765. *Heterocyclic Compounds of Nitrogen. Part VII.*[1] *The Ring-contraction of Some Cinnolines and Dihydrocinnolines.*

By L. S. Besford and J. Malcolm Bruce.

Reduction of several cinnolines with amalgamated zinc and aqueous acetic acid yields 1,4-dihydrocinnolines which are further reduced to indoles. In acidic media the dihydrocinnolines give 1-aminoindoles, but these are probably not important intermediates in the reductive ring-contraction.

The reductive ring-contraction of cinnolines (as I) to indoles (as VI; R′ = H) has been effected with several reagents,[2,3] but amalgamated zinc and aqueous acetic acid, potentially of considerable synthetical value, has been used only for 4-arylcinnolines.[4,5] It was of interest to determine whether other cinnolines could be usefully reduced to indoles with this reagent, and to obtain evidence for the mechanism of the reaction.

Reduction of 4-methylcinnoline with amalgamated zinc and aqueous acetic acid under

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[1] Part VI, Besford, Allen, and Bruce, *J.*, 1963, 2867.
[2] Jacobs, in Elderfield, "Heterocyclic Compounds," Wiley and Sons, New York, 1957, Vol. VI, pp. 159—161, and references therein.
[3] Baumgarten and Furnas, *J. Org. Chem.*, 1961, **26**, 1536.
[4] Neber, Knöller, Herbst, and Trissler, *Annalen*, 1929, **471**, 113.
[5] Bruce, *J.*, 1959, 2366.

conditions similar to those used [5] for 4-phenylcinnoline afforded 82% of skatole.   Cinnoline and cinnoline-4-carboxylic acid each gave indole in yields of, respectively, 57 and 77%.   A 4-aryl group is thus not essential for synthetically useful reductive ring-contraction. Treatment of 4-phenylcinnoline with amalgamated zinc in glacial acetic acid gave a mixture
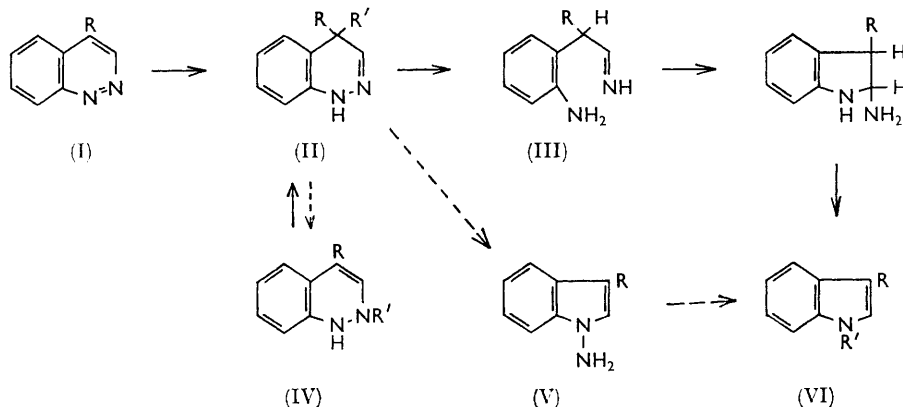
Broken arrows represent probably minor pathways.   For the sequence shown R′ = H.

of the cinnoline and its dihydro-derivative, and this, together with the observation [6] that 4-methylcinnoline under similar conditions gives only a low yield of skatole, indicates that water is necessary for smooth reduction.

Treatment of 4-phenylcinnoline with amalgamated zinc in refluxing aqueous acetic acid until the yellow colour of the cinnoline had just been discharged afforded a mixture of 3-phenylindole and, as the major component, 1,4-dihydro-4-phenylcinnoline.   4-Methyl-cinnoline similarly yielded skatole and 1,4-dihydro-4-methylcinnoline, but cinnoline and cinnoline-4-carboxylic acid each gave 1,4-dihydrocinnoline in yields of, respectively, 60 and 77%.   The latter reduction represents a convenient synthesis of 1,4-dihydrocinnoline; decarboxylation probably occurs at the dihydro-stage (II; R = H, R′ = CO_2H) since cinnoline-4-carboxylic acid is only slowly decarboxylated in boiling aqueous acetic acid, and the easy decarboxylation [7] of analogous systems, *e.g.*, 2-pyridylacetic acid,[8] is well known.   When refluxed with amalgamated zinc and aqueous acetic acid 1,4-dihydro-4-phenyl- and 1,4-dihydro-4-methyl-cinnoline gave, respectively, 77 and 53% of the corresponding indole.

These observations indicate that the dihydrocinnoline is involved in the ring-contraction, and, since it would not otherwise be isolable in good yield, that the overall reduction occurs stepwise, but they do not establish whether it is reduced in the 1,4- or the 1,2-dihydro-form (as, respectively, II; R′ = H, and IV; R′ = H), or whether it undergoes ring-contraction before reduction.   Evidence concerning these points has now been obtained.

In neutral media the dihydrocinnolines exist [1] as hydrazones (as II; R′ = H), but in acidic media prototropy could lead to contributions from the hydrazine form (as IV; R′ = H) the presence of which would be indicated in the case of 1,4-dihydro-4-phenyl-cinnoline by a decrease in the intensity of the magnetic resonance absorption (a doublet,[1] τ 5·59) due to the 4-proton.   A decrease was observed as the solvent was made progressively more acidic, but the magnitude of the change was not greater than the experimental error. A more sensitive test used 1,4-dihydro-4-methylcinnoline in a mixture of trichloroacetic acid and dioxan, but the doublet at τ 8·7 due to the methyl group persisted, and a new resonance at about τ 7·9, where absorption by the methyl group in (IV; R = Me, R′ = H)

[6] Cheorvas, M.A. Thesis, University of California, Los Angeles, 1948.
[7] Brown, *Quart. Rev.*, 1951, **5**, 131.
[8] Godfrey, in Klingsberg, '' Heterocyclic Compounds,'' Interscience, New York, 1962, Vol. 14, part 3, p. 357, and references therein.

would be expected,[1] was not observed. Contributions from the hydrazine form must therefore be small, but should be detectable by exchange for deuterium of the hydrogen atom at position 4.

Exchange experiments were carried out under conditions similar to those used for preparative reductions, although a higher proportion of acetic acid was used in order to maintain homogenous solutions. The proton magnetic resonance spectrum of an anærobic solution of 1,4-dihydro-4-phenylcinnoline in a mixture of acetic deuteroacid ($CH_3 \cdot CO_2D$) and deuterium oxide was measured initially, and then after successive periods of heating at 100°. After 90 minutes at 100° the doublet at τ 5·6 due to the 4-proton had decreased to 5% of its original intensity, in good agreement with the calculated equilibrium value; the singlet at τ 2·5 due to hydroxyl groups produced by rapid exchange at position 1 showed a corresponding increase. However, addition of water and further heating failed to intensify the τ 5·6 absorption, and the aromatic proton resonances, although now partially obscured by the hydroxyl band, changed in appearance. A precipitate, different from the dihydrocinnoline, separated. The loss of the resonance characteristic of the hydrogen atom at position 4 may therefore have been due to a reaction other than exchange with deuterium, and to check this the experiment was repeated but heating was stopped after 90 minutes: 70% of deuterated dihydro-4-phenylcinnoline was recovered. When a non-deuterated solvent system was used the doublet at τ 5·6 decreased after 90 minutes only to 87% of its original intensity, and 76% of the dihydrocinnoline was recovered. The nature of the by-product is discussed below.

In an attempt to match more closely the conditions of a preparative reduction, the foregoing exchange reaction was repeated in the presence of zinc acetate: the rate was not affected. Similar spectral changes attributable to deuterium exchange occurred, although more slowly, when glacial acetic deuteroacid was used as the solvent, but it was then possible to recover the deuterated dihydrocinnoline almost quantitatively.

An analogous experiment was performed with 1,4-dihydro-4-methylcinnoline in a mixture of tetradeutero(acetic acid) and deuterium oxide, but dioxan was added as an internal standard for comparative integration of successive spectra. Initially the solution showed an octet centred at τ 6·64 due to the 4-proton, and a doublet centred at τ 8·71 due to the methyl group. These resonances decreased in intensity as heating of the solution was continued, and a singlet, due to the methyl group of (II; R = Me, R' = D), appeared at τ 8·73 between the components of the doublet. After 90 minutes the " triplet " in the τ 8·7 region had become almost a singlet, and the octet at τ 6·64 could not be detected. However, the total absorption in the τ 8·7 region due to methyl groups progressively decreased, but the loss was balanced by the appearance of a singlet at τ 7·72 due to a product other than the deuterated dihydrocinnoline. In the early stages of the reaction the rate of exchange at position 4 of the dihydrocinnoline was 3·5 times that of by-product formation. After 12 hours at 100° a precipitate was present, and the supernatant liquid showed in the τ 6·5—10 region only a singlet at 7·72. The aromatic proton resonances were partially obscured by the hydroxyl absorption which moved upfield through them as the experiment progressed, but their appearance changed. As with the 4-phenyl compound, but more clearly, these results indicate that the hydrogen atom at position 4 of the dihydrocinnoline can be replaced by deuterium, and that an additional reaction occurs.

The materials obtained in good yield by heating 1,4-dihydro-4-phenyl- and 1,4-dihydro-4-methyl-cinnoline with aqueous acetic acid were monoacetyl derivatives containing one active hydrogen atom. The proton magnetic resonance spectrum of the methyl compound in either deuterochloroform or dioxan showed doublets in the τ 3·3, 7·6, and 8·1 regions with total intensities of, respectively, 1 : 3 : 3, the position and relative intensity of the components of each doublet depending on the concentration and the solvent (see Experimental section), but only singlets, essentially independent of concentration, were observed for solutions in dimethylformamide. The resonances in the τ 2·3—3·0 region were not

appreciably concentration-dependent, and were similar in appearance to those given by the benzenoid protons in skatole.[9]   These observations suggest the presence in deuterochloroform and dioxan of intermolecularly hydrogen-bonded species which are broken down in dimethylformamide, and are accounted for by the 1-acetamidoindole structures (VI; R = Ph or Me, R′ = NHAc).   This was confirmed for the methyl compound by synthesis from 1-nitrososkatole.   The resonances at about τ 3·3 in the case of 1-acetamidoskatole are due to the 2-proton.

Two paths may now be suggested for the formation if indoles (as VI; R′ = H) by treatment of 1,4-dihydrocinnolines with amalgamated zinc and aqueous acetic acid: either reduction to the amino-imine (as III) which then cyclises, or ring-contraction to the 1-amino-indole (as V) from which the product is derived by reduction.   That the former course may be the more important is indicated by the observation that 76% of 1,4-dihydro-4-phenylcinnoline can be recovered after heating for 90 minutes at 100° with aqueous acetic acid, whereas in the presence of amalgamated zinc, but otherwise under similar conditions, 3-phenylindole is formed in 91% yield; with 1,4-dihydro-4-methylcinnoline the recovery is 45% (formation of the 1-acetamidoindole is faster than with the phenyl compound), and the yield of skatole is 77%.

The overall reaction sequence (I)—(VI) is similar to that suggested by Jacobs,[2] although it is not certain that the 1,4-dihydrocinnoline is the species associated with the zinc at the instant of reduction.   The intermediate (III) is identical with one postulated [10] for the Fischer indole synthesis, and the subsequent steps may be similar.   Confirmation that N-2 of the cinnoline is eliminated was obtained by reduction of 4-phenyl-[2-^{15}N]cinnoline, which afforded nitrogen containing 93% of the isotopic concentration present in the nitrite used for its preparation.

That dihydro-4-methylcinnoline can be recovered almost quantitatively after treatment with glacial acetic acid, whereas in the presence of water 1-acetamidoskatole is formed suggests that this ring-contraction may involve hydrolysis of the dihydrocinnoline to a 2-hydrazinophenylacetaldehyde.   Acetylation could occur at either this or the 1-amino-skatole stage; the latter compound, like other hydrazines, is readily acetylated by acetic acid.   Treatment of 1,4-dihydro-4-methylcinnoline with aqueous hydrogen chloride yields 1-aminoskatole hydrochloride, suggesting that acid-catalysed ring-contraction of 1,4-di-hydrocinnolines may be a general reaction.   The formation [11] of 1-amino-oxindole from 3-hydroxycinnoline, probably *via* 1,2,3,4-tetrahydro-3-oxocinnoline, may be mechanistically similar.

EXPERIMENTAL

Freshly purified [1] dihydrocinnolines were used.   Zinc refers to freshly prepared amalgamated zinc wool [5] unless stated otherwise.   Glacial acetic acid was freshly distilled.   Light petroleum had b. p. 60—80° unless stated otherwise.   Solutions in organic solvents were washed with water and dried with magnesium sulphate.   Sublimation temperatures are those of the heating-bath. M. p.s are corrected.   Infrared spectra were determined with a Unicam S.P. 200 spectrometer. Proton magnetic resonance spectra were measured at 60 Mc./sec. with an Associated Electrical Industries model RS2 spectrometer except for those in tetradeutero(acetic acid) and those of the 1-aminoindoles which were obtained with a Varian A-60 spectrometer; samples were contained in tubes of 4-mm. internal diameter, and tetramethylsilane was used as internal standard unless stated otherwise.

Indoles from Cinnolines.—(*a*) 4-Methylcinnoline (201 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (1·1 c.c.) were refluxed for 1 hr., more acetic acid (0·35 c.c.) was added, and refluxing was continued for 1 hr. more.   The mixture was cooled, extracted with benzene, and the benzene-soluble material was sublimed at 40—45°/5 × 10⁻⁵ mm. to give a white solid (156 mg.),

[9] Bhacca, Johnson, and Shoolery, " NMR Spectra Catalog," Varian Associates, Palo Alto, California, 1962, spectrum no. 231.
[10] Allen and Wilson, *J. Amer. Chem. Soc.*, 1943, **65**, 611; Plieninger, *Chem. Ber.*, 1950, **83**, 273.   Cf. Allen and Van Allan, *J. Amer. Chem. Soc.*, 1951, **73**, 5850; Snyder, Merica, Force, and White, *ibid.*, 1958, **80**, 4622; Suvorov, Sorokina, and Sheinker, *J. Gen. Chem. U.S.S.R.*, 1958, **28**, 1058.
[11] Baumgarten, Creger, and Zey, *J. Amer. Chem. Soc.*, 1960, **82**, 3977.

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m. p. 30—90°, shown by optical density measurements at 224, 282, and 291 mμ to contain 96% of skatole, and from which skatole, m. p. 90—95°, identical (mixed m. p., infrared spectrum) with authentic material was isolated by crystallisation from light petroleum followed by sublimation.

(b) A mixture of cinnoline (148 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (1·1 c.c.) was refluxed for 2 hr., cooled, and diluted with water (15 c.c.). Fractional sublimation of the ethyl acetate-soluble material at 40—60°/5 × 10⁻⁴ mm. gave indole (76 mg.), m. p. and mixed m. p. 49—50°.

(c) Cinnoline-4-carboxylic acid (303 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (2·2 c.c.) were refluxed for 2·5 hr., and the mixture was worked-up as described under (b) to give indole (162 mg.).

Dihydrocinnolines from Cinnolines.—Reaction products were handled under nitrogen. (a) A mixture of 4-phenylcinnoline (189 mg.), zinc (0·4 g., washed with glacial acetic acid), and glacial acetic acid (1·1 c.c.) was refluxed for 2 hr., cooled, and diluted with water (6 c.c.). Extraction with ether gave a yellow oil from which, by crystallisation from light petroleum, sublimation at 90—100°/0·01 mm., and recrystallisation, 1,4-dihydro-4-phenylcinnoline (15 mg.) was obtained as needles, m. p. and mixed m. p. 112·5—113° The mother-liquors afforded an oil, shown by its infrared spectrum to be a mixture of 4-phenyl- and 1,4-dihydro-4-phenyl-cinnoline.

(b) A mixture of 4-phenylcinnoline (260 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (2·9 c.c.) was refluxed until the yellow colour of the cinnoline had just been discharged (9 min.), cooled, and diluted with water (10 c.c.). Extraction with ethyl acetate and sublimation of the soluble material at 90—120°/10⁻⁴ mm. gave a pale yellow solid which had τ (35% in CDCl₃) multiplets between 2·2 and 3·6 containing bands at 2·23, 2·68, and 2·77 characteristic of 3-phenyl-indole, and at 2·88, 3·53, 3·56, and 5·60 (doublet, $J = 2·5$ c./sec.) characteristic [1] of 1·4-dihydro-4-phenylcinnoline.

(c) 4-Methylcinnoline (249 mg.) was treated as described under (b), but with a reflux period of 8 min., and the product was sublimed at 80—90°/0·02 mm. to give a white solid (194 mg.) which had τ (35% in CDCl₃) multiplets between 2·8 and 3·6 containing bands attributable to skatole and 1,4-dihydro-4-methylcinnoline, 6·77 (octet, $J_1 = 7$ c./sec., $J_2 = 2·5$ c./sec.) and 8·79 (doublet, $J = 7$ c./sec.) due [1] to 1,4-dihydro-4-methylcinnoline, and 7·73 (doublet, $J = 1$ c./sec.) due [9] to skatole. The intensities of the absorptions at 8·79 and 7·73 indicated a dihydro-cinnoline : skatole ratio of 12 : 1. Treatment of the mixture with phthalic anhydride in pyridine afforded the phthaloyl derivative [1] of 1,4-dihydro-4-methylcinnoline, m. p. and mixed m. p. 187—187·5°.

(d) Cinnoline (152 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (1·1 c.c.) were refluxed for 4 min., and the mixture was worked-up as described under (b). Fractional sublimation at 50°/10⁻⁴ mm. gave a white solid (95 mg.), m. p. 81—84°, which had an infrared spectrum super-imposable on that [1] of 1,4-dihydrocinnoline.

(e) A mixture of cinnoline-4-carboxylic acid (192 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (2·2 c.c.) was refluxed for 6 min., and treated as described under (d) to give 1,4-dihydrocinnol-ine (108 mg.), m. p. 81—82·5°. The carboxylic acid was almost quantitatively recovered after being refluxed for 30 min. with aqueous 33% acetic acid, but on prolonged refluxing gave cinnoline.

Indoles from 1,4-Dihydrocinnolines.—(a) 1,4-Dihydro-4-methylcinnoline (80 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (1·1 c.c.) were refluxed for 2 hr., and the mixture was cooled, diluted with water (8 c.c.), and extracted with ethyl acetate. Removal of the solvent, and sublimation of the residue at 50°/5 × 10⁻⁵ mm. gave a white solid (38 mg.), m. p. 82—91°, the infrared spectrum of which was almost identical with that of skatole.

(b) 1,4-Dihydro-4-phenylcinnoline (103 mg.) was treated as described under (a). Sublim-ation at 70—80°/5 × 10⁻⁵ mm., and crystallisation of the sublimate from light petroleum afforded 3-phenylindole (66 mg.), m. p. and mixed m. p. 86—87°.

*Proton Magnetic Resonance Spectra** of 1,4-Dihydrocinnolines in Acidic Media.*—(a) The doublet at τ 5·6 was measured at 21° for 18% solutions of 1,4-dihydro-4-phenylcinnoline in acetone, glacial acetic acid, and 1 : 1 glacial acetic acid : trichloroacetic acid, but the decrease in intensity was less than the experimental error.

(b) The τ 7—9 region of the spectrum of 1,4-dihydro-4-methylcinnoline was measured at

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* In the presentation of proton magnetic resonance data the styles here used are: 3H to indicate an intensity corresponding to 3 protons: 3–H to indicate one proton at position 3.

$21°$ for 15% solutions in dioxan and $1:1$ dioxan : trichloroacetic acid. The doublet at $\tau\ 8\cdot7$ persisted in the acidic medium, and no new absorptions were observed. The doublet appeared at $\tau\ 8\cdot75$ for a 15% solution in methanol, and was not changed by addition of small amounts of either trichloroacetic acid or concentrated hydrochloric acid.

Deuterium-exchange and Control Experiments.—The dihydrocinnolines are readily oxidised in warm aqueous acetic acid, and solutions were therefore freshly prepared at $20°$, and degassed in the spectrometer tube which was then sealed at $0\cdot01$ mm. Heating was effected by suspending the tubes in steam above water boiling under normal pressure.

(*a*) The $\tau\ 0$—6 region of the spectrum of 1,4-dihydro-4-phenylcinnoline (50 mg.) in a mixture of acetic deuteroacid ($0\cdot25$ c.c.; $CH_3\cdot CO_2D$) and deuterium oxide ($0\cdot05$ c.c.) was measured initially and then after the solution has been heated for total periods of 30, 60, and 90 min. at $100°$. The doublet at $\tau\ 5\cdot6$ decreased to about 5% of its original intensity, and the singlet at $\tau\ 2\cdot5$ due to hydroxyl groups formed by initial rapid exchange of the 1-H of the dihydrocinnoline correspondingly increased in intensity. The resonances due to the aromatic protons showed little change. Water ($0\cdot075$ c.c.) was now added, and the spectrum was measured after additional total heating periods of 5, 35, and 65 min. The absorption at $\tau\ 5\cdot6$ did not increase in intensity, the liquid became turbid, and the aromatic proton resonances which were not obscured by the hydroxyl peak changed in appearance.

(*b*) The first part of experiment (*a*) was repeated using 1,4-dihydro-4-phenylcinnoline (50 mg.) in a mixture of acetic deuteroacid ($0\cdot2$ c.c.), deuterium oxide ($0\cdot03$ c.c.), and part ($0\cdot07$ c.c.) of a solution prepared by refluxing for 1 hr. a mixture of zinc ($0\cdot1$ g.), acetic deuteroacid ($0\cdot5$ c.c.), and deuterium oxide ($0\cdot1$ c.c.). Closely similar spectral changes were observed. The solution was then diluted with water (10 c.c.), and the precipitate was collected, washed with water, and sublimed (i) at 80—$85°/5 \times 10^{-5}$ mm. to give a white solid (41 mg.), m. p. 92—$109°$, from which needles (27 mg.), m. p. 110—$112°$ undepressed on admixture with 1,4-dihydro-4-phenylcinnoline, were obtained by crystallisation from light petroleum, and (ii) at $120°/5 \times 10^{-5}$ mm. to give 1-acetamido-3-phenylindole (3 mg.).

(*c*) Experiment (*a*) was repeated using a non-deuterated solvent system. After 90 min. at $100°$ the doublet at $\tau\ 5\cdot6$ had decreased to 87% of its original intensity, and dilution with water and sublimation of the precipitate as described under (*b*) gave 1,4-dihydro-4-phenylcinnoline (38 mg.) and 1-acetamido-3-phenylindole (4 mg.).

(*d*) Experiment (*a*) was repeated using glacial acetic deuteroacid ($0\cdot3$ c.c.). After 90 min. at $100°$ the doublet at $\tau\ 5\cdot6$ had decreased in intensity to 55% of the original, and after 200 min. to 25%; the hydroxyl resonance at $\tau\ -3\cdot2$ showed a corresponding increase. Dilution with water and sublimation gave deuterated dihydro-4-phenylcinnoline (49 mg.)

(*e*) The spectrum of 1,4-dihydro-4-methylcinnoline (49 mg.) in a mixture of dioxan (4 mg.), tetradeutero(acetic acid) ($0\cdot35$ c.c.) and deuterium oxide ($0\cdot07$ c.c.) was measured initially and after the solution had been heated at $100°$ for totals of 5, 10, 20, 30, 60, and 90 min., and 12 hr. The dioxan was used as a standard for position ($\tau\ 6\cdot30$), and for comparative integration of successive spectra. The changes which occurred are described in the text. At the end of the heating-period the precipitate (10 mg.) was collected. It had m. p. 173—$174°$ undepressed on admixture with 1-acetamidoskatole, and $\nu_{max.}$ (Nujol) 3195m, 2370s, 1417m, 1345m, and 925m cm.$^{-1}$ (the last four bands were absent or weak in the spectrum of 1-acetamidoskatole). Dilution of the mother-liquor with water (20 c.c.) gave more solid (31 mg., total 41 mg.; 92%) which had m. p. $172\cdot5$—$173°$ undepressed on admixture with 1-acetamidoskatole; $\nu_{max.}$ (Nujol) 3190s, 2370w, 1345m, and 938m cm.$^{-1}$.

(*f*) A mixture of 1,4-dihydro-4-phenylcinnoline (51 mg.), zinc ($0\cdot4$ g.), glacial acetic acid ($0\cdot25$ c.c.), and water ($0\cdot05$ c.c.) was heated at $100°$ for 90 min., cooled, and diluted with water. Extraction with ethyl acetate and sublimation at $80°/10^{-4}$ mm. gave 3-phenylindole (43 mg.).

(*g*) Experiment (*f*) was repeated with 1,4-dihydro-4-methylcinnoline (35 mg.). Sublimation at 40—$50°/10^{-2}$ mm. and then at $130°/10^{-2}$ mm. gave, respectively, skatole (24 mg.) and 1-acetamidoskatole (3 mg.).

Non-reductive Ring-contraction of 1,4-Dihydrocinnolines.—(*a*) A solution of 1,4-dihydro-4-phenylcinnoline (295 mg.) in aqueous 80% acetic acid ($2\cdot1$ c.c.) was degassed, sealed at $0\cdot01$ mm., and heated at $100°$ for 12 hr. The 1-acetamido-3-phenylindole (293 mg., 83%) which separated on cooling had m. p. $177\cdot5$—$180°$, raised by crystallisation from aqueous acetic acid and sublimation at $140°/0\cdot01$ mm. to $182\cdot5$—$183\cdot5°$ (lit.,[12] 179—$180°$) [Found: C, $76\cdot4$; H, $5\cdot9$;

[12] Alder and Niklas, *Annalen*, 1954, **585**, 97.

N, 11·3; active H, 0·40%; M (Rast), 258. Calc. for $C_{16}H_{14}N_2O$: C, 76·8; H, 5·6; N, 11·2; active H, 0·40%; M, 250]; $\nu_{max.}$ (Nujol) 3160m and 1672s cm.$^{-1}$; τ (3·8% in CDCl$_3$) 7·99, 8·21 (total 3H), and τ (6% in CDCl$_3$) 8·25 (3H).

(*b*) A solution of 1,4-dihydro-4-methylcinnoline (850 mg.) in aqueous 80% acetic acid (6 c.c.) was degassed, sealed at 0·01 mm., and heated at 100° for 16 hr. Dilution with water (50 c.c.) then gave 1-*acetamidoskatole* (882 mg., 81%), m. p. 173—174° raised to 174—175° by sublimation at 150°/10^{-4} mm. [Found: C, 70·0; H, 6·4; N, 14·7; active H, 0·57%; M (Rast), 180. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9; active H, 0·54%; M, 188]. It had $\nu_{max.}$ (Nujol) 3185s and 1677s cm.$^{-1}$; τ (7% in CDCl$_3$) 1·52, 1·92 (NH, total intensity 1H), multiplets at 2·3—2·6 and 2·7—3·0 with strongest band at 2·75 (benzenoid, 4H), 3·27, 3·38 (2-H, total intensity 1H), 7·72 (3H), 8·10, and 8·29 (total 3H). The resonances due to the 2-protons and the methyl groups were concentration- and solvent-dependent (figures in parentheses indicate the approximate relative intensities of the preceding two peaks): in CHCl$_3$, 11·3%, τ 3·34, 3·52 (1 : 1), 7·75, 7·80 (1 : 2), 8·22, 8·33 (2 : 1); 9·1%, τ 3·21, 3·45 (2 : 1), 7·71, 7·76 (1 : 1), 8·15, 8·30 (1 : 1); 5·2%, τ 3·28, 3·35 (3 : 1), 7·72, 8·05, 8·28 (1 : 1·5); 2·2%, τ 3·92, 7·72, 7·92, 8·25 (1 : 2); in dioxan, 12·1%, τ 3·09, 3·22, 7·36, 7·74 (1 : 2), 8·05, 8·39 (2 : 1); 7·1%, τ 3·08, 3·19, 7·46, 7·71 (1 : 1·5), 8·01, 8·38 (1·5 : 1); 3·7%, τ 3·08, 3·19, 7·56, 7·73 (1 : 1), 8·01, 8·39 (1 : 1); 1·5%, τ 3·05, 3·17, 7·59, 7·70, 7·97, 8·37; in dimethylformamide, 22%, τ 3·02, 7·75, 7·90; 11% and 4%, τ 2·98, 7·72, 7·86.

(*c*) 1,4-Dihydro-4-methylcinnoline (419 mg.) was refluxed for 5 min. with 30% hydrochloric acid (4 c.c.), and the material which separated on cooling was crystallised from aqueous 10% hydrochloric acid to give 1-*aminoskatole hydrochloride* (308 mg.) as plates, m. p. 146—154° (decomp.) (Found: C, 58·3; H, 6·4; Cl, 18·6; N, 14·9. $C_9H_{11}ClN_2$ requires C, 59·2; H, 6·1; Cl, 19·4; N, 15·3%). It had $\nu_{max.}$ (Nujol) 3350s (broad), 1617m, and 1595m cm.$^{-1}$, τ (16% in MeOH) multiplets between 2·2 and 2·85 with strongest line at 2·71, 7·70 (doublet, $J = 1·2$ c./sec.). Treatment of the hydrochloride with aqueous ammonia yielded 1-aminoskatole.

1-*Aminoskatole.*—1-Nitrososkatole [13] (1·5 g.) in glacial acetic acid (4·5 c.c.) was added during 15 min. to a stirred suspension of ordinary zinc dust (3 g.) in water (4·5 c.c.) at 0°, and the mixture was then stirred at 0° for 30 min., basified with aqueous 40% sodium hydroxide, and extracted with benzene. The zinc residues were separately extracted with ethyl acetate, and the extracts were combined. Removal of the solvent and sublimation of the residue at 80°/10^{-5} mm. gave a white solid from which 1-*aminoskatole* (64 mg.) was obtained by crystallisation from light petroleum (b. p. 40—60°) as needles, m. p. 59·5—60° (Found: C, 74·5; H, 7·1; N, 18·6. $C_9H_{10}N_2$ requires C, 73·9; H, 6·90 N, 19·2%); $\nu_{max.}$ (Nujol) 3260s and 1612m cm.$^{-1}$; τ (13% in CCl$_4$) multiplets at 2·4—2·75, and 2·85—3·15 with strongest band at 2·96 (total 4H), 3·39 (1H), 5·93 (NH$_2$, removed by addition of D$_2$O), 7·78 (doublet, $J = 1$ c./sec., 3H). The free base, its acetyl derivative (prepared by treatment with either acetic acid or acetic anhydride), and its hydrochloride were identical with the corresponding materials obtained from 1,4-dihydro-4-methylcinnoline.

4-*Phenyl*-[2-^{15}N]*cinnoline.*—1-*o*-Aminophenyl-1-phenylethylene (213 mg.) in aqueous 10% hydrochloric acid (3 c.c.) at 0° was treated with a slight excess of aqueous 6·5% potassium [^{15}N]nitrite (prepared [14] from potassium nitrate containing 7·95% of ^{15}N), diluted with water (10 c.c.), and the mixture was stirred at 0° for 30 min., and then basified with aqueous ammonia. Extraction with ethyl acetate gave a yellow oil which failed to crystallise, and had $\nu_{max.}$ 3400m (broad) cm.$^{-1}$. This was refluxed with phthalic anhydride (308 mg.) in pyridine (2·5 c.c.) for 3 hr., the solvent was removed, and the residue was washed with aqueous 10% sodium hydroxide and then crystallised from light petroleum to give the labelled cinnoline (80 mg.) as pale yellow needles, m. p. 65—66°, identical (mixed m. p., infrared spectrum) with 4-phenylcinnoline.

Reduction of 4-*Phenyl*-[2-^{15}N]*cinnoline.*—A mixture of the cinnoline (26 mg.), zinc (0·4 g.), and aqueous 33% acetic acid (1·1 c.c.) was refluxed for 2 hr., cooled, and filtered. The filtrate was placed in one of two bulbs blown on the lower arms of an inverted Y-tube; the other bulb contained aqueous sodium hypobromite [15] (0·6 c.c.), and the third arm carried a tap. The solutions were degassed by the freeze-pump-thaw technique, cautiously mixed at 0°, and the evolved

[13] Hodson and Smith, *J.*, 1957, 3546.
[14] Heath, *J.*, 1957, 4152.
[15] Rittenberg, "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Michigan, 1946, p. 31.

nitrogen was analysed with a Metropolitan-Vickers model MS2 spectrometer. It contained, from two separate experiments, 7·43 and 7·39% of ^{15}N.