

Peroxides of Tetrahydrocarbazole and Related Compounds.
Part VI. Some Indoleninyl Hydroperoxides.*

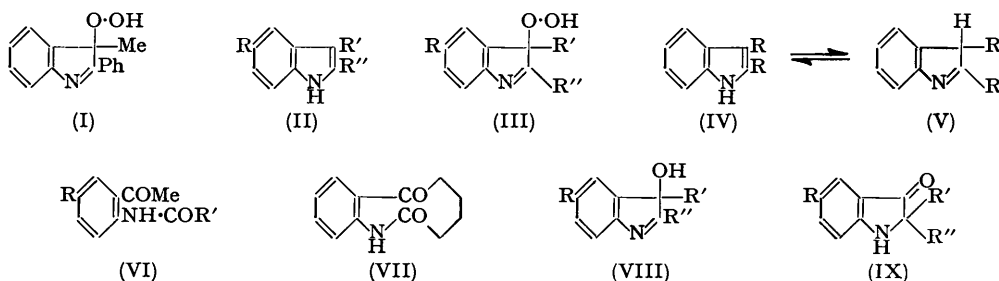
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Certain indoles, of type (II), are converted by autoxidation into indoleninyl hydroperoxides, the decomposition of which, under various conditions, yields *o*-acylamino-ketones (VI). Reduction of 2 : 3-dimethylindoleninyl hydroperoxides with sodium dithionite gives 3-hydroxy-2 : 3-dimethylindolenines, of type (VIII), which readily rearrange in hot alkaline media to 2 : 2-dimethyl- ψ -indoxyls.

THE formation of hydroperoxides is a property common to many 1 : 2 : 3 : 4-tetrahydrocarbazoles (Part IV, *J.*, 1952, 4946) but hitherto the only peroxides derived from indoles which have been described are those obtained from 2-aryl-3-methylindoles by Witkop and Patrick (*J. Amer. Chem. Soc.*, 1952, **74**, 3856; see also *Chem. Ber.*, 1952, **85**, 949). Formed in low yield by autoxidation of 2-phenylskatole, the hydroperoxide (I) was found to be more stable than tetrahydrocarbazolyl hydroperoxide, but like the latter compound, underwent acid-catalysed rearrangement, giving *o*-benzamidoacetophenone.

Experience with tetrahydrocarbazoles (*loc. cit.*) suggested that the presence of an electron-releasing substituent (R) in the benzene ring of indoles (type II) would facilitate peroxide formation and in agreement with this prediction 5-methoxy-3-methyl-2-phenylindole (II; R = OMe, R' = Me, R'' = Ph) is autoxidised in good yield to the indoleninyl hydroperoxide (III; R = OMe, R' = Me, R'' = Ph). A closer analogue of the tetrahydrocarbazoles is 5-methoxy-2 : 3-dimethylindole (II; R = OMe, R' = R'' = Me). This compound formed a hydroperoxide (III; R = OMe, R' = R'' = Me), the yield of which in small-scale experiments was almost quantitative but, as with the tetrahydrocarbazole series, purifica-



tion involved some loss. Autoxidation of 2 : 3-dimethylindole proceeded less satisfactorily but it was possible to isolate the pure hydroperoxide (III; R = H, R' = R'' = Me) in 25% yield; some of the indole was converted into a by-product of unknown structure having apparently a higher molecular weight. Reproducible results in these autoxidations were obtained only when the reactions were catalysed by traces of either benzoyl peroxide, or, better, the hydroperoxide which was being formed.

Attempts to prepare peroxides from 2-methyl-3-phenyl- and 2 : 3-diphenyl-indoles (*e.g.*, II; R = H, R' = Ph, R'' = Me; R = OMe, R' = Ph, R'' = Me; R = H, R' = R'' = Ph; R = OMe, R' = R'' = Ph) have not been successful; these indoles appear to be relatively resistant to the action of oxygen. It is interesting and possibly significant that the structural features which inhibit or prevent peroxide formation in the indole and tetrahydrocarbazole series, *viz.*, (a) *N*-substitution, (b) the presence of strongly electron-attracting groups in the benzene ring, and (c) the presence of a phenyl group in the 3-position, have been found to be necessary or desirable for successful oxidation of indoles to *o*-acylamino-ketones with chromic acid (see, *e.g.*, Atkinson, Simpson, and Taylor, *J.*, 1954,

* Part V, *J.*, 1953, 2440.

165), which, it has been suggested, depends on reduction of the aromaticity of the heteronucleus and the stabilisation of the imino-tautomer (IV) in the imino-ketimine system ($IV \rightleftharpoons V$). An alternative explanation is that successful chromic acid oxidation depends on the *absence* of an imino-group which is susceptible to homolytic fission. When a group of this type is present, *e.g.*, in indoles which readily undergo autoxidation, the first action of the oxidising agent may be to generate free N-radicals, the formation of which may well complicate or change the course of the subsequent oxidation.

Like the peroxide from 2-phenylskatole (cf. Witkop and Patrick, *loc. cit.*), 5-methoxy-3-methyl-2-phenylindolenine hydroperoxide (III; R = OMe, R' = Me, R'' = Ph) is more stable than the hydroperoxides of the tetrahydrocarbazole series towards cold aqueous acids and alkalis. With hot reagents this compound is converted into 2-benzamido-5-methoxyacetophenone (VI; R = OMe, R' = Ph) in which the presence of the benzamido-group was demonstrated by hydrolysis to benzoic acid and 2-amino-5-methoxyacetophenone, isolated as the hydrochloride. This amino-ketone was also obtained by hydrolysis of 2-acetamido-5-methoxyacetophenone (VI; R = OMe, R' = Me) which is readily formed by the decomposition of 5-methoxy-2 : 3-dimethyl-3-indoleninyl hydroperoxide (III; R = OMe, R' = R'' = Me) in hot water or benzene. 2 : 3-Dimethyl-3-indoleninyl hydroperoxide (III; R = H, R' = R'' = Me) was similarly converted by boiling water into *o*-acetamidoacetophenone. The dimethylindoleninyl hydroperoxides decomposed slowly in cold aqueous sodium hydroxide, giving the corresponding *o*-acetamidoacetophenones. Under similar conditions tetrahydrocarbazolyl hydroperoxide yields mainly 4-hydroxy-2 : 3-cyclopentenoquinoline (Part II, *J.*, 1950, 3283), probably by way of the cyclic lactam (VII) analogous to (VI).

Witkop and Patrick (*loc. cit.*) found that 3-hydroxy-3-methyl-2-phenylindolenine (VIII; R = H, R' = Me, R'' = Ph), obtained by reduction of the corresponding peroxide catalytically or with sodium borohydride, does not undergo rearrangement to 2-methyl-2-phenyl- ψ -indoxyl (IX; R = H, R' = Me, R'' = Ph) with alkalis under conditions which bring about the rearrangement of 1 : 2 : 3 : 4-tetrahydro-11-hydroxycarbazolenine. The behaviour of the 3-hydroxy-2 : 3-dimethylindolenines (VIII; R = H, R' = R'' = Me; R = OMe, R' = R'' = Me), prepared from the hydroperoxides by reduction with alkaline sodium dithionite, indicates that the stability of Witkop and Patrick's compound is due to the presence of the 2-phenyl group, and not, as these authors suggest, to the small migratory aptitude of the 3-methyl group. When heated with aqueous sodium hydroxide both 3-hydroxy-2 : 3-dimethylindolenines, which are colourless basic compounds, readily rearrange to yellow non-basic isomerides showing (in solution) the characteristic intense green fluorescence of 2 : 2-disubstituted ψ -indoxyls. These products are therefore formulated as 2 : 2-dimethyl- ψ -indoxyl (IX; R = H, R' = R'' = Me) and 5-methoxy-2 : 2-dimethyl- ψ -indoxyl (IX; R = OMe, R' = R'' = Me).

EXPERIMENTAL

The light petroleum employed had b. p. 60—80°.

5-Methoxy-3-methyl-2-phenylindole.—An alcoholic solution of the crude phenylhydrazone, obtained from propiophenone (2.6 g.) and *p*-methoxyphenylhydrazine hydrochloride (3.5 g.), was saturated with hydrogen chloride, heated under reflux for 30 min., and poured on ice. The resulting brown oil was isolated with ether and distilled, giving a yellow viscous oil, b. p. 230—240°/25 mm., which on being heated gave a sublimate of 5-methoxy-3-methyl-2-phenylindole, forming colourless needles (1.2 g.), m. p. 120°, from methanol (Found : C, 81.5; H, 6.4; N, 6.0. C₁₆H₁₅ON requires C, 81.0; H, 6.3; N, 5.9%).

5-Methoxy-2-methyl-3-phenylindole.—Similarly prepared from *p*-methoxyphenylhydrazine hydrochloride (4.25 g.) and phenylacetone (3.2 g.), 5-methoxy-2-methyl-3-phenylindole crystallised from aqueous methanol (charcoal) in colourless needles (1.4 g.), m. p. 84—85° (Found : C, 81.1; H, 6.2; N, 5.9%).

5-Methoxy-2 : 3-diphenylindole.—Prepared by the action of hot alcoholic hydrogen chloride on the *p*-methoxyphenylhydrazone of deoxybenzoin (4 g.), 5-methoxy-2 : 3-diphenylindole separated from aqueous methanol in buff prisms (2.3 g.), m. p. 155—156° (Found : C, 84.0. H, 5.5; N, 4.6. C₂₁H₁₇ON requires C, 84.3; H, 5.7; N, 4.7%).

Preparation of Peroxides.—The indole was dissolved in sufficient hot light petroleum to prevent rapid crystallisation of the compound on cooling and a trace of benzoyl peroxide or one of the indoleninyl hydroperoxides was added to the solution. When separation of the crude crystalline hydroperoxide appeared to be complete, the product was collected and recrystallised as quickly as possible from ethyl acetate–light petroleum.

5-Methoxy-3-methyl-2-phenyl-3-indoleninyl hydroperoxide formed yellow prisms, m. p. 148—150° (decomp.) (Found: C, 71.0; H, 5.5; N, 5.3; OMe, 11.6. $C_{16}H_{15}O_3N$ requires C, 71.4; H, 5.6; N, 5.2; OMe, 11.5%); the yield of crude peroxide was almost quantitative.

2:3-Dimethyl-3-indoleninyl hydroperoxide crystallised in colourless prisms, m. p. 113° (vigorous decomp.), easily soluble in cold dilute hydrochloric acid and aqueous sodium hydroxide; the yield of pure product was 25% (Found: C, 67.6; H, 6.0; N, 7.9. $C_{16}H_{11}O_2N$ requires C, 67.8; H, 6.2; N, 7.9%). A second, non-peroxidic substance subsequently separated slowly in low and variable yield from the residual reaction mixture and on crystallisation from ethanol, formed colourless, shining prisms, m. p. 225° (Found: C, 74.7; H, 6.9; N, 8.8%; M, 242).

5-Methoxy-2:3-dimethyl-3-indoleninyl hydroperoxide formed colourless prisms, m. p. 111° (decomp.) (yield of pure product, 50%) (Found: C, 63.7; H, 6.2; N, 6.9; OMe, 14.9. $C_{11}H_{13}O_3N$ requires C, 63.8; H, 6.3; N, 6.8; OMe, 15.0%).

2-Benzamido-5-methoxyacetophenone.—A solution of 5-methoxy-3-methyl-2-phenylindoleninyl hydroperoxide (200 mg.) in a mixture of methanol (8 ml.) and 2*N*-aqueous sodium hydroxide (5 ml.) was heated under reflux for 30 min. and then concentrated. On dilution with water the residual solution deposited *2-benzamido-5-methoxyacetophenone* which separated from aqueous methanol in yellow needles (115 mg.), m. p. 116° (Found: C, 71.1; H, 5.9; N, 5.3; OMe, 11.9. $C_{16}H_{15}O_3N$ requires C, 71.4; H, 5.6; N, 5.2; OMe, 11.5%). The same ketone was formed by treatment of the peroxide with hot dilute hydrochloric acid. Hydrolysis of the benzamido-ketone (100 mg.) with a boiling mixture (30 ml.) of equal amounts of water, concentrated hydrochloric acid, and acetic acid for 12 hr. gave benzoic acid, m. p. 121°, and 2-amino-5-methoxyacetophenone, isolated as its hydrochloride, m. p. 186—187°, identical with a specimen from 2-acetamido-5-methoxyacetophenone.

2-Acetamido-5-methoxyacetophenone.—When 5-methoxy-2:3-dimethylindoleninyl hydroperoxide (170 mg.) was dissolved in boiling water (30 ml.) and the solution kept at room temperature *2-acetamido-5-methoxyacetophenone* (96 mg.) slowly separated. Recrystallised from light petroleum, this compound formed long, yellow needles, m. p. 91—92° (Found: N, 6.8; OMe, 14.8. $C_{11}H_{13}O_3N$ requires N, 6.8; OMe, 15.0%). *2-Acetamido-5-methoxyacetophenone* was also obtained by decomposing the peroxide with hot benzene or with cold aqueous sodium hydroxide. Hydrolysis of 2-acetamido-5-methoxyacetophenone with hot 6*N*-hydrochloric acid for 4 hr. gave 2-amino-5-methoxyacetophenone which was isolated as the *hydrochloride*, forming buff prisms, m. p. 186—187°, from ethanol–ether (Found: N, 6.8; OMe, 15.2. $C_9H_{11}O_2N, HCl$ requires N, 6.9; OMe, 15.4%). This was shown to be the salt of a primary aromatic amine by the diazotisation test.

3-Acetamidoacetophenone.—This product (yield, 50% of theoretical), which separated from a hot solution of 2:3-dimethylindoleninyl hydroperoxide in boiling water and was also formed slowly by treatment of the peroxide with cold aqueous sodium hydroxide, crystallised from light petroleum in yellow needles, m. p. 77—78° (Found: N, 8.0. Calc. for $C_{10}H_{11}O_2N$: N, 7.9%) (Gevekoht, *Ber.*, 1882, 15, 2086, records m. p. 76—77°). The oxime separated from light petroleum in colourless needles, m. p. 153° (Auwers and Meyenburg, *Ber.*, 1891, 24, 2378, record m. p. 149—150°).

3-Hydroxy- and 3-Hydroxy-5-methoxy-2:3-dimethylindolenine.—2:3-Dimethylindoleninyl hydroperoxide (0.75 g.) was agitated with a mixture of 2*N*-aqueous sodium hydroxide (10 ml.), sodium dithionite (1 g.), and ether (15 ml.) for 1 hr., the ether layer was separated, and the aqueous liquor was extracted with more ether. Evaporation of the combined, dried, ethereal extracts gave *3-hydroxy-2:3-dimethylindolenine* as a cream crystalline solid (0.5 g.), m. p. 136—139°, which, on recrystallisation from ethyl acetate–light petroleum, formed colourless prisms, m. p. 143—144°, easily soluble in cold dilute hydrochloric acid but insoluble in cold 2*N*-sodium hydroxide (Found: C, 74.4; H, 6.8; N, 8.7. $C_{10}H_{11}ON$ requires C, 74.5; H, 6.8; N, 8.7%).

Similarly prepared from 5-methoxy-2:3-dimethylindolenine hydroperoxide, *3-hydroxy-5-methoxy-2:3-dimethylindolenine* formed pale yellow plates, m. p. 124°, from benzene–light petroleum (Found: N, 7.3; OMe, 16.7. $C_{11}H_{13}O_2N$ requires N, 7.3; OMe, 16.2%).

2:2-Dimethyl- and 5-Methoxy-2:2-dimethyl-ψ-indoxyl.—On being boiled with 2*N*-aqueous sodium hydroxide for 2—3 hr. *3-hydroxy-2:3-dimethylindolenine* was converted into *2:2-dimethyl-ψ-indoxyl* which separated from light petroleum in pale yellow needles (75%), m. p.

89—90° (Found : C, 74.5; H, 7.1; N, 8.9. $C_{10}H_{11}ON$ requires C, 74.5; H, 6.8; N, 8.7%).
5-Methoxy-2 : 2-dimethyl- ψ -indoxyl was prepared from 3-hydroxy-5-methoxy-2 : 3-dimethyl-indolenine by the same method, and on purification from light petroleum formed long yellow needles, m. p. 85—86° (40%) (Found : C, 69.1; H, 6.9; N, 7.3. $C_{11}H_{13}O_2N$ requires C, 69.1; H, 6.8; N, 7.3%). Solutions of both products in methanol exhibited a strong green fluorescence.

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