Calciferol and its Relatives. Part I. The Synthesis of a Model Conjugated Semicyclic Triene.

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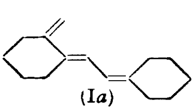
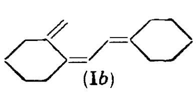
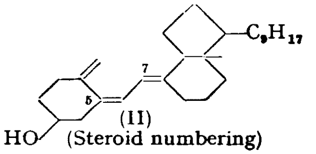
The triene, *trans*-1-2'-*cyclo*hexylidene-ethylidene-2-methylene*cyclo*hexane (I*a*), has been synthesised in two ways by application of Wittig and Schöllkopf's reaction (*Chem. Ber.*, 1954, **87**, 1318). Its unsaturated system differs from that of calciferol only in the *trans*-configuration of the central double bond.

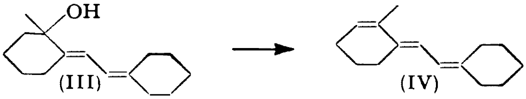
IN all but geometric detail the structure of calciferol has been known since 1935; more recently *X*-ray studies have defined it as the *cis*-5 : *trans*-7-compound (II) (steroid numbering) (Crowfoot and Dunitz, *Nature*, 1948, **162**, 608). The simplest model substance containing the remarkable unsaturated system of the vitamin is the *cis*-triene (I*b*), but neither this nor the *trans*-isomer (I*a*) has so far been described. Earlier work aimed at the synthesis of compounds of this type (Burkhardt *et al.*, *J.*, 1938, 545, 987; 1940, 10; Dimroth, *Ber.*, 1938, **71**, 1333, 1346; Dimroth and Jonsson, *ibid.*, p. 2658; Raphael and Sondheimer, *J.*, 1950, 3185) showed that the main difficulty lay in the semicyclic character of the double bonds. A double bond semicyclic to a *cyclo*hexane ring forms a system of high energy content (for references see Brown, Brewster, and Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467) and in consequence ionic eliminations designed for its introduction frequently take, under Saytzeff-type control, an alternative pathway; thus dehydration of the dienol (III) gives the monoendocyclic triene (IV) instead of the desired trisemicyclic isomer (I) (Dimroth, *loc. cit.*; cf. Inhoffen, Brückner, and Gründel, *Chem. Ber.*, 1954, **87**, 1).


(I*a*)


(I*b*)

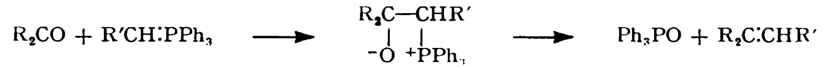


(II)
(Steroid numbering)



(III) (IV)

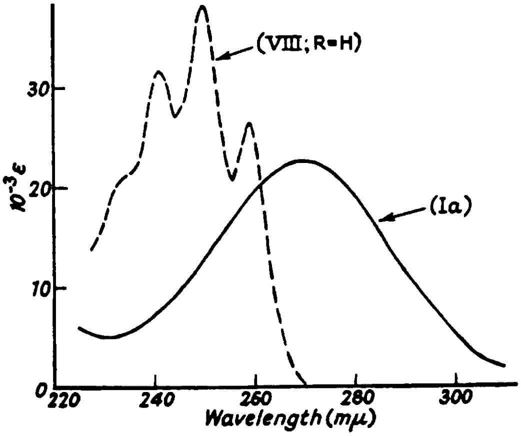
We have been engaged with experiments designed to overcome this difficulty; our first successful results were obtained by combining a proper choice of elimination method with a proper order of introduction of the three double bonds, and a synthesis of the *trans*-triene (I*a*) by this route will be described later. Wittig and Schöllkopf (*Chem. Ber.*, 1954, **87**, 1318) have meanwhile described a remarkable reaction, not subject to Saytzeff-type control, for the synthesis of olefins; it was clear to us that this reaction would be of value in synthetic work in the calciferol field. The reaction converts a carbonyl compound into an olefin in which the carbonyl-oxygen atom is replaced by an alkylidene group by the action of an alkylidenetriphenylphosphorane :



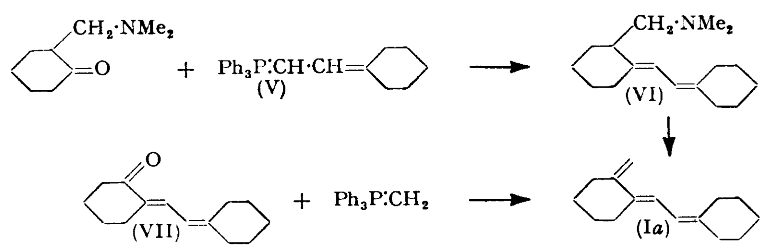
$$R_2CO + R'CH{:}PPh_3 \longrightarrow \begin{array}{c}R_2C\text{—}CHR' \\ |\quad\ | \\ {}^-O\ \ {}^+PPh_3\end{array} \longrightarrow Ph_3PO + R_2C{:}CHR'$$

and its application to synthesis of the *trans*-triene (I*a*) by the two independent routes outlined below forms the subject of the present paper.

In suitable cases Wittig and Schöllkopf obtained mixtures of *cis*- and *trans*-olefin from their reaction; thus allylidenetriphenylphosphorane and benzaldehyde gave equal amounts of *cis*- and *trans*-1-phenylbutadiene. Since we wished if possible to obtain the *cis*-triene (I*b*) it seemed appropriate to use the reaction to set up the central double bond of the triene. For this purpose the γγ-disubstituted " allylidene " compound (V) was prepared by treatment of triphenylphosphine with 2-*cyclo*hexylidene-ethyl bromide, followed by reaction of the quaternary bromide with butyl-lithium. The quaternisation proceeded, as expected, without allylic rearrangement, since the quaternary bromide showed no infrared absorption band near 890 cm.$^{-1}$ corresponding to a methylene (:CH_2) group. It was necessary to verify that reaction of the compound (V) with ketones was not attended by allylic rearrangement; there is a similarity (by no means complete) between the behaviour of alkylidenetriphenylphosphoranes and Grignard reagents, and when a Grignard reagent derived from a γ-substituted primary allyl halide reacts with a ketone, allylic rearrangement is known to take place (Roberts and Young, *J. Amer. Chem. Soc.*, 1945, **67**, 148; 1946, **68**, 1472). When the compound (V) reacted with *cyclo*hexanone, 1 : 2-di*cyclo*hexylidene-ethane (VIII; R = H) was obtained in good yield with no rearrangement. The structure of (VIII; R = H) was established by its absorption of 2·0 mols. of hydrogen in presence of palladium, by the formation of 1·6 mols. of *cyclo*hexanone on ozonolysis, and by its very characteristic light absorption (Figure and Table). The latter was closely similar to those



Light absorption of the diene (VIII; R = H) *and the triene* (I*a*) *in* EtOH.



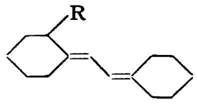
of the synthetic dienol (VIII; R = OH) (Dimroth and Jonsson, *loc. cit.*) and dihydrotachysterol (IX) (von Werder, *Z. physiol. Chem.*, 1939, **260**, 119), both compounds being known to contain a disemicyclic conjugated diene system.

Reaction of the phosphorane (V) with 2-dimethylaminomethyl*cyclo*hexanone gave a liquid basic diene (VI) which formed a homogeneous crystalline methiodide showing light absorption similar to, though less intense than, that of the diene (VIII; R = H). Only one geometrical form (VI) had therefore been produced by the reaction; this proved later to be the *trans*-form. Wittig and Schöllkopf found that the stilbene obtained by use of their method contained much more *trans*- (70%) than *cis*-isomer (30%); this indicates that steric factors may play a part in determining the *cis* : *trans* ratio, and the absence of appreciable amounts of the *cis*-isomer of (VI) may be due to the presence of the bulky dimethylaminomethyl group.

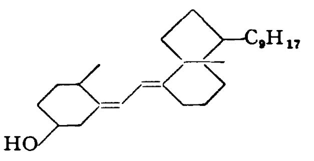
Thermal decomposition of the quaternary hydroxide derived from (VI) gave the triene (I*a*) as a crystalline solid, which absorbed 3·1 mols. of hydrogen in the presence of palladium. Its infrared absorption spectrum (liquid film) and that of calciferol (solid film) showed important similarities. Triplet C=C stretching frequencies, such as are usually shown by conjugated trienes, occur in the spectrum of calciferol at 1610, 1634, and 1653 cm.$^{-1}$; similar frequencies at 1605, 1626, and 1647 cm.$^{-1}$ are present in that of the synthetic triene. The semicyclic methylene group in calciferol causes a band at 887 cm.$^{-1}$ (out-of-plane =CH_2 deformation); a similar band at 885 cm.$^{-1}$ is present in the spectrum of the triene. A band in the spectrum of calciferol at 859 cm.$^{-1}$ is almost certainly due to out-of-plane =CH– deformation of the semicyclic methine groups; in acyclic compounds this frequency has the value 790—840 cm.$^{-1}$, but we have observed that this band has the higher frequency of 845—866 cm.$^{-1}$ in all the compounds so far examined which contain a semicyclic trisubstituted double bond (cf. Inhoffen, Brückner, Gründel, and Quinkert, *Chem. Ber.*, 1954, **87**, 1407). The diene (VI; R = H) shows a similar band at 863 cm.$^{-1}$ and the triene (I*a*) one at 866 cm.$^{-1}$.

Light absorption of semicyclic conjugated dienes.

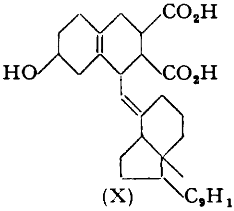
	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$
1 : 2-Di*cyclo*hexylidene-ethane (VIII; R = H)	241	31·6	250	38·1	259	26·5
Dienol (VIII; R = OH)	240	29·5	248	34·9	258	23·7
Dihydrotachysterol (IX)	242	30·2	251	40·3	261	25·9



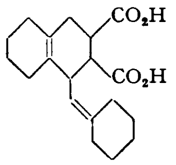
(VIII)



(IX)



(X)



(XI)

The triene (I*a*) reacted with maleic anhydride to give, after hydrolysis, the dibasic acid (XI), which has a structure analogous to that of the corresponding product (X) from calciferol (Windaus and Thiele, *Annalen*, 1935, **521**, 160). The structure of the adduct (XI) was established by the absence of a band near 890 cm.$^{-1}$ in its infrared absorption spectrum, which shows that no semicyclic methylene group is present, and by the results of ozonolysis, which gave 0·6 mol. of *cyclo*hexanone. The reaction of the triene (I*a*) with maleic anhydride was about seven times as fast as that of calciferol. This is in agreement with the *trans*-configuration assigned to the triene (I*a*); the superior reactivity of *trans*-dienes in comparison with the *cis*-isomers is well known (see, *e.g.*, Crombie, *Quart. Rev.*, 1952, **6**, 126). Evidence for the *trans*-configuration of (I*a*) is also provided by its light absorption (Figure), $\lambda_{max.}$ 269·5 mμ (ε 22,700) which is more intense and at a longer wavelength than that of calciferol, which has $\lambda_{max.}$ 265 mμ (ε 18,300); this would be expected from the more fully extended nature of the chromophore of (I*a*); the lower values observed for calciferol are not due to any steric hindrance at the 7 : 8-double bond, as shown by atomic models, but to the less fully extended chromophore and, possibly, to some slight degree of steric hindrance at the 5 : 6-double bond. The *trans*-configuration of the triene (I*a*) has further been demonstrated by its production from methylenetriphenylphosphorane and 1-2′-*cyclo*hexylidene-ethylidene*cyclo*hexanone (VII), which, from its method of preparation, almost certainly has the *trans*-configuration.

The light absorption of the synthetic triene (I*a*) provides support for the structure (II) assigned to calciferol on the basis of *X*-ray data; in particular it excludes the possibility, recently suggested by Sondheimer and Wheeler (*J. Soc. Chem. Ind.*, 1955, 714), that calciferol is the *trans*-5 : *trans*-7-isomer and that structure (II) represents precalciferol.

Modifications of the above synthetic method designed to permit the preparation of the *cis*-triene (I*b*) are being investigated.

EXPERIMENTAL

cyclo*Hexylidene-ethyltriphenylphosphonium Bromide*.—Triphenylphosphine (27·2 g.) was shaken with a solution of *cyclo*hexylidene-ethyl bromide (24·6 g.) in benzene at 0° until all had dissolved (10 min.). The mixture was kept at room temperature overnight, and the solid collected, washed with benzene, and dried. Recrystallisation from alcohol–benzene gave the quaternary *bromide* (30 g.), m. p. 164° (Found : Br^-, 17·5. $C_{26}H_{28}PBr$ requires Br^-, 17·8%).

*Di*cyclo*hexylidene-ethane*.—The quaternary bromide (10 g.), suspended in dry ether (100 c.c.), was treated under oxygen-free nitrogen with 1·3N-ethereal butyl-lithium (21·5 c.c.); the solid rapidly dissolved and the red solution was kept overnight at room temperature. After the addition of *cyclo*hexanone (2·56 g.) in ether (15 c.c.) the solution was shaken for 2 hr., and the ether removed by distillation and replaced by tetrahydrofuran; the solution was heated under reflux for 2 hr., and the tetrahydrofuran removed under reduced pressure. The residue was extracted with ether, and the ethereal solution washed with water, dried, and evaporated. Distillation of the residue gave *di*cyclo*hexylidene-ethane* (3 g.), b. p. 85—87°/0·1 mm., which separated from light petroleum (b. p. 40—60°) as colourless crystals, m. p. 45—47° (Found : C, 88·55; H, 11·55. $C_{14}H_{22}$ requires C, 88·3; H, 11·7%).

Ozonolysis. A solution of the diene (50 mg.) in chloroform (10 c.c.) was saturated with ozone at −25°, the chloroform removed under reduced pressure, and the residue heated with water at 95° for 10 min. The mixture was then shaken with silver oxide (2 g.) for 15 min. and filtered, and the filtrate was made alkaline with sodium hydroxide solution and extracted with ether, removal of which gave *cyclo*hexanone, identified as the 2 : 4-dinitrophenylhydrazone (113 mg.), m. p. and mixed m. p. 161°.

trans-1-*Dimethylaminomethyl*-2-2′-cyclo*hexylidene-ethylidene*cyclo*hexane*.—To a stirred suspension of *cyclo*hexylidene-ethyltriphenylphosphonium bromide (17 g.) in ether (200 c.c.) under oxygen-free nitrogen 1·3N-ethereal butyl-lithium (29 c.c.) was added, and stirring continued overnight. To the ice-cold solution 2-dimethylaminomethyl*cyclo*hexanone (5·8 g.) in ether (50 c.c.) was added, the stirred solution was allowed to warm to room temperature, and stirring was continued for 24 hr. After the addition of water (2 c.c.) an excess of dilute hydrochloric acid was added, the acid layer was separated and made alkaline with sodium carbonate, and the basic material extracted with ether. Distillation gave a fraction (1·7 g.), b. p. 105—125° (bath-temp.)/3×10^{-5} mm., which was treated under nitrogen with ether and methyl iodide. The *methiodide* (1·2 g.), crystallised from alcohol–benzene, had m. p. 214° (Found : N, 3·4; I, 32·3. $C_{18}H_{32}NI$, requires N, 3·6; I, 32·6%). Light absorption in alcohol : $\lambda_{max.}$ 242, 250, and 259 mμ ($10^{-3}\varepsilon$ 27·8, 31·0, and 20·3).

trans-1-2′-cyclo*Hexylidene-ethylidene-2-methylene*cyclo*hexane*.—(*a*) The above methiodide (1·2 g.) in water (30 c.c.) was shaken with silver oxide (from 3·6 g. of silver nitrate) for 4 hr., the filtered solution evaporated under reduced pressure, and the residue distilled at 60—95° (bath-temp.)/10^{-4} mm. The distillate (250 mg.) crystallised from light petroleum (b. p. 40—60°) at −40°, giving the *triene* as colourless prisms (165 mg.), m. p. 14—16° (Found : C, 89·3; H, 10·7. $C_{15}H_{22}$ requires C, 89·0; H, 11·0%).

A repetition of this experiment with crude methiodide obtained from the mother liquors gave as product a mixture containing a small amount of the above triene and larger amounts of other unsaturated materials which showed rapidly rising absorption in the far ultraviolet region; no isomer absorbing near 265 mμ was detectable.

(*b*) To a suspension of methyltriphenylphosphonium bromide (1·9 g.) in ether (50 c.c.) under oxygen-free nitrogen 1·3N-ethereal butyl-lithium (4·1 c.c.) was added and the mixture stirred for 4 hr. A solution of 2-2′-*cyclo*hexylidene-ethylidene*cyclo*hexanone (1·0 g.) in ether (10 c.c.) was then added and the mixture stirred overnight, filtered, washed with water, dried, and evaporated. Distillation at 90° (bath-temp.)/5 × 10^{-5} mm. gave the triene (0·55 g.) which after crystallisation from light petroleum (b. p. 40—60°) had m. p. 14—16° and showed ultraviolet and infrared absorption identical with that prepared by method (*a*). A portion of the triene (0·1 g.) was isomerised by aqueous-alcoholic 0·25% sulphuric acid at room temperature for 22 hr., giving an isomeric triene, $\lambda_{max.}$ (alcohol) 284 mμ (ε 39,400).

Reaction of the trans-*Triene with Maleic Anhydride.*—(*a*) A mixture of the triene (162 mg.), maleic anhydride (95 mg.), and benzene (10 c.c.) was heated under reflux for 3½ hr., filtered, and evaporated, and the residue heated at 100° for 40 min. with 10% aqueous sodium hydroxide (15 c.c.). The cooled and acidified solution was extracted with ether, removal of which gave 1-cyclo*hexylidenemethyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydronaphthalene*-2 : 3-*dicarboxylic acid* (XI) (150 mg.) which, crystallised from alcohol, had m. p. 178—180° (decomp.) (Found : C, 72·1; H, 8·0. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%).

Ozonolysis of a sample (76·7 mg.) in chloroform (10 c.c.) in the usual manner gave *cyclo*hexanone as the sole neutral product, isolated as the 2 : 4-dinitrophenylhydrazone (34 mg.).

(*b*) For comparison of the rates of reaction of the triene and calciferol with maleic anhydride, two solutions were prepared containing maleic anhydride (5·2 × 10^{-3} mole/l.); to one was added calciferol (3·69 × 10^{-5} mole/l.), to the other the triene (4·62 × 10^{-5} mole/l.). Both solutions were kept at 18°, and the logarithms of their respective optical densities at 265 and 269 mμ measured and plotted against time. Two straight lines were obtained, the ratio of whose gradients (6·9) gave the ratio of the velocity constants of the two reactions.

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