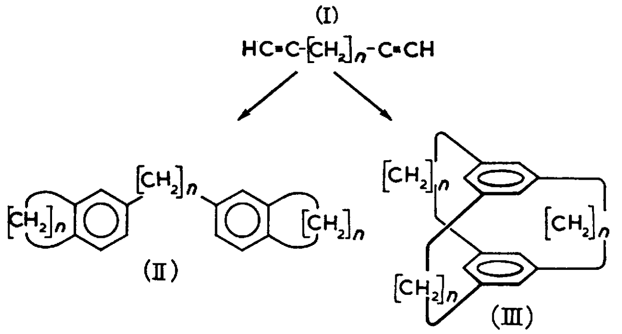
Multimacrocyclic Compounds. Part I. Novel Triply Bridged Dibenzenoid Cage Compounds

By **A. J. Hubert,** Union Carbide European Research Associates, 95 Rue Gatti de Gamond, Brussels 18, Belgium

Internal cyclotrimerisation of aromatic triynes on a Ziegler catalyst has given a series of compounds containing two aromatic rings joined by three polymethylene chains. Melting point alternation and spectral properties are similar to those of paracyclophanes.

TERMINAL diacetylenes (I) can be trimerised on Ziegler-type catalysts[1] to dumb-bell like trimers (II) and cage trimers (III).



We observed that the relative yields of the two isomers varied considerably with *n*. Isomer (II) is formed exclusively when $n < 5$, however, when $n = 5$ or 6, both (II) and (III) are obtained and when $n = 7$ only (III) could be isolated. The yields of the cage isomer (III) were low (1% or less) and could not be improved by high-dilution techniques, which favour the dumb-bell isomer (II).

We have now developed a more generally applicable stepwise synthesis of (III) which gives a much higher yield (up to 50% in the best case) of cage compounds (III), so that the homologous series ($n = 3$—7) has now been prepared. The steps involved are shown below.

$$\underset{\text{(IV)}}{3HC\equiv C\text{-}(CH_2)_nCl} \longrightarrow \underset{\text{(V)}}{\text{1,3,5 and 1,2,4-}C_6H_3[(CH_2)_nCl]_3} \xrightarrow{NaC\equiv CH/NH_3}$$

$$\underset{\text{(VI)}}{\text{1,3,5 and 1,2,4-}C_6H_3[(CH_2)_nC\equiv CH]_3} \xrightarrow[\text{high dilution}]{\text{Ziegler catalyst}}$$

$$\text{(III) (1,3,5- and 1,2,4-isomers)}$$

The trimerisation of the chloroalkyne (IV) gives the tris(chloroalkyl)benzene (V) in high yield as a mixture of 1,2,4- and 1,3,5-isomers. The reaction has to be carried out rapidly (~5 min.) at a low temperature since, if the mixture remains on the catalyst at room temperature, a vigorous reaction starts after about 15—30 min. and the trialkylbenzene is obtained by reduction of the chlorine atoms.

The time required for the substitution of the chlorine atoms by C≡CH varies with *n*; when $n = 3$, two days at room temperature (autoclave) are sufficient to complete the reaction but when $n = 9$, approximately 10% of the original chlorine is still present after 1 week. The mixture of isomeric triynes (VI) is internally trimerised at very high dilution and it is obvious that this procedure must favour the formation of the cage compounds; in fact, the yields are relatively high in several cases (Table 1).

The reaction gives a mixture of isomers as a product and isolation of the symmetrical isomer by gas chromatography for the lower members ($n = 3$ or 4), and crystallisation for the others is necessary. The cage compounds obtained by this method are identical with those obtained by direct trimerisation of the alkadiynes ($n = 5$ or 6), evidence which can be considered as structural proof for these compounds.

TABLE 1

Aromatic triynes (V)

	Yield		Found (%)			Required (%)	
n	(%)	B. p./mm.	C	H	Formula	C	H
2 [a]	62	133—135°/0·01	92·5	7·8	$C_{18}H_{18}$	92·3	7·7
3 [b]	55	160—180/0·1	—	—	$C_{21}H_{24}$	91·25	8·75
4	36	180—200/0·1	90·5	9·4	$C_{24}H_{30}$	90·5	9·5
5	35	190—220/0·01	89·55	9·85	$C_{27}H_{36}$	89·95	10·05
6	30	210—234/0·001	89·6	10·35	$C_{30}H_{42}$	89·5	10·5
7 [c]	34·5	220—250/0·001	(88·1)	(10·5)	$C_{33}H_{48}$	89·1	10·9
8 [d]	(49)	—	(81·3)	(11·1)	$C_{36}H_{54}$	88·8	11·2
9 [d]	(34·5)	—	(83·8)	(11·4)	$C_{39}H_{60}$	88·6	11·4

[a] Prepared by another method than the general procedure (see the text). [b] The pure 1,3,5 isomer was obtainable by g.l.c.—this was no more possible for the higher homologues. [c] Still contains traces of chlorine. [d] These triynes were not distillable and were obtained as impure oils still containing some chlorine by chromatography on alumina and were trimerised as such.

That the best yield is obtained when $n = 5$, is both an indication that conformational effects play a role in this reaction and furthermore, as shown in Figure 1, that the conformation of the pentamethylene chain is ideal. The m. p. (Figure 2, curve A) shows an alternation along the series which is analogous to that observed in the homologous series of macrocylic alkadiynes;[2] the m. p. for the compounds where $n = 5$ or 7

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[1] A. J. Hubert and J. Dale, *J. Chem. Soc.*, 1965, 3160.

are higher than for those where $n = 4$ or 6. Figure 1 demonstrates that the conformation of the polymethylene chain is ideal only when n is odd ($n = 5, 7$, etc.); these molecules are therefore conformationally more homogeneous and hence have a higher m. p. A similar m. p. curve is obtained for the paracyclophanes (Figure 2, curve B).

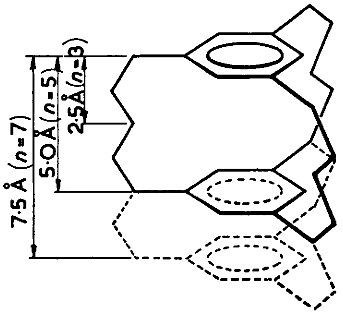

FIGURE 1

In both series, the m. p. of the member where $n = 3$ is very low and although the conformation of the chain itself appears ideal it is, in fact, too short, and the transannular repulsion between the aromatic nuclei leads to serious distortion.

The lowest known member of the paracyclophane series ($n = 2$) is even more strained, and X-ray diffraction studies,[3] ultraviolet spectra,[4] and the ease with which the compound forms a complex with tetracyanoethylene,[5] furnish evidence that the aromatic nuclei are boat shaped; the distortion decreases when $n = 3$ or 4, and is absent in the higher members.[4]

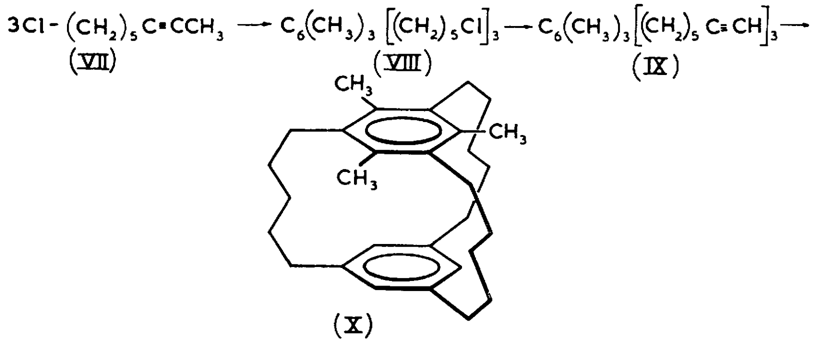

FIGURE 3

In the symmetrical cage compound (III; $n = 3$), the aromatic rings would, if the strain is homogeneously distributed, be in a chair form. This was the smallest cage compound which could be prepared since even at very high dilution only polymers were obtained for $n = 2$.

A trimethyl substituted cage compound (X) (Figure 3), in which the substituents are located on one aromatic ring, was prepared from $C_6(CH_3)_3[(CH_2)_5C{\equiv}CH]_3$ (IX) and, it is interesting to note that, the m. p. of this cage compound (260°) is very similar to that of the non-substituted compound (m. p. 265°). This shows that the conformation of the polymethylene chains is more important than symmetry in determining the m. p.

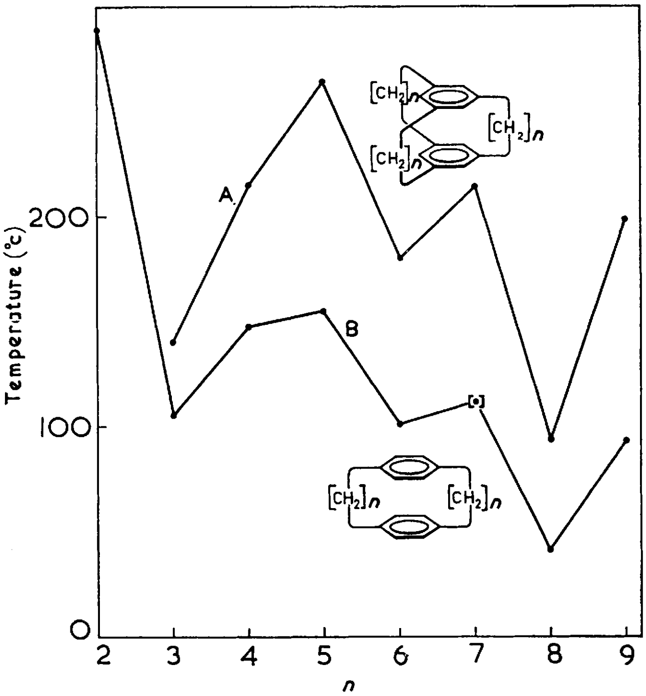

FIGURE 2 Melting points of the paracyclophanes and of the cage compounds (III)

The u.v. spectra (Figure 4) show that strain is present when $n = 3$; the absorption is weak and no vibrational structure is observed. When $n = 4$, the strain is still present but less evident and disappears completely when $n = 5$. A weak alternation is observed in these u.v. spectra; when n is odd (5 or 7) the structure is more sharply defined than when n is even (4 or 6). This can be explained by a stiffening of the chromophore when n is odd due to the rigid conformation of the polymethylene chain in these compounds. Such an effect has already been observed in the u.v. spectra of a series

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[2] J. Dale and A. J. Hubert, *J. Chem. Soc.*, 1963, 73.

[3] C. J. Brown, *J. Chem. Soc.*, 1953, 3265.

[4] D. J. Cram and co-workers, *J. Amer. Chem. Soc.*, 1959, **81**, 5971; 1964, **86**, 5722.

[5] A. J. Hubert and J. Dale, *J. Chem. Soc.*, following Paper.

of macrocyclic tetraenes,[5] where two 1,3-diene chromophores are bridged by two equal polymethylene chains.

The wavelength shift on formation of an adduct with tetracyanoethylene, which was used by Cram[4] as a method for the detection of strain in paracyclophane, shows, in the present Series, that the strain present when $n = 3$ disappears progressively as n increases. When $n = 3$, a very intense blue colour is observed, whilst for the higher members the colour is reddish, as it is for unstrained aromatic compounds. The absorption intensity of the adduct shows an interesting alternation starting from $n = 4$, that is for the unstrained molecules;

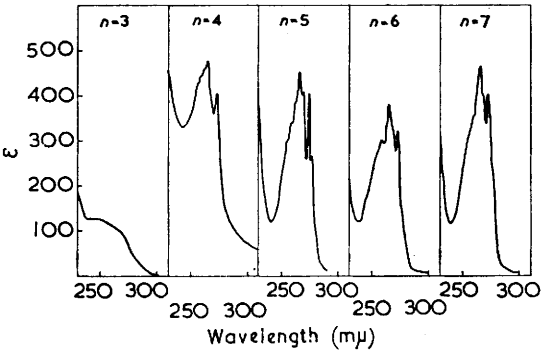

FIGURE 4 U.v. spectra of the cage compounds (III)

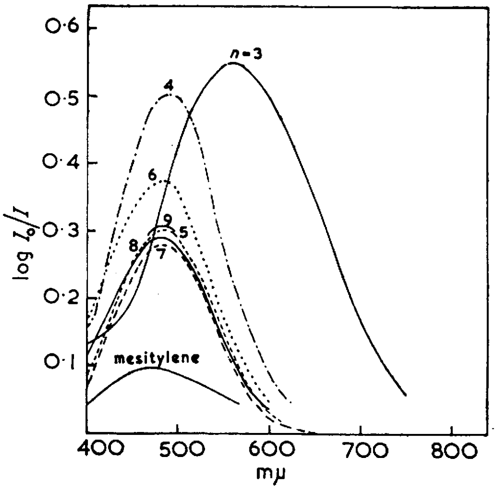

FIGURE 5 U.v. spectra of tetracyanoethylene adducts of the triply bridged dibenzenoid compounds (III)

[Hydrocarbon] = 10^{-3} m./l. [TCNE] = 2.5×10^{-2} m./l. Solvent: CH_2Cl_2

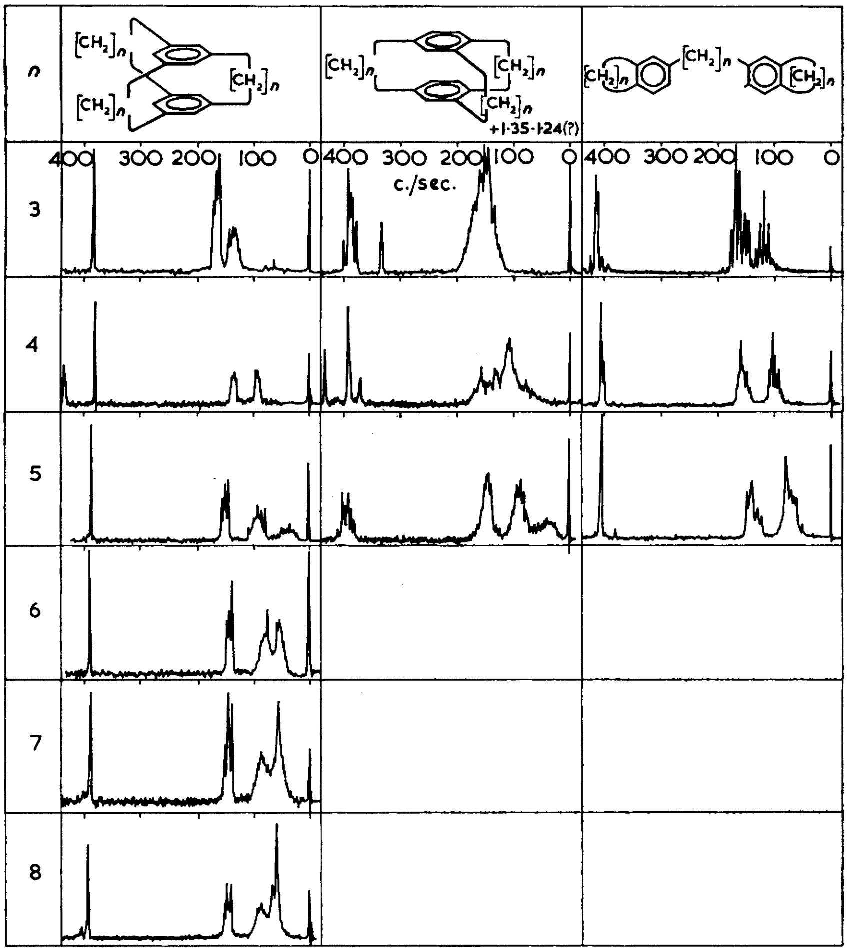

FIGURE 6 N.m.r. spectra of the triply bridged compounds as compared with their bicyclic isomers

when n is even, the absorption is higher than when n is odd. This effect is only clear for the first members ($n = 4$, 5, 6, and 7), after which it disappears. This can be explained as follows. When n is odd the conformation is ideal for the stretched polymethylene chain and, since the two aromatic rings are at a distance from each other, the interaction is small. When n is even, however, the conformation of the straight chain cannot be strain-free, the folding of the chain can occur without necessarily increasing the Pitzer-strain. The two aromatic rings can thus more easily approach each other and, by interaction, stabilise the complex; the u.v. spectra of these complexes are shown in Figure 5.

The n.m.r. spectra of cage compounds with $n = 5$ and 6 have already been discussed.[1] When $n = 5$ and 6, abnormal chemical shifts of the γ-protons in the centre of the methylene chain were observed and were interpreted as being due to the aromatic ring current, since these protons are situated, at least part of the time, between the two aromatic nuclei. When $n = 3$ and 4 (Figure 6), all the aliphatic protons are normal and models show that they must all be on the outside. For a comparison, the spectra of the compounds (II) are also reproduced.

The chemical properties of these compounds are now being studied. So far, attempts to prepare sandwich complexes with a metal, such a chromium, inside the molecule have failed. Cram[4] has reported a similar failure in attempts to prepare metal complexes with paracyclophanes.

EXPERIMENTAL

Starting Materials.—1-Chloro-3-bromopropane was a commerical product (Fluka). 4-Chlorobutan-1-ol was prepared from tetrahydrofuran,[6] 5-chloropentan-1-ol from pentane-1,5-diol,[7] and the other chlorohydrins ($n = 6$—10) from the corresponding diols.[8]

The chlorohydrins were converted with phosphorus tribromide to the 1-chloro-ω-bromoalkanes, with gave the ω-chloroalk-1-ynes (IV) upon treatment with a stoicheiometric amount of mono-sodium acetylide in liquid ammonia.[9]

General Trimerisation Procedure for Chloroalkynes (IV).—Titanium tetrachloride (5 ml.) was dissolved in dry hexane (500 ml.), and then isobutylaluminium (25 ml.) added under nitrogen. The chloracetylenic compound (50 g.) was then added with stirring during 5 min. at 0°; the temperature was controlled with a bath of solid carbon dioxide in acetone. After a further 5 min. the mixture was poured into methanol (200 ml.), water (~200 ml.) was added, and the organic layer separated and washed with further water. For the compounds where $n = 3$ and 4, the solvent was evaporated and the residue distilled in high vacuum to give the product, for higher homologues, however, decomposition became prohibitive. In this way were obtained 1,3,5- and 1,2,4-*tris*(3-*chloropropyl*)*benzene* (V; $n = 3$), b. p. 155—160°/10^{-2} mm. (Found: C, 61·5; H, 6·8; Cl, 33·0. $C_{21}H_{21}Cl_3$ requires C, 58·5; H, 6·8; Cl, 34·6%), and 1,3,5- and 1,2,4-*tris*(4-*chlorobutyl*)*benzene* (V; $n = 4$), b. p. 220—240°/0·5 mm. with decomposition.

Infrared absorption occurs at 6·25, 6·67, 11·2, 11·4, and 12·12 μ; these bands are typical for 1,3,5- and 1,2,4-trisubstituted benzene ring. The i.r. spectrum also shows that $-C{\equiv}CH$ has disappeared. The yield was almost quantitative.

In the case of the higher homologues, the crude mixture of trichloroalkyl benzene was treated directly with sodium acetylide without prior distillation. 1,3,5-*Tris*-(5-*chloropentyl*)-2,4,6-*trimethylbenzene* (and the 1,2,4-2,3,5 isomer) (VIII) were prepared by trimerisation of 8-chloro-oct-2-yne (VII).[10] The crude trichloride was used directly for the preparation of the corresponding triyne (IX) (Found: C, 65·0; H, 9·3; Cl, 24·9. $C_{24}H_{39}Cl_3$ requires C, 66·4; H, 9·0; Cl, 24·6%).

General Preparation of Trialkynylbenzenes (VI).—The trichlorotrialkylbenzene (0·5 mole) was added to sodium acetylide (2 moles) in liquid ammonia (1 l.). The mixture was shaken during 3—4 days for the compounds where $n = 3$ and 4, for 1 week where $n = 5$ and 6, and for the compounds where $n = 7$—9 for 2 weeks, since the product isolated after 1 week still contained about 30% of the theoretical amount of chlorine. The triynes could be distilled in high vacuum.

The i.r. spectra of all these triynes show the typical absorption of $-C{\equiv}CH$ at 3·0 and ~16 μ, and the $-C{\equiv}C-$ stretching band at 4·7 μ as well as at 6·25, 6·69, 11·35, and 12·1 μ, characteristic for 1,2,4- and 1,3,5-trisubstituted benzene rings.

The yields and the properties of these triynes are given in Table 1. 1,3,5- and 1,2,4-*Tris*(*pent*-4-*ynyl*)*benzene* (VI); $n = 3$) is the highest member which can be eluted without decomposition on a column (5 m.) of silicon gum-rubber at 300°. Four peaks are observed in the following ratio, 40 : 35 : 15 : 9%. The 1,3,5-isomer is the first one to be eluted.

The n.m.r. spectrum fits well with the expected structure. The aromatic protons give a single peak at 6·75 p.p.m., whilst the aliphatic protons give two groups of peaks, one at 2·62 p.p.m. corresponding to the protons of CH_2 in the α position to the aromatic nucleus, and the other at about 2·0 p.p.m. containing the signals of the other CH_2 together with the signal of the acetylenic protons which are not resolved. Measurements of the area of these peaks show that there are 3 aromatic protons, 6 protons from the α-CH_2, and 15 other protons (β-CH_2 + γ-CH_2 + acetylenic protons).

The i.r. spectrum shows the presence of $-C{\equiv}CH$ and of 1,3,5-trisubstituted benzene (6·25 and 11·4 μ) and the absence of a 1,2,4-aromatic system.

The second peak is the 1,2,4-isomer (i.r. and n.m.r.) but it has not been isolated in a pure state, and contains some 1,3,5-isomer. The two other smaller peaks are unidentified and will be studied later.

1,3,5-*Tris*(*but*-3-*ynyl*)*benzene* (VI; $n = 2$).—The procedure for the preparation of this triyne is different from that of the other triynes.

A solution of prop-2-ynyl magnesium bromide was prepared according to Sondheimer[11] from magnesium (26 g.) activated with mercuric chloride (2 g.), prop-2-ynyl bromide

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[6] *Org. Synth.*, Coll. Vol. II, 1957, 571.

[7] *Org. Synth.*, Coll. Vol. I, 1956, 533.

[8] *Org. Synth.*, Coll. Vol. III, 1955, 446.

[9] R. A. Raphael, " Acetylenic Compounds in Organic Synthesis," Butterworths Scientific Publications, London, 1955, p. 6.

[10] J. Wotiz and E. S. Hudak, *J. Org. Chem.*, 1954, **19**, 1580.

[11] F. Sondheimer, R. Wolovsky, D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, 1961, **83**, 1688.

(130 g.) in ether (500 c.c.). ω,ω′,ω″-Tribromomesitylene (47 g.)[12] was immediately added, followed by cuprous chloride (1 g.). The mixture was warmed slowly and left to stand overnight under nitrogen. The solution was then poured on to ice, acidified with hydrochloric acid, and the organic layer was separated. After evaporation of the solvent, the residue was distilled *in vacuo*. An i.r. spectrum showed peaks at 3·0 and 4·7 μ (C≡CH), at 6·25 (1,3,5-trisubstituted benzene ring), and a large band at 11·65 μ (the out-of-plane vibration of the hydrogen of the 1,3,5-trisubstituted benzene ring and the rocking of the two adjacent methylene groups are contained in this large band).

The n.m.r. spectrum confirmed the structure; a single peak is observed at 6·81 p.p.m. One group of peaks is observed at 2·65 p.p.m. (α-CH_2 to the aromatic nucleus) and one at 2·35 p.p.m. (β-CH_2). The acetylenic signal is a triplet at 1·83. The ratio of the area is 3 : 6 : 6 : 3, respectively, as expected for the structure.

TABLE 2

Cage compounds (III)

	Yield (%)				Analysis of the 1,3,5-isomer						
					Found (%)				Required (%)		
n	Crude product 1,3,5- and 1,2,4-isomers	1,3,5-Isomer	B. p./m.m.	M. p. 1,3,5-isomer	C	H	*M*	Formula	C	H	*M*
2	—	0	—	—	—	—	—	$C_{18}H_{18}$	92·3	7·7	234
3	16 [a]	9·6 [b]	180—200°/0·1 mm.	140	91·4	8·7	276	$C_{21}H_{24}$	91·25	8·75	276
4	16 [a]	3·2 [b]	180—200/0·1 mm.	213	90·7	9·4	325	$C_{24}H_{30}$	90·5	9·5	318
5	53 [a]	8·6 [c]—15 [b]	200—250/0·1 mm.	265	89·4	10·0	369	$C_{27}H_{36}$	89·95	10·05	360
6	32·5 [a]	6·6 [c]	220—240/0·1 mm.	178	89·45	10·3	390	$C_{30}H_{42}$	89·5	10·5	402
7	(22·7) [d]	9·2 [d]	—	217	89·5	10·2	349	$C_{33}H_{48}$	89·1	10·9	445
8	(31) [d]	1·2 [d]	—	95	88·4	11·4	471	$C_{36}H_{54}$	88·8	11·2	487
9	(14·6) [d]	0·65 [d]	—	208	88·2	11·5	519	$C_{39}H_{60}$	88·6	11·4	529

[a] Obtained by distillation. [b] Measured by gas–liquid chromatography. [c] Isolated by crystallisation. [d] Isolated by chromatography on alumina.

1,3,5-*Tris*(*hept*-6-*ynyl*)-2,4,6-*trimethylbenzene* (IX).—The title compound was obtained by reaction of the corresponding trichloride (VIII) with sodium acetylide in an autoclave. The yield was 50·5%, b. p. 220—240°/0·001 mm. The distilled material was directly trimerised without further purification. It still contained chlorine (2·5%).

General Preparation of Cage Compounds (III).—Titanium tetrachloride (5 ml.) was added to light petroleum (b. p. 40—60°, 1 l.) and tri-isobutylaluminium (25 ml.) added under nitrogen. A 1 l. three-necked flask fitted with a mechanical stirrer, a Soxhlet (without cartridges), and a glass stopper was used as a reaction vessel. The catalyst was added through the last neck under nitrogen. The Soxhlet was fitted with an efficient condenser connected from the top to nitrogen, and to a micropump (the Distiller's Company). The solution of triyne (∼0·5 mole) in benzene (500 ml., was injected through the condenser by way of the micropump at the speed of 7 ml./hr. The light petroleum was heated strongly under reflux, so that the Soxhlet was filled approximately every 3 min. (at most 5 min.). The solution of triyne thus entered the reaction vessel as a very dilute solution.

Fresh catalyst was prepared in the reaction vessel after 2 days in order to ensure continued activity. It was not found necessary to maintain an atmosphere of nitrogen in the apparatus once the light petroleum had been heated to reflux point.

When all the solution of triyne had been added (∼4 days) the mixture was poured into methanol and worked up as for the preparation of the trichloroalkylbenzene. The crude material was taken up in hexane and filtered through alumina, and finally, either distilled in high vacuum or purified by chromatography on alumina.

The yields and the properties of the cage compounds are given in Table 2.

1,3,19-*Trimethyltetracyclo*[9,9,5,$1^{3,19}$,$1^{9,13}$]*heptacosa*-1,3(26),9,11,13(27),19-*hexane* (X, Figure 2).—The title compound was obtained by trimerisation of the corresponding triyne (IX) under high dilution. The mixture of isomers was obtained in 13·5% yield as an oil from which 4·65% of pure 1,3,5-isomer was isolated by crystallisation, m. p. 260° (Found: C, 89·0; H, 10·7%; *M*, 388. $C_{33}H_{48}$ requires C, 89·5; H, 10·5%; *M*, 402). Absorption at 6·25 μ in the i.r. spectrum demonstrated the presence of the 1,3,5-trisubstituted benzene ring.

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[12] W. Reppe, *Annalen*, 1948, **560**, 104.