Indole Oxidation: the Dimer of 3-Hydroxy-2,3-dimethylindolenine[1]

VINOD DAVE AND E. W. WARNHOFF
Department of Chemistry, University of Western Ontario, London, Ontario

Received November 3, 1970

Chemical and spectroscopic evidence for the structure **1** of the dimer of 3-hydroxy-2,3-dimethylindolenine is presented. This evidence is based mainly on a comparison of the spectroscopic properties and reactions of both the dimer **1** and its hexadeutero analog **13**. The stereochemistry derived by consideration of n.m.r. shielding is that found by the X-ray analysis of other investigators. The various ways in which this dimer can arise are discussed critically.

Des données chimiques et spectroscopiques permettant d'attribuer la structure **1** au dimère de l'hydroxy-3 diméthyl-2,3 indolénine sont présentées. Les conclusions sont basées principalement sur une comparaison des réactions et des propriétés spectroscopiques du dimère **1** et de son analogue hexadeutéré **13**. La stéréochimie déduite par considération du blindage en r.m.n. est la même que celle trouvée par d'autres chercheurs à l'aide d'une analyse par rayons-X. Les diverses façons par lesquelles ce dimère peut se former sont discutées d'une façon critique.

Canadian Journal of Chemistry, 49, 1911 (1971)

Oxidation and rearrangement play a key role in the chemistry of indoles and indole alkaloids (1–3). The susceptibility of indoles to oxidation is well illustrated by 2,3-dimethylindole which gives rise to a dimeric oxidation product, $C_{20}H_{22}N_2O_2$ (m.p. variously reported as 213 (4), 214 (5), 222 (6), 224 (7), and 225° (8)), under a variety of conditions: simple recrystallization from petroleum ether (7), peroxide-catalyzed oxidation (8), and catalytic oxygenation–reduction (5). In an earlier investigation (5) Kershaw and Taylor suggested an imidazolidine formula **11** for this compound, but further work,[1] the details of which are now presented, definitely established the revised formula **1** as the correct structure of this product. Recently, on the basis of mechanistic considerations and spectroscopic data Berti *et al.* (7), have independently proposed this structure for the dimeric product without, however, providing unambiguous evidence to support it. Still more recently (9), an X-ray crystallographic analysis has been reported which confirms this structure and, moreover, provides the stereochemistry of this molecule.

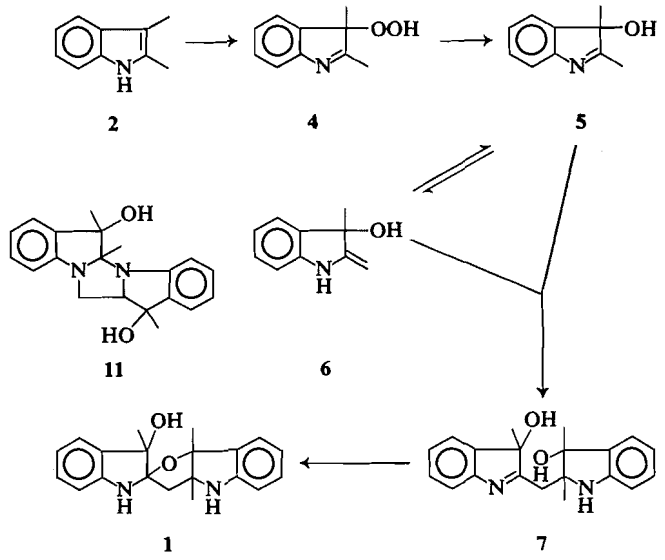
The unusual feature of the dimer as a chemical structural problem was that spectroscopy was of limited utility, and this limitation obliged the use of supplementary chemical methods. The problem became more interesting during the course of obtaining the structural evidence when an intricate rearrangement sequence was discovered (10). In this paper is presented briefly the chemical proof for the dimer structure together with observations on its chemistry, and in the accompanying paper (10) a description of the acid-catalyzed rearrangements which it undergoes.

Structure

Since the same oxidation product has also been found to arise by dimerization of 3-hydroxy-2,3-dimethylindolenine (**5**) (5), the simplest interpretation[1] of its formation would be addition of the enamine tautomer **6** to the indolenine **5** followed by intramolecular addition of a tertiary hydroxyl group in the resulting imine **7** to yield the dimer **1**, as also suggested by Berti *et al.* (7) (see Scheme 1). This structure is in accord with the two indoline chromophores of the u.v. spectrum and the absence of carbonyl absorption in the i.r. region. As expected of structure **1**, only one nitrogen atom is titratable in the methylcellosolve–water (80:20) system, and the $pK_a \sim 3.0$ found[2] corresponds to an *N*-alkylaniline (*cf.* *N*-methylaniline pK_a 3.37 in the same solvent); the basicity of the nitrogen atom of the ring-closed carbinolamine ether is weakened by the oxygen atom (expected decrease: 2–3 pK_a units (11)) to the point that it is not titratable in this solvent system. Also in agreement with structure **1**, the n.m.r. spectrum (Fig. 1) consisted of three

[1]Presented in part at the 52nd Annual Conference of the Chemical Institute of Canada, Montreal, Quebec, May 25–29, 1969.

[2]We would like to thank Dr. W. Simon, E. T. H., Zürich, for this determination.



SCHEME 1

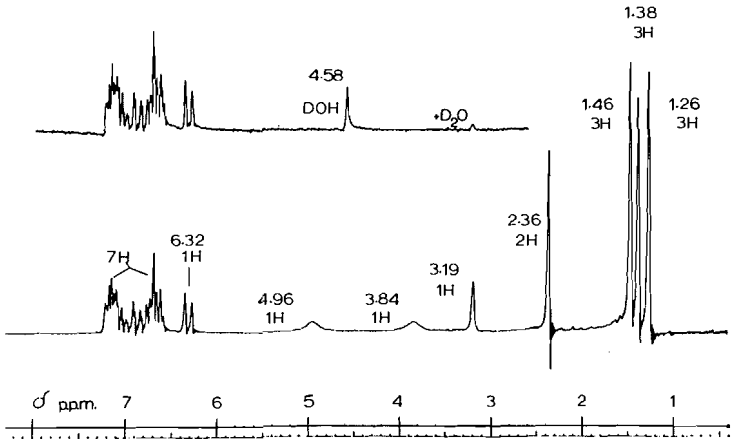
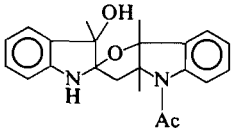


FIG. 1. The n.m.r. spectrum (100 MHz) of the dimer **1** of 3-hydroxy-2,3-dimethylindolenine in $CDCl_3$.

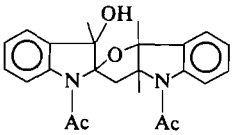
unsplit methyl peaks (δ 1.26, 1.38, and 1.46), a two-proton singlet (δ 2.36), a broad pattern from eight aromatic protons, and three separate broad one-proton peaks exchangeable with deuterium oxide (δ 3.19, 3.84, and 4.96).[3] The nature of these three exchangeable hydrogen atoms was determined by acetylation in mildly basic medium to mono-, di-, and triacetyl derivatives. The first acyl group was introduced onto the more basic indoline nitrogen atom even at room temperature,[4] but acetylation of the other two functions occurs at a convenient rate only at higher temperature. The mono- and diacetates **8** and **9** were both *N*-acyl compounds (i.r.), but the triacetate **10** was an *N,N,O*-triacyl compound (i.r.). Each of the acetates was saponified back to the dimer, and the spectra of

[3]Of course the shape and position of these peaks are solvent, temperature, and p*H* dependent. This fact and the appearance of a DOH peak corresponding to ~1H close to the lowest field peak after addition of D_2O are partly responsible for the original suggestion of the imidazolidine structure **11** (5).

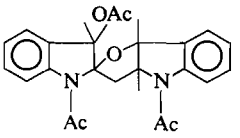
[4]Evidence that the monoacetate is indeed **8** comes from its acid-catalyzed rearrangement described in the succeeding paper (10).



8



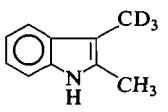
9



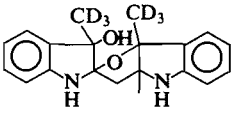
10

the acetates indicate the carbinolamine ether ring to be still intact.

That the two indolenine moieties were joined through the 2-methyl group of one was determined by preparing the dimer from 2-methyl-3-methyl-d_3-indole. The Fischer indole synthesis with butanone-4,4,4-d_3 (available from methyl iodide-d_3 and ethyl acetoacetate) and phenylhydrazine gave **12** whose n.m.r. spectrum had a single methyl peak at δ 2.28. Catalytic oxygenation–reduction to the 3-hydroxyindolenine and subsequent dimerization furnished the hexadeuterio dimer (later found to be **13**) whose n.m.r. spectrum was lacking only the two methyl peaks at δ 1.38 and 1.46 of the protio analog. The two-proton peak at δ 2.36, which is still present in the n.m.r. spectrum of the hexadeuterio dimer, must originate from the hydrogen atoms of the carbon bridge which joins the two hydroxyindolenines, and therefore this connecting carbon atom must have been a 2-methyl group.

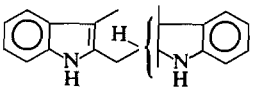


12



13

The question of whether the 2-methyl group of one indolenine unit was linked to the 2- or the 3-position of the other unit was answered by a dissolving metal reduction, a reaction considered unlikely to lead to skeletal rearrangement because of general experience with the method. The action of sodium and *t*-butyl alcohol on **1** gave six products of progressive reduction (**2** and **14–18**) two of which, desoxystereoisomers of partial formula **19**, could be used to decide between the alternative arrangements. In the n.m.r. spectrum of each of these epimeric products one methyl group was a doublet (J = 7 Hz) due to coupling with an adjacent methine hydrogen, but in the n.m.r. spectra of the analogous products from sodium–*t*-butyl alcohol reduction of the hexadeuterio dimer **13** this doublet was absent.[5] Therefore, the methyl group in **19** with an adjacent carbinyl hydrogen atom was the C-3 methyl group of the indolinyl moiety, and the desoxy compounds are the epimers **14** and **15** with the methylene bridge linking the C-2 position of each heterocyclic unit. Attachment of the two hydroxyl groups to this firmly established carbon–nitrogen skeleton in the only way possible gives **7** which would only undergo facile ring closure to **1**, the structure derived from the earlier mentioned mechanistic considerations.



19

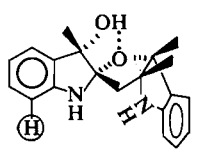
Stereochemistry

During the formation of the dimer, the addition of the enamine **6** to the imine **5** should occur mainly from the least hindered side opposite the C-3 methyl group to produce *cis* methyl groups at C-2 and -3 of the indoline, and certainly ring closure (reversible) of the carbinolamine ether ring would be expected only with the *cis* fusion of the two five-membered rings. The X-ray analysis (9) found that these methyl groups were indeed *cis*. The closure of the carbinolamine ether ring could occur in two senses to yield **20** or **21**,[6] and the actual arrangement **20** found by the X-ray determination is the only one in agreement with certain shielding effects in the n.m.r. spectra. One of the eight aromatic protons is so shielded (δ 6.32, $J \sim 7$ Hz) that it is separated from the other seven. From its position and coupling and by analogy with model indolines (12, 13) this proton is one of the two ortho to the nitrogen atom on a benzene ring. In the monoacetate of the dimer **8**, the strongly shielded proton is still present, but in the di- and triacetates **9** and **10**, this proton has been deshielded and moved back among the other seven aromatic hydrogen atoms, a known effect of acetylation on the C-7 proton of an indoline (12, 13). Therefore, this proton must be the one encircled in **20**, and the abnormal

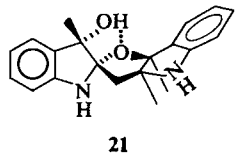
[5]The peak from the indole methyl group was also missing.

[6]Only one of the racemic pair is shown.

shielding is attributed to the orientation of the other aromatic ring. The acetyl methyl on the basic indoline nitrogen atom is strongly deshielded ($\delta \sim 2.5$–2.6) in all three acetates, but the carbinolamine *N*-acetyl methyl group in the di- and triacetates is abnormally shielded ($\delta \sim 1.9$ instead of ~ 2.2 (12)), the latter observation being in agreement only with the stereochemistry in **20**. Finally, the reaction of the dimer with formaldehyde to produce a homo dimer in which the two nitrogen atoms are linked by a methylene group (10) is only possible with **20**.



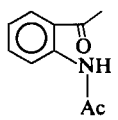
20



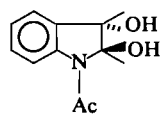
21

Formation in Other Reactions

The basic features of the mechanism leading to dimer from the 3-hydroxyindolenine **5** suggest that dimerization could also occur through the hydroperoxide **4** or a combination of **4** and **5** followed by reduction of any hydroperoxide linkages, and there is no evidence to exclude this possibility. Furthermore, thermal breakdown of the hydroperoxide regenerates some 2,3-dimethylindole which could react with more hydroperoxide to yield the hydroxyindolenine. As might then be expected, dimer is formed to some extent under a variety of conditions not initially involving the hydroxyindolenine: autoxidation of 2,3-dimethylindole in chloroform solution,[7] reaction of the indole and hydroperoxide at room temperature (8), and thermal decomposition of the hydroperoxide in boiling benzene.



22



23

[7]This reaction shows an interesting dependence on agitation (see Experimental). If the solution is allowed to stand without stirring, oxygen absorption is slow. Consequently any hydroperoxide formed has time to react with the indole to yield hydroxyindolenine and finally dimer. However, if the solution is stirred so that oxygen absorption is rapid, most of the indole is converted to hydroperoxide before much reaction of the peroxide with excess indole can occur. In this case the major product is *o*-acetamidoacetophenone (**22**) from the usual decomposition of the hydroperoxide (8).

This last reaction was done according to the conditions of Ghosal and Dutta (6) who obtained a compound,[8] $(C_{10}H_{11}NO)_n$, m.p. 220–222°, which they formulated as the 2,3-epoxide of the indole **2**, but which is undoubtedly the dimer **1** (see Experimental).[9]

However, one reaction reported to lead to the dimer does not do so on re-investigation. Although saponification of *N*-acetyl-2,3-*trans*-dihydroxy-2,3-dimethylindoline (**23**) was reported (5) to yield 2,2-dimethylindoxyl (**25**) and dimer **1**,[10] only 2,2-dimethylindoxyl was formed in our repetition of the experiment. Nevertheless, variation of the ratio of indoxyl **25** to dimer **1** with experimental conditions is to be expected. For the two competing reactions (Scheme 2), the higher the concentration of hydroxide ion or other added base, the greater the proportion of indoxyl formed. On the other hand, the imine $\rightleftharpoons$ enamine tautomerization is fast relative to dimerization and, provided the reaction medium is basic enough to maintain the equilibrium, an increased concentration of base would have little effect on the dimerization rate. Moreover, the dimerization being bimolecular in hydroxyindolenine will be slowed by dilution.

This dimerization reaction should have some degree of generality, and provided that steric factors are not unfavorable, other 3-hydroxyindolenines and indoles should undergo the same reaction.

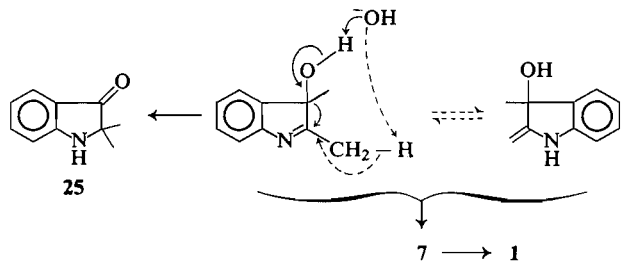
Addendum

The products of the sodium – *t*-butyl alcohol reduction are readily rationalized (Scheme 3). Whether the left hand aromatic ring of **1** or the imine group of **7** accepts electrons, the initial

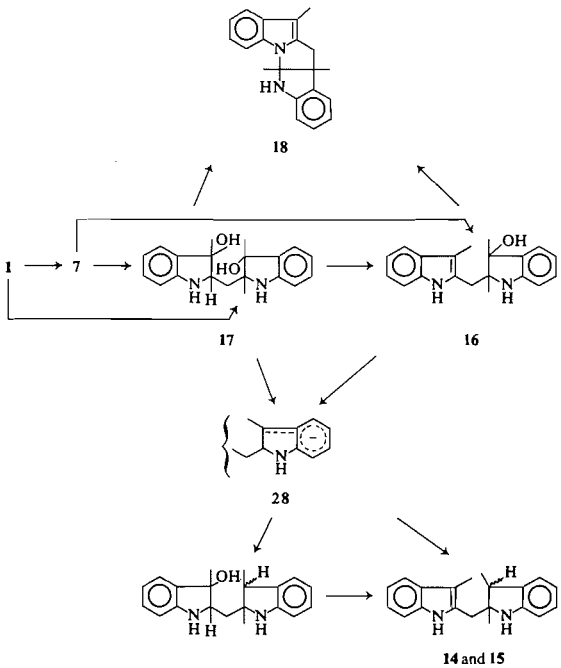
[8]In our hands treatment of the compound (actually dimer **1**) with dilute hydrochloric acid did not give *o*-acetamidoacetophenone (**22**) as reported (6), but only the rearrangement products described in the accompanying paper (10). However, treatment of the hydroperoxide **4** with dilute hydrochloric acid does give *o*-acetamidoacetophenone (see footnote 7).

[9]The difference in products from the benzene and chloroform reactions (see footnote 7) is probably mainly a function of temperature. At higher temperatures the hydroperoxide breaks down to the indole **2** which reacts with additional hydroperoxide to produce dimer via the hydroxyindolenine. In the absence of this thermal regeneration of **2** the favored reaction path of hydroperoxide is formation of *o*-acetamidoacetophenone (see footnote 8).

[10]Dimer was found after recrystallization of chromatogram fractions having the same m.p. as hydroxyindolenine **5**.

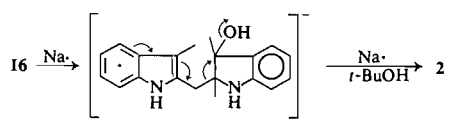


SCHEME 2



SCHEME 3

product could be diol **17**. Elimination of water would then produce the indole **16**, or possibly **7** is hydrogenolyzed directly to **16**. Similar electron addition to the aromatic ring on the right and hydroxyl elimination would remove the other oxygen function. Protonation of the carbanion **28** would occur from both sides of the benzylic carbon atom to produce both epimers **14** and **15**. 2,3-Dimethylindole could arise by reduction of the 3-hydroxyindolenine from retro Mannich scission of dimer (see footnote 12) or else by direct reductive cleavage, *e.g.*



It is not surprising that both **16** and **17** should be extremely sensitive to acid, even the traces of hydrogen chloride present in chloroform, and undergo dehydration with rearrangement to **18**, thus explaining its presence in the reduction product (see the accompanying paper, ref. 10).

Experimental

General

Melting points were determined on a Reichert–Kofler microscope hot stage and are corrected.

The i.r. spectra were recorded on a Beckman IR-10 instrument with chloroform solutions. The n.m.r. spectra were recorded on Varian A-60, T-60 and HA-100 spectrometers with ~ 10–15% (w/v) solutions in deuteriochloroform solution containing tetramethylsilane as internal standard. In the few cases where a different solvent was used, it is specified. Aromatic n.m.r. absorptions are not reported. The u.v. spectra were recorded on a Cary model 14 spectrometer with methanol solutions. Mass spectra were obtained on a Varian M-66 instrument.

Silica gel GF_{254} (Merck, Germany) was used for thin and thick layer (20 g/20 × 20 cm plate) chromatography. Thin layer plates were sprayed with a 5% solution of phosphomolybdic acid in ethanol. On thick layer plates bands were detected under a u.v. lamp. Woelm neutral, Brockman grade IV alumina, or British Drug Houses silica gel was used for column chromatography. Petroleum ether refers to the fraction of b.p. 60–80°.

Organic layers from work-up of reactions were washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and then evaporated at reduced pressure on the rotary evaporator.

The n.m.r. data are given in Table 1.

2,3-Dimethylindole (2)

This starting material was either purchased from the Aldrich Chemical Co. or was made by the Fischer indole synthesis in which a solution of methyl ethyl ketone (50 g, 0.70 mol), phenylhydrazine hydrochloride (100 g, 0.70 mol), and glacial acetic acid (500 ml) was refluxed for 3 h. The cooled solution was diluted with water, filtered, washed with water, and dried. Percolation of a petroleum ether solution of the crude product through silica gel gave 71 g (70%) of white crystalline solid, m.p. 98–100° (lit. (14) 106°).

2,3-Dimethylindolenyl-3-hydroperoxide (4)

In our hands the procedure of Beer *et al.* (8) gave miserable yields of **4**. The major product obtained was

TABLE 1. The n.m.r. data exclusive of aromatic protons*

Compound	Absorption δ
2,3-Dimethylindole (**2**)	2.20 (s, 3-Me), 2.28 (s, 2-Me) *dilute* $CDCl_3$ (13 mg/0.25 ml) 2.19 (s, 3-Me), 2.28 (s, 2-Me) CD_3COOD
2-Methyl-3-methyl-d_3-indole (**12**)	2.28 (s, 2-Me) dilute $CDCl_3$ (15 mg/0.25 ml) 2.28 (s, 2-Me) CD_3COOD
3-Hydroperoxy-2,3-dimethylindolenine (**4**)	1.40 (s, 3-Me), 2.17 (s, 2-Me) 10.97 (s, OOH)
3-Hydroxy-2,3-dimethylindolenine (**5**)	1.39 (s, 3-Me), 1.89 (s, 2-Me)
2-Hydroxymethyl-3-methylindole (**24**)	2.28 (s, Me), 4.81 (s, CH_2), 1.68 (s, OH), 8.07 (b, NH)
2-Formyl-3-methylindole (**3**)	2.72 (s, Me), 9.03 (b, NH), 10.12 (s, CHO)
2,2-Dimethylindoxyl (**25**)	1.32 (s, diMe), 4.85 (s, NH)
N-Acetyl-2,3-dimethylindole	2.15 (s, Me) 2.50 (s, Me), 2.62 (s, NCOMe)
N-Acetyl-*trans*-2,3-dihydroxy-2,3-dimethylindoline (**23**)	1.72 (s, Me), 1.91 (s, Me), 2.03 (s, Me), 4.40 (OH)
N-Acetyl-*cis*-2,3-dihydroxy-2,3-dimethylindoline (?)	1.45 (s, Me), 1.56 (s, Me), 2.23 (s, NCOMe), 4.28 (OH)
2-Acetamidoacetophenone (**22**)	2.26 (s, Me), 2.70 (s, NCOMe), 11.69 (NH)
Dimer **1**	1.26 (s, 2-Me), 1.38 (s, 3-Me), 1.46 (s, 3-Me), 2.36 (s, CH_2), 3.19 (OH), 3.84 (NH), 4.96 (NH)
Dimer-d_6 **13**	1.26 (s, 2-Me) 2.36 (s, CH_2), 3.20 (OH), 3.84 (NH), 4.95 (NH)
Dimer monoacetate **8**	1.38 (s, Me), 1.52 (s, diMe), 2.54 (s, NCOMe), 3.05 (s, OH), 3.30 and 3.54 (AB of CH_2, J = 14), 3.88 (b, NH)
Dimer diacetate **9**	1.35 (s, Me), 1.51 (s, Me), 1.73 (s, Me), 1.95 (s, NCOMe), 2.55 (s, NCOMe), 4.27 center of AB of CH_2 of which only two strongest lines visible. [OH not apparent in this spectrum]
Dimer triacetate **10**	1.32 (s, Me), 1.73 (s, Me), 1.80 (s, Me), 1.88 (s, COMe), 2.47 (s, COMe), 2.51 (s, COMe), 3.50 and 3.84 (AB of CH_2, J = 16)
Reduction product **16**	1.07 (s, Me), 1.40 (s, Me), 2.27 (s, Me), 3.10 (s, CH_2)
Desoxy indolylindoline **14**	1.06 (s, Me), 1.19 (d, 3H, J = 7), 2.24 (s, Me), 2.94 (s, CH_2), 3.35 (indoline NH), 8.53 (indole NH)
Desoxy indolylindoline **15**	1.30 (s, Me), 1.34 (d, 3H, J = 7), 2.16 (s, Me), 2.58 and 2.88 (AB of CH_2, J = 14)

*Chemical shifts are given in p.p.m. from tetramethylsilane (δ) and coupling constants in Hz; $CDCl_3$ solutions unless otherwise specified; 2-Me and 3-Me signify that the methyl group giving rise to the absorption originated from a 2- or 3- methyl group of 2,3-dimethylindole, respectively; s = singlet, d = doublet, b = broad absorption.

the hydroxyindolenine dimer **1**. However, the hydroperoxide **4** was obtained in good yield by McCapra's procedure.[11] A solution of 2,3-dimethylindole (**2**) (0.50 g), which had been freshly crystallized from aqueous methanol, was dissolved in petroleum ether (50 ml) and cooled to ~ 0°. Oxygen was bubbled in with stirring at ~ 0°, and a white crystalline solid slowly precipitated. At the end of 12 h, t.l.c. showed the absence of **2** and the presence of a single spot more polar than **2**. The solid was filtered, washed once with petroleum ether, and dried to give 0.35 g (57%) of colorless hydroperoxide, m.p. 103–108° (dec.) (lit. (8) 113° (dec.)). The compound was used without further attempted purification. It tends to decompose within a day at room temperature, but it is stable for months in a refrigerator. It also turns brown on the t.l.c. plate.

[11]We would like to thank Dr. F. McCapra, University of Sussex, Brighton, England, for sending us his experimental details before publication.

3-Hydroxy-2,3-dimethylindolenine (5)

The procedure of Beer, Donavanik, and Robertson (8) was used. To a mixture of pure hydroperoxide **4** (200 mg), ether (6 ml) and 2 *N* NaOH (3.5 ml) was added sodium dithionite (0.4 g). The mixture was stirred (magnetic bar) at room temperature for 1.5 h, diluted with ether, and separated. The organic layer was washed with water, dried, and evaporated to leave 170 mg of crystalline solid which t.l.c. showed to be composed of ~ 90% of **5** and ~ 10% of dimer **1**. The n.m.r. spectrum agreed with this analysis. Attempts at further purification by recrystallization only increased the proportion of dimer **1**.

Reactions Leading to Dimer 1

(a) Oxygenation–Hydrogenation of 2,3-Dimethylindole (2) (5)

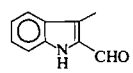
Platinum oxide (0.40 g) in ethyl acetate (200 ml) was reduced with hydrogen. The apparatus was flushed with nitrogen, and 2,3-dimethylindole (3.00 g) was added to the mixture which was stirred (magnetic bar) and oxy-

genated for 12 h (oxygen uptake ~ 400 ml). The t.l.c. showed the *complete absence* of 2,3-dimethylindole (**2**). The apparatus was flushed with nitrogen, and the mixture then hydrogenated for 30 min (hydrogen uptake ~ 400 ml). The t.l.c. at this stage revealed the *presence* of 2,3-dimethylindole (**2**) and more polar materials. The catalyst was removed by filtration, and the filtrate was evaporated at reduced pressure to leave 3.10 g of viscous brown liquid which was chromatographed on a column of 90 g of alumina.

(*i*) Petroleum ether eluted 0.70 g (23%) of **2,3-dimethylindole** (**2**), m.p. 98–100°, identical with starting material.

(*ii*) Petroleum ether – benzene (95:5) eluted 0.30 g (8.2%) of ***o*-acetamidoacetophenone** (**22**) which was recrystallized from chloroform – petroleum ether to give colorless needles, m.p. 74–75° (lit. (8) m.p. 77–78°), ν_{max} 3240 (NH), 1690 (ArC=O), and 1650 cm^{-1} ($CH_3C(=O)N$).

(*iii*) Petroleum ether – benzene (85:15) eluted 70 mg (2%) of **2-formyl-3-methylindole** (**3**) which on recrystallization from methanol gave colorless crystals, m.p. 137–139° (lit. (15) m.p. 139–140°), ν_{max} 3640 (NH) and 1650 cm^{-1} (conj. CH=O); *m/e* 159 (molecular ion).

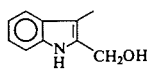


3

(*iv*) Petroleum ether – benzene (60:40) eluted 1.20 g (36%) of crude **dimer 1** which on recrystallization from methanol gave 0.70 g of colorless crystals, m.p. 195–225° (lit. (4–8) m.p. from 213 to 225°),[12] pK_a ~ 3.0 (80% methyl collosolve – 20% water), λ_{max} 245 (16 300) and 297 nm (7600); *m/e* 322 (molecular ion).

Anal. Calcd. for $C_{20}H_{22}N_2O_2$ (322.4): O, 9.92. Found: O, 10.41.

(*v*) Benzene eluted 0.15 g (4.5%) of crude yellowish **2-hydroxymethyl-3-methylindole** (**24**) which was purified by thick layer chromatography (ether–benzene (60:40) used for development) and subsequent recrystallization from chloroform – petroleum ether to give colorless crystals, m.p. 124–126° (lit. (15) m.p. 123–124°), undepressed on admixture with an authentic specimen, m.p. 125–127°, prepared by lithium aluminum hydride reduction of 2-formyl-3-methylindole (**3**), *m/e* 161 (molecular ion).



24

(b) Autoxidation of 2,3-Dimethylindole (2)

A solution of **2** (25 g) in reagent grade chloroform (400 ml) was allowed to stand undisturbed in an open beaker at room temperature for 4 days with chloroform being added occasionally to maintain the original volume. Concentration of the dark brown solution gave an oily solid which was recrystallized once from methanol and twice from chloroform – petroleum ether to yield 11 g (40%) of the dimer **1** identical in all respects with the compound obtained in section *a*.

[12]The wide m.p. range is due to thermal decomposition; see later experimental description.

If the chloroform solution of **2** in an open vessel was *stirred* (magnetic bar), the major product was *o*-acetamidoacetophenone (**22**) with only a minor amount (2–5%) of dimer **1**.

(c) Reaction of 2,3-Dimethylindole (2) and 2,3-Dimethylindolenyl-3-hydroperoxide (4)

A solution of **2** (35 mg) and **4** (35 mg) in chloroform (1 ml) was sealed under nitrogen in a tube and stored in the dark for 3 days. The t.l.c. of the reaction mixture showed the absence of hydroperoxide **4** and the presence of 2,3-dimethylindole (**2**) and dimer **1**. The n.m.r. spectrum of the mixture gave the proportion of **1**:**2** as 80:20.

When the hydroperoxide **4** alone was allowed to stand at room temperature in chloroform solution, *o*-acetamidoacetophenone (**22**) was the major product together with a minor amount of the dimer **1**.

(d) Thermal Decomposition of 2,3-Dimethylindolenyl-3-hydroperoxide (4)

The reaction was conducted according to the directions of Ghosal and Dutta (6). A solution of colorless hydroperoxide **4** (0.20 g, pure by t.l.c.) in reagent grade benzene (25 ml) was refluxed for 40 min, after which time the benzene was evaporated at reduced pressure to leave a brown oily solid. The t.l.c. (benzene–ether, 50:50) showed some remaining **4** and three other spots corresponding to **2**, **3**, and dimer **1**. Chromatography on alumina (6.0 g) yielded: (*i*) 75 mg of 2,3-dimethylindole (**2**) eluted by petroleum ether; (*ii*) 8 mg of 2-formyl-3-methylindole (**3**) eluted by petroleum ether – benzene (70:30); and (*iii*) 24 mg of dimer **1** eluted by petroleum ether – benzene (60:40). Recrystallization of the 24 mg of **1** from methanol gave colorless crystals, m.p. 195–225° (dec.)

(e) Basic Treatment of 3-Hydroxy-2,3-dimethylindolenine (5)

A solution of **5** (50 mg, 90% pure with 10% of dimer **1** as impurity) in 2 *N* aqueous NaOH (4 ml) was refluxed for 3 h. After extraction into ether, the product was washed with water and dried. Evaporation left 49 mg of yellowish solid whose t.l.c. (benzene–ether, 50:50) showed a major spot corresponding to dimer **1** and a minor spot corresponding to 2,2-dimethylindoxyl (**25**). From the n.m.r. spectrum the ratio of **1**:**25** was ~ 90:10.

Acidic Treatment of Hydroperoxyindolenine 4

A solution of the hydroperoxide **4** (100 mg) in 2 *N* HCl (1 ml) was stirred at room temperature for 1.5 h. The brownish black solution was diluted with chloroform, washed with water, dried, and concentrated to leave 38 mg of a dark brown oil. The t.l.c. in benzene–ether (50:50) gave a single significant spot of the same R_f as **22**. The n.m.r. spectrum of the crude product clearly showed it to contain about 85% of *o*-acetamidoacetophenone (**22**). No attempt was made to isolate **22**.

Acetylation of Dimer 1

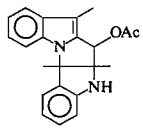
(a) Monoacetate

A mixture of dimer **1** (0.50 g), anhydrous sodium acetate (0.10 g), pyridine (5.0 ml), and acetic anhydride (3.0 ml) was stirred (magnetic bar) at room temperature for 11 days. At this point t.l.c. showed the absence of starting material **1**. The reaction mixture was poured into chloroform, washed with water, dried, and concentrated to leave 0.48 g of viscous brown liquid. The t.l.c.

(benzene–ether, 50:50) gave a spot (R_f 0.71) corresponding to *O*-acetate **26** (absent in t.l.c. of the reaction mixture before work-up), a spot (R_f 0.49) corresponding to monoacetate **8**, and two minor spots due to di- and triacetates **9** and **10**. Separation by t.l.c. (benzene–ether, 1:1, used for development) gave 0.20 g (40%) of solid which after several recrystallizations from chloroform – petroleum ether gave 50 mg of *N*-monoacetate **8**, m.p. 175–177°, ν_{max} 3530 (OH), 3380 (NH), and 1650 cm^{-1} (amide C=O); λ_{max} 248 (16 700) and 280 nm (3600); *m/e* 364 (molecular ion).

Anal. Calcd. for $C_{22}H_{24}N_2O_3$ (364.4): C, 72.51; H, 6.64; N, 7.69. Found: C, 72.36; H, 6.61; N, 7.54.

From a less polar band of the t.l.c. separation was isolated 42 mg of yellow oily solid. One recrystallization from petroleum ether gave 30 mg of *O*-acetate **26** identical (m.p., t.l.c., i.r., n.m.r.) with the authentic specimen (10). This compound was an artifact formed at some stage of the work-up procedure. It was not present if the chloroform solution of the crude product was washed with $NaHCO_3$ solution.



26

(b) Di- and Triacetates

To a stirred (magnetic bar) mixture of dimer **1** (0.30 g), anhydrous sodium acetate (0.1 g), and pyridine (2.0 ml) was added acetic anhydride (2.0 ml), and the reaction mixture was heated at 85° for 18 h. Dilution of the cooled reaction mixture with water and extraction with chloroform gave an organic layer which was washed with water, dried, and evaporated to leave 0.32 g of dark brown oil. Separation by t.l.c. (benzene–ether, 25:75, used for development) gave a band (R_f 0.34) from which 32 mg of crystalline ***N,N*-diacetate 9** was extracted. Recrystallization from ether – petroleum ether (b.p. 30–60°) gave colorless granules, m.p. 194–204°, ν_{max} 3535 (OH), and 1655 cm^{-1} (amide C=O); *m/e* 406 (molecular ion).

Anal. Calcd. for $C_{24}H_{26}N_2O_4$ (406.5): C, 70.92; H, 6.45. Found: C, 71.11; H, 6.74.

From a slightly more polar band (R_f 0.44) was extracted 48 mg of the ***N,N,O*-triacetate 10** which on recrystallization from chloroform – petroleum ether gave colorless granules, m.p. 165–188° (wide range due to stereoisomers?), ν_{max} no OH or NH absorption, 1730 (ester C=O) and 1650 cm^{-1} (amide C=O); *m/e* 448 (molecular ion).

Anal. Calcd. for $C_{26}H_{28}N_2O_5$ (448.5): C, 69.63; H, 6.29. Found: C, 69.18; H, 6.32.

Saponification of Dimer Acetates

A solution of the *N,N*-diacetate **9** (90 mg), KOH (2 pellets), and methanol (2 ml) was refluxed for 18 h. Dilution of the reaction mixture with water and extraction with chloroform gave an organic layer which was washed with water, dried, and evaporated at reduced pressure to leave 48 mg of yellowish solid. Two recrystallizations from chloroform – petroleum ether gave colorless crystals of the dimer **1**, m.p. 195–225° (dec.), undepressed on admixture with the authentic sample. The i.r. and n.m.r. spectra of the saponification product were also identical with those of authentic **1**.

The same procedure was used to saponify the *N*-monoacetate **8** and the *N,N,O*-triacetate **10**; in both cases the dimer **1** was the only product recovered.

2-Methyl-3-methyl-d_3-indole (12)

Methyl ethyl ketone-4,4,4-d_3 was prepared by modification of the *Organic Syntheses* procedure (16). To a solution of sodium (0.80 g) in absolute ethanol (17.5 ml) was added ethyl acetoacetate (4.4 g, 0.033 mol). After a 10 min reflux period, methyl iodide-d_3 (5.0 g, 0.034 mol, > 99% D) was added to the refluxing solution during 15 min. The reaction mixture was refluxed for 6 h at the end of which time it was neutral to p*H* paper. After additon of 5% aqueous NaOH (35 ml), the solution was stirred at room temperature for 5 h. Aqueous H_2SO_4 (1:1, 4 ml) was added and the acidic solution was stirred at room temperature for 15 min before refluxing for 2 h. The solution was distilled, and the fraction of b.p. 78–90° was collected. Redistillation from five pellets of NaOH gave the ketone accompanied by some ethyl alcohol. To this mixture of ketone and ethyl alcohol was added glacial acetic acid (20 ml) and phenylhydrazine hydrochloride (3.1 g, 0.021 mol). The resulting solution was refluxed for 3 h, then cooled and diluted with water. The precipitate was filtered, washed with water, dried, and percolated in petroleum ether solution through a column of 50 g of silica gel to give 1.8 g (37%) of colorless crystalline **12**, m.p. 90–96°, *m/e* 148 (molecular ion). The t.l.c. gave a single spot of the same R_f as **2**. The compound was used for subsequent reactions without further purification.

Hexadeuterio Dimer 13

The procedure of Kershaw and Taylor (5), described in section *a* under dimer preparation above, was used with 2-methyl-3-methyl-d_3-indole (590 mg). The dimer-d_6 (110 mg, 17%) obtained had identical m.p. and t.l.c. behavior as the non-deuterated material, *m/e* 328 (molecular ion corresponding to hexadeuteration).

Sodium–t-Butanol Reduction of Dimer 1

To a refluxing solution of the pure (t.l.c. and n.m.r.) dimer (4.50 g, 14.1 mmol) in *t*-butyl alcohol (150 ml) was added freshly cut sodium metal (15 g) during 0.5 h. Reflux was continued for 2.5 h. Methanol was added to the cooled solution to dissolve unreacted sodium. After the sodium had dissolved, water was added and the mixture was thoroughly extracted with ether. The ethereal solution was washed with water, dried, and evaporated to leave 4.38 g of clear brown oil composed of six compounds according to t.l.c. in benzene – petroleum ether (70:30). The crude product was chromatographed on 200 g of neutral alumina.

(*i*) Petroleum ether eluted 30 mg (1.4%) of colorless **2,3-dimethylindole (2)**, R_f 0.85.

(*ii*) Further elution with petroleum ether gave 55 mg (1.3%) of **Berti's desoxy compound 18**, R_f 0.67, which was recrystallized from chloroform – petroleum ether to give colorless crystals, m.p. 185–190°, whose n.m.r. spectrum was identical with that of the authentic synthetic specimen (see ref. 10).

(*iii*) Continued elution with petroleum ether gave a pale

yellow oil (660 mg) which was chromatographed again on six thick plates developed with benzene–ether (95:5). Extraction yielded 475 mg (11%) of colorless oil, R_f 0.54, which solidified (single t.l.c. spot). Recrystallization from chloroform – petroleum ether gave 330 mg of colorless crystals of the **indolylindoline 14**, m.p. 106–108°, ν_{max} 3480 and 3410 cm^{-1} (NH); λ_{max} 230 (33 500) and 288 nm (9900).

Anal. Calcd. for $C_{20}H_{22}N_2$ (290.4): C, 82.72; H, 7.64; N, 9.65. Found: C, 83.02; H, 7.68; N, 9.66.

(*iv*) The final petroleum ether eluates left 580 mg (14%) of colorless oily solid which on recrystallization from chloroform – petroleum ether gave 355 mg of colorless crystals of the **indolylindoline** stereoisomer **15**, m.p. 160–170°, R_f 0.44 ν_{max} 3440 and 3390 cm^{-1} (NH); λ_{max} 227 (31 900) and 285 nm (9500).

Anal. Calcd. for $C_{20}H_{22}N_2$ (290.4): C, 82.72; H, 7.64; N, 9.65. Found: C, 82.35; H, 6.92; N, 9.57.

(*v*) Elution with petroleum ether – benzene (60:40) gave 220 mg (5%) of colorless oil which was chromatographed again on four thick plates developed in petroleum ether–benzene (50:50). Extraction yielded 70 mg of colorless oil which solidified. On recrystallization from chloroform – petroleum ether the compound underwent dehydration and rearrangement to Berti's desoxy compound **18**, m.p. 178–183°, n.m.r., and u.v. spectrum identical with that of authentic synthetic **18** (see ref. 10).

(*vi*) Elution with chloroform gave 650 mg of a brown viscous mass which was chromatographed on four thick plates developed with ether–benzene (75:25). Extraction of the band at R_f 0.39 gave 55 mg of colorless solid, m.p. 162–174° (dec.) after recrystallization from methanol – petroleum ether. However, on standing in chloroform solution this product of unknown structure[13] was transformed into Berti's desoxy compound **18** before analysis.

N-Acetyl-2,3-dimethylindole

This compound was made according to a modification of the published procedure (17). A solution of 2,3-dimethylindole (4.0 g), camphor-10-sulfonic acid (40 mg), and acetic anhydride (40 ml) was refluxed for 9 h. The excess anhydride was distilled at reduced pressure, and the residue was percolated in benzene solution through a column of 100 g of silica gel. Evaporation of the eluate left 3.4 g (66%) of colorless crystalline amide which was used without further purification. A sample recrystallized from petroleum ether (b.p. 30–60°) had m.p. 68–70° (lit. (17) m.p. 74°), ν_{max} 1700 cm^{-1} (indole amide C=O); *m/e* 187 (molecular ion).

N-Acetyl-trans (and cis?) -2,3-dihydroxy-2,3-dimethylindoline (23)

The published procedure (18) was modified. To a stirred (magnetic bar) solution of *N*-acetyl-2,3-dimethylindole (2.0 g) in glacial acetic acid (3 ml) cooled in an ice–salt bath was added nitric acid (0.84 g) during 5 min. After being stirred for 1 h at room temperature, the reaction mixture was filtered to remove unreacted starting material. The filtrate was concentrated to one quarter of its volume at room temperature under reduced pressure. The residual viscous brown liquid was diluted with ether and allowed to stand overnight to complete the precipitation of solid. Filtration and washing with ether gave 0.66 g (28%) of yellowish **23** (single t.l.c. spot). Two recrystallizations from methanol gave 0.42 g of colorless crystals, m.p. 130–132° (lit. (18) m.p. 133–134°), ν_{max}(Nujol) 3420, 3300 (OH), and 1635 cm^{-1} (amide C=O); *m/e* 221 (molecular ion). The n.m.r. spectrum indicated the crystalline compound to be a mixture of the *trans* and *cis* stereoisomers. The mother liquors from the two recrystallizations were saved for the basic treatment described below.

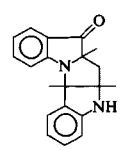
Base Treatment of N-Acetyl-trans-2,3-dihydroxy-2,3-dimethylindoline (23)

The directions of Kershaw and Taylor (5) were followed. A mixture of 130 mg of **23**, m.p. 130–132° (single t.l.c. spot), in 1 *N* aqueous NaOH solution (5 ml) was refluxed. Within a few minutes a greenish-yellow fluorescent color had appeared. At the end of 1 h the reaction mixture was cooled and extracted with benzene. The organic layer was washed with water, dried, and evaporated to leave 85 mg (90%) of yellow **2,2-dimethyl indoxyl (25)**. The n.m.r. spectrum showed the absence of starting material **23** and dimer **1**, and t.l.c. gave a single spot corresponding to **25**. The n.m.r. spectrum of the crude product contained no peaks due to the dimer **1**. Recrystallization from petroleum ether gave yellow needles, m.p. 86–87.5° (lit. (8) m.p. 89–90°), ν_{max} 3420 (NH) and 1710 cm^{-1} (indoxyl C=O).

The mother liquors from the isolation of **23** in the experiment above were treated with refluxing sodium hydroxide as described above for pure **23**. The n.m.r. spectrum and t.l.c. of the crude product did show the presence of 5–10% of the dimer **1**, but no attempt was made to isolate it.

Thermal Decomposition of Dimer 1

Dimer (0.20 g) was heated at ~ 225° in a test tube for 1 h. The t.l.c. of the dark brown residue gave only one significant spot having the same R_f as the dimer. Chromatography on a thick plate developed with benzene–ether (50:50) gave a yellow band at R_f 0.59. Extraction of the band yielded 124 mg (62%) of yellow solid whose n.m.r. spectrum unambiguously showed it to be a mixture of 2,2-dimethylindoxyl (**25**) and the dimeric indoxyl **27** (see accompanying paper, ref. 10). No attempt was made to separate the mixture.



27

We would like to thank the National Research Council of Canada for financial support. We would also like to thank Dr. A. Taylor, NRCC Atlantic Regional Laboratory, Halifax, Nova Scotia, for his very helpful cooperation.

[13]The product had the same t.l.c. R_f as **17**, the $LiAlH_4$ reduction product (7) from **1**, but it was not investigated further.

1. W. C. SUMPTER and F. M. MILLER. *In* Heterocyclic compounds with indole and carbazole systems. *Edited by* A. Weissburger. Interscience Publishers, New York, N.Y., 1954.
2. W. I. TAYLOR. Indole alkaloids. Pergamon Press, Oxford, 1966.
3. E. W. WARNHOFF. *In* Molecular rearrangements. Part 2. *Edited by* P. de Mayo. Interscience Publishers, New York, N.Y., 1964. p. 841.
4. K. M. BISWAS and A. H. JACKSON. Tetrahedron, **24**, 1145 (1968).
5. J. W. KERSHAW and A. TAYLOR. J. Chem. Soc. 4320 (1964).
6. S. GHOSAL and S. K. DUTTA. Indian J. Chem. **7**, 135 (1969).
7. G. BERTI, A. DA SETTIMO, G. DI COLO, and E. NANNIPIERI. J. Chem. Soc. 2703 (1969).
8. R. J. S. BEER, T. DONAVANIK, and A. ROBERTSON. J. Chem. Soc. 4139 (1954).
9. S. MCLEAN, E. K. STRØM-GUNDERSEN, K. S. DICHMANN, J. K. FAWCETT, and S. C. NYBURG. Tetrahedron Lett. 2645 (1970).
10. V. DAVE and E. W. WARNHOFF. Chem. Commun. 919 (1970); Can. J. Chem. This issue.
11. J. F. KING. *In* Elucidation of structures by physical and chemical methods. Part 2. *Edited by* K. W. Bentley. Interscience Publishers, New York, N.Y., 1963. p. 347.
12. K. NAGARAJAN, M. D. NAIR, and P. M. PILLAI. Tetrahedron, **23**, 1683 (1967).
13. A. M. MONRO and M. J. SEWELL. Tetrahedron Lett. 595 (1969).
14. E. FISCHER. Ann. **236**, 129 (1886).
15. W. I. TAYLOR. Helv. Chim. Acta, **33**, 164 (1950).
16. C. S. MARVEL and F. D. HAGER. Org. Syn. **1**, 248 (1948); J. R. JOHNSON and F. D. HAGER. Org. Syn. **1**, 351 (1948).
17. S. G. P. PLANT and M. L. TOMLINSON. J. Chem. Soc. 955 (1933).
18. C. M. ATKINSON, J. W. KERSHAW, and A. TAYLOR. J. Chem. Soc. 4426 (1962).