PART I

Addition Reactions of a Methyleneaziridine

PART II

Conformational Aspects of Cyclotriveratrylene

Derivatives.

A thesis in two parts submitted to the
University of Southampton
for the degree of
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bу

Brian Halton

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Summary

Part I The nature of the Favorskii intermediate has been in question for some time and it was thought that a study of 1-ethyl-2-methyleneaziridine, a nitrogen analogue of the allene oxide postulate of Cookson and Nye, could lend further evidence to the existence of allene oxides as transient species in this rearrangement by the isolation of similar adducts with 1,3-dipolarophiles.

The results obtained show that in the majority of cases where the 'intermediate' gave adducts the aziridine did not react and that in the two cases where reaction occurred the products did not correspond. The mechanism of formation of the adduct with dimethyl acetylenedicarboxylate is discussed.

Part II The structure and conformation of cyclotriveratrylene, the condensation product between veratrole and formaldehyde, has only recently been clarified. Two possible conformations, corresponding to the 'crown' and 'flexible' conformers of cyclononatriene, could exist for this ring system of three aromatic nuclei separately fused to a cyclononatriene ring but cyclotriveratrylene is shown to exist entirely in the

'crown' form. A study of the known monoketone is made and its conformation and that of the triketone, a new by-product in the oxidation, is proposed as the alternative 'flexible' arrangement.

The existence of both conformers is demonstrated in a series of derivatives. Theoretically three alcohols, the \propto -, and \circlearrowleft - and \circlearrowleft -cyclotriveratrylenols, are possible from reduction of the monoketone but only the first two could be obtained. The conformations of these and their ionisation rates are presented. Equilibria between the 'crown' and 'flexible' forms are demonstrated in the methylene- and isopropylidenecyclotriveratrylenes. General trends regarding the conformational stability of the derivatives are discussed.

CONTENTS

PART I

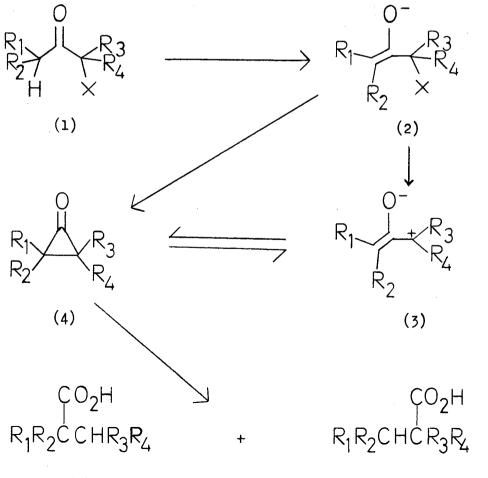
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PART I

ADDITION REACTIONS OF A METHYLENEAZIRIDINE

Introduction

In recent years much attention has been given to the Favorskii rearrangement of \propto -haloketones¹, particular emphasis being placed on the nature of the intermediate²⁻⁷. The mechanism generally accepted for an \propto -haloketone with an \propto -hydrogen atom is essentially that summarised by J. G. Burr and M. J. S. Dewar⁴, where an enolate anion (2), is formed which undergoes



(5)

(6)

unimolecular loss of halide ion to give the planar dipole or zwitterion (3). This may collapse exothermically to the cyclopropanone (4) and give the Favorskii products (5) and (6) by cleavage with base. An internal displacement of halide from (2) can lead to (4) directly. The decrease in stereospecificity with increase in polarity of the medium is understandable in terms of this mechanism.

Both A. W. Fort⁵ and M. J. Nye^{6,7} have shown that the Favorskii intermediate can be 'trapped' with suitable 1,3-dipolarophiles. When Nye treated 1,3-dibromo-1,3-diphenyl-propanone, (7), with sodium iodide in the presence of furan or cyclopentadiene stereoisomers of (8) were obtained.

When (7) was treated with sodium iodide in acetonitrile

Nye observed a peak at 1750cm⁻¹ in the infra-red (I.R.) spectrum

which can well be ascribed to the exocyclic double bond of the

allene oxide, (9). Cookson and Nye⁶ have pointed out that

the allene oxide could well be an intermediate in the Favorskii

rearrangement, as shown in the following scheme:

$$\begin{array}{c} R_1 \\ R_2 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_3 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_3 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_3 \\ R_4 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_3 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_4 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_3 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_3 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_3 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_2 \\ R_4 \\ R_4 \\ R_4 \end{array} \longrightarrow \begin{array}{c} R_1 \\ R_1 \\ R_2$$

Nye obtained adducts of the 'intermediate' with the following dipolarophiles⁹, dimethyl acetylenedicarboxylate (10), diethyl azodicarboxylate (11), tetracyanoethylene (12), and those of type (8). The dimer (13) was also observed.

The purpose of the work described here was to see if l-ethyl-2-methyleneaziridine (14), a nitrogen analogue of allene oxide, would undergo analogous addition reactions to those of the Favorskii intermediate, thus lending further evidence to the existence of allene oxides as transient species in this rearrangement.

Chapter II

The Aziridine and its Reactions with

Dipolar ophiles.

1-ethyl-2-methyleneaziridine

The aziridine (14) was first prepared by C. B.

Pollard and R. F. Parcell¹⁰ in the extension of their

work on the dehydrohalogenation of N-(2-bromoally1)
dialkylamines to N-(2-bromoally1)-alkylamines using

sodamide in liquid ammonia. Structure (15) was proposed

but was shown to be incorrect by M. G. Ettlinger and

F. Kennedy¹¹ who assigned (14) on the basis of the intense

exocyclic carbon-carbon double bond frequency at 1765cm⁻¹

in the infra-red (I.R.) spectrum. J. D. Roberts and

A. T. Bottini¹² confirmed this latter assignment by a

nuclear magnetic resonance (N M R) study of the compound.

$$CH_2 = CH - CH = N - Et$$

The mode of formation of the aziridine was elegantly demonstrated by A. T. Bottini and R. E. Olsen¹³ using tracer techniques.

The product with tetracyanoethylene (T C N E)

Treatment of the aziridine with T C N E in refluxing acetone gave 5-ethyl-1,1,2,2-tetracyano-5-azaspiro _73,2_7hexane, (16), in good yield.

The compound gave a satisfactory microanalysis for a 1:1 adduct and the structural assignment is supported by spectral data.

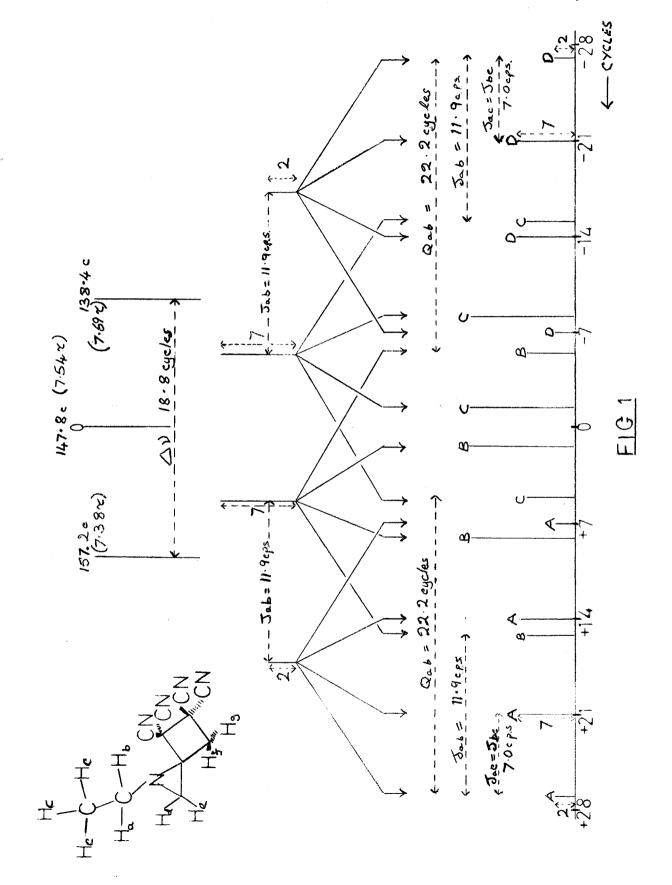
The N M R spectrum, in pyridine solution, was as follows:

7 5.98 quartet J = 14c.p.s. 2 protons H_f and H_g 7.47 singlet 1 proton H_d 7.54 multiplet of 16, J = 7.0c.p.s. 2 protons H_a and H_b 8.19 singlet 1 proton H_e 8.83 triplet J = 7.0c.p.s. 3 protons H_c

The significant factor in this spectrum is the occurrence of the multiplet of sixteen. The coupling constant, J, is 7.0 c.p.s. and therefore it is due to the methylene of the N-ethyl group (it occurs at almost exactly the same chemical shift as this group in the starting aziridine). The potential asymmetry 14 of the spiro-carbon atom causes non-equivalence of protons $_{a}^{14}$ and $_{b}^{14}$ which thus couple with coupling constant $_{ab}^{14}$ = $_{b}^{14}$ c.p.s. to give an AB 'quartet'. However each of the protons $_{a}^{14}$ and $_{b}^{14}$ will separately couple to the methyl

protons, H_c , of the N-ethyl group with the same coupling constant $J_{ac} = J_{bc} = 7.0$ c.p.s. Hence each peak of the initial AB quartet will be split further into a quartet giving the observed pattern of sixteen peaks. This is represented diagramatically in fig.1.

The unexpected singlets for protons H, and H are more difficult to explain. These protons are nonequivalent and one expects to see an AB quartet. The geminal coupling constants of cyclopropane derivatives are generally about -5 c.p.s. 15 and for spiro /3,2 7 hexane and spiro [2,2] pentane the cyclopropane ring protons show this coupling as -4.6 ± 2.0 and -3.9 ± 1.0 c.p.s. respectively 16. The effect of an electronegative atom ∞ to a CH, is to increase the geminal coupling constant in a positive sense, the effect being a maximum when the lone pairs of the hetero-atom eclipse the C-H bonds 17(a). In a three-membered ring with nitrogen as the electronegative atom the lone pair and one C-H bond are almost eclipsed and the geminal coupling constant is increased by about +4 c.p.s. 17(b), and thus in an aziridine ring the geminal coupling constant will be small and negative



 $(J_{\text{gem}} = -0.87 \text{ c.p.s. for 2-phenylaziridine}^{17(b)})$. Hence protons H_{d} and H_{e} could well be coupled with $J_{\text{de}} < 1 \text{ c.p.s.}$ On an expanded scale of 100 cycles sweep width there is evidence for coupling with $J_{\text{de}} < 0.5 \text{ c.p.s.}$

The I.R. spectrum is in agreement with the proposed structure. The compound slowly eliminated hydrogen cyanide on standing but in ethanol the decomposition was accelerated, accounting for the observed U.V. spectrum; no product was isolated.

Under these conditions it is evident that a 1,3-dipole is not formed but rather the affinity of T C N E for double bonds is exemplified.

The product with dimethyl acetylenedicarboxylate (D M A)

A solution of the aziridine and excess D M A in acetone gave, after two days at room temperature followed by chromatography over silica, a colourless crystalline compound, m.p. 93-4°, analysing for $^{\rm C}_{12}{}^{\rm H}_{15}{}^{\rm NO}_{6}$, viz. a l:l adduct plus one carbon and two oxygen atoms. The analysis was confirmed by high resolution mass spectrometry.

I.R. spectra showed carbonyl stretching frequencies at 1730, 1725 (shoulder) and 1700cm⁻¹ and N M R, one proton

On the basis of these spectra it would appear that trimethyl 1-ethylpyrrole-2,3,4-tricarboxylate,(17), could well be the compound. The U.V. spectrum showed absorption at \$\int_{\text{max}}\$ 218 (38,300) and 269 my. (\$\malepsilon\$ = 16,400) typical of pyrrole carboxylic esters. The assignment of the structure was confirmed by melting point, mixture melting point and comparison of I.R. spectra with an authentic sample supplied by Professor R. A. Nicolaus \$18,19\$.

Synthesis of the adduct with excess D M A under nitrogen led to the same yield of product (31%), whereas under carbon dioxide the yield fell to 3% showing that the

additional carbon and two oxygen atoms do not come from atmospheric carbon dioxide. When the synthesis was performed with equimolar quantities of reagents the yield of pyrrole fell to 20% indicating that more than one mole of ester is required for each mole of aziridine.

The mechanism of formation of the pyrrole (17)

One can postulate the first step in the mechanism as attack of D M A on the exocyclic double bond of the aziridine to give the spiro-compound (18), corresponding to the T C N E adduct. This would then ring-open in the usual manner to give (19) which can then close to (20) as indicated. It would appear reasonable that (20) should aromatise to the pyrrole (21).

The formation of (20) can be rationalised by the direct addition of D M A to the dipole (22) obtained by breaking the carbon-carbon bond²⁰. However once dipoles are invoked (23) and (24) should also exist in higher concentration and give rise to (26) via (25).

$$X = CO_2CH_3$$

$$Et - N \stackrel{\bigoplus}{\longleftarrow} \frac{DMA}{} (20)$$
(20)

(23) and (24) can also follow the reaction path corresponding to the 'trapping' of the Favorskii intermediate by Nye, and thus (28), the analogue of (10), would be formed.

Ph
$$\longrightarrow$$
 Ph \longrightarrow X=CO₂CH₃

Hence

Of the products (20), (21), (25), (26), (27) and (28) only the first four could react further with D M A (see below). Since (27), which would be expected to hydrolyse readily to (28), was not seen it seems unlikely that dipolar intermediates are plausible entities in this reaction. The should be noted here that apart from (17) the only isolable material was a non-crystallisable orange gum with an I.R. spectrum similar to that of (17)

From the above discussion the most plausible pathway seems $(14) \longrightarrow (18) \longrightarrow (20)$, and the latter product must in some way react further with D M A to give (17), either directly or via (21). R. M. Acheson and J. M. Vernon²¹ have shown that 1-methylpyrrole reacts with D M A as shown in scheme 1.

SCHEME 1

whereas 1,2-dimethylpyrrole reacts to give aromatic substitution in the 5 position 22 .

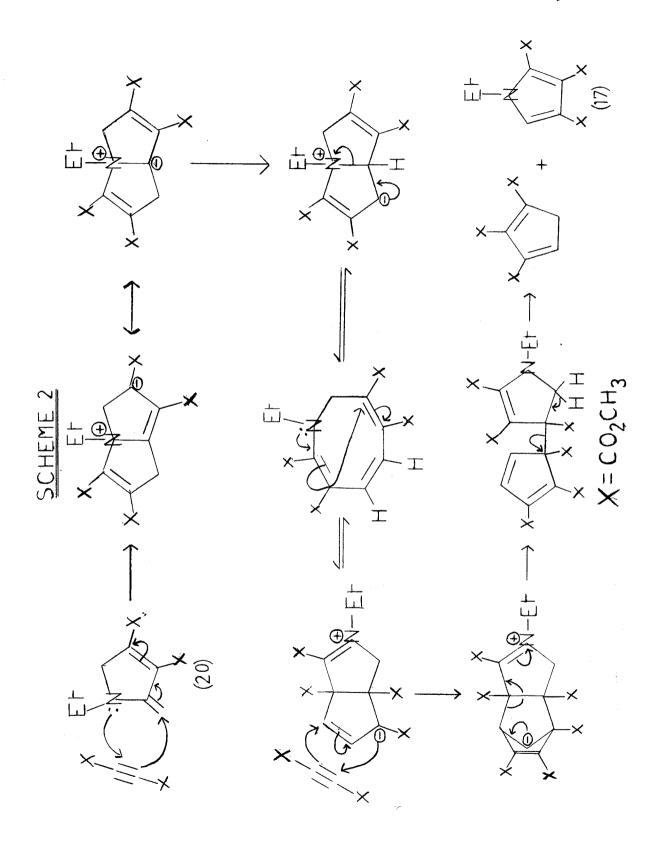
$$H_3C$$
 CH_3
 CH_3
 CH_3
 CH_3

Pyrrole (21), a possible intermediate, corresponds to the latter case but it was thought that the effect of the electron-withdrawing ester groups could well favour Diels-Alder addition in preference to substitution.

Hence the reaction product trimethyl 1-ethylpyrrole-2,3,4-tricarboxylate,(17), could be formed by a route corresponding to scheme 1, although the penta-ester (31) was not observed.

Dimethyl 1-ethyl-2-methylpyrrole-3,4-dicarboxylate (21), was synthesised²³ and treated with a slight excess of D M A under conditions identical to the formation of (17). Starting materials were recovered in 88% yield and thus (21) / and in all probability (26) should the route (23) — (26) be invoked / is not an intermediate in the formation of (17).

It is believed that the product arises by further reaction of (20) (or (25) though this is less favoured for reasons outlined before) with D M A since the process $(14) \longrightarrow (18) \longrightarrow (19) \longrightarrow (20)$ seems very reasonable indeed.



A route from (20) to the product (17) is shown in scheme 2. The cyclopentadiene tri-ester or its dimer was not observed.

Reactions with other 1,3-dipolerophiles.

Acetylenes

It was hoped that adducts of methyl propiolate and dicyanoacetylene with the aziridine would indicate the mode of formation of (17) since, in the former case, repeated additions of methyl propiolate would be less favoured than with dimethyl acetylenedicarboxylate.

With methyl propiolate the aziridine yielded only a non-crystallisable red gum which on hydrolysis gave a black tarry organic acid not further characterised. Dicyanoacetylene and the aziridine produced polymeric products shown to contain C-H and CEN bonds by their I.R. spectra in 'florube' and hexachlorobutadiene.

Enes

The only product isolated from reaction with maleic anhydride was a brown gum corresponding in behaviour to that from methyl propiolate, whereas with

acrylonitrile starting materials were recovered. Diethyl azodicarboxylate, used to 'trap' the Favorskii intermediate, produced a red, non-crystallisable gum together with some hydrazodicarboxylate. The occurrence of the latter product is to be expected ²⁴.

Dienes

Furan and cyclopentadiene, successfully used by Nye 6,7, gave only starting materials at room temperature, and even in a sealed Carius tube at 180° furan and the aziridine were recovered in 95% yield; cyclopentadiene in a sealed tube gave a thick black polymer. Bicyclo 2,2,1 heptadiene paralleled the behaviour of furan.

Conclusion.

From the reactions outlined above it is quite clear that 1-ethyl-2-methyleneaziridine does not behave in a manner analogous to the allene oxide postulate of Nye⁷. In the majority of cases where Nye obtained adducts the aziridine gave no isolable product (viz. furan, cyclopentadiene and diethyl azodicarboxylate) and in the two cases where products were identified (viz. tetracyanoethylene and dimethyl acetylenedicarboxylate) they did not correspond.

The mechanistic path to pyrrole (17) is still unknown, and whilst dipoles are thought unlikely they cannot be excluded. Reaction of the aziridine with T C N E shows the affinity of the latter for double bonds but with methyl propiolate and dicyanoacetylene dipolar intermediates (22), (23) and (24) could be postulated. That furan does not react, and cyclopentadiene only under forcing conditions, again suggests that dipoles are not present. It would seem, therefore, that whilst dipoles cannot be excluded, reaction with the exocyclic double bond of the aziridine is prefered.

Attempts to synthesise (33), the nitrogen analogue of Nye's postulated intermediate, from dibenzyl ketone trimethylhydrazonium iodide, (32), or to 'trap' a dipolar intermediate of it in situ failed and does not warrant further discussion here.

Experimental

Microanalyses were performed by Ilse Beetz, (Kronach), and Dr. H. Bieler, (Vienna).

Infra-red spectra were recorded on a Unicam
S.P. 200 spectrophotometer and calibrated against
polystyrene. Nujol mulls were employed unless otherwise
stated.

Ultra-violet spectra were recorded on a Unicam S.P. 800 spectrophotometer in 95% B.P. ethanol unless otherwise stated.

N M R spectra were run on a Varian Associates A.60 instrument operating at 40° . Deuterochloroform solutions were used, unless otherwise stated, with tetramethylsilane as internal reference. Results are expressed in τ values (TMS = 10), the proton count is in brackets and the abbreviations s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet follow.

The abbreviation Pet. ether refers to petroleum ether, b.p. $40 - 60^{\circ}$.

1-ethyl-2-methyleneaziridine (14) was prepared from
2,3-dibromopropene by the method of Pollard and Parcell
10.

It is essential that the liquid ammonia be dry, and preferable to form the sodamide in situ. A careful fractionation is necessary since the aziridine co-distils with ether.

Reaction of the aziridine with tetracyanoethylene (T C N E)

A solution of T C N E, 2.56g. (0.02 mole), purified by sublimation in vacuo and the aziridine, 1.66g. (0.02 mole) in acetone, (60 mls.) was refluxed for 2 hours. Excess solvent was removed in vacuo and the black residue purified by repeated crystallisation from chloroform to give a 2.52g. (60%) yield of (16), m.p. 155-6° (decomp.), as colourless needles.

I.R. 2275, 2250, 1200, 1125, 800 cm $^{-1}$.

U.V. λ_{max} 233 (1200); 283 (230); 319 my. (ϵ = 240).

(Accounted for by loss of H-C=N from the molecule. Extinction coefficients increased on standing probably due to opening of the cyclobutene ring followed by polymerisation).

NMR_(pyridine)
$$\tau$$
 5.98 (2) q J = 14 c.p.s.; 7.47 (1) s; 7.54 (2) m J = 7.0c.p.s.; 8.19 (1) s; 8.83 (3) t J = 7.0c.p.s.;

Analysis: C₁₁H₉N₅ requires C 62.55; H 4.26; N.33.17 % found C 61.44; H 4.55; N 32.1 %

Reaction of the aziridine with dimethyl acetylenedicarboxylate (D M A)

A solution of the aziridine, 2.00g. (0.025 mole), and D M A, 7.11g. (0.05mole), in acetone, (30 mls.), was stood at R. T. for 2 days. Excess solvent was removed in vacuo and the residual black viscous oil chromatographed over silica, 300g. Pet. ether-benzene (1:1) eluted excess D M A and benzene-ether mixture (9:1) a viscous yellow/orange oil which solidified on standing. Continuation of the chromatography to 100% acetone gave non-solidifiable orange gums. The benzene-ether (9:1) fraction was recrystallised from ether to give 1.95g. (31%) yield of (17) as a colourless crystalline solid, m.p. 93-4°.

I.R. (CHCl₃) 1730, 1725(sh), 1700, 1535, 1235, 1058cm⁻¹.

U.V. λ_{max} 218 (38,300); 269 m/ ($\epsilon = 16,400$).

NMR 72.60 (1) s; 5.65 (2) q J = 7.5 c.p.s.;

6.10 (3) s; 6.20 (3) s; 6.25 (3) s;

8.60 (3) t J = 7.5 c.p.s.

Analysis: C₁₂H₁₅NO₆ requires C53.53, H 5.57, N 5.20 % found C53.54, H 5.53, N 5.30 %

Mass spectrum.Molecular formula $^{\rm C}_{12}{}^{\rm H}_{15}{}^{\rm NO}_{6}$

m.p., mixture m.p. and comparison of I.R. spectrum with an authentic sample showed the compound to be trimethyl l-ethylpyrrole-2,3,4-tricarboxylate, (17).

Synthesis of dimethyl 1-ethyl-2-methylpyrrole-3,4-dicarboxylate(21) was performed by the method of Kornfield and Jones²³, the diethyl

ester being transesterffied to the dimethyl ester in the usual manner.

Yield 59% m.p. 90 - 20

I.R. (CHCl₃) 1715, 1695, 1200cm⁻¹.

 $U.V. \lambda_{max}$ 217 (12,000), 258m/ ($\epsilon = 9,000$)

NMR $\sim 2.80 (1) \text{ s}; 6.17 (2) \text{ q}.$ J = 7.0 c.p.s.;

6.18 (3) s; 6.24 (3) s; 7.65(3) s;

8.68(3) t. J = 7.0 c.p.s.

Analysis: C₃₁H₁₅NO₄ requires C 58.67; H 6.67; N 6.22 % found C 59.19; H 6.67; N 6.14 %

Treatment of (21) with D M A

The procedure was identical to the reaction of the aziridine with D M A. Pet. ether-benzene (1:1) eluted D M A and benzene-ether (9:1), (21), in 86% yield.

Reaction of the aziridine with

- (i) methyl propiolate
- (ii) maleic anhydride
- (iii) diethyl azodicarboxylate
- (iv) furan
- (v) cyclopentadiene
- (vi) bicylo-heptadiene and
- (vii) dicyanoacetylene²⁶.

The Procedure was as for the reaction of the aziridine with D M $\mbox{A.}$

Reactions (i), (ii) and (iii) yielded non-crystallisable gums which gave tarry organic acids on hydrolysis; (iv), (v) and (vi) showed no reaction. Reaction (ii) under reflux conditions gave the same product. In sealed Carius tubes at 180°C. (iv) and (vi) showed no change but (v) gave a thick black polymer. (vii), used in ether at RT and -70°, gave a black polymer with T.R. (florube) 2200, 1455cm⁻¹.

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PART II

CONFORMATIONAL ASPECTS OF CYCLOTRIVERATRYLENE

DERIVATIVES

Chapter I

Cyclotriveratrylene

The condensation of veratrole with formaldehyde in the presence of strong acids has been known for some time. The product was considered by G. M. Robinson to be 2,3,6,7-tetramethoxy-9,10-dihydroanthracene, (1),1

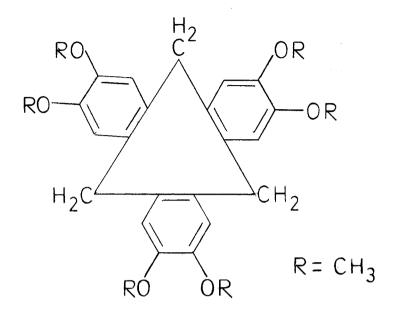
and this structure was widely accepted 2 . More recent studies by A. Oliverio and C. Casinovi 3 proved that the product did not have the dihydroanthracene structure and that in the formula $C_9H_{10}O_2-I_n$ n was greater than 2. Their conclusion was based on the fact that the properties of the condensation product differed from those of 2,3,6,7-tetramethoxy-9,10-dihydroanthracene synthesised by an unambiguous route 4 . The condensation product could

be oxidised to a crystalline ketone, the process being reversed by Clemmensen reduction; only trace amounts of 2,3,6,7-tetramethoxy-anthraquinone were observed.

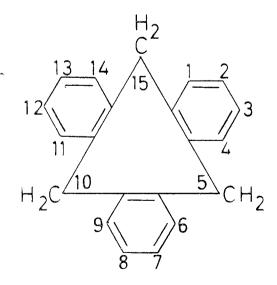
On treating veratrole with less than the required quantity of formaldehyde Oliverio and Casinovi isolated (2), and when this was treated further with formaldehyde the original condensation product was obtained. Robinson,

in her work, reported that $3,3^{\circ},4,4^{\circ}$ -tetramethoxydiphenylmethane condensed with formaldehyde to give (1). Coupling
this with their own observations, the Italian workers concluded
that the condensation product was a hexamer, (3), $^{\circ}$ $_{54}^{\circ}$ $_{60}^{\circ}$ $_{12}^{\circ}$ $_{12}^{\circ}$ $_{13}^{\circ}$ $_{14}^{\circ}$ $_{15}^{\circ}$ $_{15}^{\circ}$

erystallographic data but unfortunately no direct molecular weight determination was made. Recently A. S. Lindsey has shown that the condensation product between veratrole and formaldehyde is, in fact, a cyclic trimer, (4), ${}^{\text{C}}_{27}{}^{\text{H}}_{30}{}^{\text{O}}_{6} \text{ m.p. } 233\text{-4}^{\text{O}}_{\text{,}} \text{ and that an error of a factor of two was incurred by the Italian workers.} His results are based$



CYCLOTRIVERATRYLENE (4)



CYCLOTRIBENZYLENE (5)

on molecular weight determinations on the condensation product and the monoketone derived from it.

The parent system, (5), has been named

"Cyclotribenzylene" and numbered as shown, and the trimeric condensation product, (4), "cyclotriveratrylene"

(10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo
_a,d,g_7cyclononene)⁵.

That the condensation product is indeed a trimer has been verified by H. Erdtman, F. Haglid and R. Ryhage who determined the mass spectrum of cyclotriveratrylene⁶. These workers also identified the by-product, m.p. 316°, obtained in the condensation, and mentioned by Oliverio and Casinovi, as the cyclic tetramer, (6).

As a result of Lindsey's work three general methods are available for the synthesis of substituted cyclotribenzylenes

- (i) the reaction of 1,2-disubstituted benzenes with 3,3',4,4'-tetra-alkoxy-6,6'-bischloromethyl-diphenylmethanes⁵. (see P.37).
- the condensation of suitable 1,2-disubstituted
 benzenes with formaldehyde in the presence of 70%
 sulphuric acid e.g. veratrole¹, 2-ethoxyanisole¹⁰,
 1,2-diethoxy-and dibutoxybenzene¹⁰, methylenedioxybenzene¹¹ (the product has been converted to
 cyclotriveratrylene thus demonstrating the cyclotribenzylene ring structure).

RO OR

$$CH_2 H_2C$$

$$CH_2 H_2C$$

$$CH_2 H_2C$$

$$CH_3$$

$$RO OR$$

$$R = CH_3$$
(6)

(iii)
$$H_3CC OCH_3$$

$$CH_2CH$$

$$AcOH H_2SO_4$$

Condensation of 3,4-disubstituted benzyl alcohols or halides.

Cyclotriveratrylene (87%)

veratrylene (and cyclotribenzylene) have been made 5-9.

This novel ring system of a cyclononatriene ring with three benzene rings separately fused can adopt two possible conformations, (7) and (8), corresponding to the 'crown' and 'flexible' conformations of cyclononatriene respectively.

Examination of Dreiding and Courtauld models lead to the conclusion that steric requirements favour the 'crown' conformation (7). In this case the geometry is essentially pyramidal, the aromatic rings forming three sides of a pyramid with the methylene hydrogens close together at the apex.

"CROWN"
(7)

 $R = CH_3$

"FLEXIBLE"
(8)

The alternative 'flexible' conformation (8), can be made from Dreiding models without deformation of the methylene C—H bonds from the normal tetrahedral valency⁵, but with the Courtauld models some deformation does occur. The possibility of pseudorotation in (8) leads to an abnormally close approach of each methylenic hydrogen atom to the aromatic T cloud (estimated to be 1.4 Å from the plane of the aromatic ring from Dreiding scale models). In cyclonomatriene itself the preferred conformation is the 'crown' 12.

The nuclear magnetic resonance spectrum (N M R) of cyclotriveratrylene, in deuterochloroform solution 5,6 , shows signals at τ 3.21, 5.36, 6.19 and 6.52 in the integrated ratio 2:1:6:1. The singlets at τ 6.19 and 3.21 correspond to the eighteen protons of the methoxyl groups and the six protons of the aromatic nuclei respectively. The τ 6.52 and 5.36 signals occur as doublets (or an AB quartet centred at τ 5.94), J = 14 c.p.s., and correspond to the six protons of the methylene groups. The 'crown' conformation (7), is rigid with the methylene protons non-equivalent. These should give rise to the observed characteristic signal pattern, the hydrogen atoms located at the centre of the 'crown' having the larger chemical shift (see P.67). The methylene protons of

the 'flexible' conformation (8), would give rise to a singlet if pseudorotation were rapid, or a much more complex signal if this were slow. After heating to 200° cyclotriveratrylene showed no evidence of inversion to the 'flexible' conformation nor the presence of other forms 13.

Our interest in this system stemmed from the reported physical properties of the monoketone derived from cyclotriveratrylene⁵ and the apparent non-existence of the 'flexible' conformation.

For convenience a 'fold-out' of the 'crown' and 'flexible' conformations of cyclotriveratrylene has been included at the end of this work and the conformations of the various derivatives will be referred to this.

The abbreviation C T V will be used for cyclotriveratrylene.

Chapter II

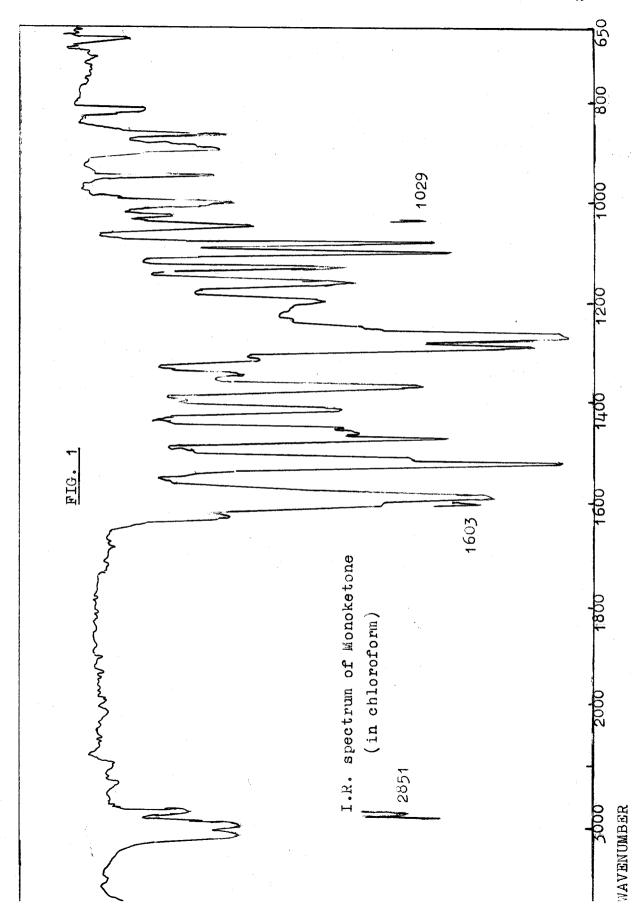
The Oxidation Products of Cyclotriveratrylene

C T V yields a crystalline monoketone, $C_{27}H_{28}O_{7}$, m.p. 214°, together with trace amounts of 2,3,6,7-tetramethoxyanthraquinone on chromic acid oxidation^{3,5}. Lindsey characterised the monoketone (which gives C T V on Clemmensen reduction³) by its I. R. (1630cm⁻¹) and U. V. \angle 238 (4.50), 286 (4.15) and 326 m μ (log ϵ = 4.16)7 spectra, its molecular weight and the formation of a 2,4-dinitrophenylhydrazone. The spectroscopic measurements were reported as consistent with the proposed structure of C T V, but no conformation was assigned to the ketone.

The oxidation of C T V was repeated and, in addition to the monoketone, a higher melting product, m.p. 287 - 90°, was obtained; no 2,3,6,7-tetramethoxyanthraquinone was isolated.

The Monoketone.

The U. V. and I. R. spectra of the monoketone were found to be identical with those of an authentic sample supplied by Dr. Lindsey. Fig. 1 shows the I. R. spectrum of the monoketone in chloroform solution. The band at 1630cm⁻¹



was assigned by Lindsey to the carbonyl stretching frequency but since this absorption is weak compared to the remainder of the spectrum the strong band at 1585cm⁻¹ would be a much more reasonable assignment. This is supported by the disappearance of the band on reduction of the ketone to alcohol. The 1630cm⁻¹ band is probably due to C = C ring vibrations of the conjugated aromatic nuclei since this also disappears on reduction of the monoketone.

Thus with a carbonyl frequency of 1585cm⁻¹ and U. V. absorption at 238, 284 and 326 m/ there is little doubt that the carbonyl group is conjugated with the aromatic rings. Table I illustrates the known variation of carbonyl frequency with conjugation and Table II the similarity of the U. V. chromophore of the monoketone to those of benzophenones.

The wavelength at which a ketonic group absorbs in the I. R. is known to depend on three additive factors 15,16

- (i) conjugation
- (ii) inductive effects and
- (iii) ring strain.

Thus conjugation will move the absorption to longer wavelength (a lower wavenumber) as will electron-donating substituents and increase in ring size.

Table 1

Compound	$y_{c=c}$.cm ⁻¹	Solvent
Acetone	1718	cc1 ₄
Acetophenone	1692	cc1 ₄
Benzophenone	1669	CHC1 ₃
3,31,4,41-tetramethoxy-6,	1654	CHC1 ₃
6'-dimethylbenzophenone'.	Commanded in the command of the comm)

Table II

Compound	\(\lambda\) max (95%	
	ethanol)	log ε
3,31,4.41-tetramethoxy-	278 m/u	4.45
benzophenone ¹⁴	312 "	4.42
3,31,4,4 -tetramethoxy-	235 "	4•37
-6,6%-dimethylbenzophenone	284 "	3•98
	322 "	4.01
monoketone	238 "	4•50
	284	4•15
	326 "	4•16

Electron-withdrawing substituents and decrease in ring size cause a shift to shorter wavelengths.

J. O. Halford 17 has shown that equation (1) holds for aliphatic ketones,

 $v = 1278 + 68k - 2 \cdot 20$ (1) where v is the carbonyl frequency in the I. R., k the carbonyl stretching force constant for an aliphatic ketone and equals 10.2 ± 0.3 (%%0⁵ dynes/cm) and Ø the carbon-carbonyl-carbon angle in degrees. k is almost independent of \emptyset . The substitution in 3,31,4,41-tetramethoxy-6,6'-dimethylbenzophenone and the monoketone is almost identical, the two methyl groups of the benzophenone replacing the methylene groups and the third aromatic ring of the monoketone. That the same chromophore is present in both these compounds is evidenced by the almost identical U. V. spectra. It would seem reasonable, therefore, to assume that the same conjugative and inductive effects operate on the carbonyl groups of both compounds. The difference in the carbonyl stretching frequency of the monoketone and of the tetramethoxydimethylbenzophenone (69cm⁻¹) must then be ascribed to ring strain effects. Applying equation (1) to the hypothetical case of an aliphatic ketone whose carbonyl stretching frequency is

moved to a lower wavenumber by 69cm⁻¹ due to ring strain effects

the C - CO - C angle is calculated as 146°. A plot of carbonyl frequency against C - CO - C angle for cyclo-butanone (1782cm⁻¹, 92°), cyclopentanone (1751cm⁻¹, 108°) cyclohexanone (1717cm⁻¹, 117°) and cycloheptanone (1705cm⁻¹, 128°)¹⁶ extrapolated to a frequency of 1649cm⁻¹ predicts a C - CO - C angle between 140° and 150°, in good agreement with the above. Thus in the monoketone we can expect considerable widening of the C - CO - C angle.

Examination of Deiding models of the monoketone lead to several important conclusions. Firstly, if the conformation were 'crown' then the carbonyl group and the aromatic rings would be held rigidly orthogonal \(\sum_{\cong}() \), see fold-out in direct contradiction to the observed spectra. Secondly, conjugation can occur in the 'flexible' conformation, (10). With a C - CO - C angle of 135° the Dreiding model still shows that conjugation cannot occur in the 'crown' conformation. With this angle of 135° inversion of the 'flexible' conformation is readily possible and the two adjacent aromatic nuclei are held at an angle of about 34° (estimated from Dreiding scale models) to the plane of the carbonyl group,

in reasonable agreement with 4,4'-dimethoxybenzophenone where this angle is 38°16. With a C - CO - C angle of 120° Dreiding models show that the angle of the aromatic rings to the plane of the carbonyl group is about 43°. Conformation (11) has, therefore, been assigned to the monoketone. It is analogous to the twist conformation of cyclohexanone and has C₂ symmetry.

The N M R spectrum of the monoketone, in deutero-

RO
$$RO$$
 OR OR $R = CH_3$ H H

chloroform, shows three two-proton singlets at 2.57, 3.20 and 3.46 τ , a twelve-proton singlet at 6.10 τ and a tenproton singlet at 6.20 τ , the characteristic quartet of the 'crown' conformation being absent. In pyridine solution the methylene protons show as a sharp singlet at 5.95 τ

as would be expected for a rapidly inverting molecule.

The Dreiding model of the monoketone shows that the molecule can be inverted from the 'flexible' to the 'crown' conformer and vice versa, although the processes are difficult. N M R spectra were run at various temperatures but no evidence for the 'crown' conformer was observed. is believed that in derivatives of C T V with the C_5 carbon atom tetrahedral the preferred conformation is 'crown'. Several attempts were made to prepare ketal and thicketal derivatives since these could be readily hydrolysed to the ketone in the N M R spectrometer probe. Should the hydrolysis yield the 'crown' ketone as a transient species its presence might well be observed the characteristic quartet for the ${\bf C}_{10}$ and ${\bf C}_{15}$ methylene protons. no ketonic derivatives could be made.

Attempts to demonstrate the change in conformation on oxidation of one of the methylene groups of two other cyclotribenzylenes were made. The hexa-acetate (13), obtained by demethylation of C T V to the hexa-phenol (12), followed by acetylation, was resistant to oxidation in anhydrous acetic acid (both (12) and (13) have the 'crown' conformation).

The condensation product of methylenedioxy-benzene with formaldehyde has been shown to have the same ring system

as C T V by conversion to it. Oxidation of this compound could not be effected due to its almost total insolubility

(12)
$$R = H$$

(13)
$$R = CH_3CO$$

in most organic solvents. That this compound is a trimer was confirmed by its mass spectrum (M W = $402 \cdot 107 \pm 0 \cdot 004$; $^{\rm C}_{24}{}^{\rm H}_{18}{}^{\rm O}_{\rm 6}$ requires $402 \cdot 1103$) which paralleled exactly that reported by Erdtman $^{\rm 6}$ for C T V. Due to its insolubility no N M R spectrum could be obtained but it would appear only reasonable to assign the 'crown' conformation to it.

The By-product

In addition to the monoketone, chromic acid oxidation of C T V yielded 5% of a higher melting product.

N. K. Anand 13 first observed this product but did not characterise it. A complete separation of the higher melting product from the monoketone could not be effected by chromatographic techniques. However, when the mixture was treated with excess of alcoholic alkali the higher melting compound dissolved and could be recovered on acidification, thus effecting complete separation from the monoketone.

The I. R. spectrum of the by-product (fig. 2) showed strong carbonyl bands at 1750 and 1598cm⁻¹ with a weaker band at $1658cm^{-1}$. The compound absorbed at 226 (4.62), 258 (4.64), 308(4.26) and 353 m μ (log ϵ = 3.96) in the U. V. indicative of conjugation stronger than in the monoketone.

Because of 'salt' formation with alkali and carbonyl bands at 1750 and 1598cm⁻¹ the lactone structures (14) and (15), arising by Baeyer-Villiger oxidation of C T V, were thought possible. Each of these would be expected to ring open to a substituted benzoate with alkali. The N M R spectrum, in deuterochloroform, (Fig. 3, P.58) could be

explained in terms of either (14) or (15), the two methylene protons being 'hidden' under the methoxyl protons. However, recovery of the by-product by acidification of the alkaline solution threw doubt on the lactone structures since lactonisation across the 1 and 9 positions of a hydroxy-carboxylic acid is unexpected.

The analytical data could be interpreted for two compounds as shown below.

		C%	H%	OMe%
Found for the	(i)	65•91	5.11	36-73
by-product	(ii)	65•55	4.83	38-27
	(iii)	65•92	4.79	37·26
Calculated for C2	7 ^H 26 ^O 9	65 • 58	5 • 30	37.66
Calculated for C	27 ^H 26 ^O 8	67.75	5•48	38 • 92
A diketone				
Calculated for C2	7 ^H 24 ^O 9	65•83	4.92	37•82
_A triketone				

The diketone ${}^{\rm C}27^{\rm H}26^{\rm O}8$ was eliminated but the differences between the lactones (14) and (15) and the possible triketone were thought too small to make any definite assignment of structure and hence a mass spectrum of the by-product was

determined¹⁸. The mass spectrum showed, unequivocally, that the molecular formula was $^{\rm C}_{27}^{\rm H}_{24}^{\rm O}_9$, corresponding to a loss of six hydrogen atoms and a gain of three oxygen atoms from C T V.

A re-examination of the I. R. spectrum (fig. 2) indicated that the 1658cm⁻¹ band could well be due to a third carbonyl band and the triketone structure (16) has been assigned to the by-product. The conformation (17) is essentially that of the monoketone (11), but skew

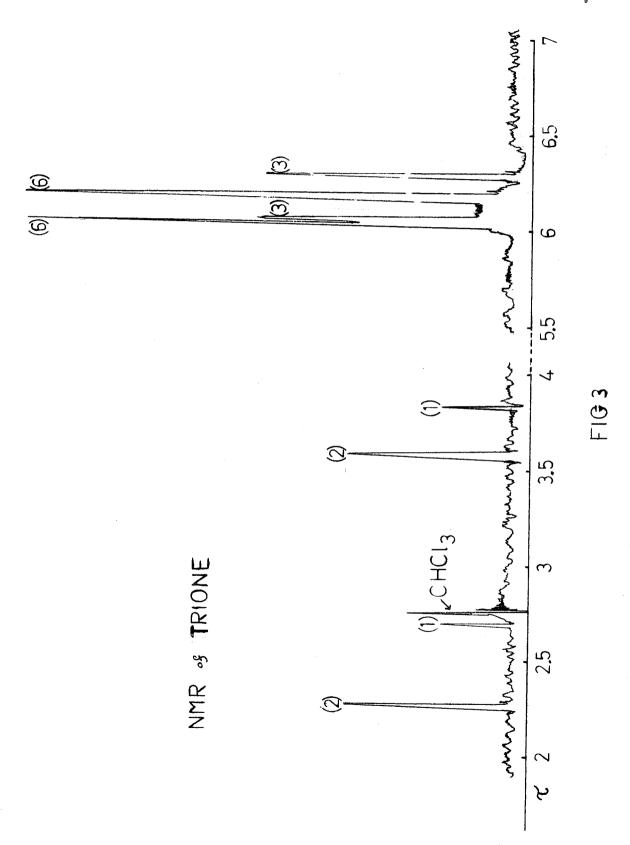
Two of the three carbonyl groups are conjugated with the aromatic rings (I. R. frequencies 1598 and $1658 \,\mathrm{cm}^{-1}$). On lines of argument parallel to those used for the monoketone the $1598 \,\mathrm{cm}^{-1}$ carbonyl, $C = O_a$, will have a widened carbon-carbonyl-carbon angle similar to that in the monoketone. A normal C = CO = C angle is to be expected for the $1658 \,\mathrm{cm}^{-1}$ carbonyl, $C = O_b$. Carbonyl $C = O_c$ is nonconjugated and its high frequency, $1750 \,\mathrm{cm}^{-1}$, is explicable in terms of the adjacent rings A and C being conjugated and acting as electron-withdrawing substituents, thus causing a shift to shorter wavelength. Slight compression of the $C = CO_c = C$ angle is possible.

Examination of Dreiding models of the trione with one C - CO - C angle of 135° lead to the conclusion that the

RO OR
$$RO$$
 OR $R = CH_3$ (16)

- symmetrical system (cf. (8), fold-out) is not as extensively conjugated as the 'flexible' skew conformation (17). Conformation (17) is characterised by the following data estimated from Dreiding scale models.
- (i) Carbonyl C = O_a is conjugated to rings A and B with a widened C CO C angle (cf. monoketone). The angle that the plane of ring A makes with the plane of the carbonyl group is less than that for ring B.
- (ii) Carbonyl C = C, is conjugated to ring C but only slightly to ring B. The stretching frequency (1658cm⁻¹) is very close to that for 3,3',4,4'-tetramethoxy-6,6'-dimethylbenzophenone (1654cm⁻¹)⁵ and there is either more conjugation than the models indicate or else the C CO_b- C angle is widened.
- (iii) Carbonyl C = 0_c is not conjugated to either ring A or ring C.
- (iv) The hydrogen atoms H_a and H_b are equivalent as are H_a , and H_b .
- (v) H_c is not equivalent to H_c* since the former is ortho to a conjugated carbonyl whilst the latter is ortho to a non-conjugated carbonyl group.

The N M R spectrum of the triketone, in deuterochloroform solution, (fig. 3), is in agreement with the



proposed structure and conformation. The resonances have been assigned as follows, the signals due to the aromatic protons being ascribed by a consideration of the shielding and deshielding effects of the carbonyl and methoxyl groups and by analogy with the monoketone.

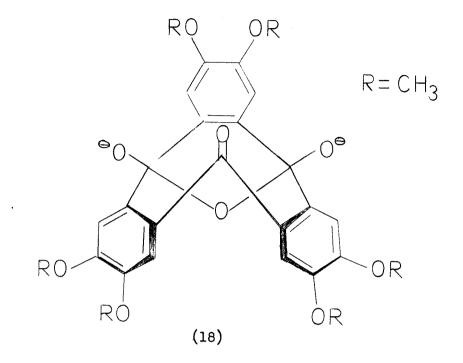
て	2 · 29	H _a and H _b
	2.70	H _C
	3.58	Ha' and Hb'
	3·83	H _c •
	6.04	Methoxyl protons Ra and Rb
	6.06	Methoxyl protons R _c •
	6.18	Methoxyl protons R _a and R _b
	6 • 28	Methoxyl protons R _c

On the basis of conformation (17) the U. V. spectrum of the trione is difficult to interpret since it indicates conjugation through three aromatic nuclei i.e. through ring A, C = O_a , ring B, C = O_b and ring C. The angle of the plane of ring B to the plane of the carbonyl C = O_b is large,~55° (estimated from Dreiding models) but would be reduced if the C = CO_b = C angle is widened, and whether this is sufficient for the chromophore still to be effective is open to question. It should, however, be noted that the angles of the plane of ring A and of ring C to the non-

conjugated carbonyl $C = 0_c$ are much larger and, $\sim 80^\circ$.

No diketone was observed and it would appear that once two of the methylene groups in C T V have been oxidised the third is oxidised readily. When the monoketone was treated with excess sodium dichromate in refluxing acetic acid a 20% yield of trione was obtained. No D N P derivative of the triketone could be obtained. Attempts to establish the structure of the by-product by chemical methods were unsuccessful. reduction, under conditions similar to those used for the monoketone³, gave a black deposit whose I. R. spectrum indicated the absence of C T V. Hydrogenolysis experiments, using platinum oxide and 10% palladium on charcoal as catalysts, did not produce C T V, the process trione $triol/s \longrightarrow C T V being expected since the triol/s$ produced would be benzhydrylic.

The formation of a water soluble 'salt' from the triketone is surprising and its nature is still unknown. That excess alkali is necessary to its formation was demonstrated by attempted syntheses with one, two, three and five moles of potassium hydroxide in methanol (5% solution). Only in the last case did 'salt' formation occur. The U. V. spectrum of the 'salt' in water, showed absorption at 256 (4.7), 282 (4.4), 315 (4.3) and 376 mm



(log $\epsilon \sim 4$ 2), evidence of conjugation stronger than in the trione. Because of this spectrum structures similar to (18), \angle cf. (19) 19 7 must be excluded.

Since the salt could not be synthesised in the absence of excess base no analytical data are available.

I. R. spectra could not be obtained and N M R spectra were non-reproducible although the samples still showed the same U. V. spectrum. Attempts to methylate the 'salt'

with methyl iodide or dimethyl sulphate failed, the trione being obtained. This was probably due to the presence of traces of acid sufficient to effect neutralisation.

Chapter III

The \propto -, β -, and χ -Cyclotriveratrylenols

There appears little doubt that cyclotriveratrylene and the monoketone derived from it exist entirely in the 'crown' and 'flexible' conformations respectively. A consideration of models of cyclotriveratrylenol, the secondary alcohol expected from reduction of the monoketone, leads to the conclusion that theoretically three conformers (20), (21) and (22) (see fold-out) could exist.

(20), ~-Cyclotriveratrylenol, has the 'flexible' conformation being derived directly from the monoketone.

(21), 3-Cyclotriveratrylenol, is the 'crown' isomer with the hydroxyl group pointing away from the apex of the pyramidal structure and corresponding to an equatorial substituent. (22), 8-Cyclotriveratrylenol, is also 'crown' but in this case the hydroxyl group is 'in' corresponding to an axial substituent and the models show this to be a very crowded arrangement with the oxygen to hydrogen 'in' distance about 1.2 A

Reduction of the monoketone with lithium aluminium hydride (LiAlH₄), or sodium borohydride, gave different products under different conditions ²⁰.

(i) Reaction followed by a neutral or alkaline work-up.

Treatment of the monoketone with excess of LiAlH4, or borohydride, in tetrahydrofuran, followed by the addition of sodium sulphate crystals or 5% sodium hydroxide solution to destroy the excess reagent, effected complete reduction of the monoketone. Thin-layer chromatography (T L C) showed two products A and B with $R_{\hat{\mathbf{f}}}$ values of 0.37 and 0.12 respectively, eluted with benzene-acetone mixture (4:1). The relative proportions of A and B varied and were shown to depend on the method of evaporation of the solution. With no heating and evaporation in vacuo only trace amounts of B were present but with evaporation in vacuo from a warmed flask B constituted about one half of the mixture, the relative proportions being estimated by comparison of the T L C plates. Column chromatography of the reaction products resulted in total conversion to B and even on standing the product mixture at room temperature for twenty-four hours the conversion of A to B was almost complete.

An effective separation of the products was obtained by utilising their solubility differences in tetrahydrofuran. Compound B was readily soluble whereas A was only slightly soluble and thus filtration of the solution gave pure A. A could be stored at -70° for several days without conversion to B.

The stable product - Compound B.

B could be obtained pure to T L C by crystallisation of the product mixture from benzene containing trace amounts A colourless crystalline solid, m.p. 236 - 70 of chloroform, The I. R. spectrum in nujol showed an OH band resulted at 3500cm⁻¹ and the absence of the carbonyl band at 1585cm⁻¹. The U. V. spectrum was almost identical to that of C T V, absorption occurring at 234 (4.54) and 291 m μ (log ϵ = 4.03) C T V: 234 (4.52) and $294 \text{ my} (\log \epsilon = 4.01) 7.$ should be noted here that, in the U. V., C T V, and hence product B, exhibits a bathochromic shift of about 6 mm from the monomeric unit, 4,5-dimethylveratrole, The extinction coefficients of C T V are four times greater than the monomeric unit even though only three units are joined together. behaviour is consistent with the structure of C T v^5 and parallels that of the paracyclophanes where extinction coefficients are increased due to distortion of the aromatic rings from a planar configuration and to T -electron interaction between the aromatic rings 21.

Microanalysis was consistent with a mono-alcohol of C T V, $C_{27}H_{30}O_7$, and the N M R spectrum, in deuterochloroform, showed the characteristic quartet for the C_{10} and C_{15} methylene protons of the 'crown' conformation, at almost exactly the

same chemical shift as in C T V (see Table III). The geminal coupling constant, -14.0 c.p.s. (sign assumed), is the same for this alcohol and for C T V. Because of

Table III

N M R Spectra of the Cyclotriveratrylenols

сту	& -alcohol (21)	∝ =alcohol (20) ^a
	3.07 (1) s	2•83 (2) s
3•21 (6) _s	3°21) (6) 3°24)	3•32 (4) s
	3•24	3∘92 (1) s
	5·26 (1)s OH ^c	
5•36 (3)d ^b	5°35 (2)d ^b	5•96 (2)d ^d
6•19 (18) s	6•15) (18) 6•18)	6.13 (18) s
6°52 (3)d ^b	6°52(2)d ^b	6*24 (2)d ^d

All spectra were run in deuterochloroform solution. The figures show respectively, position in \mathcal{C} (T M S = 10), number of protons and multiplicity of absorptions (s = singlet, d = doublet etc.). Anydroxyl resonance not seen. AB quartet J = 14.0 c.p.s. OH = hydroxyl resonance. AB quartet J = 15.5 c.p.s.; Peaks 1, 2 and 4 visible.

its stability and the similarity of the N M R spectrum to that of C T V the 'crown' conformation with hydroxyl group 'out', β -cyclotriveratrylenol (21), has been assigned to compound B. The geminal coupling constant for the β -alcohol and C T V is in fair agreement with the dihedral angle between the methylene groups and each adjacent p orbital of the benzene rings (110 \pm 5°, estimated from Dreiding scale models) after allowance for some opening of the C α - CH₂ - C angle α - C angle

The doublets at 5.35 and 5.36 Υ in the e-alcohol and C T V respectively, are probably due to the methylene protons over the centre of the 'crown'. This stems from a consideration of the one-proton singlet at $3.07\,\Upsilon$ in the N M R spectrum of the e-alcohol. This signal was assigned to the 'in' proton of the tertiary group viz. RCHOHR. Benzhydrol and diphenylmethane 24 show a chemical shift difference, \triangle , of 1.88 Υ for the corresponding proton.

viz. Ph CHOHPh
$$4 \cdot 20 \, \Upsilon$$
 $\triangle = 1.88 \, \Upsilon$ Ph CH₂ Ph $6 \cdot 08 \, \Upsilon$

Applying this to the α -alcohol and C T V the corresponding proton in the latter should occur at about 4.9% in fair agreement with the observed doublet at 5.36% (see Table III).

In dimethyl sulphoxide (D M S 0) two one-proton doublets at 3.25 and 4.35 τ (J = 2.5 c.p.s.) were observed. Addition of deuterium oxide caused the higher field signal to vanish and the 3.25τ signal to coalesce to a singlet as would be expected for a secondary alcohol 25,26.

Treatment of & -cyclotriveratrylenol with acetic anhydride in pyridine gave rise to an acetate (21a), m.p. 215 - 7°, with the expected analytical and spectral data. The reaction was slow and incomplete and separation of the derivative from the starting material proved difficult, fractional crystallisation being the most efficient method. Oliverio and Casinovi³ claimed an acetate, m.p. 220°, by reductive acetylation of the ketone. Since &-cyclotriveratry-lenol is the stable alcohol the acetate derived from it and that obtained by the Italian workers are, in all probability the same compound, &-cyclotriveratrylenyl acetate (21a).

The Unstable product - Compound A.

Crystallisation of compound A, obtained by filtration of the tetrahydrofuran solution, resulted in 100% conversion to B, established as @-cyclotriveratrylenol (21), and thus it would appear that A is a conformational isomer since there is no asymmetric centre in the molecule.

When A was slowly heated the melting point observed was that of (21), $236 - 7^{\circ}$. However, when a sample was placed in a melting point apparatus pre-heated to 215° immediate melting, followed by re-solidification and final melting at $236 - 7^{\circ}$, was observed. With the apparatus at 205° opacity and melting at $236 - 7^{\circ}$ resulted and thus the melting point of A must lie between 205 and 215° .

The I. R. spectrum of A, in nujol, showed an OH band at 3500cm^{-1} but, like the β -alcohol, the band was very weak in solution spectra. The N M R spectrum. in deuterochloroform, / Table III P.66 Compound (20) 7 showed a two-proton singlet at 2.83 %, a four-proton singlet at 3.32τ , a one-proton singlet at 3.92τ and a nineteen-proton singlet at 6.13 together with three resonances at 5.78, 6.04 and 6.41 r integrated to 2.5 protons. The latter three peaks are explicable in terms of an AB quartet (J = 15.5 c.p.s.) with doublets at 5.96 and 6.13% corresponding to the four methylene protons, the third peak of the quartet being hidden under the methoxyl signal. This was verified by the spectrum in pyridine where signals occurred at 5.48, 5.74, 5.90, 6.21 and 6.28 %. two resonances corresponded to the eighteen methoxyl protons and the former three to the first, second and third peaks of

an AB quartet (J = 15.5 c.p.s.) integrated for 3.5 protons The fourth peak was, in this case, hidden under the methoxyl signal.

In D M S O two one-proton doublets (J = 4.0 c.p.s.) at 4.17 and 4.37 were observed. Addition of deuterium oxide caused the higher field signal to vanish and the 4.17 doublet to coalesce to a singlet, behaviour paralleling that of the e-alcohol.

The U. V. spectrum of A paralleled that of C T V and the ℓ -alcohol but with a hypsochromic shift of about 4 m μ , absorption occurring at 230 (4.48) and 288 m μ (log ϵ = 4.04). The absorption at 230 m μ was a shoulder on the solvent absorption whereas in C T V and (21) the 234 m μ absorption was a distinct peak.

Compound A must be either α - or δ -cyclotriveratrylenol In the δ -alcohol, (22), the methylenic 'in' hydrogens are in very close proximity ($\sim 1\cdot 2$ Å) to the hydroxyl oxygen atom and one would expect these protons to be markedly moved downfield in the N M R spectrum, the quartet becoming AX i.e. the chemical shift difference $\Delta \gg J$. The geminal coupling constant, J, should not differ greatly from C T V or the β -alcohol, since the dihedral angle for the methylene protons is the same viz. $110 \pm 5^{\circ}$. The U. V. chromophore in the δ -alcohol would be the same as in C T V and the δ -alcohol,

the relative positions of the aromatic nuclei being unaffected. These predictions from examination of models oppose the observed data.

Examination of Dreiding models of
 -cyclotriveratrylenol (20) lead to predictions in agreement with the observed data. The methylene hydrogen atoms are non-equivalent since, on pseudorotation, one hydrogen atom from each methylene group approaches the hydroxyl group more closely than the other. If the pseudorotation were rapid a quartet would be observed, if slow a more complex signal pattern would arise, all four methylene protons being non-equivalent. The dihedral angles between the methylene groups and the p orbital of the adjacent aromatic ring are not all equal as in the case of C T V and the g - and δ -alcohols. In (20) protons H_a and H_b have the same dihedral angle of 110 + 50 (estimated from Dreiding scale models). Proton H_c has a dihedral angle of about 5° and H_d one of 105 \pm 5°. From the plot of geminal coupling constant, J, versus the angle between the ${\tt CH}_2$ and the axis of the p orbital (dihedral angle)²⁷, the following data for the coupling constant are obtained.

Dihedral Angle	J in c.p.s.
5°	-15∘5 to -18∘0
105°	-11.0 to -13.8
110°	-10.8 to -13.5

An averaging effect will operate and, allowing for some opening of the C - CH₂ - C angle (a negative contribution to the coupling constant), the observed value of 15.5 c.p.s. is in good agreement.

The U. V. spectrum of the \propto -alcohol could be expected to show a smaller bathochromic shift from 4,5-dimethylveratrole than C T V since the relative positions of the aromatic chromophores are different, π -electron interaction being possible between only two of the rings as compared to three in C T V.

The spectral evidence is, then, in agreement with compound A being \propto -cyclotriveratrylenol (20), and this is favoured since it corresponds to a more direct reduction of the monoketone (11) to (20a) to (20), and is in agreement with the ease of conversion to the α -alcohol.

(ii) Reduction followed by an acidic work-up

Treatment of the monoketone with excess LiAlH₄ or borohydride, in benzene, followed by the addition of dilute acid to destroy excess reagent and chloroform to effect solution, gave rise to four products B, C, D and E with R_f values 0.21, 0.25, 0.48 and 0.63 respectively, eluted with chloroform-ethyl acetate (19:1). The products could not be separated by column chromatography.

$$H_3CO$$
 H_3CO
 H_3C

$$H_3CO$$
 H_3CO
 H_3CO
 H_4
 OCH_3
 OCH_3
 OCH_3

An alternative diagramatic representation of the flexible conformation. H_a and H_d approach the -OH more closely than H_b and H_c on pseudorotation.

Preparative scale T L C effected a separation of B, D and E ____eluted with benzene-acetone (4:1)__7. C was present only in trace amounts and was never isolated.

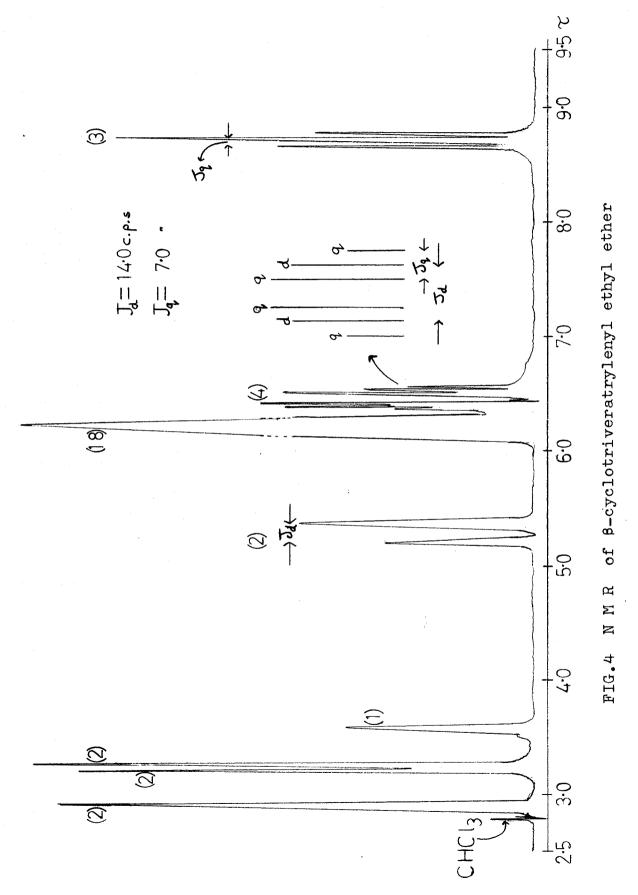
Compound B.

This was shown to be identical to (3 -cyclotriveratrylenol by mixed spots on T L C plates, mixture melting point and comparison of spectral data.

Compound D.

Recrystallisation of D, extracted from the T L C silica with A. R. acetone, gave a colourless crystalline solid, m.p. $212 - 4^{\circ}$, pure to T L C. The I. R. spectrum showed the absence of a hydroxyl group and the ketonic band at 1585cm^{-1} was not present, the remainder of the spectrum being similar to the alcohols. The U. V. spectrum showed absorption at $235 \ (4.52)$ and $292 \text{ m/m} \ (\log \epsilon = 3.97)$ almost identical to C T V and the ϵ -alcohol, the 235 absorption being a distinct peak typical of the 'crown' conformation. The compound did not analyse for $C_{27}H_{30}O_{7}$ and the possibility of its being the δ -alcohol seemed slight.

The N M R spectrum, in deuterochloroform, is shown in fig. 4 (measured on a Varian Associates HR 100 instrument). It is consistent with a 'crown' conformation, the C₁₀ and



c₁₅ methylene protons showing as an AB quartet with doublets at 5.29 and 6.47 τ (J = 14.0 c.p.s.). The signals occur at almost the same chemical shift as in C T V and the σ -alcohol (c.f. Table III, P.66). The higher field doublet is superimposed over a quartet centred at 6.46 τ (J = 7.0 c.p.s.) and corresponding to two protons coupled to the three-proton triplet at 8.71 τ . Because of the chemical shifts the quartet and triplet were suspected of being due to an 0-ethyl group.

A re-examination of the analytical data showed agreement with $^{\text{C}}_{29}^{\text{H}}_{34}^{\text{O}}_{7}$ a gain of two carbon and six hydrogen atoms from the monoketone. Due to reasons analogous to those used for the $^{\text{C}}_{\text{C}}$ -alcohol, compound D has been assigned as $^{\text{C}}_{\text{C}}$ -cyclotriveratrylenyl ethyl ether (23).

The occurrence of this product can be explained in terms of ionisation of cyclotriveratrylenol to the carbonium ion, in dilute acid, and reaction of this with the ethanol added to chloroform as stabiliser __but see P.79_7.

Compound E.

Although this compound had the largest R_f value of the four products and formed a distinct band on the preparative scale T L C plate extraction of it from the T L C silica always gave rise to a mixture of D and E. The relative proportions

of D and E in a series of reductions were shown to differ and this was demonstrated by evaporation of the chloroform solution in three ways:

- 1. Concentrated to dryness in vacuo at room temperature.
- Concentrated to dryness in vacuo from a warmed flask.
- 3. Concentrated to 5 mls. by distillation at atmospheric pressure.and to dryness by 2.

T L C showed that utilising 1 the proportion of E was large and D small, using 2 the proportions were approximately equal and with 3 the proportion of D was much larger than E.

The I. R. spectrum of the product mixture obtained by method 1 above showed no hydroxyl group or monoketone and a qualitative U. V. spectrum showed absorption at 234 and 290 mm.

The behaviour of E paralleled that of the α -alcohol, being readily inverted to the α -ether and thus α -cyclotriveratrylenyl ethyl ether, (24), is proposed for the structure and conformation of this compound.

(iii) Reduction followed by an acidic work-up in the absence of ethanol.

Treatment of the monoketone, in tetrahydrofuran, with excess LiAlH₄ or borohydride, followed by the addition of dilute mineral acid to destroy excess reagent, gave rise

to two products, T L C showed these to be the α - and ε -alcohols, the proportions depending on the mode of evaporation.

The Y-alcohol

From the above results evidence for the &-alcohol (22) was slight. It is conceivable that product C, obtained only in trace amounts and never isolated could be this compound.

It was hoped that Grignard reduction of the monoketone could conceivably afford (22). Treatment of the monoketone with t-butyl magnesium chloride, under nitrogen, effected reduction and gave a bright green solid. TLC showed the presence of eight products none of which could be separated. This result is surprising since one would expect alcohol to be formed and 2-methylprop-1-ene to be evolved if reduction did occur. A gas was evolved but corresponded to less than the theoretical volume. Isopropyl magnesium bromide, also known to effect reduction, gave similar products (but see Chapter IV).

It would appear, then, that reduction of the monoketone gives rise to a -cyclotriveratrylenol (20) as the kinetic product and because of its instability this inverts in conformation to the stable a-cyclotriveratrylenol, the thermodynamic product. That &-cyclotriveratrylenol was

not obtained is not too surprising in view of the crowded arrangement of this 'crown' conformer.

The mode of formation of the ethers.

Treatment of the α -alcohol with ethanol, in chloroform containing traces of dilute mineral acid, gave, after one hour, three products shown by T L C to be the α - and β -ethers and the β -alcohol. The β -ether predominated. Similar treatment of the β -alcohol gave rise to a small quantity of β -ether but only after fourteen hours.

The kinetics of ionisation of the α - and β-cyclotriveratrylenols

The relationship between the solvolysis rate of an arenesulphonate and the stretching frequency of the corresponding carbonyl compound has been shown by C.S. Foote, to be linear for a large variety of dissimilar compounds 28,29. Since the carbonyl frequency of the monoketone is exceptionally low a correlation between it and the solvolysis rate of the -tosylate seemed desirable. This would not only provide a check on the carbonyl frequency but, if the correlation were correct, would usefully extend Foote's plot. However, the

 α -alcohol is unstable and one would predict even less stability in the α -tosylate if it could be synthesised. From the plot of the acetolysis rate of the tosylate versus carbonyl frequency extrapolation indicated that the α -tosylate would solvolyse with a rate constant of about $10^{10}~{\rm sec}^{-1}$ at 25° . Coupling this with the known instability of the α -alcohol no attempt to synthesise the tosylate was made.

One would expect the difference in solvolysis rates of the α - and β -tosylates to be paralleled in the ionisation rates of the α - and β -alcohols. Thus with both ionisation rates and the solvolysis rate of the β -tosylate (from the stable β -alcohol) the rate for the unstable α -tosylate could be computed.

From the qualitative experiments on the synthesis of the α - and β -ethers it appeared that ionisation of the α -alcohol was much more rapid than that of the β -alcohol. This is predicted from Foote's correlation and is not too surprising since the 'flexible' conformation is much closer to planarity than the 'crown' conformation, thus affording the carbonium ion much more readily.

The acid catalysed ionisation rates of α - and β -cyclo-triveratrylenol have been determined. The technique is

fully described in the Experimental Section. Product analysis was by T L C separation of the alcohol from the ether and a determination of the relative proportions of these (and hence the percentage of residual alcohol) from the U. V. spectra, using the extinction coefficients previously determined for the absorption at 291 mm.

T L C plates were eluted with benzene-methanol mixture (9:1) and the compounds were extracted from T L C silica with 95% B.P. ethanol in graduated flasks, the volume of silica being neglected. Where unstable α -conformers were produced the solution was left to allow inversion to the 'crown' conformation.

Solubility problems precluded the use of 'standard' solvents for the kinetic runs, the only suitable solvent being bromoform-ethanol mixtures (4:1) and (1:1). The concept of Z-values as a measure of solvent polarity has been introduced by E. M. Kosower³⁰. The position of the charge-transfer (c - t) band of 1-ethyl-4-carbomethoxy-pyridinium iodide was found to be very sensitive to the nature of the solvent employed. Determination of the transition energy of the c - t absorption-band afforded a constant for the particular solvent. A good correlation between these constants and the Y-values³¹⁻³³ of the same solvents was obtained. Thus the charge-transfer energy for the pyridinium

iodide provides an empirical measure of the solvent polarity and is known as a Z-value.

1-Ethyl-4-carbomethoxypridinium iodide was synthesised and the Z-values of bromoform and bromoform-ethanol mixture (4:1) determined from the c - t absorption-band position utilising equation (2)

$$Z = 2.859 \times 10^{-5} \bar{\nu}$$
 _____(2)

where $\bar{\nu}$ is the c - t absorption position in wavenumbers. The Z-values obtained were: Bromoform 77.5 (uncorrected for 'salt' concentration); Bromoform-ethanol (4:1) 78.1 (independent of 'salt' concentration). Ethanol has a Z-value of 79.6 and it was fortuitous to find that the two solvents have almost the same polarity. Rates determined in any bromoform-ethanol mixture will, therefore, correspond very closely to those measured in ethanol, a 'standard' solvent.

The conditions employed in the determination of the rate constants are listed below:

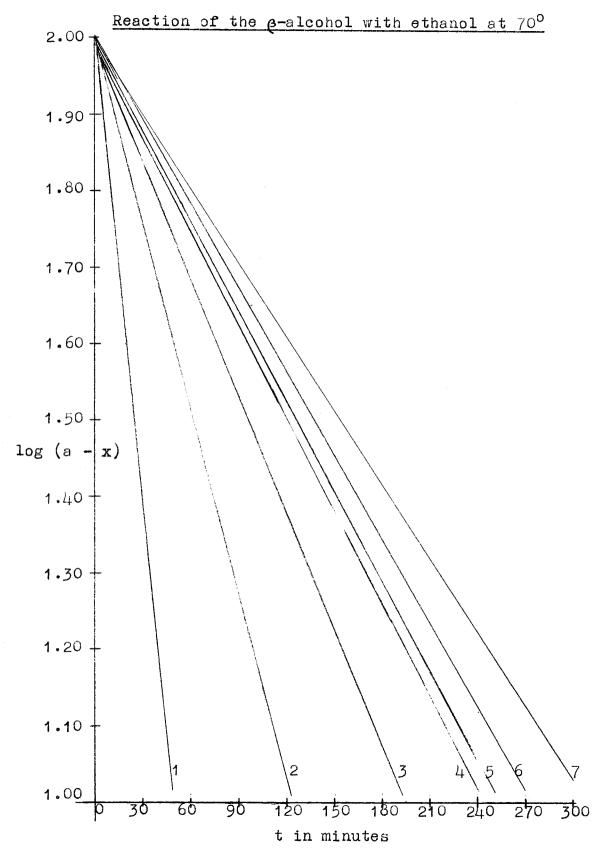
- (i) A solution of alcohol, 60.0 mg. in 5 mls. of solvent (i.e.0.0258M) was used.
- (ii) The bromoform-ethanol mixture (4:1) was 3.44 and the (1:1) 8.60 M with respect to ethanol.

- (iii) A standard solution of hydrochloric acid in the solvent was made up by absorption of dry hydrogen chloride, dilution and standardisation.
- (iv) The following correction for the acidity of the solvent, determined by potentiometric titration, was made.

Bromoform-ethanol (4:1) $9.33 \times 10^{-4} \text{ N}$. Bromoform-ethanol (1:1) $5.39 \times 10^{-4} \text{ N}$.

- (v) Two 'runs' at each acid concentration were followed
- (vi) The rate constant, k and the standard deviation, σ, are the result of a 'least-squares' plot of log (a x) versus t / derived from equation (2) / as processed by a Ferranti Pegasus Computer. σ is expressed as a percentage of the average log (a x) value, the error being assumed to arise in determining the relative proportions of alcohol and ether. The rate constant for a first order process is given by equation (3),

where a is the initial cyclotriveratrylenol concentration and x the ether concentration at time t. (a - x) \propto % alcohol remaining.



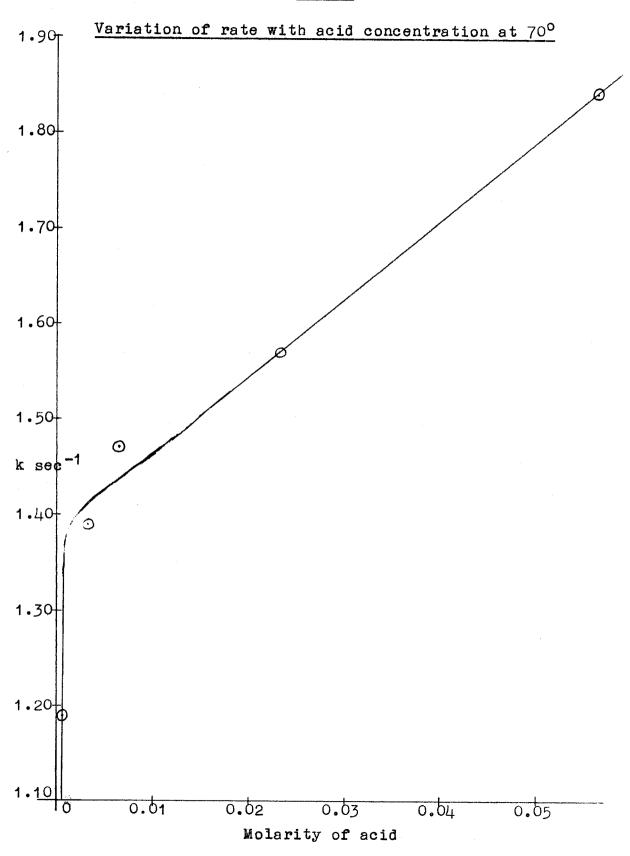
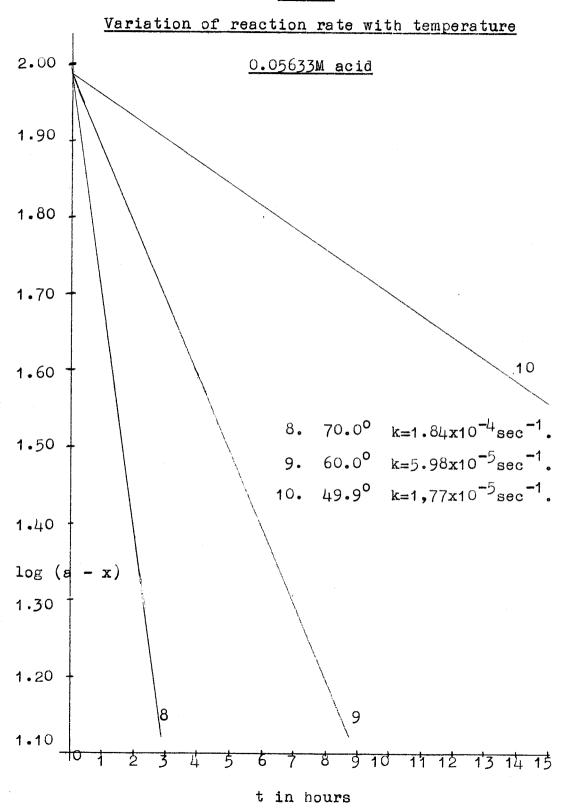
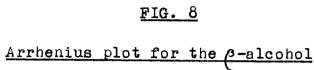
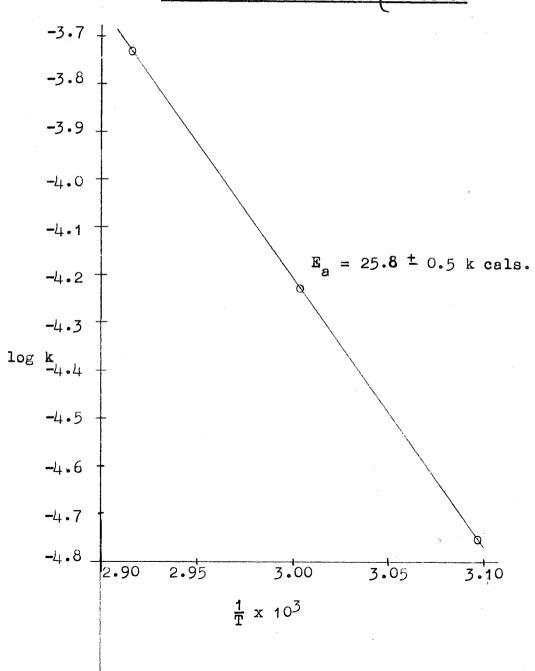


FIG. 7







The results for &-cyclotriveratrylenol are shown graphically in figs. 5, 6, 7 and 8 and the rate constants in Table IV. In general the plots were linear to 85% reaction or beyond, indicative of first order kinetics.

The rate does show an acid dependence (fig. 6) but with an acid concentration greater than 0.06 M deviation from linearity occurs and is probably due to increased polarity of the solvent. This dependence on acid concentration is to be expected if the process:

 $R - OH \longrightarrow R - OH_2 \longrightarrow R^+ + H_2O$ is occurring.

Rates of ionisation of β-cyclotriveratryenol in bromoformethanol (4:1) at 70°

	Acid Molarity	K sec ⁻¹	0%
1.	0•2779	6.67 x 10 ⁻⁴	2•22
2.	0•1105	3°00 "	1.03
3.	0•05630	1.84 "	0.81
4.	0•02309	1•57 **	0•38
5•	0.00647	1•47 "	0•30
6.	0.00315	1.29 #	1.97
7.	³⁶ 0∙000538	1•19 "	1.02

^{*}In bromoform ethanol (1:1).

The activation energy for the process, E_a , was determined by measuring the rate at three temperatures, (fig. 7). Using equation (4) where A is the Arrhenius factor and T the absolute temperature, a plot of log k against $^1/_T$ gives E_a as 25.8 ± 0.5 k.cals (fig. 8) $k = Ae^{-E_a/RT}$

The T L C plates from the kinetic runs with short halflives showed the presence of both \propto - and \circlearrowleft -ethers. The process can be rationalised as:

 β -alcohol \longrightarrow \angle carbonium ion \angle \longrightarrow α -ether \longrightarrow β -ether the carbonium ion intermediate being the same as in the α -alcohol.

before it became clear. The time for this varied in the range 8 - 10 minutes and the reaction was presumed to proceed as the alcohol dissolved. Using the nomograph for first order kinetics 34 the rate lies in the range $2.9 - 3.5 \times 10^{-3}$ sec⁻¹, the upper limit being favoured.

The rate of ionisation of the g-alcohol at 70° in the (1:1) solvent was determined as $1 \cdot 19 \times 10^{-4} \text{ sec}^{-1}$ (Plot 7 fig. 5, P.84). Knowing the activation energy the rate of ionisation of the g-alcohol at 25 and 12.8° was calculated by use of equation (4) as:

$$k \frac{25}{6} = 4.04 \times 10^{-7} \text{ sec}^{-1}$$
.
 $k \frac{12.8}{6} = 6.38 \times 10^{-8} \text{ sec}^{-1}$.

Thus

and

$$45,500 < \frac{k\alpha}{kc} < 55,000$$

$$\frac{k\alpha}{kc} \sim 5 \times 10^4$$

The solvolysis rate of the &-tosylate has not been obtained. Attempted synthesis of this compound by the standard procedure, at either 0° or room temperature, failed. The alternative method of synthesis from the sodium or potassium salt of the &-alcohol was also without success. With potassium, in refluxing benzene, the salt was not formed whereas with sodium hydride and trityl sodium some reaction

did occur but addition of tosyl chloride failed to give an isolable product. The trityl sodium reaction was reminiscent of that of the monoketone with t-butyl magnesium chloride, a highly coloured mixture of eight products being obtained. That the c-tosylate could not be synthesised is difficult to understand particularly since the c-acetate was made. The possibility of other derivatives such as the methyl sulphonate remain to be exploied.

The correlation of tosylate solvolysis rate with carbonyl frequency predicted a rate constant of about $10^{10} \, \mathrm{sec}^{-1}$ at 25° for the α -tosylate. Assuming a carbonyl frequency of $1730 \, \mathrm{cm}^{-1}$ for the hypothetical 'crown' ketone the solvolysis rate constant of the β -tosylate should be about $10^{-9} \, \mathrm{sec}^{-1}$ at 25° . The rate difference between the α - and β -tosylates is, therefore, about 10^{19} , clearly greater than that observed between the ionisation of the alcohols. In the absence of the β -tosylate rate, or the rate of a corresponding derivative, the conclusions between the predicted and the observed rate differences are difficult to make.

Chapter IV

Olefinic Derivatives of Cyclotriveratrylene

The existence of the 'flexible' conformation of C T V derivatives with the C_5 carbon atom tetrahedral (α -cyclotriveratrylenol) and trigonal-planar (monoketone) has been established. A derivative of the 'crown' conformation with an sp hybridised C_5 carbon atom had not been observed. It was hoped that replacement of the carbonyl group of the monoketone with methylene and isopropylidene groups would invert the stability of the conformations due to increased steric compression and thus allow isolation of a 'crown' conformer.

Treatment of the monoketone with methyl magnesium iodide gave rise to two products whose R_f values were 0.91 and 0.77 in chloroform-ethyl acetate mixture (19:1). The compound with R_f value 0.77 predominated. Chromatographic techniques failed to effect a separation of the products. The I. R. spectrum of the product mixture showed the absence of both hydroxyl and ketonic bands.

The N M R spectrum of the mixture, in deuterochloroform, (fig. 9), indicated the presence of the two compounds in the in the proportions 7:3 and the signal pattern was ascribed to

the two compounds in the following way:

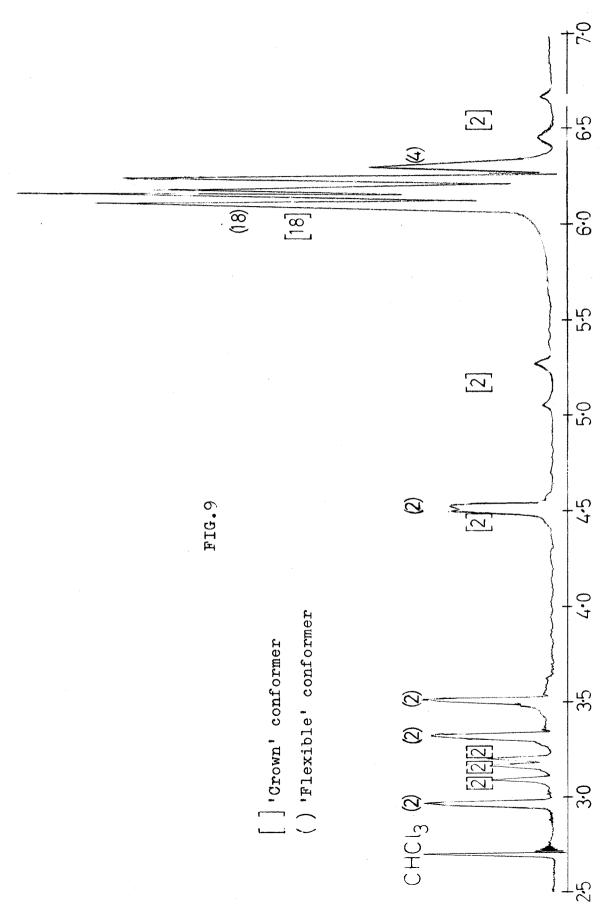
Compound I (\sim 70%).

6.30 (4) s.

Compound II (\sim 30%)

Compound I was obtained pure by its solubility difference from compound II in ethanol. Compound II was readily soluble whereas compound I was only partly soluble and filtration afforded I pure to T L C.

The N M R spectrum of I was in agreement with the assignment from that of the mixture. Attempted crystallisation of I gave rise to a mixture of I and II in approximately the same proportions as the product mixture. The conversion of I to a mixture of I and II occurred within a week at room temperature, indicative of an equilibrium process. N M R spectra were run on a solution of pure I and after one week at room temperature the proportion of II had risen from zero to a constant value of twenty-four percent.



N M R of the Methylenecyclotriveratrylenes

The N M R spectrum of the product mixture obtained by evaporation of the ethanol solution at room temperature showed an increased proportion of II. The resonance signals of II occurred at the same chemical shifts as in the original mixture. A series of spectra on a sample enriched in compound II showed that equilibration to I was complete within 30 hours at room temperature. The same equilibrium mixture viz. 76% I and 24% II was obtained as with the transition I \longrightarrow II.

The equilibrium mixture analysed for $C_{28}H_{30}O_6$, a loss of one oxygen atom and a gain of one carbon and two hydrogen atoms from the monoketone. Coupling this with the absence of a hydroxyl band in the I. R. spectrum and the presence of two equilibrating forms the products are proposed as the methylenecyclotriveratrylenes (25) and (26). The tertiary alcohol, expected as a precursor to these compounds, must have dehydrated during work-up.

Compound I has been assigned the 'flexible' conformation (25) which is supported by the occurrence of a four-proton singlet at 6.30 τ in the N M R spectrum due to the C₁₀ and C₁₅ ring protons. Compound II has been assigned the 'crown' conformation (26). The C₁₀ and C₁₅ methylenic proton signals occur as the characteristic AB quartet at almost the same chemical shift as these protons in C T V and the β -alcohol.

The rate constants and the equilibrium constant for the process

have been determined by standard N M R techniques. A sample enriched in (26) was allowed to equilibrate in the spectrometer probe at the normal operating temperature of 40°. Spectra were run at suitable time intervals.

Using equation (5), where Co, Ce and Ct are respectively the concentration of 'crown' conformer at zero time, at

In
$$\frac{(c_1 - c_e)}{c_t - c_e} = k_{-1} \frac{c_o}{c_e} t$$
 (5)

equilibrium and at time t, a plot of log $(C_t - C_e)$ against t gives k_1 (fig. 10).

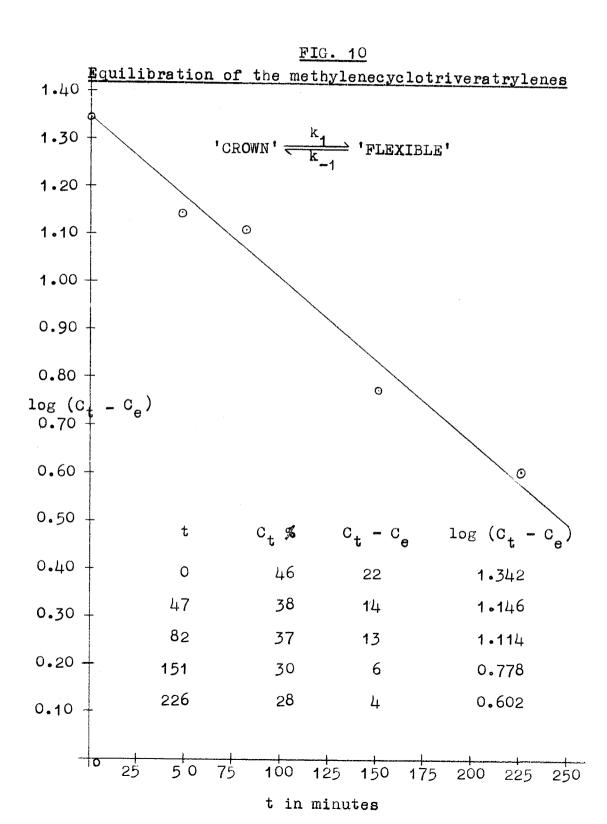
The results obtained were:

$$k_{-1}^{40} = 6.8 \pm 0.6 \times 10^{-5} \text{ sec}^{-1}$$

$$k_1^{40} = 2.1 \pm 0.6 \times 10^{-4} \text{ sec}^{-1}$$

$$K = \frac{k_1}{k_{-1}} = \frac{\sqrt{\text{flexible}}}{\sqrt{\text{crown}}} = 3.2$$

When the monoketone was treated with methyl lithium one product was obtained together with traces of unreacted starting material. Attempted purification by column chromatography resulted in conversion of the product to a mixture of (25) and



(26), but crystallisation from benzene-cyclohexane mixtures afforded a pure colourless crystalline compound. On rapid heating the product showed a melting point of 118 - 20° with the evolution of vapour, resolidification and final melting at 179 - 182°. With slow heating the melting point was in the range 164 - 170° with evolution of vapour. On drying in vacuo at room temperature a mixture of (25) and (26) resulted and thus no microanalytical data could be obtained. However, the conversion to (25) and (26) and the melting point data indicated the compound to be the expected sertiary alcohol.

The N M R spectrum in D M S O showed a one-proton singlet at $4.56\,\tau$ which disappeared on addition of deuterium oxide, behaviour expected for a tertiary $\operatorname{alcohol}^{25,26}$. In deuterochloroform the ring methylene hydrogens showed as an AB quartet consisting of a pair of doublets at 5.84 and 6.80τ (J = 15.5 c.p.s.) analogous to that observed for the ∞ -alcohol (20), (cf Table III P.66). The methyl group occurred as a singlet at 8.02τ .

The compound is proposed as the tertiary alcohol with the 'flexible' conformation, (27). The conformational assignment is supported by the observed AB quartet with a geminal coupling constant of 15.5 c.p.s. The U. V. spectrum $\angle 231$ (4.44); 286 m \oplus (log \in = 3.99) $\angle 7$ parallels that of the \triangle -alcohol and is typical of the 'flexible' conformation.

The alternative 'crown' conformers, with either the hydroxyl or the methyl group 'in' would appear unlikely since no evidence for the %-alcohol was observed.

The resonance signals for the aromatic protons occurred at 2.47, 2.72, 3.33, 3.54, and $3.60 \, \tau$, in deuterochloroform. The integrated ratio was 1:1:2:1:1 respectively. It is possible that these different chemical shifts could be caused by a slowed pseudorotation compared to α -cyclotriveratrylenol. The anomaly could be clarified by a series of spectra at different temperatures.

Treatment of the monoketone with either isopropyl magnesium bromide or isopropyl lithium gave rise to a mixture of six products, the solid being yellow. Benzene-chloroform mixture (1:1) eluted all six products on column chromatography. T L C showed that the first fraction collected consisted of only two compounds, the slower running component being present in low yield. The R_f values were close to those of the methylenecyclotriveratrylenes (25) and (26).

The N M R spectrum of the mixture was analogous to that of the methylenecyclotriveratrylene mixture and accounted for the presence of two compounds in the proportions 88 and 12%. Compound I_B (12%)

7 3.010 (2) s; 3.45 (2) s; 3.55 (2) s; 6.08 (4) s; 6.15 - 6.20 (18); 8.82 (6) s.

Compound IJa

The behaviour of the mixture paralleled that of the methylene compounds, IIa equilibrating with Ia. Crystal-lisation of the mixture from benzene-chloroform mixtures yielded a colourless crystalline solid, m.p. $193 - 6^{\circ}$, analysing for $C_{30}H_{34}^{\circ}O_6$. By their similarity to the methylenecyclotriveratrylenes the compounds have been assigned as the isopropylidenecyclotriveratrylenes, Ia being the 'flexible' conformer (28) and IIa the 'crown' conformer (29). The N M R spectrum supports these conformations, The single at $6.08 \times 10^{\circ}$ is due to the four methylenic hydrogen atoms in the 'flexible' conformer and the characteristic AB quartet, occurring as doublets at 5.54 and $6.58 \times 10^{\circ}$ (J = 13.5 c.p.s.), is due to the same protons in the 'crown' conformer.

The U. V. spectrum of IIa supports the proposed conformation, (29). Absorption occurred at 233 (4.50) and 292 mm ($\log \epsilon = 4.00$), almost identical to that of C T V. The 233 mm peak was distinct and typical of the 'crown' conformation. In the discussion on the conformation of the monoketone it was pointed out that the carbonyl group would be held rigidly

orthogonal to the aromatic rings in the 'crown' conformation. That conjugation does not occur through an sp² hybridised

C₅ carbon atom of a C T V derivative in the 'crown' form is amply demonstrated by the isopropylidene derivative whose stable conformer is 'crown'.

Conclusion.

The conformations of a series of cyclotriveratrylene derivatives have been established and, from these, various factors influencing the stability of the conformers are When the C5 carbon atom is tetrahedral the evident. preferred conformation appears to be 'crown' provided that at least one substituent is hydrogen (e.g. C T V and the (3-alcohol); With a trigonal-planar C5 carbon atom the preferred conformation is 'flexible' since this allows conjugation with the adjacent aromatic nuclei (e.g. mono-Steric compression with the ortho nuclear and triketones). hydrogen atoms also plays an important part. It is not severe in the case of the methylene derivative but increase in the size of the substituents inverts the stability of the conformations, the 'crown' predominating with large R (e.g. the isopropylidene derivative).

The apparent non-existence of the 8-alcohol is not altogether unexpected since this arrangement is very crowded. The 'crown' conformers of the tertiary alcohol (27) were not observed probably for the same reason.

That the &-tosylate has eluded us is surprising in view of having obtained the &-acetate. It is conceivable that steric requirements preclude the existence of bulky

derivatives. The ionisation rates of the - and -alcohols are not analogous to the predicted tosylate solvolysis rates. Acceleration in the case of the -alcohol is conceivable since the activation energy for the process of conformational inversion is not high and the rate is faster than had been expected. However, no definite conclusions can be made until such time as a full correlation with Foote's work is made.

Syntheses of the parent cyclotribenzylene system have been attempted but without success. Attempts to reduce the hexa-phenol (12), by the zinc-dust melt and zinc-dust in pyridine methods gave only phenolic smelling gums.

Experimental

The general points described for the experimental section of Part I (P. 24) apply here. In addition the following should be noted.

Thin-layer chromatography plates were prepared according to the method of E. Stahl³⁶ using silicagel G containing 2% of luminous pigment ZS super (Riedel-de Haën). Analytical plates (5 x 20 cm) were made to a thickness of 10 thou and preparative scale plates (20 x 20 cm) to a thickness of 1 - 2 mm. The compound positions were identified by viewing under a low pressure mercury lamp.

Chapers I and II

Cyclotriveratrylene, C T V, (7), (10, 15-dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo /a, d, g/cyclononene) was prepared by the method of Robinson¹.

m.p.
$$233 - 4^{\circ}$$
 /Lit⁵ 234° /7.

N M R 73.21 (6) s; 5.36 (3) d. J = 14.0 c.p.s.;

6.19 (18)s; 6.52 (3) d. J = 14.0 c.p.s.

Oxidation of C T v^3 C T v, 6g. (13.3 m.moles), was dissolved in boiling glacial acetic acid (50 mls.) and sodium dichromate, 4g. (13.3 m.moles), in water (20 mls.), was added dropwise over 30 - 40 mins. The solution was refluxed for a further3 hours

when hot water (100 mls.) was added. After 2 days at R. T. the product was filtered off, dried and crystallised from aqueous dioxan. The golden brown crystalline product was chromatographed over 8" of Woelm neutral alumina in a 1" diameter column. The first fractions of benzene eluted the monoketone (11) whilst later fractions and continuation to 100% chloroform eluted a mixture of the mono- and tri-ketones.

Those benzene fractions showing the absence of a 1750cm⁻¹ band in the I. R. spectrum were crystallised from benzene to yield 1.9 g. (29%) of the monoketone (11) as colourless prisms. The remaining combined fractions were refluxed with potassium hydroxide, 2·lg, in methanol (21 mls.) for 2 hours. suspension was diluted with water (50 mls.) and extracted with chloroform (2 x 50 mls.). The combined chloroform extracts were dried over magnesium sulphate, evaporated to dryness in vacuo and crystallised from benzene to give a further 0.76g. (14%) yield of monoketone (11). The aqueous fraction was acidified with dilute hydrochloric acid, extracted with chloroform (3 x 30 mls.), dried over magnesium sulphate after washing the combined organic fractions with sodium bicarbonate and water, and evaporated to dryness in vacuo. Crystallisation from benzene gave the triketone (17) as a colourless crystalline solid, 0.36g. (5.4%).

The Monoketone (10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo /a, d, g/cyclononen-5-one), (11).

Total yield 2.66 g. (43%).

m. p. $213 - 4^{\circ}$ /Lit⁵ $213 - 4^{\circ}$].

I. R. (CHCl₃) (fig. 1 P.43) 1630, 1600, 1585, 1289, 1270, 1095, 1075 cm⁻¹.

U. V. λ_{max} 238 (4.50); 284 (4.15); 326 m μ (log ϵ = 4.16).

NMR 2057 (2) s; 3020 (2) s; 3046 (2) s; 6010 (12) s; 6020 (10) s。

N M R (pyridine) 25.95 (4)s; 6.17 (12) s; 6.34 (6) s.

Mass spectrum: M. W. 464.183+ 0.001

 $^{\text{C}}_{27}^{\text{H}}_{28}^{\text{O}}_{7}$ requires 464.1834.

Analysis: C₂₇H₂₈O₇ requires C 69.81; H 6.08; OCH₃ 40.09 %. found C 69.67; H 5.89; OCH₃ 39.24 %.

The Triketone, (17) (10,15-dihydro-2,3,7,8,12,13-hexamethoxy--5H-tribenzo / a, d, g / cyclononen-5,10 %-trione).

Yield 0.36g. (5.4%).

m.p. $287 - 90^{\circ}$

I. R. (CHCl₃) (fig. 2, P.52) 1750, 1658, 1598, 1520, 1475, 1378, 1305, 1250, 1095 cm⁻¹.

U. V. λ_{max} 227 (4.62); 258 (4.64); 308 (4.26); 353 m/m (log $\epsilon = 3.96$).

N M R (fig. 3, P.58)

N M R (pyridine)

~ 6.18 (3) s; 6.21 (6) s; 6.38 (6) s; 6.42 (3) s.

Mass spectrum:

Molecular formula C27H24O9.

Analyses: C₂₇H₂₄O₉ requires C 65.83; H 4.92; OCH₃ 37.82 % found C 65.91; H 5.11: OCH₃ 36.73.

65.55; 4.83; 38.27.

65.92; 4.79; 37.26.

Attempted formation of ketal and thicketal derivatives of the monoketone (11).

Treatment of the monoketone with either ethylene glycol or trimethyl orthoformate or ethane dithiol, in refluxing benzene or toluene with one crystal of para-toluene sulphonic acid and azeotropic separation of any water formed, failed to yield any derivative even after 3 days.

Demethylation of C T V to 10,15-dihydro-2,3,7,8,12,13-hexa-hydroxy-5H-tribenzo/a, d, g/cyclononene, (12), and treatment with acetic anhydride and pyridine to give the hexa-acetate, (13), was by the method previously described 5.

The hexaphenol, (12).

I. R. 3400 (broad), 1605, 1520, 1280 cm⁻¹.

N M R_(pyridine) γ 5.15 d. J = 14 c.p.s; 6.39 d. J = 14 c.p.s.

The hexa-acetate, (13).

NMR \sim 2.86 (6) s; 5.34 (3) d. J = 14 c.p.s.; 6.35 (3) d. J = 14 c.p.s; 7.77 (18)s.

Attempted oxidation of the hexa-acetate, (13), using the method described for C T V gave partial hydrolysis to the hexaphenol. Under anhydrous conditions the starting material was recovered in 85% yield.

The condensation of methylenedioxybenzene³⁷ with formaldehyde was by the method of Garofano and Oliverio¹¹. A 9g.(23%) yield of cyclotrimethylenedioxybenzylene, (C T M B) was obtained.

$$m.p. > 360^{\circ}$$
.

I. R. 1607, 1590, 1240, 1042 cm⁻¹.

U. $V_{\circ}(\text{dioxan}) \lambda \text{ max}$ 238 (4.59) and 299 m μ (log ϵ = 4.40). Mass spectrum: M.W. 402.107 + 0.004

^C24^H18^O6 requires **4**02.1103.

Due to its almost total insolubility in organic solvents no other spectral data could be obtained.

Attempted oxidation of CTMB by the method used for CTV failed, CTMB being recovered in 95% yield. A prolonged reflux time of 24 hours had no effect.

Oxidation of the monoketone, (11).

The monoketone, 1.16 g. (2.5 m.moles), was dissolved in refluxing glacial acetic acid (10 mls.) and sodium dichromate, 0.5g.(1.7 m.moles), in water (3 mls.), was added. Using the procedure adopted for the oxidation of C T V a 0.25g. (20%) yield of trione, (17), was obtained.

Attempted conversion of the trione, (17), to C T V by Clemmensen reduction³ and standard hydrogenolysis techniques using Adam's catalyst and 10% palladium on charcoal failed.

Conversion of the trione, (17), to its *salt*

The trione, (17), 210 mg. (0.42 m.moles), was treated with potassium hydroxide, 22 mg. (0.40 m.moles), in methanol (2mls.), and refluxed for 12 hours. The resulting suspension was diluted with water (10 mls.) and extracted with chloroform (10 mls.). The organic fraction gave a 98% recovery of trione and evaporation of the aqueous fraction in vacuo gave no product. Using two and three times the quantity of base gave the same results.

With the same quantity of trione and 120 mg. of base the chloroform extract contained no product and the aqueous fraction gave a 100% yield of pale green 'salt' which when dried at 100° turned orange.

U. V. λ max. 256 (4.68); 282 (4.42); 315 (4.35); 376 m/m ($\log \epsilon \sim 4.17$).

N M R spectra of samples showing the same U. V. were non-reproducible.

Attempted methylation of the 'salt'.

- (i) Treatment of the 'salt' with excess, freshly distilled, methyl iodide (1 ml.) in A. R. methanol (5 mls.), dried over potassium carbonate, at R. T. overnight gave 100% conversion to the trione. (m.p., mixture m.p., comparison of I. R. spectra).
- (ii) Treatment of the 'salt' with excess dimethyl sulphate, dried over potassium carbonate and re-distilled, in 30% alcoholic alkali gave a 15% yield of trione (m.p. mixture m.p., comparison of I. R. spectra), the 'salt' being recovered in 85% yield.

Chapter III

Reduction of the monoketone, (11), with lithium aluminium hydride
Li Al H, or sodium borohydride.

(i) Reduction followed by a neutral or alkaline work-up.

The monoketone, (11), 1.16g. (2.5 m.moles), was dissolved in dry tetrahydrofuran, T H F, (70 mls.) and LiAlH₄, 130 mg.

(3.3 m.moles), added. The solution was stirred at ca. 35° for 1 hour. Excess LiAlH₄was destroyed by the addition of

sodium sulphate crystals, water, or 5% sodium hydroxide solution, and the solution filtered. Evaporation of the solvent in vacuo gave rise to a mixture of (20) and (21) in 84% yield.

The product was stirred in T H F (40 mls.) for 1 hour and filtered to yield (20) pure. Crystallisation of the mixture, from benzene, gave (21) pure.

R_f /chloroform-ethyl acetate(19:1) 0.39

m.p.: With the apparatus at 215° immediate melting followed by re-solidification and final melting at 236 - 7° occurred.

With the apparatus at 205° spacity and melting at 236 - 7° occurred.

I. R. 3500, 1605, 1522, 1270, 1220, 1100, 1090 cm⁻¹.

U. V. λ max. 230 (sh) (4.48) and 283 m μ (log ϵ = 4.04).

NMR \sim 2.83 (2) s; 3.22 (4) s; 3.92 (1) s; 5.96 (2) d. = = 15.5 c.p.s.; 6.13(18) s; 6.24 (2) d. = 15.5 c.p.s.

*Peaks 1, 2, and 4 of an AB quartet visible.

N M R (pyridine) ~ 5.53 (2) d. J = 15.5 c.p.s.; 6.07 (2) d. $\sim J = 15.5$ c.p.s.; 6.21 and 6.28 (18).

*Peaks 1, 2, and 3 of an AB quartet visible.



N M R(DMSO)
$$\sim$$
 2.91 (2) s; 3.23 (4) s; 4.17 (1) d. J = 4.0 c.p.s.; 4.37 (1) d. J = 4.0 c.p.s.; 6.29 (18) s.

Addition of deuterium oxide caused the 4.37% signal to vanish and the 4.17% signal to coalesce to a singlet 25,26 .

@ -Cyclotriveratrylenol, (21).

 R_f /chloroform-ethyl acetate (19:1) 0.21. m.p. 236 - 7°.

I. R. 3500, 1605, 1520, 1260, 1090 cm⁻¹.

U. V. λ_{max} . 234 (4.52) and 291 my (log $\epsilon = 4.01$).

NMR \sim 3.07 (1) s; 3.21 and 3.24 (6); 5.26 (1) OH;

5.35 (2) d. J = 14.0 c.p.s.; 6.15 and 6.18 (18);

6.52 (2) d. J = 14.0 c.p.s.

N M R_(DMSO) $^{2.79}$ (2) s; $^{2.94}$ (2) s; $^{3.00}$ (2) s;

3.25 (1) d. J = 2.5 c.p.s.; 4.35 (1) d. J = 2.5 c.p.s.;

5.30 (2) d. J = 14.0 c.p.s.; 6.30 (18) s.

Addition of deuterium oxide caused the 4.35τ signal to vanish and the 3.25 doublet to coalesce to a singlet 25,26.

Analysis: C₂₇H₃₀O₇ requires C 69.79; H 6.28: OCH₃ 38.66 %.

found C 69.51; H 6.48; OCH₃ 39.89 %.

The proportions of (20) and (21) varied depending on whether the T H F solution was warmed or not during evaporation in vacuo.

Characterisation of & -cyclotriveratrylenol (21).

The alcohol was characterised as its acetate (21a) prepared by reaction with acetic anhydride in pyridine in the usual manner.

m.p. $215 - 7^{\circ}$

I. R. 1735, 1265, 1235 cm⁻¹.

NMR ~ 2.05 (1) s; 2.87 (2) s; 3.16 (4) s; 5.14 (2) d.

J = 14 c.p.s;6.18 (18)s; 6.34 (2) d.J = 14 c.p.s.;

7.78 (3) s.

Analysis: $^{\text{C}}_{29}^{\text{H}}_{32}^{\text{O}}_{8}$ requires $^{\text{C}}_{68 \cdot 50}$; $^{\text{H}}_{6 \cdot 29}$; $^{\text{OCH}}_{3}$ $^{36 \cdot 61}$ %. found $^{\text{C}}_{69 \cdot 10}$; $^{\text{H}}_{6 \cdot 21}$; $^{\text{OCH}}_{3}$ $^{35 \cdot 72}$ %.

The acetate could not be obtained 100% pure, some &-alcohol always remained.

(ii) Reduction followed by an acidic work-up and extraction with chloroform.

The reduction was performed as in (i) above, benzene or T H F being used as solvent. Excess LiAlH, was destroyed with dilute hydrochloric acid and chloroform was added to effect solution. The organic solution was filtered, washed with water, dried over magnesium sulphate, and evaporated in vacuo. Four products B, C, D, and E, with R_f values /chloroformethyl acetate (19:1) 7 0.21, 0.25, 0.48 and 0.63 respectively, were obtained in 90% yield. The products were separated by preparative scale T L C eluting with chloroformethyl acetate (19:1) or benzene-acetone (4:1) and extraction from the silica with A. R. acetone.

Product B: identified as @-cyclotriveratrylenol, (21), by m.p., mixture m.p. and comparison of I. R. spectra with a sample from method (i) above.

<u>Product C:-</u> this was never isolated and was present only in trace amounts.

<u>Product D</u>:- (3-cyclotriveratrylenyl ethyl ether, (23).

m.p. 212 - 4°.

I. R. 1605, 1520, 1260, 1095 cm⁻¹.

U. V. λ max. 235 (4.52) and 292 m μ (log $\epsilon = 3.97$).

N M R (Varian Associates HR 100 instrument) (fig. 4,P. 75)

2.88 (2) s; 3.22 (2) s; 3.26 (2) s; 3.59 (1) s; 5.29 (2) d. J = 14.0 c.p.s.; 6.20 (18) s; 6.46 (2) q. J = 7 c.p.s.; 6.47 (2) d. J = 14.0 c.p.s.; 8.71 (3), t. J = 7 c.p.s.

Analysis: C₂₉H₃₄O₇ requires C 70.41; H 6.93 %.
found C 69.93; H 6.85 %.

Product E:- ≪- cyclotriveratrylenyl ethyl ether, (24).

The compound formed a distinct band on the T L C plate but after extraction a mixture of (23) and (24) was always obtained. The proportions of (23) and (24) varied depending on whether the chloroform solution was warmed or not during evaporation in vacuo.

 $v. v. \lambda_{mex} 232 \text{ (sh)}$ and 290 m μ .

(iii) Reduction followed by acidic work-up.

The reduction was performed as in (i) above the excess LiAlH, being destroyed by dilute hydrochloric acid. Evaporation of the T H F in vacuo gave rise to two products (20) and (21).

The same results were obtained for methods (i), (ii) and (iii) using sodium borohydride but a prolonged reaction time of 20 hours was necessary to effect complete reduction.

Attempted Grignard reduction of the monoketone.

The monoketone, (11), 1.16g. (2.5 m.moles), in T H F (60 mls.), was added dropwise, under nitrogen, to 10 m.moles of t-butyl magnesium chloride at 0°. The solution was stirred for 3 hours, poured into ice-water containing hydrochloric acid and the aqueous layer extracted with chloroform. Evaporation of the organic faction gave a mixture of eight products (T L C), the solid being bright green.

Z-values.

1-Ethyl-4-carbomethoxypyridinium iodide was synthesised by the reported method 30.

m.p.
$$212 - 3^{\circ}$$
 /Lit³⁰ $211 - 2^{\circ}$ 7.

U. V. (Unicam SP 700 instrument)

bromoform-ethanol (4:1)

Molarity	λ max	Z
41·8 µM	27,300 cm ⁻¹	78-05
51.2 "	27,300 "	78-05
102.4 "	27,250 "	77-91

U. V. Bromoform, λ max 27,100 cm⁻¹ Z = 77.5

Ethanol was purified by prolonged refluxing over calcium oxide and fractional distillation, the fraction, b.p. 78.4 - 78.7°, being collected. The bromoform was purified by redistillation and filtration through neutral alumina.

Solutions of hydrochloric acid in the (4:1) and (1:1) solvent mixtures were prepared by bubbling anhydrous hydrogen chloride into the solutions, dilution and standardisation against standard sodium methoxide in methanol.

The (1:1) and (4:1) solvent mixtures were standardised by the same method but by potentiometric titration using a Metrohm E.350 pH meter. The (1:1) solvent was $5.38 \times 10^{-4} \text{N}$ and the (4:1) $9.33 \times 10^{-4} \text{N}$ in hydrogen ion.

The &-alcohol, (21), was purified by recrystallisation from benzene and drying in vacuo at 100° for 8 hours. It was pure to T L C. The \approx =alcohol, (20), was prepared as above and stored at -70°. A solution of alcohol, 60.0 mg. (25.8 m.M), in 5 mls. of solvent was employed, the ethanol

concentration being essentially unaltered by the reaction.

The reaction flask was sealed with a serum cap and samples removed with a syringe. For the 3-alcohol cooling to R. T. effectively stopped the reaction but for the calcohol excess alkali was introduced into the syringe barrel, the needle not coming into contact with the base. The sample thus obtained was applied to an analytical T L C plate and eluted with benzene-methanol (9:1). The bands of compound were scraped into graduated flasks and extracted from the silica with 95% B.P. ethanol, U. V. spectra being run on the filtered solutions. The absorption at 291 mp. was followed and the proportions of compounds determined by use of the previously measured extinction coefficients.

The results are given in figs. 5 - 8 and Table IV

(P.84 - 88). Using equation (6), where a is the absorbance

E the extinction coefficient, c the concentration and 1

the path length, c can be calculated. The concentration

a = ε cl $\int_{-\infty}^{\infty} 0.0 = \varepsilon$ cl $\int_{-\infty}^{\infty} (6)$ of product and starting material from the T L C plate can be obtained from the two spectra. e.g. for run 1 (fig. 5).

t mins.	moles R-OH	moles R-OEt	Total moles	% R-OH	log %
30	23 · 53	8 · 84	32×37	72	1.861
63	8 · 75	8 · 36	17:11	51	1.709
93	6.31	12·29	18.60	34	1.530
120	5.01	15.71	20.72	24	1.384
152	2·96	14-40	17 36	17	1.232
210	1.82	17/6A	19.50	9	0 970
270	0-90	16.77	17-67	5	0 · 708
00	nil	R-Oft only		0	_

Attempts to synthesise the &-tosylate by:(i) treatment of the &-alcohol with para-toluene sulphonyl chloride (tosyl chloride) in pyridine at 0° and R. T. for 10 and 6 days respectively gave starting material in 95% yield. (ii) refluxing the &-alcohol in toluene with potassium metal failed to form the salt. (iii) treatment of the &-alcohol with a slight excess of sodium hydride in refluxing xylene followed by the addition of tosyl chloride gave only starting material and by (iv) treatment of the &-alcohol with excess trityl sodium followed by the addition of tosyl chloride gave a green product consisting of eight compounds (T L C).

Chapter IV

Reaction of the monoketone, (11), with methyl magnesium iodide

A solution of methyl magnesium iodide (10 m.moles) in ether (10 mls.) was prepared by the standard procedure. To this was added over 30 mins., with stirring, a solution of the monoketone, 1.16g (2.5 m.moles), in dry T H F (50 mls.). The solution was stirred at R. T. for 14 hours, then poured into ice-water (300 mls.) containing dilute hydrochloric acid (10 mls. 4N). The aqueous layer was extracted with ether (3 x 100 mls.) and the combined ethereal extracts washed with water, dried over magnesium sulphate and evaporated to dryness at R. T. to yield an equilibrium mixture of (25) and (26). Crystallisation from benzene-pet. ether mixture gave a colourless crystalline solid, m.p. 183 = 5°, (0.88g., 77%). (25) was obtained pure by its insolubility in ethanol.

> 7 2.96 (2) s; 3.32 (2) s; 3.51 (2) s; 4.53 (2) s; 6.10 (6) s; 6.19 (6) s; 6.23 (6) s; 6.30 (4) s.

- U. V. λ max 233 (4.34); 284 (4.18); 298 m/ (log ϵ = 4.11).

& -Methylenecyclotriveratrylene, (26).

N M R (fig. 9, P.94) 24%.

7 3.09 (2) s; 3.16 (2) s; 3.20 (2) s; 4.50 (2) s; 5.18 (2) d. J = 13.5 c.p.s.; 6.15 and 6.19 (18); 6.53 (2) d. J = 13.5 c.p.s.

Analysis of equilibrium mixture:

 $C_{28}H_{30}O_6$ requires C 72.71; H 6.54 %. found C 72.33; H 6.53 %.

Equilibration (26) \longrightarrow (25) see P. 96-7.

Reaction of the monoketone with methyl lithium

Methyl lithium (17.5 m.moles) in ether (10 mls.) was prepared by the method of H. Gilman³⁹. To this was added a solution of the monoketone, 1.16g. (2.5 m.moles), in dry T H F (70 mls.), over 30 mins. the whole being under nitrogen. After stirring for 3 hours the solution was poured slowly into ice-water (300 mls.) and extracted with chloroform (3 x 100 mls.). The combined organic extracts were dried over magnesium sulphate and evaporated to dryness at R. T. Crystallisation from benzene-cyclohexane gave 5-methyl-10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo
/ a,d,g/cyclononen-5-ol, (27), (0.88g, 75%), as a colourless crystalline solid.

m.p. (rapid heating) 118 - 20°, resolidification and m.p. 179 - 82°.

I. R. 3500 (broad), 1610, 1520, 1255, 1090 cm⁻¹.

U. V.
$$\lambda$$
 max. 231 (sh) (4.44) and 286 my (log ϵ = 3.99).

NMR α 2.47 (1) s; 2.72 (1) s; 3.33 (2) s; 3.54 (1) s; 3.60 (1) s; 5.84 (2) d. J = 15.5 c.p.s.; 6.11 (6) s; 6.15 (6) s; 6.29 (6) s; 6.80 (2) d. J = 15.5 c.p.s.; 7.70 (1) 0H; 8.02 (3) s.

NMR (DMSO) 2.48 (1) s; 2.74 (1) s; 3.17 (2) s; 3.46 (1) s; 3.53 (1) s; 4.56 (1) s.

Addition of deuterium oxide caused the 4.56% signal to vanish 25,26.

Heating in vacuo gave the equilibrium mixture of (25) and (26).

Reaction of the monoketone with isopropyl magnesium bromide or isopropyl lithium.

The procedures were identical to those for methyl struggard and methyl lithium respectively. TLC showed the presence of six compounds in the green product mixture. Dehydration by heating in vacuo at 100° or by azeotroping in toluene with one crystal of para-toluene sulphonic acid did not effect dehydration. Chromatography of the mixture over 9° of Woelm neutral alumina in a 1° diameter column gave the equilibrium mixture of the α and α -isopropylidenecyclotriveratrylenes, (28) and (29), with

the first fraction of benzene-chloroform (1:1). Continuation of the chromatography eluted the remaining products as a mixture. (28) and (29) crystallised from benzene as colourless plates, m.p. 193 - 6°.

I. $R_{\circ}(\text{CHCl}_3)$ 3020, 2960, 2850, 1605, 1520, 1470, 1260, 1105 cm⁻¹. U. V. λ_{max} 233 (4.50) and 292 m μ (log ϵ = 4.00). N M R on equilibrium mixture.

(28), 12% of mixture.

(29), 88% of mixture.

Analysis: C₃₀H₃₄O₆ requires C 73.45; H 6.99; OCH₃ 37.96 %. found C 72.90; H 6.66; OCH₃ 38.29 %.

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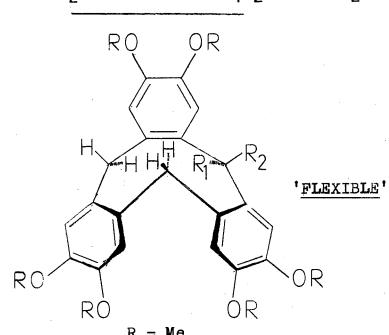
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R = Me

(7)
$$R_1 = R_2 = H$$
. (22) $R_1 = OH$, $R_2 = H$.

(9)
$$R_1 R_2 = -0.$$
 (23) $R_1 = H$, $R_2 = OEt$.

(21)
$$R_1 = H$$
, $R_2 = OH$. (26) $R_1 R_2 = CH_2$.
(21a) $R_1 = H$, $R_2 = OAc$. (29) $R_1 R_2 = CMe_2$.



R = Me

(8)
$$R_1 = R_2 = H$$
. (25) $R_1 R_2 = \text{CH}_2$.

(10)
$$R_1 R_2 = -0$$
. (27) $R_1 = CH_3$, $R_2 = OH$.

(20)
$$R_1 = H$$
, $R_2 = OH$. (28) $R_1 R_2 = CMe_2$.

(24)
$$R_1 = H$$
, $R_2 = OEt$.