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Chemistry of Cyclotriveratrylene. I. Formation of Cyclotriveratrylene from Veratrylamine N-Tosylates[1,2]

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Acid treatment (60% $HClO_4$) of veratrylamine N-tosylates (Va—d) as well as condensation of veratrole and formalin or of veratrylalcohol in the presence of strong acids was proved to give cyclotriveratrylene (III) mainly. On the other hand, the similar reaction of Va with various acids in organic solvents was found to afford both III and cyclotetraveratrylene (IV) in moderate yield.

It had widely been accepted in the literature[4] that condensation of veratrole and formalin or of veratrylalcohol in the presence of strong acids (concd. H_2SO_4, hydrochloric acid) afforded 2,3,6,7-tetramethoxy-9,10-dihydroanthracene (I).[5]

However later studies by Italian chemists[6] have shown that the product does not possess a dihydroanthracene structure but is a hexamer (II) which contains six veratrole nuclei.

More recently, re-examinations by A.S. Lindsey,[7] and by H. Erdtman and his co-workers[8] have independently established that it contains three veratrole nuclei rather than six, must possess the "crown" conformational structure, and is named as cyclotriveratrylene (III). At the same time, cyclotetraveratrylene (IV)[8,9] which contains four veratrole nuclei has also been obtained as a by-product.

During the course of our attempted Pomeranz–Fritsch reaction on N-veratrylethanolamine and its derivatives under a variety of conditions, we have found[2,10] that acid treatment of its N-tosylate, N-veratrylethanolamine N-tosylate (Va), affords a crystalline product, mp 234—237°, whose structure is assigned as cyclononatriene (III). Furthermore, the similar reaction of Va was proved to give both III and IV.

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2) The preliminary communication of this work appeared in *Chem. Pharm. Bull.* (Tokyo), **16**, 177 (1968).
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5) G.M. Robinson, *J. Chem. Soc.*, **107**, 267 (1915).
6) A. Oliverio and C. Casinovi, *Ann. Chim.* (Rome), **42**, 168 (1952) [*C.A.*, **47**, 7457a (1953)]; C. Casinovi and A. Oliverio, *ibid.*, **46**, 929 (1956) [*C.A.*, **51**, 7341b (1957)].
7) A.S. Lindsey, *Chem. Ind.* (London), **1963**, 823; *J. Chem. Soc.*, **1965**, 1685.
8) H. Erdtman, F. Haglid and R. Ryhage, *Acta Chem. Scand.*, **18**, 1249 (1964).
9) J.D. White and B.D. Gesner, *Tetrahedron Letters*, **1968**, 1591.
10) After publication of our communication, identity of cyclononatriene with cyclotriveratrylene reported by H. Erdtman, *et al.* was secured by comparison of their physical constants (mp, NMR and MS spectra). Therefore, we adopted hereafter the common name of cyclotriveratrylene in place of cyclononatriene for the compound (III).

Such an example as this facile formation of III and IV from Va was rarely encountered.[11] Therefore the present paper was concerning the formation of III and IV from some kinds of veratrylamine N-tosylates.

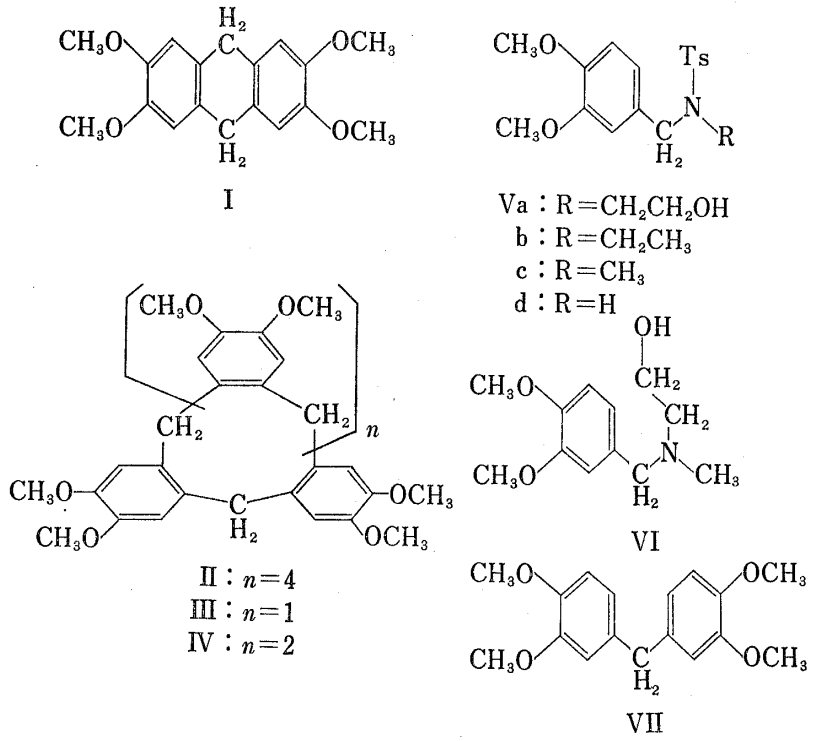

Chart 1

The preparation of the starting material (Va) was performed by means of refluxing a benzene solution of N-veratrylethanolamine[12] with *p*-tosyl chloride in the presence of K_2CO_3. N-Tosylates (Vb—d)[13] of N-ethylveratrylamine, N-methylveratrylamine, and veratrylamine were prepared from the corresponding amines with *p*-tosyl chloride by Schotten–Baumann method.

A suspension of Va in 60% $HClO_4$ was stirred at room temperature for 4 hr (immediate violet coloration displayed). The reaction mixture was diluted with ice–water and the product was taken up in $CHCl_3$. Usual work–up of the $CHCl_3$ layer gave a crystalline mass, which was recrystallized from CCl_4 to furnish colorless feathery crystals (III),[14] mp 234—237°, in 80.4% yield.

Furthermore, in order to examine the effect of substituents (including hydrogen) on nitrogen atom, the same reaction as described above on Vb–d was performed to afford only III in 83.3%, 84.0%, and 89.3% yield, respectively. In every cases IV was not isolated. Treatment of N-methylveratrylethanolamine (VI) with 60% $HClO_4$ was fruitless. Results were shown in Table I.

The foregoing finding suggested that this reaction was certainly not dependent on the length or the presence of N-alkyl group, but on both N-tosyl and *p*-methoxyl group.[11]

11) Sunagawa, *et al.* have found that reaction of 2-(3,4-dimethoxybenzylamino)pyrimidine with hot 10% HCl affords 2,3,6,7-tetramethoxy-9,10-dihydroanthracene which might be indentical with III [G. Sunagawa, T. Ichii and N. Yoshida, *Pharm. Bull.* (Japan), 3, 109 (1955)].
12) R. Baltzly and O. Kauder, *J. Org. Chem.*, 16, 173 (1951).
13) O. Hoshino, S. Sawaki and B. Umezawa, unpublished data.
14) In a large scale run, the same reaction at room temperature gave a small amounts of IV besides III, though III was the sole product at 10—15°.

Table I

	Compound (g)	Conditions			Product III g (%)
		Reaction temperature	Reaction time (min)	60% $HClO_4$ (ml)	
Va	0.4	R.T.[a]	240	40	0.1323 (80.4)
Vb	0.349	R.T.	120	5	0.125 (83.3)
Vc	0.335	R.T.	120	5	0.126 (84.0)
Vd	0.16	R.T.	120	5	0.067 (89.3)

a) at room temperature

On the other hand, White, *et al.*[9] have shown that a solution of veratrylalcohol in AcOH containing a few drops of concd. H_2SO_4, when heated at 90°, affords III (68%) and IV (16%), and also that treatment of veratrole with 70% H_2SO_4 in formalin at 0° yields III and IV in approximately the same proportions. However, in the reaction of Va—d with 60% $HClO_4$ III was formed almost exclusively. Thereupon, employment of solvent in this reaction seemed to be favourable to the formation of IV, and the possibility was confirmed as follows. Namely, treatment of Va with various acids in organic solvents[15] at room temperature or under reflux afforded both III (22—56%) and IV (11—30%), mp 334—337° (decomp.), irrespective of acids and solvents. Results were shown in Table II.

Table II

Compound Va (g)	Conditions				Products	
	Reaction temperature	Reaction time (min)	Acids (ml or g)	Solvents (ml)	III g (%)	IV g (%)
0.365	R.T.[a]	120	95% H_2SO_4 (1.0)[b]	AcOH (15)	0.061 (40.7)	0.025 (16.7)
0.365	R.T.	300	60% $HClO_4$ (5.0)[b]	AcOH (15)	0.079 (52.7)	0.018 (12.0)
0.365	R.T.	120	BF_3·etherate (1.0)[b]	C_6H_6 (15)	0.067 (44.7)	0.038 (26.0)
0.365	reflux	120	*p*-TsOH (0.35)[c]	$CHCl_3$ (15)	0.066 (44.0)	0.017 (11.3)
0.351	reflux	30	*p*-TsOH (0.344)[c]	C_6H_6 (30)	0.081 (56.2)	0.03 (20.8)
0.365	reflux	60	*p*-TsOH (0.35)[c]	$C_6H_5CH_3$ (15)	0.034 (22.7)	0.02 (13.3)
0.365	reflux	120	*p*-TsOH (0.35)[c]	AcOH (15)	0.037 (24.7)	0.021 (14.0)
0.365	reflux	60	BF_3·etherate (1.0)[b]	C_6H_6 (15)	0.053 (35.3)	0.045 (30.0)

a) at room temperature b) ml c) g

Assuming that cleavage of carbon–nitrogen bond in Va was accelerated both by protonation on nitrogen atom and the effect of *p*-methoxyl group to give veratrylcarbonium cation as an intermediate, condensation of which would yield both III and IV, strength of acids might be responsible for this reaction. This assumption, however, could not be proved partly because no definite change on products was observed under varying acidic conditions used. Among other things the finding that the condensation products (III) and (IV) also were obtained in the reaction with *p*-toluenesulfonic acid was to be remembered.

Moreover re-examination on veratrole and formalin or on veratrylalcohol with 60% $HClO_4$ was carried out. In this case again III was produced mainly. In addition condensation of bis-(3,4-dimethoxyphenyl)methane (VII)[5] and formalin in the presence of 60% $HClO_4$

15) However, standing at room temperature or refluxing a methanolic solution of Va and 35% HCl or a solution of Va and *p*-toluenesulfonic acid in tetrahydrofuran or dioxane all failed to give the condensation products (III) and (IV).

or 95% H_2SO_4 was found to furnish III in 69.8% or 45.5% yield, respectively, although Lindsey[7] claimed that III could not be prepared by this route. Results were shown in Table III.

Table III

Compound (g)		Conditions: Reaction temperature	Reaction time (min)	60% $HClO_4$ (ml)	37% HCHO (ml)	Product III g (%)
Veratrole	1.0	R.T.[a]	120	5.0	1.2	0.766 (70.2)
Veratrylalcohol	1.5	R.T.	120	6.0	—	0.474 (35.3)
VII	0.47	R.T.	120	2.5	3.0	0.33 (69.8)
	1.17	R.T.	120	—[b]	2.0	0.556 (45.5)

a) at room temperature b) 95% H_2SO_4 (0.15 ml)

Thus the fact that acid treatment of veratrylamine N-tosylates (Va—d) as well as that of veratrole or VII and formalin or of veratrylalcohol afforded III mainly was found. Furthermore the finding that IV was formed in organic solvents was noteworthy and seemed to be the useful method for preparation of IV so far. Considering that with BF_3·etherate III and IV were obtained, the generation of veratrylcarbonium cation would be indispensable. Viewed from this point, the above reaction would reasonably be interpreted as a kind of Friedel–Crafts reaction, though the reason why III was formed predominantly remained ambiguous.

Experimental[16]

N-Veratrylethanolamine N-Tosylate (Va)——A mixture of veratraldehyde (20 g) and ethanolamine (8 g) in absolute toluene (100 ml) was refluxed for 3 hr. After removal of the solvent under reduced pressure, the crystalline mass obtained was recrystallized from EtOAc to give colorless plates (19 g), mp 109—111° (lit.[12] mp 105.5—106.5°).

To a stirred solution of the Schiff base (10 g) obtained above in MeOH (100 ml), $NaBH_4$ (2 g) was added and the mixture was gently refluxed for 1 hr. Then to the residue obtained after evaporation of the solvent under reduced pressure, 10% NaOH solution was added and the product was taken up in ether. The ether layer was dried (K_2CO_3). Evaporation of the solvent furnished N-veratrylethanolamine, mp 55.5—57.5°; oxalate (MeOH), colorless prisms, mp 180—181.5°. *Anal.* Calcd. for $C_{13}H_{19}O_7N$: C, 51.82; H, 6.36; N, 4.65. Found: C, 51.58; H, 6.40; N, 4.65; picrate (EtOH), yellow prisms, mp 151—154° (lit.[12] mp 155—156°).

To a stirred solution of the free amine (4 g) obtained above and K_2CO_3 (4 g) in absolute benzene (100 ml), *p*-TsCl (4 g) was added. After 5 hrs' reflux of the mixture with stirring and removal of the solvent under reduced pressure, to the resultant residue, water was added and the product was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with 10% HCl and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a crystalline mass which was recrystallized from benzene to yield Va, mp 122—123°, 4.1 g (63.3%) as colorless prisms. *Anal.* Calcd. for $C_{18}H_{23}O_5NS$: C, 59.18; H, 6.33; N, 3.83. Found: C, 59.11: H, 6.49; N, 3.83.

N-Methylveratrylethanolamine (VI)——A solution of the free amine (3 g) obtained above, 90% HCOOH (5 g) and 37% HCHO (5 g) was heated at 95° for 3 hr. After removal of the solvent under reduced pressure, the residue was treated with 10% NaOH solution and the product was taken up in ether. The ether layer was dried (K_2CO_3). Evaporation of the solvent gave an oil which was distilled to afford colorless liquid (2 g), bp 175—180°/3 mmHg (bath temperature); picrate, mp 103—106° (iso-PrOH). *Anal.* Calcd. for $C_{18}H_{22}O_{10}N_4$: C, 47.58; H, 4.88; N, 12.33. Found: C, 47.50; H, 4.80; N, 11.90.

Cyclotriveratrylene (III) from Va——i) A suspension of Va (0.4 g) and 60% $HClO_4$ (40 ml) was stirred at room temperature for 4 hr. The reaction mixture displayed immediate violet coloration. After comple-

16) All melting points were uncorrected and measured on a Yanagimoto micro melting point measuring apparatus. Nuclear magnetic resonance (NMR) spectra were taken with a JNR-C-60S and a JNR-4H-100 spectrometers in $CDCl_3$ using Me_4Si as internal standard. Mass spectra (MS) were measured with a Hitachi mass spectrometer Model RMU-6E. Infrared (IR) spectra were obtained with a Hitachi EPI-S_2 infrared spectrometer.

tion of the reaction, the reaction mixture was diluted with ice–water and the product was taken up in $CHCl_3$. The $CHCl_3$ layer was washed successively with brine, 5% K_2CO_3 solution and brine, and dried ($MgSO_4$). Removal of the solvent gave a crystalline mass which was recrystallized from CCl_4 to furnish III, mp 234—237°, 0.1323 g (80.4%) as colorless feathery crystals. *Anal.* Calcd. for $C_{27}H_{30}O_6$ (mol. wt.=450.51): C, 71.98; H, 6.71. Found: C, 71.86; H, 6.67. NMR τ: 6.15 (18H, S., $-OCH_3\times6$), 6.43, 5.18 (each 3H, AB quartet, J=13.5 cps, $=CH_2\times3$), 3.11 (6H, S., aromatic ring protons). MS: *m/e* 451 (parent peak).

ii) A solution of Va (0.351 g) and *p*-TsOH (0.344 g) in benzene (30 ml) was refluxed for 30 min. The reaction mixture was washed with cold saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Removal of the solvent gave a pale yellow mass which was fractionally recrystallized from benzene to furnish III, 0.081 g (56.2%) (readily soluble in benzene) and colorless crystals (IV), mp 328—337° (decomp.), 0.03 g (20.8%) (less soluble in benzene), respectively. The latter was twice recrystallized from benzene–$CHCl_3$ to give colorless needles, mp 334—337° (decomp.). *Anal.* Calcd. for $C_{36}H_{40}O_8$ (mol. wt.=600.68): C, 71.98; H, 6.71. Found: C, 71.76; H, 6.76. NMR τ: 6.38 (8H, S., $=CH_2\times4$), 6.20 (24H, S., $-OCH_3\times8$), 3.38 (8H, S., aromatic ring protons). MS: *m/e* 600 (parent peak). Physical constants (NMR and MS) of this compound agreed well with that of cyclotetraveratrylene (IV) reported by Erdtman, *et al.*[8]

In the case of other conditions, the same treatment of the reaction mixture as described above except washing with 10% KOH solution instead of saturated $NaHCO_3$ solution afforded results shown in Table II. Identification of the products was performed by comparison of each IR spectrum ($CHCl_3$).

III from Vb—d——After a solution of Vb—d in 60% $HClO_4$ was stirred at room temperature, the same treatment of the reaction mixture as described in (i) except washing with 10% KOH solution in place of 5% K_2CO_3 solution gave results shown in Table I. The product from each reaction was identical with III by comparison of each IR spectrum ($CHCl_3$).

III from Veratrole and Formalin or Veratrylalcohol——A suspension of veratrole and 37% HCHO or of veratrylalcohol in 60% $HClO_4$ was stirred at room temperature. The same work-up of the reaction mixture as described in (i) afforded results shown in Table III. Characterization of the product was performed by comparison of each NMR spectrum.

III from Bis(3,4-dimethoxyphenyl)methane (VII)[5]——A mixture of VII and 37% HCHO in 60% $HClO_4$ or 95% H_2SO_4 was stirred at room temperature and the same treatment as described in (i) gave results shown in Table III. Identification of the product was carried out by comparison of each NMR spectrum.

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