solution, formed almost black, lustrous needles, m. p. 128—130° (Found: C, 56·65; H, 3·95; N, 12·3. $C_{16}H_{15}ON,C_6H_3O_7N_3$ requires C, 56·65; H, 3·85; N, 12·0%).

(*c*) 4-*p*-Hydroxyphenyl-3-methylcinnoline gave an aqueous alkaline solution which, after ether-extraction, deposited a solid which did not melt at 330° (evidently the sodium salt of the cinnoline). The ether-extract yielded 3-p-*hydroxyphenyl-2-methylindole*, which crystallised from benzene in almost colourless prisms, m. p. 135—136° (Found: C, 80·2; H, 5·8; N, 7·0. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9; N, 6·3%), soluble in cold 2N-sodium hydroxide, but not in aqueous ammonia or sodium carbonate. The pH 8 fraction was an oil which (in alcohol) gave unreduced cinnoline, m. p. 238—241° (identified by mixed m. p.).

(*d*) 3-Phenyl-4-*p*-anisylcinnoline gave a crystalline mixture, m. p. 47—70°. Digestion with ether afforded, with heavy losses, a less soluble fraction, m. p. 132—145° (unchanged by recrystallisation from alcohol), which was not further purified.

(*e*) The extract of the alkaline mixture from the reduction of 3-phenyl-4-*p*-hydroxyphenylcinnoline and also the pH 8 fraction yielded unchanged material, m. p. and mixed m. p. 283—286°, but unidentified products were also present.

(*f*) 4-*p*-Anisylcinnoline gave a glassy resin which could not be obtained crystalline or converted into a crystalline picrate or hydrochloride

(*g*) By extraction of the alkaline solution, 4-*p*-hydroxyphenylcinnoline yielded 3-p-*hydroxyphenylindole*, which crystallised from benzene in small golden prismatic needles, m. p. 152—154° (Found: C, 79·75; H, 5·2; N, 6·8. $C_{14}H_{11}ON$ requires C, 80·35; H, 5·3; N, 6·7%); the solubility of this substance in alkalis was similar to that of its homologue described in (*c*). The pH 8 fraction was an oily solid from which 4-*p*-hydroxyphenylcinnoline was isolated (m. p. 234—235° alone and mixed with an authentic specimen).

(*h*) The ether extract from the reduction of 4-methylcinnoline gave an oily solid which on recrystallisation from ligroin (b. p. 40—60°) yielded skatole, m. p. 95·5—96·5° (Found: C, 82·0; H, 7·5; N, 10·6. Calc. for C_9H_9N: C, 82·4; H, 6·9; N, 10·7%). The ligroin filtrates were evaporated, and the residue was treated with picric acid in benzene and the resultant solid recrystallised from alcohol, from which 4-methylcinnoline picrate separated in dark green prismatic needles, m. p. 177—178° alone and mixed with an authentic specimen (this vol., p. 811).

(*i*) In the case of 7-chloro-4-methylcinnoline, skatole separated directly when the mixture was poured into water, and was collected and identified (m. p. 96·5° alone and when mixed with the sample described above). The picrate, soft red needles from alcohol, had m. p. 177—178° (Marion and Ashford, *Canad. J. Res.*, 1945, **23**, B, 26, give m. p. 182°) (Found: C, 50·0; H, 3·4. Calc. for $C_9H_9N,C_6H_3O_7N_3$: C, 50·0; H, 3·4%). It turned yellow on standing in the air, and after 3 days had m. p. 225—230°. The aqueous filtrate from the skatole was extracted with ether, yielding an oil from which 4-methylcinnoline was isolated as picrate (m. p. 170—173°, not depressed when mixed with authentic material).

(*j*) Ether-extraction of the product from 6-chloro-4-methylcinnoline gave an oil, from which skatole (m. p. 95—96°) was isolated by means of ligroin (b. p. 40—60°) (picrate, m. p. 172—174°, not depressed by admixture with the specimen described above). The first ligroin filtrate was evaporated and the residue converted into the picrate, which was digested with alcohol; the green solid so obtained had m. p. 185—187° (6-chloro-4-methylcinnoline picrate has m. p. 154—156°; this vol., p. 811) and gave marked depressions in m. p. when mixed with the picrates of skatole and 4-methylcinnoline.

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