171. *Indoles. Part I. The* Bz-*Nitro-2 : 3-dimethylindoles and Their Use in Preparing Nitro-2-aminoacetophenones.*

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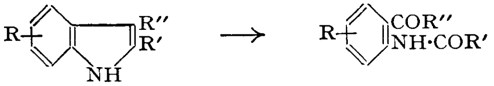
The oxidation of the *Bz*-nitro-2 : 3-dimethylindoles to nitro-2-aminoacetophenones has been examined. It offers a preparative method for obtaining 3-nitro- and 5-nitro-2-aminoacetophenone. 4-*Nitro*- and 6-*nitro*-2 : 3-*dimethylindole* and 4-*nitro*- and 6-*nitro*-2-*aminoacetophenone* are described, and the nitration of *N*-acetyl-2 : 3-dimethylindole has been reinvestigated.

Various modes of oxidation of indole derivatives have been studied [the formation of indigo and related substances is well known, and among others the autoxidation to indole ethers is noteworthy (Oddo, *Gazzetta*, 1916, **46**, I, 323; 1920, **50**, II, 268; Taffoli, *Atti X° Congr. intern. Chim.*, 1939, **3**, 369; Plancher and Colacicchi, *Atti R. Accad. Lincei*, 1911, **20**, I, 453)], but relatively few examples are known of oxidative ring fission of the type



Jackson (*Ber.*, 1881, **14**, 885) obtained acetylanthranilic acid by the action of alkaline permanganate on 2-methylindole, and the formation of the same product through an intermediate ether by autoxidation in sunlight has been observed (Baudisch and Haschek, *Ber.*, 1916, **49**, 2579), but only recently has this type of ring opening been exploited to any extent. Witkop and his collaborators found that ozone converted indole into anhydrotris-(2-aminobenzaldehyde), whilst 2-methylindole in formamide solution gave 2-acetamidobenzaldehyde. Under similar conditions skatole, 2 : 3-dimethylindole, and 3-ethylindole were ozonised to give, respectively, 2-formamido- and 2-acetamido-acetophenone and 2-formamidopropiophenone. Besides ozone, perbenzoic and peracetic acids were used, and the reaction applied to certain alkaloid derivatives (Witkop and Graser, *Annalen*, 1944, **556**, 103; Witkop and Fiedler, *ibid.*, 1947, **558**, 91; Witkop, *ibid.*, 1947, **558**, 98). Koelsch, using chromic acid in acetic acid solution, obtained 5-bromo-2-benzoyl-*N*-acetylbenzanilide from 6-bromo-1-acetyl-2 : 3-diphenylindole (*J. Amer. Chem. Soc.*, 1944, **66**, 1983), and with the same reagent converted 2 : 4- and 2 : 6-dicarbethoxy-3-(2′-carbethoxyethyl)indole into ethyl β-(6-carbethoxy-2-ethoxalylaminobenzoyl)propionate and the 4-carbethoxy-compound respectively (*J. Org. Chem.*, 1943, **8**, 295). Plant and his co-workers have effected similar ring openings with this reagent, converting 1 : 6-diacetyl-2 : 3-dimethylindole into 2 : 5-diacetylacetanilide, and 1-acetyl-2 : 3-dimethylindole into 2-acetamidoacetophenone (Gaudion, Hook, and Plant, *J.*, 1947, 1631). The indole heterocycle has also been opened in the same sense by Plant (*J.*, 1940, 283, etc.) by the device of adding the elements of nitric acid to the indole C_2–C_3 double bond, and degrading the product with alkali. It will be noticed that in the oxidations with chromic acid mentioned above the *N*-acetyl derivatives of the indoles were used, except in the cases where the indole *Bz*-ring contained the strongly electron-attracting carbethoxy-group.

This oxidative fission of the indole heterocycle appeared to us to offer a possibly easy route to substituted 2-aminoacetophenones useful in various connections, more particularly in the present instance for the synthesis of 4-hydroxycinnolines (Schofield and Simpson, *J.*, 1945, 520, and other papers of the same series), and to analogous 2-aminobenzophenones, and in the present communication we describe its application to the preparation of all four isomeric nitro-2-aminoacetophenones. Hitherto the most readily available of these compounds has been 5-nitro-2-aminoacetophenone (Simpson *et al.*, *J.*, 1945, 646; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405) but its preparation requires 2-aminoacetophenone, not very easily obtained in quantity, as starting material. This preparation yields small amounts of 3-nitro-2-aminoacetophenone as a minor product under certain conditions (Simpson, *J.*, 1947, 237), but no satisfactory preparative method was hitherto available for this compound. 4-*Nitro*- and 6-*nitro*-2-*amino*-

acetophenone have not previously been described, although Plant and Whitaker (*J.*, 1940, 283) mention the crude acetyl derivative of the former.

Ethyl methyl ketone *o*- and *p*-nitrophenylhydrazones have been used in the Fischer synthesis of 7- and 5-nitro-2 : 3-dimethylindole by Bauer and Strauss (*Ber.*, 1932, **65**, 308), and the second example has also been described by Plant and Tomlinson (*J.*, 1933, 955). We find the conditions described by the German workers to be preferable, and the yields of these indoles so obtained are 44% and 57%, respectively, based on the parent nitroanilines. The same authors (*loc. cit.*) also carried out the cyclisation of the corresponding *m*-nitrophenylhydrazone, isolating from the resulting mixture a product, m. p. 126°. From the same reaction Plant and Tomlinson (*loc. cit.*) obtained the second isomer, m. p. 142°. This second substance was identical with the compound formed by nitration and subsequent hydrolysis of 1-acetyl-2 : 3-dimethylindole, and Plant and Whitaker (*loc. cit.*) later proved it to be 6-nitro-2 : 3-dimethylindole. They further purified the compound isolated by Bauer and Strauss, raising its melting point to 130°, found that it depressed the melting point of their 6-nitro-compound, and thus concluded it to be 4-nitro-2 : 3-dimethylindole. In re-examining these results we found the conditions of Bauer and Strauss for the cyclisation of the *m*-nitrophenylhydrazone again to be preferable, giving 32% of mixed isomers based on *m*-nitroaniline. With a view to obtain as nearly as possible quantitative separation of each isomer present in the mixture, we investigated the possibility of separation by adsorption on alumina, a technique which proved successful in the closely related carbazole series (Barclay and Campbell, *J.*, 1945, 530). Adsorption from benzene, and elution with benzene–pyridine mixture gave almost quantitative recovery of two isomeric nitro-2 : 3-dimethylindoles, the least strongly adsorbed being a crimson compound, m. p. 172—173°, and the more strongly adsorbed an orange solid, m. p. 141—142°, the two occurring in the ratio 5 : 8, approximately. This result clearly rendered it necessary to orient the compounds afresh, both for the present purpose and as a check on the direction of nitration of 1-acetyl-2 : 3-dimethylindole as studied by Plant and Whitaker (*loc. cit.*).

As noted above, electron-attracting groups in the indole *Bz*-ring appear to render possible oxidative fission of the hetero-ring without the need for protecting the compound by acetylation. This proved to be the case with the nitro-2 : 3-dimethylindoles. By the action of chromic acid in acetic acid upon 5- and 7-nitro-2 : 3-dimethylindole, 5- and 3-nitro-2-acetamidoacetophenone were obtained in yields of 25% and 22% based on the parent nitroanilines. Clearly, the method, which is economical in time, is of great preparative value for these compounds, and in our experience is superior to previous methods. The nitro-2 : 3-dimethylindoles, m. p. 141—142° and 172—173°, originating from *m*-nitroaniline were likewise oxidised to isomeric nitro-2-acetamidoacetophenones, m. p. 126—127° and 143—144° respectively, and thence, by hydrolysis, provided the related 2-amino-ketones, m. p. 162—163° and 74—75°. The first of these, by diazotisation and reduction with hypophosphorous acid, gave *p*-nitroacetophenone, m. p. 81°, identified by hypochlorite oxidation to *p*-nitrobenzoic acid. To summarise, the Fischer cyclisation of methyl ethyl ketone *m*-nitrophenylhydrazone provides 4-nitro-, m. p. 172—173°, and 6-nitro-2 : 3-dimethylindole, m. p. 141—142°, in the approximate ratio of 5 : 8, from which may be obtained 6-nitro-, m. p. 74—75°, and 4-nitro-2-aminoacetophenone, m. p. 162—163°. The compound, m. p. 130°, previously assumed to be 4-*nitro*-2 : 3-*dimethylindole* must have been impure.

The problem of the cyclisation of the arylhydrazones of unsymmetrical ketones has not been extensively investigated, and in most of the cases on record one product only seems to be formed (van Order and Lindwall, *Chem. Reviews*, 1942, **30**, 69). One exception is found in the ring closure of methyl ethyl ketone phenylhydrazone, which Korczynski, Brydowna, and Kierzek (*Gazzetta*, 1926, **56**, 903) report to give 2 : 3-dimethylindole and 2-ethylindole in the approximate ratio of 4 : 1. The present work shows that in the case of the nitrophenylhydrazones of methyl ethyl ketone the product isolated from the cyclisation contains substances arising from ring closure in one way only. Again, the case of Fischer cyclisation of *m*-substituted arylhydrazones does not appear to have received much attention from the point of view of determining the proportions of 4- and 6-substituted isomers formed. According to Hollins ("Synthesis of Nitrogen Ring Compounds," London 1924, p. 96) the reactive position in a *m*-substituted arylhydrazone is "probably that which is *para* to the substituent group." Steric considerations make this not unlikely (since Fischer indolisation appears to be independent of the electronic characteristics of substituents in the aryl nucleus) and it certainly received support in the present instance. However, Barclay and Campbell (*loc. cit.*) find the products from *cyclo*hexanone *m*-nitrophenylhydrazone to occur in equal proportions, though this does not appear to be so with the analogous *m*-bromo-compound, and indeed, in the example investigated by Koelsch (*loc. cit.*)

a larger yield of the 4-substituted indole than of the 6-isomer (3 : 2) was isolated. The significance of this last result is doubtful in view of the crystallisation processes used in purifying the substances, and in general, the precise determination of the proportion of isomers formed in such reactions is rendered difficult by the far from quantitative yields and the fact that the solubilities of the isomers in the cyclisation medium, if it be a liquid, are not necessarily the same.

We have repeated the nitration of 1-acetyl-2 : 3-dimethylindole according to Plant and Whitaker (*loc. cit.*), and find the product to be 6-nitro-1-acetyl-2 : 3-dimethylindole formed in 14% yield. The homogeneity of this product was established by hydrolysis to 6-nitro-2 : 3-dimethylindole which underwent no resolution on an alumina column.

Other examples of the type of oxidation reaction described are being investigated, especially its application to the formation of 2-aminobenzophenones, and will be described later, as will the cinnolines derived from these new aminoacetophenones.

EXPERIMENTAL.

(Melting points are uncorrected.)

Nitrophenylhydrazines.—The *o*- and *m*-compounds were obtained in yields of 72% and 65% respectively by the method of Muller *et al.* (*Helv. Chim. Acta*, 1937, **20**, 1468), whilst *p*-nitrophenylhydrazine resulted in 72% yield according to Vogel (" A Text-Book of Practical Organic Chemistry," London, 1948, p. 609).

Nitrophenylhydrazones.—Methyl ethyl ketone *o*-, m. p. 72—73° (95%), *m*-, m. p. 98—99° (84%), and *p*-nitrophenylhydrazone, m. p. 124—125° (91%), resulted when the ketone and hydrazine were heated in equivalent amounts for 1 hour at 95° and the product was crystallised from ethanol (Plant and Tomlinson, *J.*, 1933, 955).

Fischer Cyclisations.—7-Nitro-, m. p. 158—160° (44%), 5-nitro-, m. p. 184—185° (57%), and a mixture of 4- and 6-nitro-2 : 3-dimethylindole (32%) were obtained by heating the nitrophenylhydrazones (10 g.) with hydrochloric acid (100 c.c., *d* 1·18) for 4 hours at 95°, collecting the product, and washing it with hydrochloric acid. On a larger scale (*ca.* 50 g. of hydrazone) the yields from the *o*- and *m*-compounds fell to 28% and 26% respectively (yields are based on the corresponding nitroanilines) (Bauer and Strauss, *loc. cit.*)

Chromatographic Separation of 4- *and* 6-*Nitro*-2 : 3-*dimethylindole.*—A filtered solution of the crude mixture (15 g.) from the Fischer cyclisation of methyl ethyl ketone *m*-nitrophenylhydrazone in benzene (500 c.c.) was adsorbed on alumina (60 cm. × 3·5 cm. of type " H," supplied by Messrs. Peter Spence Ltd.), and the adsorbate developed with benzene until separation into a lower, orange band and an upper, red band occurred. The lower band was quickly eluted with benzene (2·89 g., m. p. 171—172°), and after a middle fraction had been collected (5·49 g., m. p. 125—130°), the remainder of the upper layer was washed out with benzene–pyridine (10 : 1) (5·65 g., m. p. 132—135°). The first fraction was homogeneous, and crystallisation from dilute ethanol gave crimson plates of 4-*nitro*-2 : 3-*dimethylindole*, m. p. 172—173° (Found : C, 63·10; H, 5·11. $C_{10}H_{10}O_2N_2$ requires C, 63·16; H, 5·26%). Similarly, 6-nitro-2 : 3-dimethylindole, m. p. 141—142°, was obtained from the third fraction in orange leaflets (Found : C, 62·98; H, 5·15%). Re-adsorption and elution of the middle fraction using benzene permitted complete separation, giving 2·49 g. more of the 4- and 2·98 g. more of the 6-compound. Thus the total yields of these were 5·38 g. and 8·63 g., respectively, an approximate ratio of 5 : 8.

3-*Nitro*-2-*aminoacetophenone.*—7-Nitro-2 : 3-dimethylindole (22 g.) in acetic acid (200 c.c.) was treated gradually with chromic anhydride (20 g.) in water (20 c.c.), the temperature not being allowed to rise above 40°. The solution was left overnight, diluted with water, and extracted with chloroform. The washed and dried (Na_2CO_3) extract left a sticky solid (13·7 g.) on concentration, which crystallised from benzene to give almost pure 3-nitro-2-acetamidoacetophenone, m. p. 151—152° (10·7 g., 42%). Hydrolysis (Simpson, *J.*, 1947, 237) gave 3-nitro-2-aminoacetophenone, m. p. 94—95° (7·7 g.). On a smaller scale (0·5 g.) the oxidation yielded 50% of the acetamido-compound (22% based on *o*-nitroaniline).

5-*Nitro*-2-*aminoacetophenone.*—In the same way 5-nitro-2 : 3-dimethylindole (9 g.) gave 5-nitro-2-acetamidoacetophenone (4·5 g. of once crystallised material, m. p. 139—141°, 43%), providing 5-nitro-2-aminoacetophenone (3·5 g.), m. p. 153—154°, on hydrolysis (Simpson *et al.*, *J.*, 1945, 646). On the smaller scale (1 g.) the yield of acetamido-compound was 45% (25% based on *p*-nitroaniline).

4-*Nitro*-2-*aminoacetophenone.*—Oxidation of 6-nitro-2 : 3-dimethylindole (3 g.) as above gave a sticky brown solid, which provided the acetamido-compound (0·9 g., 26%) on crystallisation from benzene. 4-*Nitro*-2-*acetamidoacetophenone* separated from dilute alcohol in pale yellow needles, m. p. 126—127° (Found : C, 54·62; H, 4·48. $C_{10}H_{10}O_4N_2$ requires C, 54·04; H, 4·53%). Hydrolysis of this compound (0·9 g.) by refluxing with alcohol (10 c.c.), concentrated hydrochloric acid (5 c.c.), and water (5 c.c.) on the steam-bath for ½ hour, followed by basification with ammonia, gave the free amine (0·7 g.). 4-*Nitro*-2-*aminoacetophenone* crystallised from dilute alcohol in fine orange needles, m. p. 162—163° (Found : C, 53·69; H, 4·43. $C_8H_8O_3N_2$ requires C, 53·33; H, 4·44%). This amine (0·2 g.) in acetic acid (2 c.c.) and sulphuric acid (1 c.c. of *ca.* 30N), was diazotised at 0° with powdered sodium nitrite (0·1 g.), and the solution treated with hypophosphorous acid (2 c.c. of 15%) after being diluted with iced water (10 c.c.). After standing overnight at 0° the solution was basified with sodium hydroxide and extracted with ether. The dried extract (Na_2SO_4) yielded *p*-nitroacetophenone (0·08 g.), m. p. 80—81° after crystallisation from dilute alcohol. This ketone (0·05 g.) was heated at 95° for 1 hour with sodium hydroxide solution (10 c.c. of 2N) and sodium hypochlorite prepared from sodium hydroxide (0·5 g.) in water (5 c.c.). Acidification with hydrochloric acid gave *p*-nitrobenzoic acid (0·02 g.), which separated from water in colourless leaflets, m. p. 237—238°, alone and mixed with an authentic specimen.

6-*Nitro*-2-*aminoacetophenone*.—4-Nitro-2 : 3-dimethylindole (1 g.) on oxidation provided 0·35 g. (30%) of once crystallised (benzene) acetamido-compound. 6-*Nitro*-2-*acetamidoacetophenone* formed pale yellow needles, m. p. 143—144°, from aqueous ethanol (Found: C, 54·30; H, 4·67%). Hydrolysis of this substance (0·25 g.) with hydrochloric acid (10 c.c. of 6N) at 95° for ½ hour, followed by basification with ammonia gave 6-*nitro*-2-*aminoacetophenone* (0·20 g.), which separated in fine yellow needles, m. p. 74—75°, from dilute alcohol (Found: C, 53·23; H, 4·51%).

Nitration of 1-*Acetyl*-2 : 3-*dimethylindole*.—Nitration of the indole (4 g.) according to Plant and Whitaker (*loc. cit.*) gave 0·70 g. (14%) of product, m. p. 165—167°. One crystallisation from alcohol raised the m. p. to the constant value, 167—168°. Hydrolysis of the acetyl compound (0·5 g.) with alcoholic potash gave 6-nitro-2 : 3-dimethylindole (0·25 g.), m. p. 139—140°, which proved to be homogeneous when applied to an alumina column in benzene solution, giving quantitative recovery on elution.

The authors are indebted to the Chemical Society, I.C.I. Ltd., and the Council of University College, Exeter, for financial aid, and to the Department of Scientific and Industrial Research for a maintenance grant to one of them (R. S. T.).

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[*Received, September 7th,* 1948.]