Cinnolines and Other Heterocyclic Types in Relation to the Chemotherapy of Trypanosomiasis. Part VII. Intermediates.*

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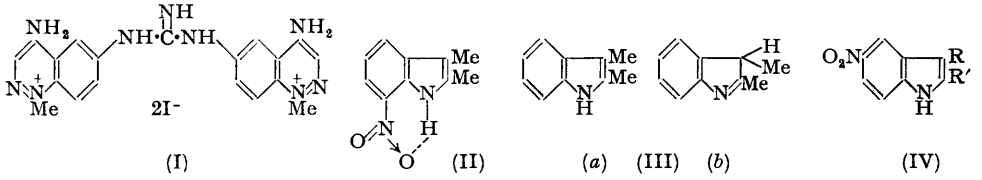
High yields of *o*-aminoacetophenones are obtained on the large scale *via* the *NN*-diacetyl derivatives by the oxidation of 1-acetyl-2 : 3-dimethylindoles. A suggested explanation, supported by nitration studies, involves the reduced aromaticity of the hetero-ring and stabilisation of the imino-form of the possible imino-ketimine system.

As part of the programme of syntheses of bis-heterocyclic quaternary salts for test as trypanocidal agents we prepared analogues of (I) (Part VI, *J.*, 1952, 2617) having the guanidine bridge across the 5 : 5′-, 7 : 7′-, and 8 : 8′-positions. This paper describes routes to suitably substituted intermediates and includes work on the large-scale preparation of 2-amino-5-nitroacetophenone for conversion into (I).

Oxidation of the appropriate 2 : 3-dimethyl-*Bz*-nitroindoles with chromic acid in acetic acid has been used by Schofield and Theobald (*J.*, 1949, 796) as a method for obtaining the corresponding 2-amino-*Bz*-nitroacetophenones. Application of the technique to our preparative problem was initially disappointing; considerable manipulative difficulties were encountered in the large-scale separation by chromatography (alumina) of 2 : 3-di-



(I) (II) (*a*) (III) (*b*) (IV)

methyl-4(and 6)-nitroindoles and attempts to influence the proportion of each isomer by varying the condensing agent were unsuccessful. Moreover, at the oxidation stage, our yield of pure 2-acetamido-5-nitroacetophenone was considerably lower than that given by Schofield and Theobold (*loc. cit.*) for the partially purified material, but in the case of 2-acetamido-3-nitroacetophenone our yield from 2 : 3-dimethyl-7-nitroindole was appreciably better than that reported and in sharp contrast to that from other nitroindoles (see Table). That these results were not due to the different stabilities of the products towards the reagent was shown by the negligible variation in the amounts obtained when different times of reaction were used. In seeking a reason for the single high yield we noted the possibility of intramolecular hydrogen bonding as in (II), this being consistent with the fact that the observed volatility is higher than that of 6-nitro-2 : 3-dimethylindole; the presence of similar bonding in 7-nitrobenziminazole has been established (Rabinowitz and Wagner, *J. Amer. Chem. Soc.*, 1951, **73**, 3030). Similar " protection " of 2 : 3-diphenylindoles, by *N*-acetylation before oxidation, was considered essential by Ritchie (*Proc. Roy. Soc. N.S.W.*, 1946, **80**, 33); and Weissgerber (*Ber.*, 1913, **46**, 651) observed the beneficial effect in the indole series of *N*-benzoylation before either halogenation or oxidation to anthranilic acid derivatives. Similar results have been observed in this work (see Table).

Our attempts to oxidise 2 : 3-dimethylindole with a variety of reagents were unsuccessful (contrast the small-scale oxidations with ozone, Witkop, *Annalen*, 1944, **556**, 103) but the *N*-acetyl derivative was smoothly oxidised by chromic acid in acetic acid to *o*-diacetylaminoacetophenone; *o*-acetylaminoacetophenone was never isolated from this experiment, in contrast to the findings by Gaudion, Hook, and Plant (*J.*, 1947, 1631). Moreover, oxidation of the 1-acetyl-2 : 3-dimethyl-*Bz*-nitroindoles, formed only under vigorous

* Part VI, *J.*, 1952, 2617.

conditions, gave only the corresponding *o*-diacetylaminoacetophenones, in agreement with the isolation by Koelsch (*J. Amer. Chem. Soc.*, 1944, **66**, 1983) of *N*-acetyl-2-benzoyl-5-bromobenzanilide from oxidation of 1-acetyl-6-bromo-2 : 3-diphenylindole. These results can be explained by consideration of the tautomerism (III*a* ⇌ *b*) possible in the indole nucleus. Stabilisation of the species (III*a*) which, on the assumption that (III*a*) and

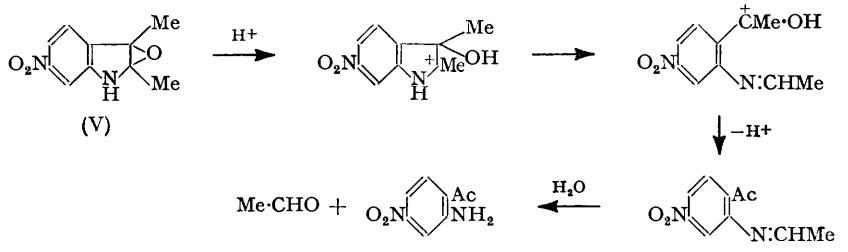
Yields of o-acetamidoacetophenones from oxidations of indoles.

	Bz-Substituent				
	Nil	4-NO_2	5-NO_2	6-NO_2	7-NO_2
2 : 3-Dimethylindole.					
Yield (%) [a]	Nil	30(30)	28(43)	26(26)	72(42)
1-Acetyl-2 : 3-dimethylindole.					
Yield (%)	55	85 [b]	78 [b]	90 [b]	—

[a] Figures in parentheses are the yields obtained by Schofield and Theobald (*loc. cit.*), whose 5-nitro-compound had m. p. 139—141°. Our product had m. p. 152—153° as reported by Bauer and Strauss (*Ber.*, 1932, **65** 308). [b] Yield over two stages, *i.e.*, to the aminoacetophenone.

(III*b*) are oxidised at approximately equal rates, is essential to high yields of *o*-amino-ketone derivatives, can be achieved either by substitution of the mobile imino-hydrogen atom (acetylation) or by hydrogen-bonding (as in II). A third method of achieving this stability is evident from the high yields of *o*-aminobenzophenones obtained by Schofield and Theobald (*J.*, 1950, 1505) from 3-phenylindoles (cf. Ritchie, *loc. cit.*). In these cases the decisive factor appears to be the ability of the 3-phenyl group to be conjugated with the double bond (2 : 3) of (III*a*) but not with that (1 : 2) of (III*b*). This idea was tested by oxidation of (IV; R = Ph, R′ = Me; and R = Me, R′ = Ph), in only the latter of which is the species (III*b*) stabilised by conjugation of the heterocyclic double bond with the phenyl substituent; as was expected, the yield of *o*-amino-ketone derivative from the former was considerably greater (75% and 39%, respectively). It may be concluded that successful oxidation of indole derivatives to those of *o*-amino-ketones depends, primarily, on reduction of the aromaticity of the nucleus and subsequent stabilisation of the imino-tautomer in the imino-ketimine system.

These suggestions presuppose the existence of a triad system –NH·C:C– unsaturated in the manner associated with aliphatic olefinic bonds, as distinct from the purely aromatic type. Evidence to support this was found in reactions of indoles and their *N*-acetyl derivatives. Thus oxidation of 6-nitro-2 : 3-dimethylindole with chromic acid in formamide yielded a non-ketonic compound, $C_{10}H_{10}O_3N_2$, which when refluxed with dilute hydrochloric acid gave 2-amino-4-nitroacetophenone and acetaldehyde. This behaviour is consistent with the compound's being the epoxide (V), treatment with acid resulting in the following changes:



Further evidence of reduced aromatic character in the hetero-ring comes from nitration experiments (see below): 2 : 3-dimethylindole is nitrated at $C_{(5)}$ (*para* to the ring-N), but 1-acetyl-2 : 3-dimethylindole undergoes, not only substitution at $C_{(4)}$ and $C_{(6)}$ (*meta* to the ring N), but also reactions about the $C_{(2)}$–$C_{(3)}$ double bond.

Our failure to adapt Schofield and Theobald's methods (*loc. cit.*) to large-scale experiments led to our evaluation of other routes as well as to the above investigation on the requirements for good results from the oxidation of indoles. Cyclisation of phenyl-

hydrazones to indoles by means of boron trifluoride complexes (Snyder and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 2452) was most valuable and after improvements in the isolation procedure 2 : 3-dimethylindole became available in large quantities. Nitration of the crude product by Bauer and Strauss's method (*loc. cit.*) gave the 5-nitro-derivative which was either purified by an improved technique or acetylated directly for the next (oxidation) stage; this route is considered the best available for production of 2-acetamido-5-nitroacetophenone in quantity. 1-Acetyl-2 : 3-dimethylindole (Borsche and Groth, *Annalen*, 1941, **549**, 238) has been nitrated by Plant and his co-workers (*J.*, 1933, 955; 1940, 283) and by Schofield and Theobald (*loc. cit.*) who confirmed the low yield (14%) of 1-acetyl-2 : 3-dimethyl-6-nitroindole. The yield of this main product has been raised to 32%, and appreciable amounts (10%) of the 4-nitro-isomer were isolated, but in spite of numerous variations (about 55 orienting experiments) we were unable to improve this result; a number of by-products, on which work is still in progress, were also isolated from this nitration. The accessibility of the precursors makes this route to 1-acetyl-2 : 3-dimethyl-6-nitroindole a serious competitor to that involving chromatography of mixed 2 : 3-dimethyl-4(and 6)-nitroindoles.

Experimental

M. p.s were determined on a Kofler block and are corrected. Complete details of orienting experiments can be found in A. Taylor's Ph.D. Thesis (Manchester), 1952.

Nitrophenylhydrazines.—The *o*- and *m*-compounds were obtained in yields of 70% and 80% respectively on a 200-g. scale by the method of Muller *et al.* (*Helv. Chim. Acta*, 1937, **20**, 1468); in the former case it was better merely to stir the intermediate hydrazo-sulphonic acid with hot concentrated hydrochloric acid to obtain the hydrochloride rather than to attempt a complete recrystallisation from this reagent. In the case of the *m*-compound, neutralisation of the solution of the diazotised amine before its reduction was omitted; conversion of the hydrazo-sulphonic acid into the hydrazine hydrochloride was carried out by dissolving the former in the minimum amount of hot water, adding an equal volume of concentrated hydrochloric acid, and cooling.

3-*Methyl*-5-*nitro*-2-*phenylindole.*—(*a*) Propiophenone *p*-nitrophenylhydrazone (6·5 g.) was heated with hydrochloric acid (65 c.c.; *d* 1·18) for 4 hr. on a steam-bath. The cold reaction mixture was diluted with water (200 c.c.) and extracted with chloroform, and the washed (sodium carbonate, water) and dried (Na_2SO_4) extract was evaporated. The residual oil gave orange crystals from benzene–light petroleum (b. p. 60—80°); 3-*methyl*-5-*nitro*-2-*phenylindole* formed long pale yellow needles, m. p. 193°, from benzene (Found: C, 71·7; H, 4·7; N, 11·6. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). Concentration of the mother-liquor gave propiophenone (1·55 g.), b. p. 127—129°/35 mm. (semicarbazone m. p. and mixed m. p. 173°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 188°). Extraction of the original aqueous reaction liquor after partial (to pH 6) and complete basification gave only further specimens of the indole.

(*b*) A solution of the hydrazone (2 g.) in acetic acid (20 c.c.) was treated with boron trifluoride–acetic acid (13·6 c.c.) and heated to boiling; spontaneous refluxing occurred for 5—10 min., heating was resumed for 20 min., and the mixture poured into water (300 c.c.). The residue obtained by evaporation of a washed (sodium carbonate, water) and dried chloroform extract was dissolved in benzene and chromatographed on alumina (10 × 3 cm.), to give a sticky solid, m. p. 178—180° (1·2 g.), having the smell of propiophenone. Recrystallisation from benzene gave the same indole (0·4 g.) as in (*a*).

2-*Methyl*-5-*nitro*-3-*phenylindole.*—Benzyl methyl ketone *p*-nitrophenylhydrazone (5·1 g.), acetic acid (50 c.c.), and hydrochloric acid (50 c.c.; *d* 1·18) were refluxed together for 2 hr. The cold mixture was extracted with chloroform, and the extract washed with sodium carbonate solution and water, dried (Na_2SO_4), and evaporated to dryness. A solution of the residue (4 g.) in benzene (100 c.c.) was percolated through alumina (8 × 3·5 cm.) to give crystalline material (1 g.), m. p. 195—196°, from which 2-*methyl*-5-*nitro*-3-*phenylindole*, m. p. 197—198°, was obtained as yellow needles by recrystallisation from benzene (Found: C, 71·3; H, 4·65; N, 11·35%.

2 : 3-*Dimethyl*-7-*nitroindole.*—(*a*) Ethyl methyl ketone *o*-nitrophenylhydrazone (25 g.) was heated with concentrated hydrochloric acid (250 c.c.; *d* 1·18) at 95° for 4 hr. The product was filtered off, washed with concentrated hydrochloric acid and water, and digested with hot benzene,

and the dried extract chromatographed in hot benzene on alumina (Spence and Co., Grade " H "; 30 × 4·5 cm.). Most of the pure indole was contained in the first coloured eluate (1 l.) and *ca.* 10% was obtained, contaminated with a bright red crystalline solid, m. p. *ca.* 194°, on further elution (500 c.c.); the latter fraction was neglected for preparative purposes. 2 : 3-Dimethyl-7-nitroindole, m. p. 164°, crystallised from benzene in golden leaflets which gradually changed to rhombs (yield, 40%; average of 20 experiments).

(*b*) A solution of the hydrazone (25 g.) in glacial acetic acid (250 c.c.) was refluxed with boron trifluoride–acetic acid (20 c.c.) for 30 min. The solid (21 g.), m. p. 145—150°, isolated by dilution with water was purified as in (*a*) (yield 35%), but the red compound, m. p. 194°, was not noted.

2 : 3-*Dimethyl*-4(*and* 6)-*nitroindoles*.—(*a*) Ethyl methyl ketone *m*-nitrophenylhydrazone was cyclised with hydrochloric acid as described above, a crude product, m. p. 128—130°, being reprecipitated by water from an alcoholic solution after treatment with carbon. A filtered solution of this material (56 g.) in 1 : 1 benzene–light petroleum (b. p. 80—100°; 800 c.c.) was chromatographed on alumina (70 × 2", 1900 g.; " Grade H "); the lower orange band was eluted with the mixed solvent, to give the 4-isomer (8·5 g.), m. p. 175°, and the crimson upper band was finally removed with ether, to give the 6-isomer (23·7 g.), m. p. 142°.

(*b*) The *m*-nitrophenylhydrazone (2 g.) was treated with boron trifluoride as for the *o*-compound (above) but gave a tar which was purified by reprecipitation from the solution in acetic acid by addition of water after treatment with carbon; the flocculent yellow solid (0·31 g., 16%) had m. p. 128—129°.

2 : 3-*Dimethylindole*.—A solution of ethyl methyl ketone phenylhydrazone (102 c.c.; dried but not distilled, excess of ketone having been removed under reduced pressure) in acetic acid (150 c.c.; contained in a 2-l. flask fitted with a wide, efficient condenser) was treated with boron trifluoride–acetic acid complex (78 c.c.) and heated on a steam-bath. At the first sign of boiling the flask was plunged into a cooling bath (solid carbon dioxide–alcohol) and when the vigorous reaction subsided the hot slurry was poured into water (*ca.* 1 l.); 2 : 3-dimethylindole was filtered off, washed with water, and dried over sulphuric acid and then sodium hydroxide, six experiments giving 518 g. (95%), m. p. 108—109°; this material can be recrystallised from light petroleum (b. p. 60—80°) (500 c.c./100 g.).

2 : 3-*Dimethyl*-5-*nitroindole*.—The crude foregoing material (225 g.) and urea (16 g.) were dissolved in cold sulphuric acid (2 l.; *d* 1·84) with mechanical stirring and treated at 0° (±5°) with a cold solution of potassium nitrate (160 g.) in sulphuric acid (800 c.c.; *d* 1·84), added during 20 min. Stirring was continued for 5 min., the mixture poured on crushed ice (*ca.* 15 kg.), and the precipitated solid washed with sodium acetate solution and water. The dry crude product (275 g.), m. p. *ca.* 170°, crystallised from alcohol in brown needles, m. p. 185—187° (50% yield); better purification was obtained if the crude material (140 g.) was digested with boiling benzene (total 8 l.) and decanted through a short column of alumina (200 g.; " Grade H ") prepared in hot benzene. Concentration of the eluate gave golden needles, m. p. 190°, of pure 2 : 3-dimethyl-5-nitroindole (43%).

1-*Acetyl*-2 : 3-*dimethylindole* (cf. Borsche and Groth, *loc. cit.*).—2 : 3-Dimethylindole (250 g.) was refluxed with acetyl chloride (1 l. of " AnalaR "; an ordinary quality gives a much lower yield) for 4 hr., excess of the reagent removed under reduced pressure, and the residue distilled at 130°/0·2 mm. Recrystallisation from alcohol (200 c.c.) gave colourless crystals, m. p. 74° (75%).

1-*Acetyl*-2 : 3-*dimethyl*-Bz-*nitroindoles*.—(*a*) The 5-nitro-indole (100 g.; m. p. 190°), anhydrous sodium acetate (100 g.), and acetic anhydride (1 l.) were refluxed together for 5½ hr. and the suspension poured into hot water (10 l.) with mechanical stirring. After cooling, the solid was filtered off, washed, and recrystallised from ethanol (charcoal). 1-*Acetyl*-2 : 3-*dimethyl*-5-*nitroindole* formed pale yellow needles, m. p. 109° (105 g., 86%) (Found: C, 60·4; H, 4·9; N, 12·05. $C_{12}H_{12}O_3N_2$ requires C, 62·2; H, 5·1; N, 12·1%).

(*b*) 2 : 3-Dimethyl-4-nitroindole (5 g.) similarly yielded the 1-*acetyl* derivative, m. p. 102°, as long yellow needles from alcohol (Found: C, 62·5; H, 4·85; N, 12·25%). A solution of this material (1 g.) in benzene (30 c.c.) was eluted from alumina (15 × 3·5 cm.) with benzene, to give the deacetylated compound (0·8 g.), m. p. and mixed m. p. 172°.

2-*Amino*-3-*nitroacetophenone*.—2 : 3-Dimethyl-7-nitroindole (10 g.) in acetic acid (100 c.c.) was treated with stirring at 25—30° with chromic anhydride (10 g.) in water (10 c.c.). The mixture was stirred overnight, diluted with water (220 c.c.), and extracted with chloroform, and the washed and dried (Na_2SO_4) extract was concentrated to 20 c.c. and diluted with ether (60 c.c.). The precipitated pale yellow solid gave colourless needles of 2-acetamido-3-

nitroacetophenone (8·5 g.), m. p. 152°, from ether–chloroform. Hydrolysis with alcohol–water–concentrated hydrochloric acid under reflux gave the amino-ketone, m. p. 94—95° (72%).

o-*Diacetylaminoacetophenone*.—A stirred solution of 1-acetyl-2 : 3-dimethylindole (1 g.; m. p. 74—75°; prepared according to Plant and Tomlinson, *loc. cit.*) (Found : C, 76·95; H, 7·35; N, 7·65. Calc. for $C_{12}H_{13}ON$: C, 77·0; H, 7·0; N, 7·5%) in acetic acid (20 c.c.) was treated during 5 min. with an aqueous solution of chromic anhydride (0·75 g. in 0·75 c.c.). The temperature rose to 30° and after 2 hr.' stirring the mixture was heated to 70° for 5 min., cooled, and diluted with water (*ca.* 80 c.c.). Unchanged material (0·14 g.), m. p. and mixed m. p. 75—76°, was precipitated and ether-extraction of the basified (sodium carbonate) filtrate gave an oil (0·71 g.); this furnished aggregates of colourless needles (0·36 g.), m. p. 84—86, of o-*diacetylaminoacetophenone* which formed colourless plates, m. p. 85—86°, from water or aqueous alcohol (Found : C, 65·3; H, 5·8; N, 6·6. $C_{12}H_{13}O_3N$ requires C, 65·75; H, 6·0; N, 6·4%). Identical material was obtained by refluxing *o*-acetamidoacetophenone with acetic anhydride for 30 min., concentration under reduced pressure, and recrystallisation of the residue from ether–light petroleum (b. p. 40—60°). The diacetylamino-compound was also converted into *o*-acetamidoacetophenone by hydrolysis (refluxing 2N-hydrochloric acid) and re-acetylation (warm acetic anhydride).

o-*Aminoacetophenone*.—A stirred solution of 1-acetyl-2 : 3-dimethylindole (40 g.) in acetic acid (40 c.c.) was treated, during 30 min. below 30° (chiefly 19—21°), with aqueous chromic anhydride (40 g. in 40 c.c.) and stirred for ½ hr. after the addition. Extraction (chloroform) of the diluted mixture and evaporation of the washed and dried extract gave an oil (37 g.) which was hydrolysed by refluxing 2N-hydrochloric acid for 1 hr.; two runs were combined and distilled, to give pure *o*-aminoacetophenone (30 g.), b. p. 90°/0·05 mm.

2-*Diacetylamino*-5-*nitroacetophenone*.—1-Acetyl-2 : 3-dimethyl-5-nitroindole (8·9 g.) was oxidised as above at 25° and stirred overnight before dilution and working up. The bulk of the monoacetamido-ketone was precipitated by ether from a chloroform solution, and material in the mother-liquors was recovered by evaporation and chromatographed in benzene on a carbon column. The first distinct fraction (1·07 g.), m. p. 86°, gave pure 2-*diacetylamino*-5-*nitroacetophenone* (0·7 g.), m. p. 93°, from alcohol (Found : C, 54·25; H, 4·55; N, 10·45. $C_{12}H_{12}O_5N_2$ requires C, 54·6; H, 4·55; N, 10·6%).

2-*Amino*-5-*nitroacetophenone*.—The 1-acetylindole (56 g.) was oxidised as in the preceding examples at 28° ± 1° and the readily crystallising oil (isolated by chloroform-extraction) was hydrolysed with refluxing alcohol–water–concentrated hydrochloric acid (equal vols.) to yield, by basification, the amino-ketone (34 g., 78%), m. p. 150—152°. The same product was obtained by oxidation of 2 : 3-dimethyl-5-nitroindole (7 g.; m. p. 190°) and hydrolysis of the intermediate *o*-acetamido-ketone (2·3 g., 28%). For preparative purposes, crude 2 : 3-dimethyl-5-nitroindole (100 g.; m. p. *ca.* 170°) was oxidised below 40° (experiments with the pure indole showed no change in yield from experiments at 18° ± 2° or 34° ± 2°). Ten runs, poured into water (4 l.), yielded, by filtration ("Supercel") and extraction of the dried filter-cake with hot benzene, a solid (349 g.), m. p. 138—145°, and a semi-solid (124 g.); chloroform-extraction of the mother-liquors gave similar fractions (30 g. and 47 g. respectively). Separate hydrolysis of the solid fractions furnished the amino-ketone (246 g., 24% based on 2 : 3-dimethylindole), m. p. 148—150° (pure, m. p. 154°); similar hydrolysis of the semi-solids gave material (40 g.) of m. p. 130—140°.

2-*Diacetylamino*-4-*nitroacetophenone*.—1-Acetyl-2 : 3-dimethyl-6-nitroindole (12 g.) was oxidised as usual at 25—26°; the almost colourless solid obtained by chloroform-extraction gave 2-*diacetylamino*-4-*nitroacetophenone*, m. p. 142°, as colourless plates from methanol (Found : C, 54·65; H, 4·5; N, 10·55%). Hydrolysis as above gave the amino-ketone, m. p. and mixed m. p. 164—165°.

2-*Amino*-4-*nitroacetophenone*.—Oxidation of the 1-acetyl-indole (56 g.) as in the preceding experiment and hydrolysis of the residue obtained by chloroform-extraction gave the amine (38 g.), m. p. 164—165°. The same compound was obtained by oxidation of 6-nitro-2 : 3-dimethylindole as described by Schofield and Theobald (*loc. cit.*).

2 : 3-*Epoxy*-2 : 3-*dimethyl*-6-*nitroindolenine*.—A solution of chromic anhydride (2 g.) in water (3 c.c.) was added during 9 min. to a well-stirred suspension of the indole (3 g.) in formamide (30 c.c.) at 2—5°. After being stirred overnight (temperature rising to 14°) the mixture was diluted with water (100 c.c.) and extracted with chloroform, and the washed and dried (Na_2SO_4) extract was concentrated to small volume. Addition of ether precipitated an orange solid which was recrystallised from alcohol, to give the *epoxide* (0·37 g.) as orange needles, m. p. 134° (Found : C, 58·0; H, 5·1; N, 14·1. $C_{10}H_{10}O_3N_2$ requires C, 58·2; H, 4·9; N, 13·6%).

Hydrolysis of this compound with refluxing 3N-hydrochloric acid (5 parts) and alcohol (1 part) in an apparatus connected to sodium acetate-buffered dimedone solution gave acetaldehyde (m. p. and mixed m. p. of dimedone derivative, 139—140°). No acetaldehyde was detected in an experiment from which the epoxide was excluded. Basification of the mixture gave 2-amino-4-nitroacetophenone, m. p. and mixed m. p. 166°.

2-*Diacetylamino*-6-*nitroacetophenone*.—A suspension of 1-acetyl-2 : 3-dimethyl-4-nitroindole (1·55 g.) in acetic acid (15 c.c.) was oxidised, as usual, at 25—28°. Evaporation of the washed and dried (Na_2SO_4) chloroform extract gave a solid (1·65 g.), m. p. 139—140°; 2-*diacetylamino*-6-*nitroacetophenone*, m. p. 146—147°, separated from ethanol in colourless plates (Found : C, 54·6; H, 4·55%).

2-*Amino*-6-*nitroacetophenone*.—Oxidation as in the previous experiment (13·5 g.) and hydrolysis of the crude product (12·8 g.) gave, by basification and chloroform-extraction, the amino-ketone (10·2 g., 85%), m. p. 74°. The same compound was obtained *via* 2-acetamido-6-nitroacetophenone, obtained by oxidation of 2 : 3-dimethyl-4-nitroindole according to Schofield and Theobald (*loc. cit.*).

2-*Amino*-5-*nitrobenzophenone*.—2-Methyl-5-nitro-3-phenylindole (3 g.) was oxidised, as usual, at 25° and the crude material (2·75 g.), m. p. 152°, obtained by extraction with chloroform was recrystallised from ethyl acetate to give colourless needles of the *acetamido-ketone*, m. p. 159° (Found : C, 63·45; H, 4·8; N, 9·55. $C_{15}H_{12}O_4N_2$ requires C, 63·5; H, 4·25; N, 9·9%). Hydrolysis with refluxing alcohol (20 c.c.) and hydrochloric acid (6N; 12 c.c.) gave the crude amine (95%), m. p. 158°. 2-Amino-5-nitrobenzophenone, m. p. 163·5°, formed yellow blades from ethyl acetate (Found : C, 64·75; H, 3·7; N, 12·0. Calc. for $C_{13}H_{10}O_3N_2$: C, 64·5; H, 4·15; N, 11·6%). Schofield and Theobald (*loc. cit.*) give m. p. 160—161°.

2-*Benzamido*-5-*nitroacetophenone*.—3-Methyl-5-nitro-2-phenylindole (0·3 g.), oxidised, as usual, at 24° ± 2°, yielded by chloroform-extraction a solid (0·15 g.), m. p. 185—190°. Recrystallisation from chloroform–ether gave colourless needles (0·13 g. 38·5%), m. p. and mixed m. p. 194—195°.

Volatility of 2 : 3-*Dimethyl*-6- *and* -7-*nitroindole*.—In a sublimation apparatus consisting of a " cold finger " dipping into a flask connected to a water pump, the weighed, finely powdered indole was heated at 107° ± 0·25° (bath) for exactly 2 hr. (pressure constant ± 1 mm.). The sublimate was washed from the finger with chloroform and the residue on evaporation to dryness was weighed. The sublimate from the 7-nitro-indole weighed 5·8 mg., that from the 6-nitro-isomer 1·0 mg.

Nitration of 1-*Acetyl*-2 : 3-*dimethylindole*.—A solution of 1-acetyl-2 : 3-dimethylindole (100 g.) in acetic acid (200 c.c.) was added simultaneously, but at a slightly lower rate, with a solution of nitric acid (50 c.c.; *d* 1·49) in acetic acid (200 c.c.) to well-stirred propionic acid (200 c.c.) at −10° during 40 min. 1-Acetyl-2 : 3-dimethyl-6-nitroindole (35 g., 30%), m. p. 169°, was filtered from the mixture, washed with acetic acid (2 × 10 c.c.), then water (2 × 300 c.c.), and dried at 70°. The filtrate and washings were diluted with water (800 c.c.) and extracted with chloroform (3 times). This extract was washed until acid-free, with sodium carbonate solution (washings rejected), then with 10% sodium hydroxide solution (3 × 500 c.c.; " A "), and finally with water, dried (Na_2SO_4), and evaporated. The residual red gum was chromatographed in benzene on alumina (7 × 22·5 cm.). Elution with benzene (6 × 500 c.c.) gave 2 : 3-dimethyl-4-nitroindole (10·2 g., 10%), m. p. and mixed m. p. 171°; further elution with ether (" anastheticus ") gave 2 : 3-dimethyl-6-nitroindole (2·5 g., 2%), m. p. and mixed m. p. 140°. The contents of the washings " A " are being examined and will be discussed in a future publication.

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