Autoxidation of 2,3-Dialkylindoles

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Autoxidation of 2,3-dimethylindole leads to the formation of an oxidized dimer **6***a*, and 2-methyl-3-ethylindole gives rise to the corresponding product **6***c* under the same conditions. In contrast, 2-ethyl-3-methylindole resembles 2,3-diethylindole in behavior and forms 2-acetyl-3-methylindole via the 3-hydroperoxyindolenine, which is an isolable intermediate. Some of the side reactions which occur under autoxidative conditions have been studied, and an attempt has been made to give a satisfactory unified rationalization of our results and those obtained for related autoxidations by numerous other workers.

L'autoxydation du diméthyl-2,3 indole conduit à la formation d'un dimère oxydé **6***a* et celle du méthyl-2 éthyl-3 indole conduit, sous les mêmes conditions, au produit correspondant **6***c*. Au contraire, l'éthyl-2 méthyl-3 indole ressemble par son comportement au diéthyl-2,3 indole et conduit à l'acétyl-2 méthyl-3 indole via l'hydroperoxy-3 indolénine qui est un intermédiaire isolable. Certaines réactions secondaires qui se font sous les conditions de l'autoxydation ont également été étudiées. Ces résultats, ainsi que ceux d'autres auteurs concernant des réactions d'autoxydation analogues ont été rationalisés d'une façon satisfaisante.

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The autoxidation of indoles and related oxidations by peroxy compounds have led to results of chemical interest and biochemical significance. The oxidation of 2,3-disubstituted indoles (**1**) has led to a variety of products, the nature of which has been shown to depend on the reaction conditions and the nature of the substituents (1–7). Isolable products from the autoxidation of compounds of general formula **1** have included 3-hydroperoxyindolenines (**2**), 3-hydroxyindolenines (**3**), compounds (**4**) in which the substituent at C-2 has been oxidized (corresponding products have been obtained from indoles carrying a heteroatom at C-2), and compounds (**5**) in which the heterocyclic ring has been opened oxidatively, as well as rearrangement, condensation, or cleavage products derived from these. It is widely accepted that a common reaction pathway starts with the conversion of the indole (**1**) to the 3-hydroperoxyindolenine (**2**), frequently isolable, which then leads on to the other products listed; there is, however, a considerable range of opinion about the details of the latter steps.

In 1954 Beer *et al.* (1*a*) showed that the simplest dialkylindole of this class, 2,3-dimethylindole (**1***a*), on autoxidation formed the hydroperoxide (**2***a*) and a second non-peroxidic product of higher molecular weight. Leete (2*a*) reported that the corresponding hydroperoxy derivative (**2***b*) could be obtained from 2,3-diethylindole (**1***b*) under specified autoxidation conditions, while 2-acetyl-3-ethylindole (**4***b*) was isolated under other conditions. Since **2***b* could be converted to **4***b* thermally it was implicated as an intermediate, and an intramolecular mechanism for this conversion, requiring a cyclic or quasi-cyclic intermediate, was proposed. He noted that, in contrast, the dimethyl analog **2***a* failed to undergo the corresponding reaction. This interpretation was criticized by Taylor (2*b*) who pointed out that the transformation represented a special case of a family of reactions in which a substituent at C-3 in an enamine tautomer (such as **2′**) was displaced by an external nucleophile. (In this proposal, although the enamine tautomer was a key intermediate, it was invoked only to effect allylic activation at C-3.) He showed, furthermore, that a small amount of the aldehyde **4***a* could, in fact, be isolated in the dimethyl case; it followed that the same pathway was, therefore, open in the dimethyl series as in the diethyl series, but the enamine tautomer was less readily formed in the former case since it lacked the stabilization of an alkyl substituent. An alternative mechanism proposed by Wasserman and Floyd (3) also required the enamine intermediate, but utilized its nucleophilic character to attack the hydroperoxy substituent intramolecularly.

Our interest in this area was aroused when we observed that a sample of 2,3-dimethylindole

(**1***a*) which had been stored in air for some time had become contaminated with a considerable amount of an impurity which, on isolation and purification, appeared to be the non-peroxidic autoxidation product originally described by Beer *et al.* (1*a*). From its analysis, mass spectrum, and other spectroscopic characteristics, which have now been described in detail elsewhere (1), we concluded that the product corresponded in composition to two molecules of **1***a* plus two oxygen atoms, that it was a bisindoline in which one methyl group of the original four had become a methylene bridge, the remaining three being tertiary in the product, and that two NH groups and one OH group were present, the second oxygen being, therefore, disubstituted and probably part of a bridge. These data strongly suggested that the product had structure **6***a* (without the stereochemical implications represented), but other structural possibilities could be envisaged and the stereochemistry was by no means established. Although the recent work of Dave and Warnhoff (1*d*) shows that our pessimism was unwarranted, we originally considered that it would be difficult, if not impossible, to establish unequivocally the structure and stereochemistry of this molecule on chemical and spectroscopic grounds since we expected it to be particularly susceptible to rearrangement. We turned, therefore, to X-ray analysis and, with the collaboration of our colleagues in crystallography, established the total structure **6***a* by direct methods which dispensed with the necessity of preparing a heavy atom derivative or perturbing the molecule in any way (1*c*).

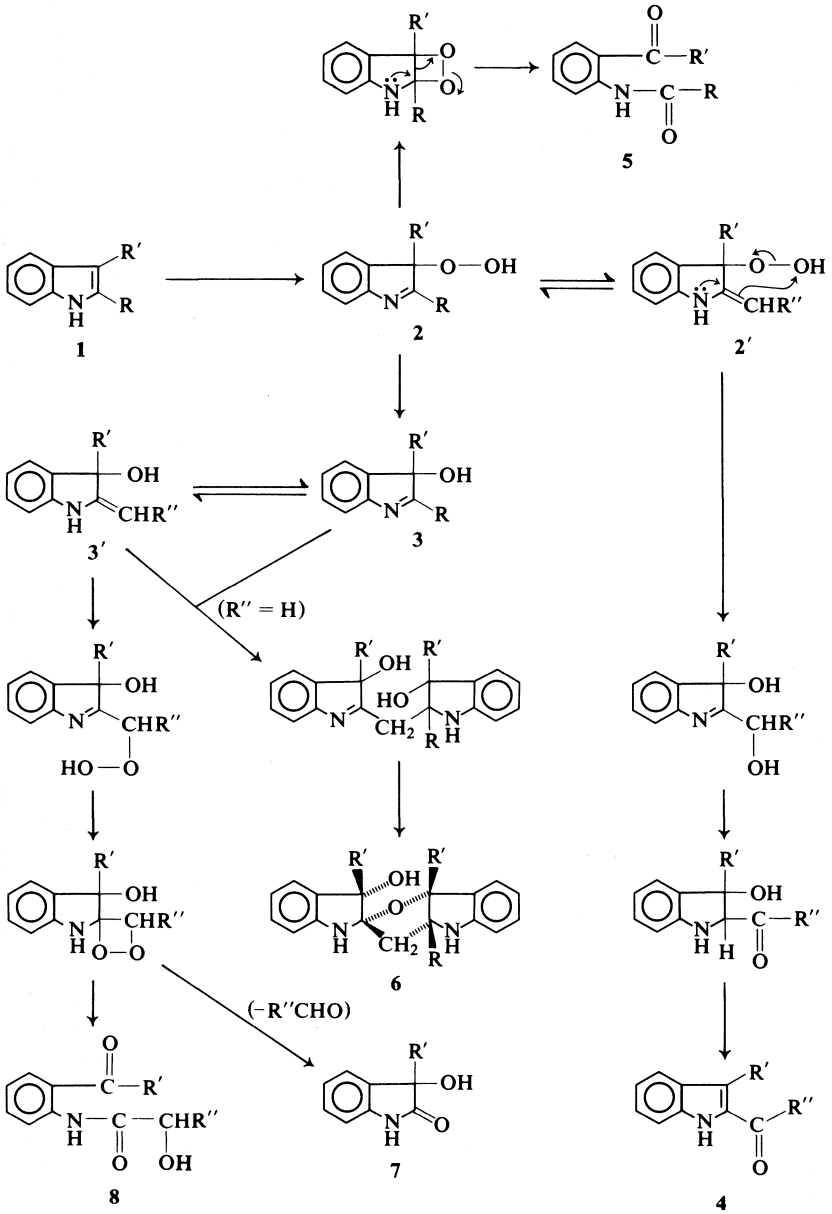
One observation, which, as we noted in our preliminary communication (1*c*), caused us some concern, was that the n.m.r. signal for the bridge methylene protons was a singlet in a variety of solvents and at a range of temperatures when determined at 60 or 100 MHz; even the addition of tris(dipivalomethanato)europium did not cause the signal to split.[1] We can now report, however, that at 220 MHz the protons do appear as an AB pattern with a coupling constant of 13 Hz, but even here the internal chemical shift is only 6.5 Hz, and as a consequence the multiplet is near the practical limits of resolution.

It is abundantly clear that **6***a* results from a reaction sequence quite different from any followed by 2,3-diethylindole, and there is good evidence to suggest that the difference can be attributed to the presence of a 2-methyl substituent in the precursor **1***a*. In order to probe the generality of the proposal that the autoxidation of 2,3-dialkylindoles follows a distinctive pathway when the substituent at C-2 is a methyl rather than an ethyl or other alkyl group, we have studied the behavior of the isomers 2-methyl-3-ethylindole (**1***c*) and 2-ethyl-3-methylindole (**1***d*).

When a solution of **1***c* in benzene was stirred in air, **1***c* slowly underwent autoxidation to afford a single isolable product which we have identified as **6***c*, the analog of the dimeric product, **6***a*, obtained on autoxidation of 2,3-dimethylindole. The i.r. and u.v. spectra of **6***c*, $C_{22}H_{26}N_2O_2$, m.p. 157–160°, were very similar to those of **6***a*, and the n.m.r. spectra differed in the manner expected: seven aromatic protons of **6***c* appear as a complex pattern between τ 2.6 and 3.3 and one is more highly shielded, appearing as a doublet, $J \simeq 8$ Hz (with further fine splitting), at τ 3.63, the unsplit methyl signal is at τ 8.60, the methylene protons show an extremely close correspondence to those of **6***a*, appearing in the 100 MHz spectrum as a singlet at τ 7.62, and the protons of the ethyl groups appear as two three-proton triplets, each with $J \simeq 8$ Hz, at τ 8.90 and 9.09 and a complex pattern, corresponding to four protons in the region τ 7.8 to 8.5, recognizable as two overlapping methylene quartets which have been further split because of the diastereotopic relationship between each pair of protons.

In contrast, the 2-ethyl-3-methyl isomer **1***d* as a solution in benzene appeared to undergo autoxidation more rapidly than **1***c* under the same conditions and afforded in good yield a product identified as the hydroperoxy derivative **2***d*. The compound, $C_{11}H_{13}NO_2$, m.p. 109–111°, showed the spectroscopic characteristics appropriate for its structure and the expected close correspondence to the values reported for **2***b* (2*a*). In ethyl acetate containing acetic acid **2***d* was transformed into 2-acetyl-3-methylindole (**4***d*), a reaction completely analogous to that of 2,3-diethylindole (**2***a*). When the hydroperoxy compound **2***d* was first reduced to the hydroxyindolenine **3***d* and this compound was subjected to further autoxidation, we isolated 3-methyl-3-

[1]We thank Dr. Marie L. Roy for this determination.



	R	R′	R″
a	Me	Me	H
b	Et	Et	Me
c	Me	Et	H
d	Et	Me	Me

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hydroxyoxindole (**7***d*), a product obtained previously by Wasserman and Floyd (3) from the autoxidation of 2-isopropyl-3-methylindole. Our present result shows that **7***d* is formed from **3***d* rather than directly from the hydroperoxy compound **2***d*, and arises from a further, and essentially independent autoxidation reaction.

It is clear that the autoxidation of 2,3-dialkylindoles leads to a diverse array of products, the outcome of any specific oxidation being strongly dependent on variables related to structure and reaction conditions. Nevertheless, we believe that it is now possible to account for all of the observed products in a unified manner and in mechanistic terms which consistently assign nucleophilic character to enamines and electrophilic character to the carbon atom of imines (see Chart 1). There appears to be little doubt that the 3-hydroperoxy compound **2** is the initial product in all of these autoxidations and is the key intermediate leading to all observed products; it clearly arises by electrophilic attack of oxygen on the "enamine" **1**. A reaction that may ensue is the reduction of the hydroperoxy group to the hydroxy group of **3**, perhaps coupled with oxidation of a molecule of **1** to afford a further molecule of **3**. Products of formula **4** can be satisfactorily accounted for in the manner proposed by Wasserman and Floyd (3); this requires the formation of the enamine tautomer (**2′**) of **2**, followed by intramolecular electrophilic attack of the terminal oxygen of the hydroperoxy group on the enamine, leading to transfer of a hydroxyl group, and then tautomerism and dehydration as shown. Products of formula **5**, which are commonly found as reaction products, particularly when an acid catalyst is present, are best explained by the intramolecular nucleophilic attack of the terminal oxygen of the hydroperoxy group of **2** on the imine function (perhaps protonated), leading to the peroxide shown which can then open, with the assistance of the electrons on nitrogen, to afford **5**. (It is worth noting that the O—O bond of a peroxide, besides being able to break homolytically, may cleave heterolytically in either direction and the terminal oxygen of a hydroperoxy group may be either electrophilic or nucleophilic.) On the basis of the evidence we presented earlier, the formation of products of formula **7** is explained as resulting from the further autoxidation of **3**, the reduction product of **2**, by electrophilic attack of oxygen on its enamine tautomer **3′** leading to the hydroperoxy intermediate which then undergoes cyclization and cleavage in the manner shown, a sequence which is the complete analog of that leading to **5**. This route is different in detail from the one proposed by Wasserman and Floyd (3), but is consistent with the pattern of behavior we have described for other reactions in this series and provides a ready explanation for the isolation of compounds of type **8** reported by these authors if it is supposed **7** and **8** arise from a common peroxide intermediate which is cleaved in the first case with the assistance of electrons on nitrogen, and in the second case, leading to **8**, with the assistance of electrons on the 3-hydroxy function. It may be noted further that intermolecular electrophilic attack at the exocyclic double bond of an enamine such as **2′** or **3′** is, of course, a route that is always open (6), but in compounds of formula **1** the indole is effectively the exclusive "enamine" tautomer available and reaction occurs at C-3, and when the hydroperoxy function is present as in **2′**, intramolecular attack, transferring a *hydroxyl* group to the enamine is the preferred reaction mode (and leads on to **4**). It is when neither of the latter situations prevails, as is the case in **3**, that intermolecular electrophilic attack on the C-2 substituent becomes a significant reaction, leading to the introduction of a *hydroperoxy* function in the present case, and to the sequence of reactions which afford **7** and **8**. The obvious and generally accepted route to dimeric products of form **6** requires the coupling of tautomers **3** and **3′**, utilizing the nucleophilic character of the latter, followed by intramolecular nucleophilic attack by a hydroxyl group on the imine function (possibly protonated) formed in the intermediate. As written, this sequence implies the initial reduction of **2** to **3**, but the chronology is not obligatory since the corresponding coupling between the tautomers **2** and **2′** could occur first and be followed by the reduction and cyclization steps. Dave and Warnhoff (1*d*) have reported results which suggest that the route requiring initial reduction of **2** is favored, but do not establish this point conclusively. In any event, there is no evidence for the formation of dimeric products of type **6** except when the

2-substituent is methyl. Previous explanations for the difference between the autoxidation behavior of 2,3-dialkylindoles (**1**) where the 2-substituent is methyl and that of analogs where the 2-substituent is some other alkyl moiety, although they have differed in mechanistic details, have all depended on assumptions regarding the relative readiness with which intermediates such as **2** and **3** form their enamine tautomers. The above discussion suggests that these explanations must be at best incomplete since at least some enamine tautomer must be present to generate **6**. The more attractive explanation that presents itself in the light of all of the above evidence is that the bimolecular coupling process is inhibited when the substituent (R) on the imine is larger than methyl and the substituent (R′′) on the enamine is consequently larger than hydrogen. As a result, alternative pathways, particularly those resulting from intramolecular processes, prevail when the 2-substituent in **1** is larger than methyl, and only 2-methyl derivatives lead to dimeric products of type **6**.

We believe that the course of all of the reactions within the category we have been concerned with can now be accounted for with the minimum of mechanistic assumptions. It is clear that other reaction pathways may also be available in specific cases, and that the products we have described may themselves be subject to further autoxidation, one illustration being provided in the very recent work of Dave and Warnhoff (1*d*).

Experimental

Melting points were determined on a Thomas–Kofler micro hot stage. Spectrometers used routinely were: a Perkin–Elmer Model 237B for i.r. spectra (carbon tetrachloride solvent unless otherwise indicated) and the wavelengths (in μ) of significant peaks are reported; a Unicam SP. 800 for u.v. spectra (methanol solvent) and wavelengths (in mμ) of absorption bands are reported, followed by the extinction coefficient (ε) in parentheses; a Varian HA-100, A-60, or T-60 for n.m.r. spectra (chloroform-*d* solvent unless otherwise indicated) and chemical shifts are reported on the τ scale, followed in parentheses by an account of the multiplicity and number of protons concerned; a CEC 21-490 for mass spectra and the *m/e* values of significant peaks are reported, followed in parentheses by their relative intensities. An AEI MS-902 mass spectrometer was used to make accurate mass measurements. The 220 MHz spectrum was recorded on the Varian HR-220 at the Canadian 220 MHz N.M.R. Center.

Autoxidation of 2-Methyl-3-ethylindole (1c)

The preparation of 2-methyl-3-ethylindole was based on the method of Pikl and Julian (8*a*): the phenylhydrazone of 2-pentanone was heated with a catalytic amount (*ca.* 1%) of cuprous chloride at 180–200° for 4 h, and 2-methyl-3-ethylindole was obtained as an oil (in 22% yield from 2-pentanone) by vacuum distillation of the reaction mixture. It showed: i.r. ($CHCl_3$) 2.89; n.m.r. 2.20–3.05 (complex; 5), 7.28 (q, J = 7 Hz; 2), 7.73 (s; 3), 8.80 (t, J = 7 Hz; 3). Picrate m.p. 154–157° (lit. (8*b*) m.p. 148–150°).

A 4% solution of 2-methyl-3-ethylindole in benzene was stirred in an open beaker and fresh solvent was added periodically to keep the volume approximately constant. After 1 week the product was precipitated as a white powder by the addition of petroleum ether; the yield corresponded to about 13% conversion and the mother liquor contained principally unchanged **2***c*. The product, **6***c*, was recrystallized three times from a benzene–hexane solution and obtained as colorless prisms, m.p. 157–160° (prior sublimation).

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.11; H, 7.60; N, 8.08.

Mass spectrum: 350 (8), 332 (1), 191 (4), 160 (32), 159 (100), 144 (38); i.r. 2.80, 2.94, 6.20; u.v. 244 (14 500), 297 (4300); n.m.r. 2.6–3.3 (complex; 7), 3.63 (d, $J \simeq 8$ Hz, with further fine splitting; 1), 6.72 (s; 1), 7.62 (s; 2), 7.8–8.5 (complex; apparently two overlapping quartets, $J \simeq 8$ Hz, with further splitting; 4), 8.60 (s; 3), 8.90 (t, J = 8 Hz; 3), 9.09 (t, J = 8 Hz; 3).

Autoxidation of 2-Ethyl-3-methylindole (1d)

2-Ethyl-3-methylindole was prepared by a method similar to that described for **1***c*: the phenylhydrazone of 3-pentanone was heated under nitrogen with a catalytic amount of cuprous chloride to 100–140° for 3 days and the reaction mixture was vacuum distilled. After recrystallization from 60–70° petroleum ether, the product (**1***d*) was obtained in 50% yield as crystals m.p. 64–68° (lit. (9) m.p. 66°); i.r. 2.87; n.m.r. 2.20–3.10 (complex; 5), 7.26 (q, J = 7 Hz; 2), 7.78 (s; 3), 8.78 (t, J = 7 Hz; 3).

A 1% solution of 2-ethyl-3-methylindole in benzene was stirred in the manner described above. After 1 day the solid (corresponding to 70% conversion) which had precipitated was collected on a filter, washed, and dried. This material, m.p. 109–111° after recrystallization from acetone, was identified as 2-ethyl-3-hydroperoxy-3-methylindolenine (**2***d*); mass spectrum: 191 (38), 173 (100); u.v. 219 (17 000), 225 (inflection; 12 500), 259 (3300).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.16; H, 6.84; N, 7.25.

A 1% solution of **2***d* in 20 ml ethyl acetate containing 2 ml acetic acid was kept in the absence of air for 2 days. Solvent was removed under reduced pressure and the brown residue was dissolved in methylene chloride and washed free of acetic acid. The solid obtained from the methylene chloride was chromatographed on a column of neutral alumina and eluted with benzene. This afforded a crystalline product (yield corresponding to 45% conversion), which was recrystallized from benzene and obtained as colorless needles, m.p. 150–152°, identified

as 2-acetyl-3-methylindole (lit. (10) m.p. 146.5°); i.r. 2.89, 6.05; u.v. 237 (15 000), 310 (19 500); n.m.r. 0.77 (broad; 1), 2.1–3.0 (complex; 4), 7.40 (s; 6; in presence of benzene this signal moved upfield and split into two singlets of equal intensity).

*Autoxidation of 2-Ethyl-3-hydroxy-3-methylindole (**3d**)*

2-Ethyl-3-hydroxy-3-methylindole was prepared by shaking an ethereal solution of the hydroperoxy compound **2***d* (1.00 g) with a solution of sodium hydrosulfite (2.6 g) in 30 ml of 10% aqueous sodium hydroxide for 50 min. Evaporation of the ether layer afforded a yellow solid (0.71 g) which, after two recrystallizations from acetone–hexane, formed colorless needles, m.p. 79–83°; i.r. 2.77, 3.15 (weak); u.v. 219 (19 000), 224 (inflection), 256 (3600); n.m.r. 2.3–3.0 (m; 4), 6.35 (broad; 1), 7.53 (q, J = 7 Hz; 2), 8.53 (s; 3), 8.83 (t, J = 7 Hz; 3); the high resolution mass spectrum showed the molecular ion of mass 175.0996 (Calcd. for $C_{11}H_{13}NO$: 175.0997), but combustion analysis gave poor and unreproducible results, the best of which was:

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.76; H, 7.04; N, 8.04.

A solution of 2-ethyl-3-hydroxy-3-methylindolenine (0.25 g) in 200 ml of benzene was stirred in an open beaker for 36 h. After a small amount of amorphous precipitate had been removed by filtration, evaporation of the benzene left a brown tar from which 3-hydroxy-3-methyloxindole (**7***d*) (40 mg; 18%), m.p. 159–165° (lit. m.p. 161.5–162.5° (3); 163–165° (11)), was recovered by crystallization from benzene and recrystallization from benzene–acetone; i.r. ($CHCl_3$) 2.80, 2.91, 5.78; u.v. 252 (6000), 286 (1350); n.m.r. (acetone-d_6) 2.5–3.3 (complex; 4), 8.53 (s; 3).

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