783. *Calciferol and its Relatives. Part II.** *An Alternative Synthesis of* trans-1-2′-cyclo*Hexylidene-ethylidene-2-methylene*cyclo*hexane.*†

By B. Lythgoe, S. Trippett, and J. C. Watkins.

The secondary alcohol (IV) and the tertiary amine (V) have been prepared and their elimination reactions studied. 1 : 4-Elimination of water from the alcohol gives the diconjugated triene (VI), whereas 1 : 4-elimination of dimethylamine from the amine (V) gives the triconjugated triene (I) named in the title.

THE triconjugated triene, *trans*-1-2′-*cyclo*hexylidene-ethylidene-2-methylene*cyclo*hexane (I) is of interest because of the similarity of its unsaturated system to that present in calciferol. In Part I * two routes were described for the preparation of the triene, both of which made use of Wittig and Schöllkopf's olefin synthesis [1] to introduce one of the double bonds. In the present paper we describe an alternative synthesis in which the double bonds are introduced solely by classical ionic elimination reactions.

Formulæ (II)—(V) represent intermediates which might, in theory, be converted into the desired triene by elimination of appropriate oxygen and nitrogen functions. For each, however, alternative elimination pathways are open, which may be preferred because of the high energy of double bonds semicyclic to a *cyclo*hexane ring. Thus the readily accessible tertiary alcohol (II) has been shown [2] to lose water, giving not the triene (I), but an isomer in which the newly formed double bond is cyclic. Milas and Alderson [3] studied a simpler analogue of the amino-alcohol (III), and in the light of their results it is very probable that successive (indirect) elimination of water and dimethylamine would yield the desired triene (I). However, the preparation of this amino-alcohol by a Grignard reaction is apparently excluded by the allylic rearrangement which is known to take place when Grignard reagents derived from γ-substituted primary allyl halides react with

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* Part I, *J.*, 1955, 4016.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

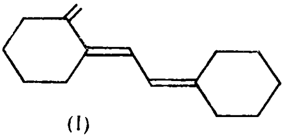
[1] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.

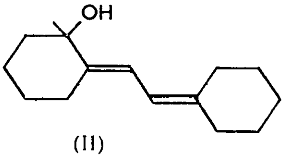
[2] Dimroth, *Ber.*, 1938, **71**, 1346.

[3] Milas and Alderson, *J. Amer. Chem. Soc.*, 1939, **61**, 2534.

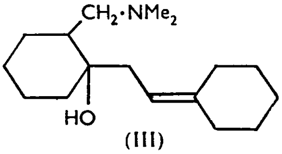
ketones;[4] no other simple route to the amino-alcohol (III) seems available. Accordingly we have studied the preparation and elimination reactions of the compounds (IV) and (V).

By using the abnormal Grignard reaction of allylic halides mentioned above, the alcohol (IV) was easily obtained. 1-Bromomethyl*cyclo*hexene formed a magnesium derivative which reacted with *cyclo*hexylideneacetaldehyde, giving the alcohol (IV) which, although no doubt a mixture of stereoisomers, formed a crystalline α-naphthylurethane, and its structure was confirmed by infrared bands at 888 (semicyclic methylene group) and 848 cm.$^{-1}$ (semicyclic trisubstituted double bond).


(I)



(II)



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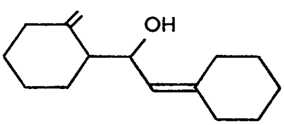
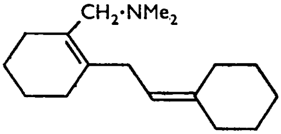
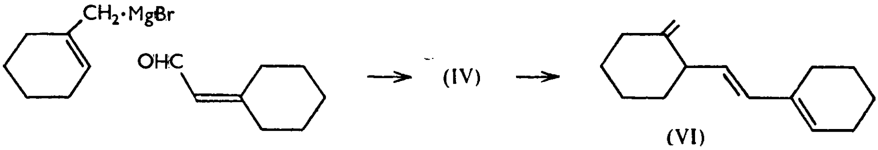


(IV)



(V)

Two paths are theoretically open for its dehydration: 1 : 2-elimination, leading to the desired triene (I), and 1 : 4-elimination across the semicyclic trisubstituted double bond, leading to the diconjugated triene (VI). Dehydration took place readily in the presence of phosphoric oxide in light petroleum, the product consisting almost exclusively of the triene (VI), which showed the expected dienoid light adsorption at 234 mμ and infrared bands at 888 (semicyclic methylene group) and 967 cm.$^{-1}$ (*trans*-CH:CH). This preferential 1 : 4-elimination was not unexpected. The reaction probably follows a mechanism approximating to the E_1 type and subject to the generalised Saytzeff rule. One of the newly formed double bonds is purely acyclic, the other cyclic; both have less energy than the semicyclic trisubstituted double bonds present in (I). Thus the only factor favouring the 1 : 2-elimination reaction leading to the desired compound (I) is the triconjugation of the latter's triene system, but this factor will be of little significance because of the unfavourable *s-cis*-configuration of the semicyclic methylene group in relation to the other two double bonds. It seemed possible that 1 : 2-elimination from a structure of type (IV) might be promoted by altering the reaction mechanism, and with this aim we attempted to convert the alcohol (IV) into the bromide from which other suitable derivatives might be obtained. However, treatment with phosphorus tribromide caused anionotropic rearrangement to the corresponding tertiary bromide, and this approach was not further pursued.



Compounds of type (V) contain a dimethylaminomethyl*cyclo*hexene system, which we proposed to create by partial reduction of a suitable benzylamine. The route was first explored in model experiments. *m*-Methoxyphenylmagnesium bromide and *cyclo*hexylidene-ethyl bromide gave m-2′-*cyclo*hexylidene-ethylanisole (VII; R = H). Reduction with sodium and alcohol in liquid ammonia, followed by mild acid hydrolysis, gave 3-2′-*cyclo*hexylidene-ethyl*cyclo*hex-3-enone (VIII; R = H), whose structure was established

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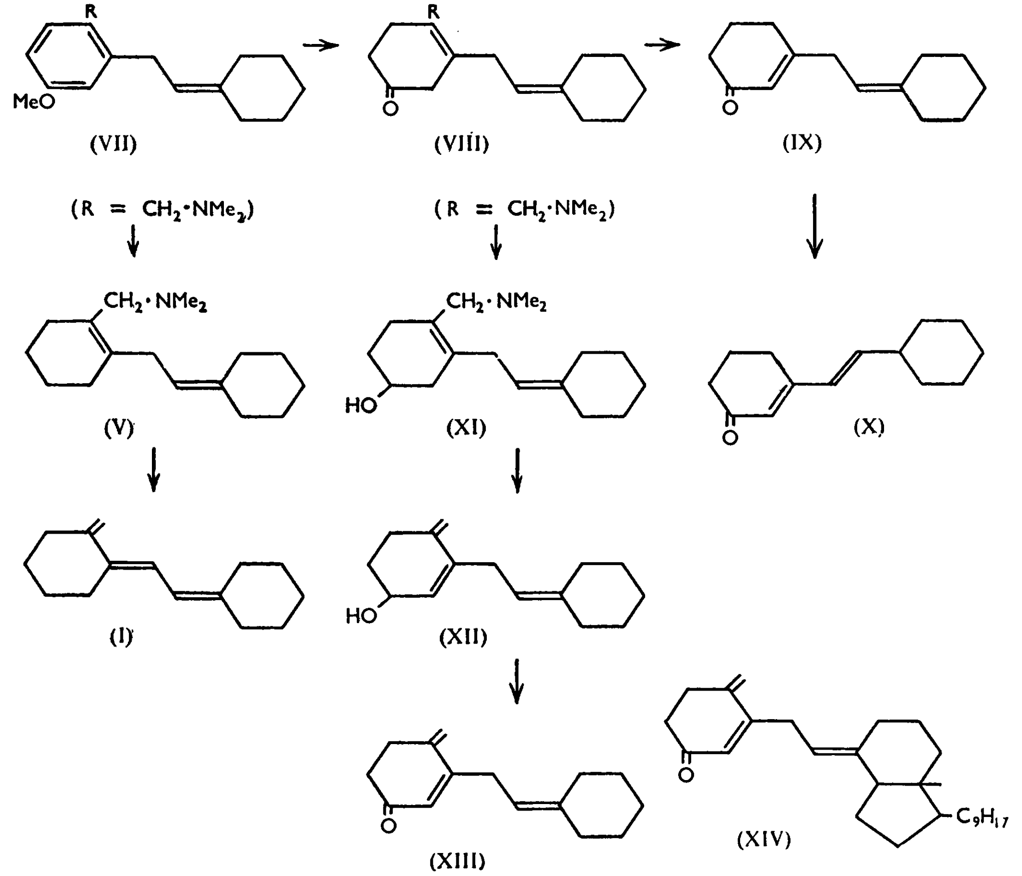
[4] Roberts and Young, *J. Amer. Chem. Soc.*, 1945, **67**, 148; 1946, **68**, 1472.

by lack of selective light absorption above 220 mμ and by stepwise isomerisation by acid, first to the unsaturated ketone (IX), and thence to the conjugated dienone (X). These displayed the expected light absorption maxima at 235 and 281 mμ respectively and were both characterised as semicarbazones.



By extension of the method, 2-bromo-4-methoxy-*NN*-dimethylbenzylamine was converted into its magnesium derivative, which with *cyclo*hexylidene-ethyl bromide gave the amine (VII; $R = CH_2{\cdot}NMe_2$). During reduction of this with sodium and alcohol in liquid ammonia some over-reduction, accompanied by loss of the methoxyl group, took place, as previously observed [5] in parallel cases. After mild acid hydrolysis the product was reduced with lithium aluminium hydride to convert the ketone (VIII; $R = CH_2{\cdot}NMe_2$) into the alcohol (XI), and the mixture so obtained was separated by chromatography on alumina into hydroxylic and non-hydroxylic fractions. The latter contained 2-dimethylaminomethyl-1-2′-*cyclo*hexylidene-ethyl*cyclo*hexene (V), originating in the loss of methoxyl function mentioned above; it was isolated as its crystalline methiodide which showed no selective light absorption above 220 mμ. Thermal decomposition of the corresponding quaternary hydroxide gave the desired triene (I), $\lambda_{max.}$ 270 mμ (ε 21,200); material purified by recrystallisation as described in Part I has $\lambda_{max.}$ 269·5 mμ (ε 22,700). The infrared absorption spectra of the two samples were identical. The overall yield of the triene (I) was very low, and for preparative purposes the present route is much inferior to those already described.

The alcohol (XI) present in the hydroxylic fraction from the chromatogram could not

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[5] Birch, *J.*, 1946, 593; 1947, 1642.

be obtained crystalline either as such or as a derivative. The crude material was converted into the methiodide and thence into the quaternary hydroxide, which was decomposed by heat, giving a mixture of two materials showing light absorption at 234 and near 273 mμ severally. The minor component, which was responsible for the absorption near 273 mμ, may well have been the desired 5-hydroxy-derivative of (I), but we were unable to purify it. The component responsible for the light absorption at 234 mμ was identified as the diconjugated trienol (XII) as follows. Manganese dioxide did not attack the crude alcohol (XI), but oxidised the product from its Hofmann degradation, causing disappearance of the selective light absorption at 234 mμ and giving the conjugated dienone (XIII), characterised as the semicarbazone. The latter had $\lambda_{max.}$ 293 mμ, which agrees with that of the semicarbazone of the analogue (XIV), the product of Oppenauer oxidation of calciferol.[6] The contrast in the elimination of the amine (V) and its hydroxy-derivative (XI) is surprising, but may possibly be due to the allylic disposition of the hydroxyl group in stabilising the transition state leading to the alcohol (XII).

EXPERIMENTAL

1-*Hydroxymethyl*cyclo*hexene*.—1-Cyano*cyclo*hexene[7] (57 g.), 95% alcohol (100 c.c.), and concentrated sulphuric acid (32 c.c.) were heated together under reflux for 72 hr., the cooled mixture was poured into water, and the product extracted with ether. The washed and dried ethereal solution was evaporated, distillation of the residual oil giving ethyl *cyclo*hex-1-ene-carboxylate (57 g.), b. p. 104—111°/25 mm. This was added dropwise to a stirred suspension of lithium aluminium hydride (10·5 g.) in ether (300 c.c.) so that the ether refluxed gently, and stirring was then continued for ½ hr. Excess of hydride was decomposed by water, the cooled mixture poured into 10% hydrochloric acid (1·2 l.) with stirring, and the product isolated with ether. Distillation under reduced pressure gave 1-hydroxymethyl*cyclo*hexene (34 g.), b. p. 96°/18 mm. The phenylurethane[8] had m. p. 96° (Found: C, 72·7; H, 7·3; N, 6·15. Calc. for $C_{14}H_{17}O_2N$: C, 72·7; H, 7·4; N, 6·1%).

1-1′-*Hydroxy*-2′-cyclo*hexylidene*-*ethyl*-2-*methylene*cyclo*hexane* (IV).—1-Hydroxymethyl*cyclo*hexene (10 g.) in light petroleum (25 c.c., b. p. 40—60°) was cooled to −12°, stirred, and treated dropwise with phosphorus tribromide (9 g.) in light petroleum (8 c.c.). The mixture was kept at −12° for 1 hr., then at room temperature for 24 hr., after which it was poured into ice-water and extracted with ether. The ethereal solution was washed with ice-cold aqueous sodium hydrogen carbonate and with water, dried, and evaporated. Distillation of the residue under reduced pressure gave 1-bromomethyl*cyclo*hexene (9 g.), b. p. 86—87°/17 mm. A portion (6·9 g.) was converted into the Grignard reagent by reaction with powdered magnesium (7 g.) in ether (65 c.c.). Ether (32 c.c.) was then distilled off and replaced by benzene (32 c.c.), after which a solution of *cyclo*hexylideneacetaldehyde (1·7 g.) in ether (5 c.c.) and benzene (5 c.c.) was added slowly with stirring. The mixture was stirred and heated under reflux for ½ hr., then cooled and poured into 10% aqueous ammonium chloride (200 c.c.). The product was isolated with ether in the usual manner and its solution in light petroleum (200 c.c.; b. p. 40—60°) chromatographed on neutral aluminium oxide (200 g.; deactivated by addition of 10 g. of water). The column was washed with more light petroleum (400 c.c.) and with benzene–light petroleum (400 c.c.; 2 : 1), and the filtrates were discarded; elution with benzene (600 c.c.) then gave 1-1′-*hydroxy*-2′-cyclo*hexylidene-ethyl*-2-*methylene*cyclo*hexane* (1·67 g.) as a colourless oil (Found: C, 82·0; H, 11·2. $C_{15}H_{24}O$ requires C, 81·8; H, 11·0%). It showed no selective light absorption above 220 mμ. The α-*naphthylurethane* separated from light petroleum as rosettes of needles, m. p. 98—100° (Found: C, 80·0; H, 8·2; N, 3·75. $C_{26}H_{31}O_2N$ requires C, 80·2; H, 8·0; N, 3·6%).

Dehydration. A solution of the above alcohol (46 mg.) in light petroleum (1 c.c.; b. p. 60—80°) containing phosphoric oxide (30 mg.) was warmed under reflux for 2 hr., then kept at room temperature for 24 hr., and filtered. Evaporation gave an oil with $\lambda_{max.}$ 234 mμ (ε 16,500 in EtOH) and an inflection at 273 mμ (ε 3000). Its infrared absorption spectrum showed no band near 3300 cm.$^{-1}$ (absence of OH group) but showed *inter al.* bands at 1650 (m), 888 (vs) and 967 (s) cm.$^{-1}$.

m-2′-cyclo*Hexylidene-ethylanisole* (VII; R = H).—To a solution of the magnesium

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[6] Trippett, *J.*, 1955, 370.

[7] Bhattacharyya, *J. Indian Chem. Soc.*, 1945, **22**, 85.

[8] Kohler, Tishler, Potter, and Thompson, *J. Amer. Chem. Soc.*, 1939, **61**, 1057.

derivative prepared from *m*-bromoanisole (25·4 g.) and magnesium (3·1 g.) in ether (200 c.c.) a solution of 2-*cyclo*hexylidene-ethyl bromide (21·5 g.) in ether (100 c.c.) was added slowly with stirring, and the mixture was heated under reflux for 2 hr., then cooled and decomposed with water. The product was isolated with ether and distilled under reduced pressure, giving m-2′-cyclo*hexylidene-ethylanisole*, b. p. 114—118°/0·4 mm. (Found: C, 83·5; H, 9·5. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%).

Reduction of m-2′-cyclo*Hexylidene-ethylanisole with Sodium in Liquid Ammonia.*—A solution of the above compound (7·8 g.) in alcohol (40 c.c.) and ether (50 c.c.) was added to liquid ammonia (700 c.c.) with stirring, which was continued for 4 hr. during the portionwise addition of sodium (11 g.). From the final colourless solution ammonia was allowed to evaporate, then water (300 c.c.) was added cautiously and the crude product (7·8 g.) was isolated with ether. Its ultraviolet absorption showed the presence of about 5% of unreduced material. A portion (5·7 g.) dissolved in alcohol (200 c.c.) containing 3N-sulphuric acid (14·5 c.c.) was kept at room temperature for 15 min., then diluted with water and extracted with ether. The concentrated ether extract (40 c.c.) was shaken twice with saturated aqueous sodium hydrogen sulphite (50 c.c.) for 15 hr. and the bisulphite compound separated by centrifugation. It was decomposed with N-sodium carbonate, and the product was isolated with ether and distilled under reduced pressure, giving 3-2′-cyclo*hexylidene-ethyl*cyclo*hex-*3*-enone* (2 g.), b. p. 104—106°/0·2 mm. (Found: C, 81·9; H, 10·1. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%). It showed no specific absorption above 220 mμ. Attempts to characterise it as the semicarbazone caused partial conversion into the semicarbazone of the αβ-unsaturated isomer, as shown by the light absorption of the product.

Isomerisation.—The unconjugated ketone (500 mg.), alcohol (80 c.c.), and 3N-sulphuric acid (20 c.c.) were boiled together under nitrogen for 1 hr. From the cooled and diluted solution the product was extracted with ether, and the ethereal extract was shaken with saturated sodium hydrogen sulphite in order to free it from starting material. The ethereal solution was washed, dried, and evaporated, and the residue treated with a solution of semicarbazide acetate in aqueous alcohol. Recrystallisation of the product from alcohol gave 3-2′-cyclo*hexylidene-ethyl*cyclo*hex-*2*-enone semicarbazone*, m. p. 170—171° (Found: C, 68·6; H, 9·1; N, 16·0. $C_{15}H_{23}ON_3$ requires C, 68·9; H, 8·9; N, 16·1%). Light absorption in EtOH: max. at 268 mμ (ε 28,900). The ketone, obtained by treatment with pyruvic acid in aqueous acetic acid in the usual manner, showed $\lambda_{max.}$ 235 mμ (ε 12,500 in EtOH). A portion (110 mg.) in alcohol (40 c.c.) containing 3N-sulphuric acid (10 c.c.) was heated under reflux under nitrogen for 24 hr. The product, isolated in the usual way, was a colourless oil, b. p. 160° (bath-temp.)/0·2 mm., which had $\lambda_{max.}$ 281 mμ (ε 17,800 in EtOH). Reaction with semicarbazide gave 3-2′-cyclo*hexylvinyl*cyclo*hex-*2*-enone semicarbazone* which formed leaflets (from alcohol), m. p. 203° (Found: C, 69·05; H, 8·8; N, 15·9. $C_{15}H_{23}ON_3$ requires C, 68·9; H, 8·9; N, 16·1%). It showed λ_{max} 298 mμ (ε 41,800 in EtOH).

2-*Bromo-*4*-methoxy-*NN*-dimethylbenzylamine.*—A stream of hydrogen chloride was passed through a vigorously stirred suspension of *m*-bromoanisole (72 g.) in 40% aqueous formaldehyde (60 g.) at 40° for 4 hr. The product was extracted with chloroform, and the extract washed, dried, and evaporated. Fractional distillation of the residue under reduced pressure gave 2-*bromo-*4*-methoxybenzyl chloride* (52 g.), b. p. 107°/1 mm. (Found: C, 41·1; H, 3·75. C_8H_8OClBr requires C, 40·8; H, 3·4%), and 5-*bromo-*2 : 4*-di(chloromethyl)anisole* (10 g.), b. p. 130—135°/1 mm., which separated from light petroleum (b. p. 40—60°) as needles, m. p. 79° (Found: C, 38·3; H, 3·5. $C_9H_9OCl_2Br$ requires C, 38·1; H, 3·2%).

The above monochloromethyl compound (21·4 g.) was heated under reflux for 1½ hr. with 25% aqueous dimethylamine (27 c.c.) and alcohol (180 c.c.). The alcohol was then removed and the mixture shaken with 3N-sulphuric acid and ether. The acid phase was made strongly alkaline with aqueous sodium hydroxide, and the product isolated with ether and distilled, giving 2-bromo-4-methoxy-*NN*-dimethylbenzylamine (13 g.), b. p. 88°/0·5 mm. The *picrate* separated from alcohol as yellow prisms, m. p. 135—138° (Found: C, 40·25; H, 3·8; N, 12·1. $C_{16}H_{17}O_8N_4Br$ requires C, 40·6; H, 3·6; N, 11·8%).

2-2′-cyclo*Hexylidene-ethyl-*4*-methoxy-*NN*-dimethylbenzylamine* (VII; R = $CH_2{\cdot}NMe_2$).—To magnesium (5·9 g.) in ether (10 c.c.) ethyl bromide (1 g.) was added and, when vigorous reaction had set in, a nitrogen atmosphere was maintained above the stirred mixture during the gradual addition of a mixture of the above tertiary base (30 g.), ethyl bromide (12·4 g.), and ether (150 c.c.). When this was complete the stirred mixture was heated under reflux for 1 hr., a solution of 2-*cyclo*hexylidene-ethyl bromide (49 g.) in ether (50 c.c.) was added slowly, and stirring and heating were continued for a further 2 hr. The mixture was cooled and treated with water (200 c.c.), the ether layer was washed and evaporated, and the residue extracted with 3N-sulphuric acid. The acid extract was made alkaline and the product isolated with ether and distilled, giving 2-2′-cyclo*hexylidene-ethyl-4-methoxy-*NN-*dimethylbenzylamine* (13 g.), b. p. 137—144°/0·3 mm. (Found: C, 78·1; H, 9·9; N, 5·9. $C_{18}H_{27}ON$ requires C, 79·1; H, 9·9; N, 5·9%). The methiodide formed plates (from alcohol–ether), m. p. 194° (decomp.).

Reduction of 2-2′-cyclo*Hexylidene-ethyl-4-methoxy-*NN-*dimethylbenzylamine with Sodium in Liquid Ammonia.*—A solution of the tertiary base (3·56 g.) in alcohol (14·5 c.c.) and ether (12 c.c.) was added to stirred liquid ammonia (150 c.c.), and sodium (5·5 g.) was added in small portions during 4 hr., after which stirring was continued for a further 4 hr. and the remaining blue colour finally discharged by adding alcohol (2·5 c.c.). When the ammonia had evaporated water (150 c.c.) was added to the stirred mixture, from which the crude product (3·44 g.) was isolated with ether. It was hydrolysed by keeping its solution in 0·28N-sulphuric acid at room temperature for ½ hr., and the product obtained by making the solution alkaline was isolated with ether. A solution of the hydrolysis product (3·25 g.) in ether (40 c.c.) was added slowly to a stirred suspension of lithium aluminium hydride (0·5 g.) in ether (10 c.c.), and the mixture was warmed under reflux for 1 hr. Excess of hydride was decomposed with saturated aqueous sodium sulphate, and the mixture was treated with anhydrous sodium sulphate and filtered, the solid residue being well washed with ether. Evaporation of the filtrate and washings gave a colourless oil (3·2 g.) which was dissolved in light petroleum (10 c.c.; b. p. 40—60°) and passed through neutral alumina (130 g.; deactivated by addition of 5% of water). The column was washed successively with light petroleum (500 c.c.; b. p. 40—60°), with light petroleum–benzene (1 : 1; 4 × 300 c.c.), with benzene (600 c.c.), and finally with 1 : 99 methanol–benzene (300 c.c.).

trans-1-2′-cyclo*Hexylidene-ethylidene-2-methylene*cyclo*hexane* (I). Evaporation of the first light petroleum–benzene eluate (300 c.c.) gave an oil (410 mg.) which on treatment with methyl iodide in benzene furnished 2-*dimethylaminomethyl-*1-2′-cyclo*hexylidene-ethyl*cyclo*hexene methiodide* as plates (from alcohol–ether), softening at 168°, resolidifying above 170°, and remelting at 230—255° (decomp.) (Found: C, 55·65; H, 8·5; N, 3·7. $C_{18}H_{32}NI$ requires C, 55·5; H, 8·3; N, 3·6%). It showed no specific light absorption above 220 mμ. A portion (36 mg.) was shaken in aqueous methanol (1 c.c.) with silver oxide (46·5 mg.) for ½ hr., then the filtered solution was evaporated and the residue distilled at 110°/0·5 mm. The distillate consisted of *trans*-1-2′-*cyclo*hexylidene-ethylidene-2-methylene*cyclo*hexane and had $\lambda_{max.}$ 270 mμ (ε 21,200), $\lambda_{min.}$ 230 mμ (ε 5700). Its infrared absorption spectrum was identical with that of authentic material prepared as described in Part I.

3-2′-cyclo*Hexylidene-ethyl-4-methylene*cyclo*hex-2-enone* (XIII). Evaporation of the 1 : 99 methanol–benzene eluate from the chromatogram yielded an oil (1·25 g.) consisting of crude 4-dimethylaminomethyl-3-2′-*cyclo*hexylidene-ethyl*cyclo*hex-3-en-ol. A portion (343 mg.) was converted in the usual manner into the methiodide and thence into the quaternary hydroxide, which was distilled at 130—140°/0·5 mm., giving a colourless viscous oil (192 mg.) showing $\lambda_{max.}$ 234 and 274 mμ in EtOH. It was shaken in light petroleum (10 c.c.; b. p. 40—60°) with manganese dioxide [9] (2 g.) for ¾ hr., after which the solution was filtered and evaporated and the product distilled at 110—130° (bath-temp.)/0·5 mm. Treatment of the distillate with semicarbazide in aqueous alcohol gave 3-2′-cyclo*hexylidene-ethyl-4-methylene*cyclo*hex-2-enone semicarbazone* as needles (from alcohol), m. p. 203—204° (Found: C, 70·5; H, 8·2; N, 15·5. $C_{16}H_{23}ON_3$ requires C, 70·3; H, 8·5; N, 15·4%). Light absorption: max. at 293 mμ (ε 34,500 in $CHCl_3$).

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THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.
DEPARTMENT OF ORGANIC CHEMISTRY,
THE UNIVERSITY, LEEDS, 2.

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[9] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.