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Macrocyclic Condensation Products of Veratrole and Resorcinol

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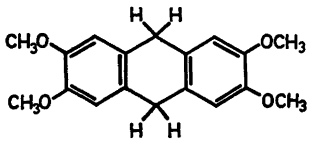
The acid catalysed condensation of veratrole with formaldehyde gives two crystalline compounds. A spectrometric investigation indicates their structures to be (*3*) and (*6*), respectively. The main product from the condensation of resorcinol with acetaldehyde is similarly shown to be (*7*).

When veratryl alcohol [1] or veratrole and formaldehyde are treated with strong acids, a high melting condensation product *A* (m.p. 237°) is formed. This compound was considered by G. M. Robinson [2] to be 2,3,6,7-tetramethoxy-9,10-dihydroanthracene (*1*).

Some thirty years ago one of us (H.E.) briefly investigated this compound and several other phenol condensation products in connection with studies on the structure of some lignans. It was observed that compound *A* could be distilled *in vacuo* without decomposition and that small amounts could be distilled at ordinary pressure with only slight decomposition. This could be expected for a compound such as *1*.



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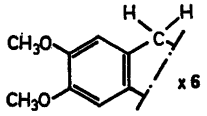

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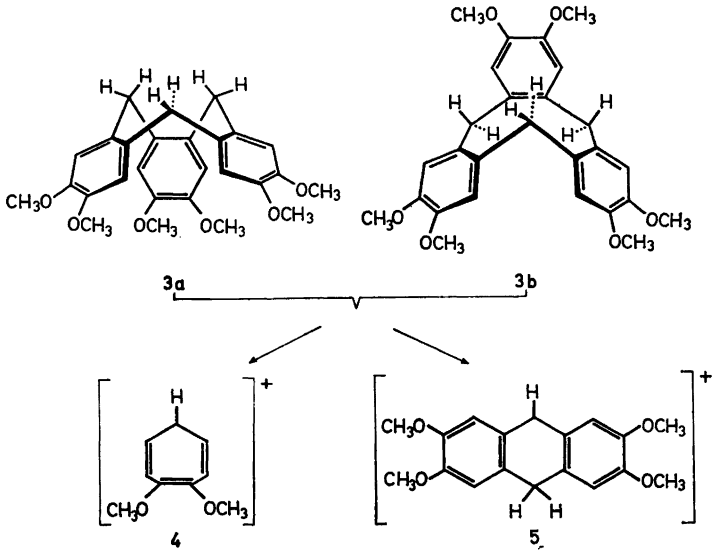
2,3,6,7-Tetramethoxy-9,10-dihydroanthracene has since been synthesised by Italian chemists [3] and found to possess properties different from those of *A* (*e.g.*, m.p. 212—213°). A re-investigation [4] of the structure of *A* indicated that the molecule contains not less than six veratrole nuclei and possesses structure *2*. It seemed strange that such a compound (mol.wt. 900) should be

easily distillable and an examination of the molecular weight of the veratrole condensation product appeared highly desirable.



Such an examination has recently been carried out by Lindsey,[5] who showed that the product contains only three veratrole nuclei. He discussed the possible conformations of the compound and concluded that the structure of *A* is *3* and that it must possess the "crown" conformation *3a*. Lindsey's conclusions are confirmed by our independent mass spectrometric and nuclear magnetic resonance investigations.

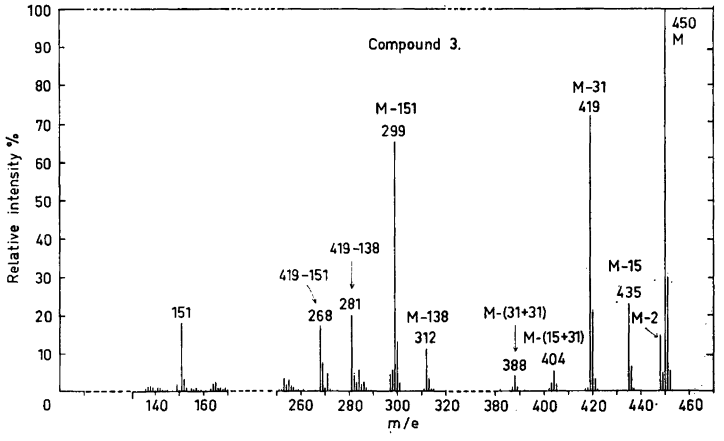


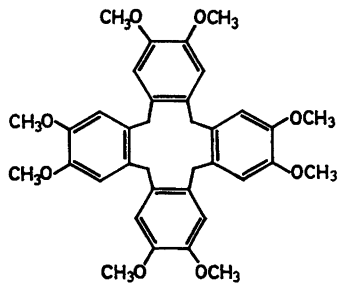
Fig. 1. Masspectrum of compound 3.

Table 1. Metastable ions of compound 3.

Diffuse peaks *m	Break down reaction
446	$450^+ \rightarrow 448^+ + 2$
385	$450^+ \rightarrow 419^+ + 31$
358	$419^+ \rightarrow 388^+ + 31$
188	$419^+ \rightarrow 281^+ + 138$
186.5	$388^+ \rightarrow 269^+ + 119$
172	$419^+ \rightarrow 268^+ + 151$

The mass spectrum of *3* (Fig. 1) exhibits a molecule ion peak at *m/e* 450, which is also the base peak. There are other peaks indicating loss of 15 and 31 mass units. The peaks at *m/e* 151 and *m/e* 299 (sum 450) arise from the fission of the molecule with formation of the ions $\frac{1}{3}M + 1$ and $\frac{2}{3}M - 1$, respectively. The former is probably a dimethoxytropylium ion (*4*) and the latter might be the ion *5*. Table 1 shows the fragmentation reactions of the molecule indicated from diffuse peaks due to metastable ions. The ion *m/e* 448 obviously results from elimination of 2 H. Many of the ions of lower masses are formed from the ion *m/e* 419, which is produced by loss of a methoxyl group.

The nuclear magnetic resonance spectrum of *3* (in deuterochloroform) exhibits four signals at 6.83, 4.67, 3.84, and 3.48 ppm (tetramethyl silane as internal standard) with the integrated ratio 2:1:6:1. The sharp singlet at 3.84 ppm corresponds to the eighteen protons of the methoxyl groups and the signal at 6.83 ppm to the six protons of the aromatic nuclei. The signals at 4.67 and 3.48 ppm appear as doublets ($|J| = 14$ cps) and correspond to the six protons of the methylene groups. The Dreiding model of conformation *3a* indicates that such a "crown" conformation is rigid. The methylene protons are unequal and should give rise to the observed characteristic signal pattern. (It may be that the doublet at 4.67 ppm is due to the protons located in the "centre" of the crown). Other possible conformations of *3*, such as *3b*, are not rigid. The protons of the methylene groups of such a conformer would give rise either to one single band, if the conformational transformations were



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rapid, or to a much more complex signal pattern, if these transformations were slow.

Oliverio and Casinovi [4] mentioned the formation of a by-product, m.p. 316°, when veratrole is condensed with formaldehyde and we have also investigated this compound. It has the same composition as *3* and can also be sublimed *in vacuo* without decomposition.

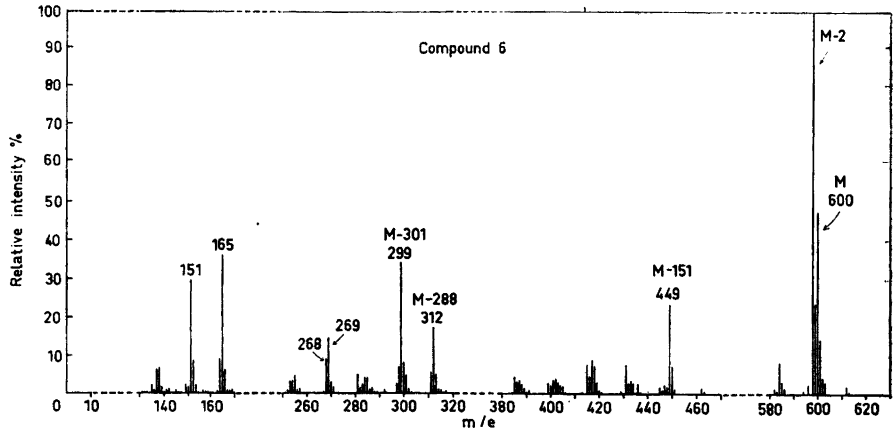


Fig. 2. Masspectrum of compound 6.

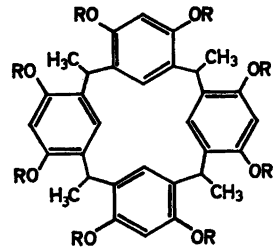
As can be seen from Fig. 2 this compound is the "tetramolecular" product (*6*) of molecular weight 600. The base peak is here a fragment *m/e* 598. A diffuse peak at *m/e* 596 indicates the reaction: $600^+ \rightarrow 598^+ + 2$ H. Two other metastable ions at *m/e* 291.5 and 161 may be due to the reactions $600^+ \rightarrow 418^+ + 182$ and $600^+ \rightarrow 312^+ + 288$, respectively.

The ions "151" and "449" (sum 600) indicate fission of the molecule with formation of the ions $\frac{1}{4}$M + 1 and $\frac{3}{4}$M − 1. Not unexpectedly there are great similarities in the fragmentation patterns of *3* and *6*.

The NMR spectrum of compound *6* exhibits only three signals, at 6.59, 3.78, and 3.60 ppm with the integrated ratio: 1:3:1. The signal at 6.59 ppm corresponds to the eight protons of the aromatic rings. The 24 protons of the methoxyl groups appear at 3.78 ppm and the eight methylene protons give rise to the peak at 3.60 ppm. This is in full accordance with the very flexible structure *6* in which all the aromatic, methoxyl and methylene protons are groupwise equivalent.

A compound derived from methylenedioxybenzene by condensation with formaldehyde, m.p. >360° (decomp.), has been described [6] and is probably the methylenedioxy analogue of *3*.

Niederl and Vogel [7] described a compound obtained from resorcinol by condensation with acetaldehyde in the presence of sulphuric acid and suggested the structure *7* (R = H) for this substance. On methylation with dimethyl sulphate, they obtained a "methyl ether monohydrate", m.p. 256°. We have repeated their condensation procedure but prefer to mix the starting materials at 0° and let the reaction mixture stand for a week at room temperature. The



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recrystallised (ethanol) condensation product, obtained in about 90 % yield, was methylated with diazomethane. (Dimethyl sulphate and alkali gave mainly partially methylated products.) The melting point of the methyl ether *7* (R = CH_3) was found to be 326—328°. Like compounds *3* and *6* this methyl ether could be sublimed *in vacuo*.

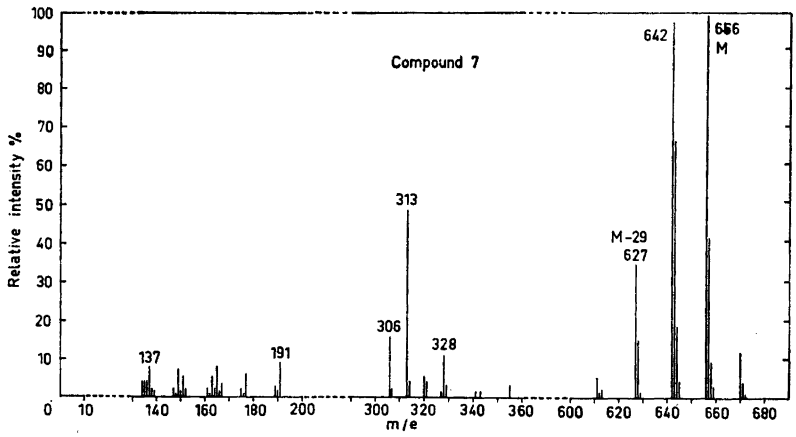

Fig. 3. Masspectrum of compound 7.

The mass spectrometric examination (Fig. 3) showed that the molecule contains four aromatic nuclei (*7*, R = CH_3). The molecular ion peak * (base peak) was found to be 656. (Mol.wt. for $C_{40}H_{48}O_8$ = 656.) The second largest peak was M — 14.

The peak at *m/e* 328 may be a doubly charged ion M^{2+} or a fragment $(M/2)^+$. The ion *m/e* 313 may be due to a fragment *m/e* 328 — 15. No diffuse peaks due to metastable ions were found in this mass spectrum.

Similar compounds have been obtained by condensing resorcinol or pyrogallol with aromatic aldehydes.[9,10]

* The correct counting of the mass numbers of the molecule ion and fragment ions were made by using an internal fluorocarbon standard.[8]

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