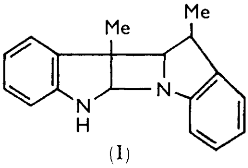
194. *Indoles. Part V.* 3-Alkylindole Dimers.*

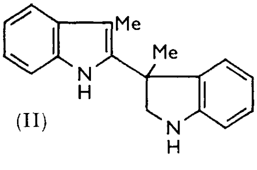
By G. F. Smith and A. E. Walters.

Structure (III) is proposed for the skatole dimer. The action of mineral acid on 2-methyl-, 3-n-propyl-, 3-isopropyl-, and 3-t-butyl-indole, and on tryptamine is discussed.

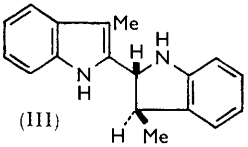
Oddo and Crippa [1] found that skatole is converted in high yield into a dimer by the action of dry hydrogen chloride in ether. They assigned structure (I) to the dimer. Schmitz-Dumont [2] showed the presence in it of an indole and of an indoline nucleus and, on insufficient experimental evidence, proposed structure (II).



(I)



(II)



(III)

We have obtained degradative evidence which shows skatole dimer to have structure (III). (The stereochemistry shown is based only on a theoretical argument; see below.) The dimer forms a methyl-methiodide, which is cleaved by sodium in liquid ammonia to a base, $C_{20}H_{24}N_2$, characterised as the crystalline picrate: the base is oxidised by chromic

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* Part IV, *J.*, 1960, 4574.

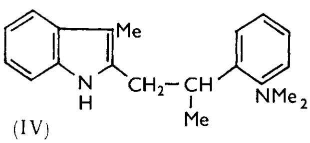
[1] Oddo and Crippa, *Gazzetta*, 1924, **54**, 339; Oddo, *ibid.*, 1933, **63**, 898.

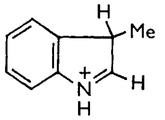
[2] Schmitz-Dumont, *Annalen*, 1934, **574**, 267.

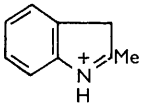
acid to methylsuccinic acid. This, together with the observations that the base has an ultraviolet spectrum indicative of an aromatic indole nucleus, that it does not give a colour with Ehrlich's reagent, and that it is derived from two mol. of skatole, can only be interpreted in terms of structure (IV), which leads to structure (III) for the original dimer. Attempts to carry out the Hofmann degradation of the skatole dimer along the lines used for the indole dimer[3] were unsuccessful.

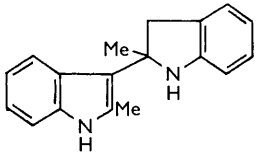
The mechanism of dimerisation can be visualised as attack by the electrophilic iminium carbon atom in ion (V) on position 2 of an unprotonated skatole molecule. Attack by the less hindered side of cation (V) will be favoured, leading to the stereochemistry shown in structure (III).

It is of interest that 2-methylindole cannot be made to dimerise:[2] the main reason for this is almost certainly the reduced electrophilic character of the iminium carbon atom in ion (VI), in comparison with the corresponding atom in ion (V), owing to the electron-releasing nature of the methyl group, possibly coupled with a steric hindrance effect; it is paralleled by the lower electrophilic activity of methyl ketones than of aldehydes. That the failure of 2-methylindole to dimerise is not due to a lower susceptibility of position 3 to electrophilic attack is proved by the formation of mixed dimers between 2-methylindole and indole and between 2-methylindole and skatole in which the 2-methylindole moiety retains its aromaticity:[4] this means that 2-methylindole is susceptible to electrophilic attack by the normally reactive 3-protonated 2-unsubstituted indole cations.


(IV)


(V)


(VI)


(VII)

The product which 2-methylindole would form if it dimerised, base (VII), has been prepared by Witkop and Patrick[5] by reducing the 2-methylindole autoxidation product with lithium aluminium hydride. We have found that base (VII) parallels the indole dimer in that it dissociates on dry distillation at ordinary pressure to two mol. of 2-methylindole (in 68% yield): the dimer (III) is thermally much more stable, for it can be distilled largely unchanged. This dimer (III) does, however, dissociate under acid-catalysis: distillation of a solution of the dimer in dilute hydrochloric acid leads to skatole in 91% yield (1·82 mol.).

We have explored the limitations of the dimerisation reaction in various 3-substituted indoles. We find that dimerisation is markedly subject to steric hindrance. Thus, whereas, as might be expected, 3-n-propylindole dimerises as easily as skatole (the reported failure of 3-ethylindole to dimerise[6] must be an error), neither 3-isopropylindole nor 3-t-butylindole dimerises. This failure is most probably due to steric hindrance of approach of the electrophilic reagent to position 2 by the bulky 3-substituent in the unprotonated molecule. On the other hand models show that approach of a nucleophilic reagent to position 2 of a 3-protonated molecule is quite open: it should therefore be possible to produce mixed dimers; for instance, indole and 3-t-butylindole should give 2-methyl-3-(3-t-butyl-2-indolinyl)indole.

Dimerisation is also prevented by the presence of a formal positive charge in the 3-side-chain: thus tryptamine cannot be dimerised. Even after one month at 15° in 15% aqueous hydrochloric acid, tryptamine was recovered completely unchanged (complications due to autoxidation were avoided by working in an evacuated sealed tube; under

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[3] Hodson and Smith, *J.*, 1957, 3544.

[4] Noland and Hammer, *J. Org. Chem.*, 1960, **25**, 1525.

[5] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 713.

[6] Schmitz-Dumond and Geller, *Ber.*, 1933, **66**, 766.

the same conditions, an 85% yield of the skatole dimer was obtained after 4 days); this cannot be due to a steric effect in view of the ease with which the isosteric 3-n-propylindole dimerises, but must be due to a field effect of the side-chain ammonium-nitrogen atom which prevents protonation at position 3, the first step in a dimerisation.

3-n-Propylindole, first prepared as a liquid by Brown *et al.*,[7] has now been obtained crystalline (m. p. 29°) by reduction of 3-propionylindole with lithium aluminium hydride. 3-t-Butylindole is a new compound (m. p. 67—68°) and was synthesised by the action of t-butyl bromide on indolylmagnesium bromide.

EXPERIMENTAL

trans-1,1,3-*Trimethyl*-2-(3-*methyl*-2-*indolyl*)*indolinium Iodide* (*Skatole Dimer Methyl-methiodide*).—A mixture of the skatole dimer (3 g.), dry acetone (100 c.c.), methyl iodide (10 g.), and anhydrous potassium carbonate (10 g.) was refluxed for 18 hr. The acetone and excess of methyl iodide were then boiled off, and the residue was washed with ether and then with cold water. Crystallisation of the residual solid from ethanol yielded the pure *iodide* as prisms, m. p. 211—212° (3·9 g., 82%) (Found: C, 57·3; H, 5·7; N, 6·75. $C_{20}H_{23}IN_2$ requires C, 57·5; H, 5·6; N, 6·7%), $\lambda_{max.}$ 221, 277, and 292 (infl.) mμ (ε 55,000, 13,300, and 11,000 respectively) in EtOH.

2-(2-o-*Dimethylaminophenylpropyl*)-3-*methylindole* (IV).—A solution of the above iodide (520 mg.) in dry liquid ammonia (100 c.c.) was treated with an excess of freshly cut sodium, and the blue solution left for 1½ hr. The excess of sodium was then decomposed by the addition of ammonium chloride, the ammonia was allowed to evaporate, and the residue was partitioned between ether and water. The ether solution yielded a pale yellow viscous liquid (350 mg., 96%). This was treated with a solution of picric acid (275 mg.) in ethanol; a picrate crystallised (463 mg., 74%). Recrystallisation from ethanol gave the pure *picrate* as yellow prisms, m. p. 175—176° (Found: C, 60·3; H, 5·4; N, 13·2. $C_{26}H_{27}N_5O_7$ requires C, 59·9; H, 5·2; N, 13·4%), $\lambda_{max.}$ 283·5 and 292 mμ (ε 9400 and 8900) in EtOH.

Oxidation of base (IV). A solution of the above base (recovered from the picrate) (1·2 g.) and of chromium trioxide (10 g.) in 10% sulphuric acid (100 c.c.) was heated on the steam-bath for 1 hr. Excess of oxidising agent was reduced by sulphur dioxide, and the mixture extracted with ether (3 × 50 c.c.). The extracted material (40 mg.) was partially crystalline; it was refluxed in ethanol (4 c.c.) containing one drop of sulphuric acid for 3 hr., most of the ethanol was removed *in vacuo*, and the residue partitioned between ether and water. The ether extract yielded a pleasant smelling liquid (47 mg.), a solution of which in dry ether was added to anilinomagnesium bromide (prepared from 93 mg. of aniline) in ether. The mixture was refluxed for 30 min., then treated with excess of dilute hydrochloric acid, and the whole thoroughly extracted with ether. The extract yielded a partially crystalline product (58 mg.), crystallisation of which from aqueous ethanol yielded methylsuccindianilide as needles, m. p. and mixed m. p. 199° (25 mg.).

3-*n-Propylindole*.—3-Propionylindole (3·8 g.) was added to a solution of lithium aluminium hydride (1·0 g.) in ether (100 c.c.), and the mixture refluxed for 5 hr. Working up in the usual manner yielded the crude 3-n-propylindole as a pale yellow oil (3·3 g.). The product distilled at 153—154°/15 mm. and crystallised from pentane at 0°, to give the pure 3-*n-propylindole* as needles, m. p. 29° (Found: C, 82·8; H, 8·3. $C_{11}H_{13}N$ requires C, 83·0; H, 8·2%), $\lambda_{max.}$ 224, 281, and 291 mμ (ε 32,200, 5700, and 5100 respectively) in EtOH. The infrared spectrum was identical with that of non-crystalline 3-n-propylindole obtained by hydrogenation of 3-allylindole.[8]

Dimerisation of 3-*n-Propylindole*.—A solution of 3-n-propylindole (0·52 g.) in dry ether (100 c.c.) was treated with a slow stream of pure dry hydrogen chloride for 2 hr. The pink crystals which separated were filtered off and partitioned between aqueous sodium hydroxide and ether. The ether layer yielded the dimer as a pale yellow viscous liquid (0·45 g., 87%), $\lambda_{max.}$ 226, 285, and 292 mμ (ε 40,700, 13,200, and 12,300 respectively) in EtOH. The *hydrochloride* of this dimer crystallises from a small volume of ethanol as needles, m. p. 160—162° (Found: C, 74·1; H, 7·8; Cl, 10·0. $C_{22}H_{27}ClN_2$ requires C, 74·4; H, 7·7; Cl, 10·0%).

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[7] Brown, Jones, and Henbest, *J.*, 1952, 3174.

[8] Brown, Ph.D. Thesis, Manchester, 1951.

3-*t*-*Butylindole*.—A stirred solution of indolylmagnesium bromide (from 19·2 g. of indole) in di-isopropyl ether (100 c.c.) was slowly treated with a solution of t-butyl bromide (21 c.c.) in di-isopropyl ether (50 c.c.). The mixture was stirred for 15 hr. under reflux, the Grignard complex decomposed with ammonium chloride solution, and the organic layer separated. This yielded a brown viscous liquid (26·4 g.) which distilled over a wide range (128—169°/9 mm.). The highest fraction, b. p. 158—169°/9 mm., was carefully redistilled to give a fraction, b. p. 166—169°/9 mm. (3·9 g.), which in benzene afforded a *picrate* (5·5 g.), as red needles, m. p. 105·5—107° (from benzene) (Found: C, 53·3; H, 4·4; N, 13·4. $C_{18}H_{18}N_4O_7$ requires C, 53·7; H, 4·5; N, 13·9%).

Decomposition of the picrate between aqueous ammonia and ether, and filtration of the ether solution through a column of alumina, yielded the crystalline base. Recrystallisation from pentane gave pure 3-*t*-*butylindole* as polyhedra, m. p. 67—68° (Found: C, 82·9; H, 8·7; N, 7·9. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1%), $\lambda_{max.}$ 222·5 and 282·5 mμ (ε 32,600 and 5560) in EtOH.

We thank Dr. B. Witkop for a specimen of the base (VII). One of us (A. E. W.) is indebted to the D.S.I.R. for a Maintenance Award.

DEPARTMENT OF CHEMISTRY, THE UNIVERSITY, MANCHESTER, 13. [*Received, July 25th,* 1960.]