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MACROCYCLIC CONDENSATION PRODUCTS OF INDOLE AND SIMPLE ALDEHYDES

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Abstract—Under strongly acid conditions the reaction between indole or 1-methylindole with formaldehyde gives cyclooligomeric products in small yields. The corresponding products are also formed by simple acid treatment of 3,3'-diindolylmethane and 3,3'-di(1-methylindolyl)methane. The reaction between indole and aromatic aldehydes gives dimeric products.

WHEN 3,3'-diindolylmethane or indole are condensed with formaldehyde under strongly acid conditions, a high-melting product (m.p. 410°) is formed. Supported only by elemental analysis, Maas and von Dobeneck[1,2] assigned to it the dimeric structure 1. The mass spectrum (Fig 1) of this condensation product exhibits, however, a parent ion peak at *m/e* 516, indicating a tetrameric rather than a dimeric structure.

A closely related reaction, the condensation of veratrole with formaldehyde, gives a product (m.p. 237°) which was at first considered to be 2,3,6,7-tetramethoxy-9,10-dihydroantracene.[3] Lindsey[4,5] and Erdtman *et al.*[6] showed independently that the product was a cyclic trimer (Mw 450, MS), cyclotriveratrylene (2), in the crown conformation. A by-product (m.p. 316°) from the synthesis of cyclotriveratrylene was assigned a tetrameric structure (Mw 600, MS) with a flexible conformation.[6] Interestingly, Cookson *et al.*[7] have recently shown that oxo- and hydroxy-derivatives of cyclotriveratrylene may occur in saddle conformations.

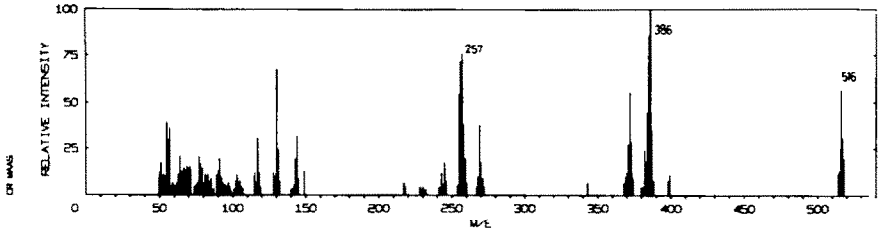
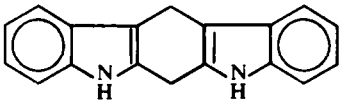
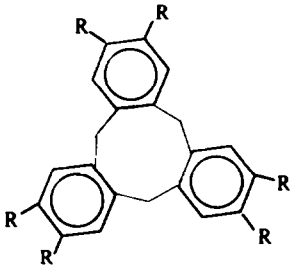


FIG 1

Four different configurational tetrameric isomers should, at least theoretically, be formed during the condensation reaction between indole and formaldehyde. The mere fact that the starting material (e.g. 3,3'-diindolylmethane) contains a preformed 3,3'-methylene bridge does not prove the existence of 3,3-bridges in the final tetramer, as protonated 3,3'-diindolylmethane may undergo rearrangement (cf Ref 8–10) and give 2,3'-diindolylmethane. The situation is further complicated by the rapid acid catalysed



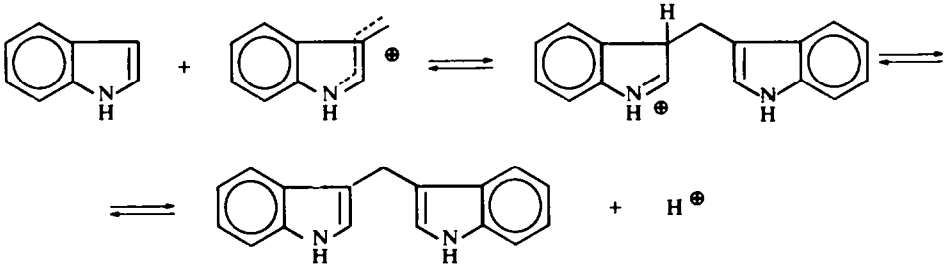
1



2: R = OCH_3

cleavage of 3,3'-diindolylmethane (Scheme 1). (The tetramer can, in fact, be obtained from such a solution without addition of formaldehyde. This easy cleavage of the 3,3'-methylene bridge may also explain why triethyl orthoformate can substitute for formaldehyde as the C_1-donor in the condensation[11]). The full structure of the tetramer is not yet known for certain, but NMR data indicate a symmetric structure with four 2,3-bridges.

SCHEME 1



A similar acid-catalysed reaction between 1-methylindole and formaldehyde gave a condensation product **3** which also could be synthesized by treatment of 3,3'-di(1-methylindolyl)methane with strong acid. The mass spectrum of this product (Fig 2) exhibits a parent ion peak at *m/e* 429, indicating a cyclic trimeric structure (**3a** or **3b**). For both configurations one saddle and one crown conformation is possible. Although the two possible configurations of the trimeric condensation product both resemble the

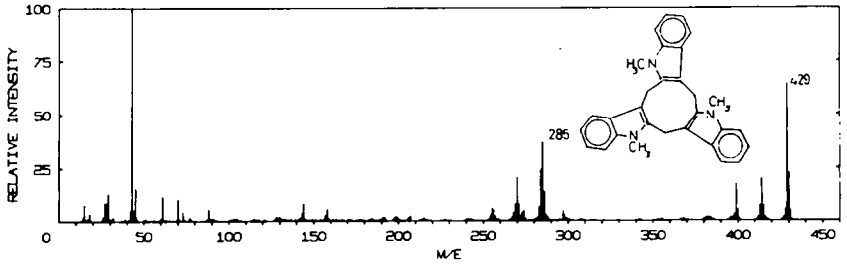


FIG 2

structure of cyclotriveratrylene (2), the NMR spectra of the two compounds are quite different. In the NMR spectrum of **3** (Fig 3) the signals from the Me groups and from the methylene bridges appear as two singlets at $\tau = 6{\cdot}47$ and $\tau = 5{\cdot}99$ respectively. Contrary to this, the signals from the methylene protons in the NMR spectrum of cyclotriveratrylene appear as two doublets in the ratio 1 : 1 at $\tau = 5{\cdot}33$ and $\tau = 6{\cdot}52$ which proves that cyclotriveratrylene has the rigid crown conformation. For this reason a crown conformation of **3** (either **3a** or **3b**) seems to be less likely. The NMR data are probably in closest agreement with a saddle conformation of **3a**. The saddle conformation of **3b** can not, however, be rigorously excluded as a possible structure of **3**, since the nonidentical methylene and Me protons may give overlapping signals. The shape and location of the singlets in the NMR spectrum of **3** change very little in the temperature range from $-25°$ to $+100°$, using pyridine as solvent. At $-35°$ a broadening of the peaks was observed, which may indicate that the saddle–saddle inversions at this temperature are slow. Studies have not been made at still lower temperatures owing to the low solubility.

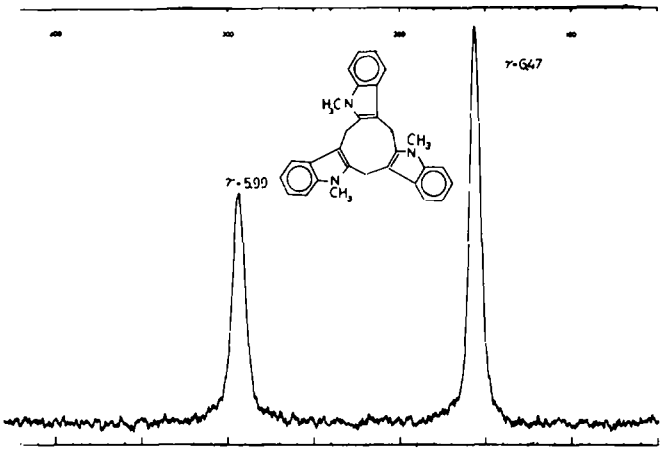
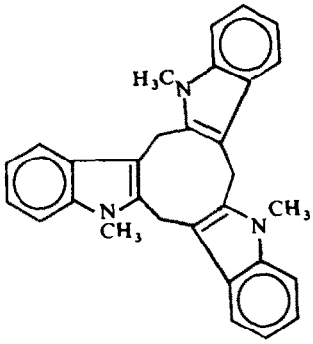


FIG 3

The mass spectrum (Fig 4) of the condensation product from indole and benzaldehyde* exhibits a parent ion peak at *m/e* 410 indicating a dimeric product which has tentatively been given structure **4**. This assignment is based only on NMR data. In order to give further support to the structure an X-ray investigation is in progress using crystals from the condensation product of indole and *p*-bromobenzaldehyde. In this connection it is interesting to note that Noland and Wenkiteswaran[12] have suggested structure **5** to a condensation product from indole and acetophenone.

Compound **4** is not the only product formed in the condensation between 3,3-diindolylmethane and benzaldehyde. A second, more soluble, compound (m.p. 305–

* The same product is formed with 3,3′-diindolylmethane and benzaldehyde as starting materials. A reaction which again illustrates the easy cleavage of 3,3′-diindolylmethane.



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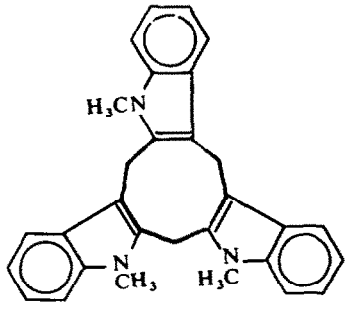
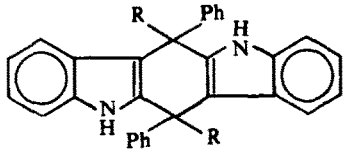
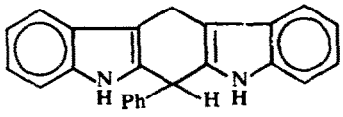


3b



4: R=H
5: R=CH_3



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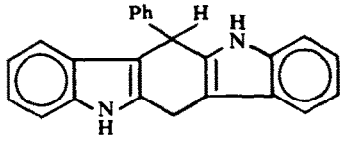

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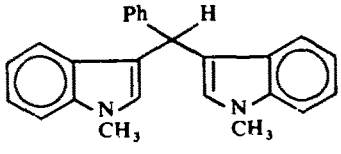

8

307°) could also be isolated. Maas[1] considered it to be 6,12-dihydro-6-phenyl-indolo[2,3-b]carbazole (**6**). The MS-determined mol wt is in agreement with this formulation. However, in view of the easy cleavage of the 3,3'methylene bridge in the starting material, 5,11-dihydro-5-phenyl-indolo[3.2-b]carbazole (**7**) cannot be excluded as an alternative.

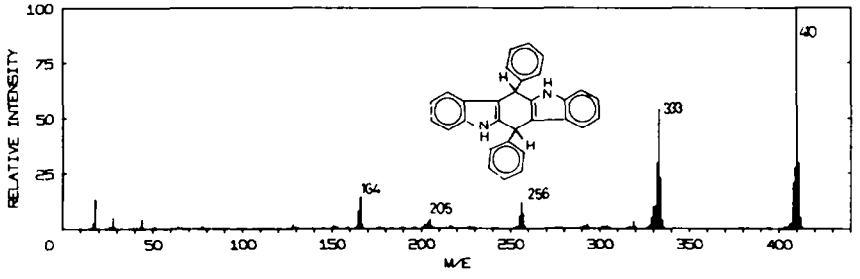

FIG 4

Attempts to prepare the N,N-dimethyl analogue of **4** from 1-methylindole and benzaldehyde, under the same conditions as for **4**, only gave a precipitate of 3,3'-di(1-methylindolyl)phenylmethane (**8**).

Why small changes in the starting material result in macrocycles with different ring sizes is not clear. Maybe it is due merely to solubility. If so, it should be possible to regulate the degree of oligomerization by using different solvents. (So far we have only used methanol.)

EXPERIMENTAL

Tetramer from indole and formaldehyde. Sulphuric acid (6·5 ml) was added during 2 min to a stirred soln of indole (11·7 g, 0·1 mole) and 38% formaldehyde (16 ml, 0·1 mole) in MeOH (900 ml). The pink soln was refluxed for 1 hr on a water bath using an efficient reflux condenser to avoid loss of dimethoxymethane. The ppt was filtered off, washed with MeOH and crystallized twice from pyridine, yield: 1·9 g (15%), m.p. 410°. The same tetramer can be prepared with 3,3'-diindolylmethane[13] and formaldehyde or with 3,3'-diindolylmethane only as starting material, yield 22% and 15% respectively; $NMR_{(DMSO-d6)}$: $\tau = 5{\cdot}1$ (s, 8, CH_2). The Spectrum was recorded at 120°.

Cleavage of 3,3'-diindolylmethane. Sulphuric acid (0·8 ml) was added to pure 3,3'-diindolylmethane (1·0 g) in MeOH (50 ml). A sample for TLC (silica gel GF, $CHCl_3$/EtOH 99:1) was immediately taken. The chromatogram showed the presence of indole ($R_f = 0{\cdot}84$). (3,3'-Diindolylmethane $R_f = 0{\cdot}65$).

Trimer (**3**) *from 1-methylindole and formaldehyde.* The same method was used as for the tetramer above. The crude product was extracted with EtOAc at 25°. The insoluble material was crystallized from EtOH/pyridine (1:1) to give colourless needles, yield: 3·4 g (24%), m.p. 275° dec. Maas,[1] under similar conditions, obtained a compound (m.p. 317°) which may be a conformer or a different oligomer.

Addition of MeOH to the EtOAc extract gave a ppt containing several compounds. No attempts have been made to separate this mixture.

Dimer (**4**) *from indole and benzaldehyde.* The same method as above was used. The crude product was crystallized from pyridine and then from N,N-dimethylformamide (DMF). The dimer crystallized with three mole crystal-DMF which could be removed with reduced press (10 mm, 100°), yield: 7·6 g (37%), m.p. 353–355° (Lit.[14] m.p. 353–355°); $NMR_{(DMSO-d6)}$: $\tau = 4{\cdot}25$ (s, 2, CH). The spectrum was recorded at 140°, using CAT.

Reaction of 3,3'-diindolylmethane with benzaldehyde. Sulphuric acid (1·0 ml) was added during 2 min to a stirred soln of 3,3'-diindolylmethane (2·46 g, 0·01 mole) and benzaldehyde (1·06 ml, 0·01 mole) in MeOH (200 ml). The pink soln was refluxed for 0·5 hr. After 20 hr at 25° the ppt was filtered off, and

recrystallized from pyridine and then from DMF. The crystal-DMF was removed with reduced press (10 mm, 100°), yield: 0·75 g (37%), m.p. 353–355°.

This product is identical with the dimer (**4**) obtained from indole and benzaldehyde. Under very similar conditions Maas obtained a product (m.p. 392–394°) with a suggested mol wt of 757.

After addition of water (500 ml) to the MeOH filtrate, the mixture was extracted with ether. The residue, after removal of the solvent, was crystallized twice from benzene, yield: 0·72 g (21%), m.p. 305° dec (Lit.[1] 306°).

The mass spectrum was dominated by the parent ion peak at *m/e* 334 (100%), a fragment ion peak at *m/e* 257 (52%) and their isotopic peaks.

The data so far available are not sufficient for deciding between structures **6** and **7**.

3,3′-*Di*(1-*methylindolyl*)*phenylmethane* (**8**). Sulphuric acid (3·3 ml) was added during 2 min to a stirred soln of 1-methylindole (6·55 g, 0·05 mole) and benzaldehyde (5·3 ml, 0·05 mole) in MeOH (400 ml). The soln was refluxed 1 hr on a water bath. The ppt was filtered off, washed with MeOH and crystallized from benzene/cyclohexane 1:1, yield: 5·1 g (60%), m.p. 202–203°. (Found: C, 85·9; H, 6·2; N, 8·0. Calc. for $C_{25}H_{22}N_2$: C, 85·7; H, 6·3; N, 8·0%).

3,3′-Di(1-methylindolyl)phenylmethane is sensitive to light and air. The NMR spectrum ($CDCl_3$, 40°) showed three singlets located at $\tau=6{\cdot}42$ (6 H, N—CH_3), $\tau=4{\cdot}13$ (1 H, CH) and $\tau=3{\cdot}48$ (2 H, 2- and 2′-hydrogen on the indole rings).

Note added in proof

After the completion of this work* a paper,† describing some pyrrole analogues of **3**, has appeared. As concluded by the German group the pyrrole derivatives also occur in saddle conformations.

The mass spectrum of the dimer from indole and benzaldehyde was also studied and conclusions similar to ours were drawn.

Furthermore, failure to obtain a defined product from the condensation of indole and formaldehyde was reported. We have also sometimes encountered difficulties to reproduce this condensation. The reason for this is however not clear.

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