Tetrahedron Letters, Vol 33, No 25, pp. 3591-3594, 1992
Printed in Great Britain

0040-4039/92 $5.00 +
Pergamon Press Ltd

Cyclo-oligomerization of Veratryl Alcohol with Trifluoroacetic Acid

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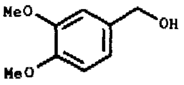
Abstract: Treatment of veratryl alcohol with a dilute solution of trifluoroacetic acid in chloroform yields a mixture of oligomers. Four major products have been separated and identified as the new cyclohexaveratrylene **6** and cyclopentaveratrylene **5**, in addition to the known cyclic tetramer **4** and cyclic trimer **3**.

A compound first obtained in 1915 from 3,4-dimethoxybenzyl alcohol (veratryl alcohol)**1** by the action of sulfuric acid in acetic acid was considered to be the dihydroanthracene **2**, a dimeric condensation product.[1] This constitution was widely accepted until an unequivocal synthesis of **2** rendered it untenable.[2] An alternative proposal that this condensation product possessed six veratryl units[3] was called to question by Lindsey,[4,5] Goldup *et al.*,[6] and Erdtman *et al.*[7] who established the "trimeric" nature and structure **3** with rigid crown (C_{3v}) conformation. These conclusions have been supported by PMR[8,9] and crystal structure evidence.[10]

The homologous cyclotetraveratrylene **4** has been isolated by chloromethylation of veratrole,[3,6] and as a by-product (16% yield) of **3** from **1** under Lindsey's conditions.[11,12] In a comprehensive review of cyclophenylenes,[13] attention is drawn to the fact that in the acid-catalyzed formation of **3** and **4** from **1**, the formation of higher cyclic oligomers "that have neither been isolated nor characterized so far" is very likely. We report here the realization of this prediction.

Treatment of veratryl alcohol **1** with a dilute solution of trifluoroacetic acid in chloroform at or below room temperature, followed by solvent removal yielded a residual solid, whose ^{1}H NMR spectrum indicated the presence of four major symmetrical products. In particular, the aryl proton region of the spectrum gave singlet signals at δ6.82 (attributable to **3**), 6.60 (broad, attributable to **4**), 6.57 and 6.49 shown after isolation to correspond to the cyclopentamer **5** and cyclohexamer **6** respectively. These four oligomers were separated by solubility differential and fractional crystallization to give **3**, **4**, **5**, and **6** in isolated yields of 19, 42, 13 and 5% respectively;[14] their ^{1}H and ^{13}C NMR spectra are reported in tables 1 and 2.



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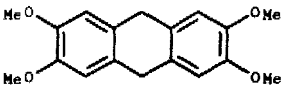

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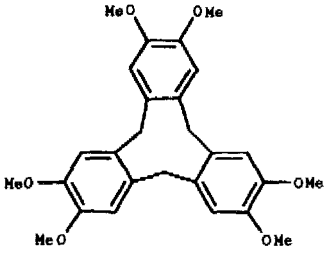

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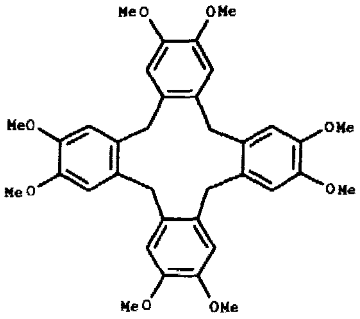

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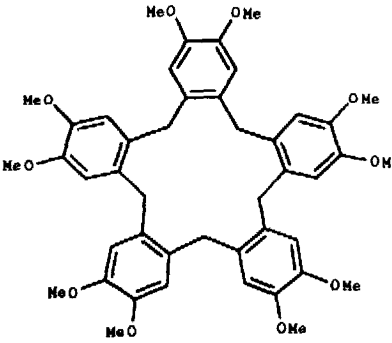

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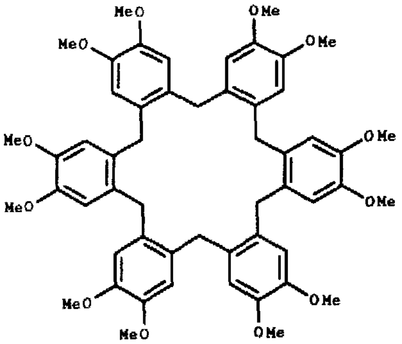

6

It is now well established[15] that cyclotriveratrylene **3**, which has been variously described as cone-,[16] saucer-,[17] and umbrella-[6] shaped, exists as a single rigid crown conformer of C_{3v} symmetry, with characteristic AB multiplicity of the methylene bridge

Table 1. ^1H NMR Chemical Shifts for Oligomers **3**, **4**, **5** and **6** in $CDCl_3$ (δ_{ppm}) at 300 MHz

Oligomer	Temp. °C	ArH	OMe	CH_2
Trimer **3**	19	6.82 s	3.83 s	4.74 d (J 13.7 Hz) and 3.53 d (J 13.7 Hz)
Tetramer **4**	19	6.4-6.9 br.	3.4-4.0 br.	under OMe
	50	6.60 s	3.77 s	3.61 s
Pentamer **5**	19	6.57 s	3.75 s	3.68 s
Hexamer **6**	19	6.49 s	3.73 s	3.63 s

Table 2. ^{13}C NMR Chemical Shifts for Oligomers **3**, **4**, **5** and **6** in $CDCl_3$ (δ_{ppm}) at 75 MHz

Oligomer	Temp. °C	Ar<u>C</u>OMe	Ar<u>C</u>	Ar<u>C</u>H	OMe	CH_2
Trimer **3**	19	147.63	131.71	113.03	55.96	36.41
Tetramer **4**	19	147.14	131.45	114-119 br. and 109-113 br.	55.90	34.80
	40	147.44	131.65	113.88	56.06	34.84
Pentamer **5**	19	147.21	130.74	113.73	55.98	36.14
Hexamer **6**	19	147.26	130.82	113.21 and 113.00	55.99 and 55.83	35.28
	50	147.74	131.11	113.90	56.18	35.34

protons. In contrast, the cyclotetramer **4** in solution at ambient temperature has a flexible structure with pseudo-rotation about the methylene carbon atoms resulting in interchange of the intra- and extra-annular methylene protons.[11,12] The ambient temperature ^{1}H NMR spectra of the new oligomers, cyclopentamer **5** and cyclohexamer **6** also reveal equivalence of methylene protons pointing consequently to conformational mobility. These two cyclo-oligomers also provide interesting 15- and 18-membered carbocyclic analogues of the widely studied oxygen crown ethers and may be precursors for the polybenzo[15] and [18] annulenes.

Acknowledgments: We wish to thank Dr. Andrew Tyler of the Harvard University Chemistry Department Mass Spectrometry Facility [funded by grants from N.I.H. (1 SIO RR06716-01) and N.S.F. (CHE-9020043)] for providing high-resolution analytical data. A grant from Merck, Sharp and Dohme Research Laboratories which supported this work is also gratefully acknowledged.

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14. A solution of trifluoroacetic acid (10% v/v) in chloroform (150 ml) was added over 10 min. to 3,4-dimethoxybenzyl alcohol (3.0 g) cooled in an ice-water bath, and the mixture allowed to stand for one day. The solvent was removed under reduced pressure to yield a froth solid, shown to consist of four major products (shown in the sequel to be **3**, **4**, **5** and **6**) by examination of the ^{1}H NMR spectrum. Trituration with benzene (40 ml) gave a solid (1.8g, mp 327-334 °C) and filtrate A. This solid (mixture of **3**, **4** and **5**) was boiled with benzene (50 ml) and filtered to give solid *cyclotetraveratrylene* **4** (1.27 g, mp 336-339 °C) whose mp was raised to 346-348 °C on recrystallization from benzene-chloroform (lit. mp 334-337 °C,[18] 319-321 °C,[12] 316 °C[2])[19] and filtrate B (0.37g, mixture of **5** and **6**).

    Evaporation of filtrate A gave a solid (1.2 g, mixture of **3**, **5** and **6**) which on trituration with benzene gave filtrate C (1.08 g mixture of **3** and **5**) and a solid (0.12g, mixture of **5** and **6**). This solid and that obtained from filtrate B were combined and boiled with ethyl acetate (70 ml). The insoluble solid (0.16 g) so obtained on crystallization from the same solvent gave *cyclohexaveratrylene* **6** as felted needles (mp 311-313 °C, M/e 900.4092;[20] calc. for $C_{54}H_{60}O_{12}$, 900.4086) and filtrate D. Evaporation of filtrate D afforded a solid (0.33g) and crystallization from ethyl acetate gave *cyclopentaveratrylene* **5** (0.30 g)as felted solid mp 268-270 °C, M/e 750.3406; calc. for $C_{45}H_{50}O_{10}$, 750.3405.

    Filtrate C (mixture of **3** and **5**) upon evaporation and crystallization from ethyl acetate gave additional **5** (0.13g, mp 268-270 °C). The solid obtained from evaporation of the filtrate was crystallized from benzene to yield *cyclotriveratrylene* **3** as needles (0.56g), mp235-236 °C (lit. mp 234 °C[5], 234-237 °C.[18])
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19. The disparity in reported melting points may be attributable to polymorphism or presence of minor quantities of oligomers undetected in the ^{1}H NMR spectrum.
20. Fast atom bombardment mass spectra were run on a JEOL SX-102 mass spectrometer and associated data system. Accurate mass measurements were obtained at 10,000 mass resolution and appropriate ions from the FAB spectrum of polyethylene glycol were used as internal mass markers.

(Received in USA 21 February 1992)