163. *Calciferol and its Relatives. Part IV.* A Non-photochemical Synthesis of a Model* cis-*Triene.*

By I. T. HARRISON and B. LYTHGOE.

The bicyclic αβ-unsaturated lactones (III) and (IV) were studied as possible intermediates for a synthesis of the *cis*-triene (II), a simple model for calciferol.

The γ-lactone (III) was transformed in four steps into the *cis*-dienol (XIV) and thence into the *cis*-dienone (XV). This sequence, in conjunction with the conversion of (XV) into (II) described in the preceding paper, provides a new synthesis of the model *cis*-triene by a non-photochemical route.

THE present work continues that of the preceding paper in seeking methods to secure the *cis*-configuration of the central double bond of trienes of the calciferol type. The photochemical method there described provided a rational partial synthesis of calciferol, but one which did not completely satisfy us because a photochemical route (admittedly complex) was already available in the normal preparation from ergosterol. We have therefore investigated an alternative approach to calciferol (I), independent of photochemical reactions. As before, the initial experiments were carried out on model compounds, and we now report a second synthesis of the model *cis*-triene (II), based on the established method [1] of preparing *cis*-ethylenic compounds by ring-opening of cyclic unsaturated intermediates.

The bicyclic αβ-unsaturated lactones (III) and (IV) appeared to be suitable as intermediates for this purpose. They contain one ring of the triene (II) and its attached *cis*-semicyclic double bond, together with functional groups at positions appropriate for construction of the rest of the triene molecule. The γ-lactone (III) is obtained [2] by dehydrating 2-oxo*cyclo*hexylacetic acid, but the δ-lactone (IV) was described only very recently. Belleau [3] has prepared it by a Prins reaction between trioxan and *cyclo*hex-1-enylacetic acid in dioxan containing sulphuric acid. The method by which the lactone (IV) was prepared for the present work differs from Belleau's and will be reported in a separate paper.

We shall describe first our experiments on the δ-lactone (IV). It is a bicyclic analogue of the lactone [4] (VI), which Linstead and his associates [5] have shown can be converted

---

* Part III, Harrison and Lythgoe, preceding paper.

[1] For examples, see Crombie, *Quart. Rev.*, 1952, **6**, 101 (p. 135).

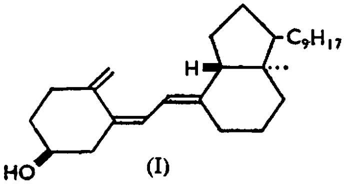
[2] Newman and VanderWerf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.

[3] Belleau, *Canad. J. Chem.*, 1957, **35**, 673.

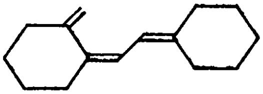
[4] Haynes and Jones, *J.*, 1946, 954.

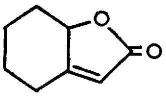
[5] Eisner, Elvidge, and Linstead, *J.*, 1953, 1373.

into hexa-*cis*-2-*trans*-4-dienoic acid by treatment with methanolic sodium methoxide. If the bicyclic lactone reacted in the same way it would give the *cis*-dienoic acid (V) which contains two of the double bonds of the triene (II) and obvious facilities for constructing the third. However, neither under Linstead's conditions nor under others more vigorous was any conjugated dienoic acid obtained from the bicyclic lactone (IV); the course of the reaction was not determined, but the light absorption of the dienoic acid would have allowed even small amounts to be detected. The high energy of the semicyclic methylene double bond in compound (V) was, of course, expected to make the reaction more difficult than that studied by Linstead. Alternative methods of opening the lactone ring of (IV) were therefore used, as shown below.

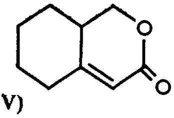


(I)

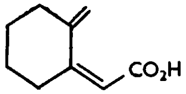

(II)



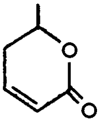
(III)



(IV)

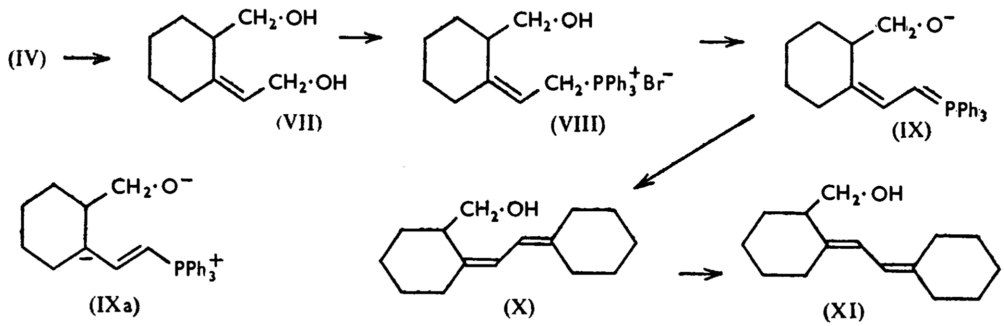


(V)



(VI)

The δ-lactone (IV) was reduced with lithium aluminium hydride to the diol (VII), characterised as the di-*p*-nitrobenzoate. The *cis*-geometry was retained during this reduction, as during similar reduction [6] of *cis*-crotonic acid. Next, we wished to replace the allylic hydroxyl group of the diol by a bromine atom, whilst leaving the rest of the molecule unchanged. Reagents permitting a unimolecular replacement mechanism were expected to cause some geometric inversion, so we chose triphenyl phosphite benzylobromide as the reagent; Landauer and Rydon [7] have shown that the corresponding methiodide converts *neo*pentyl alcohol into the iodide without rearrangement. There is also evidence in Rydon's work that such reagents attack allylic primary alcohols more rapidly than ordinary primary alcohols, which in turn react more rapidly than ordinary secondary alcohols. We found that reaction of the diol (VII) with slightly more than 1 mol. of triphenyl phosphite benzylobromide effected the replacement of the allylic hydroxyl group fairly selectively, and when the crude product was treated with triphenylphosphine it gave the crystalline phosphonium bromide (VIII).



The derived Wittig [8] reagent (IX), obtained by the action of butyl-lithium (1·9 mols.), reacted with *cyclo*hexanone, giving the *cis*-dienol (X) together with a small amount of the

---

[6] Hatch and Nesbitt, *J. Amer. Chem. Soc.*, 1950, **72**, 727.
[7] Landauer and Rydon, *J.*, 1953, 2224.
[8] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.

trans-isomer (XI). Three features of this reaction deserve mention. First, it will be noted that no protection was necessary for the hydroxyl group of (VIII); the reaction may be compared with that described in Part III, where the unprotected hydroxyl group was present in the ketonic, instead of the phosphorane, component. Secondly, it will be noted that the phosphorane component (IX) is a resonant structure, to which the form (IXa) contributes. In this form the *cis*-double bond has become a single bond; this implies that in the actual molecule the *cis*-double bond has only partial double-bond character, so that its resistance to torsion is less than that of an isolated double bond. It would therefore be expected to undergo geometric inversion relatively easily, and this probably accounts for the production of the *trans*-isomer (XI): in practice it was advisable to generate the reagent (IX), and also to bring it into reaction with *cyclo*hexanone, at low temperatures, as otherwise a larger proportion of the unwanted *trans*-isomer (XI) was obtained. Finally, we have observed that, in Wittig reactions where, as in the present example, a new double bond is formed in conjugation with an existing one, the intermediate zwitterion decomposes readily at room temperature, so that the thermal decomposition frequently used is unnecessary.

The *cis*-dienol (X) was readily freed from the *trans*-isomer (XI) by crystallisation, and then had $\lambda_{max.}$ 242, 250, and 259 mμ (ε 34,300, 38,800, and 27,400 in EtOH). The *trans*-isomer (XI) was best separated as the 3 : 5-dinitrobenzoate, which showed ultraviolet absorption closely similar to those of the *cis*-dienol (X) and its 3 : 5-dinitrobenzoate. This confirms the gross structure of both isomers, since triple maxima at these positions are characteristic[9] of derivatives of di*cyclo*hexylidene-ethane. The *cis*-configuration of the isomer (X) was established by the inversion of its 3 : 5-dinitrobenzoate into that of the *trans*-isomer (XI) in the presence of iodine.

The conversion of *cyclo*hexylmethanol into methylene*cyclo*hexane, formally a dehydration, must be performed indirectly because of the semicyclic nature of the new double bond. Superficially, it appears that the *cis*-dienol (X) could be similarly converted into the desired triene (II), and more readily because of the conjugation present in the triene. We were, however, unable to effect this change. The methods attempted may be summarised as follows. (*a*) *cyclo*Hexylmethyl iodide gives[10] methylene*cyclo*hexane when treated with a base. We were unable to obtain the iodide corresponding to the dienol (X) by treating the dienol with triphenyl phosphite methiodide, or by treating the toluene-*p*-sulphonate with sodium iodide. Direct elimination from the toluene-*p*-sulphonate by reaction with bases was likewise attempted without success; atomic models show that approach to the relevant hydrogen atom is seriously hindered. (*b*) The toluene-*p*-sulphonate of the dienol, unlike that of *cyclo*hexylmethanol, could not be quaternised by treatment with trimethylamine, so that the Hofmann elimination method, by which the *trans*-isomer of the triene (II) has been prepared,[9] was inapplicable here. Displacement reactions at the hydroxymethyl-carbon atom of derivatives of the dienol (X) are, it appears, sterically hindered. (*c*) Pyrolysis[11] of the acetate of the dienol (X) left it unchanged or, under more vigorous conditions, decomposed it completely. (*d*) Whereas benzyl *cyclo*hexylmethyl ether and butyl-lithium give methylene*cyclo*hexane[12] the triene (II) could not be similarly obtained from the benzyl ether of the dienol (X). With the failure of these attempts work on the above route was brought to an end.

We then returned to the bicyclic γ-lactone (III) which we had reduced in earlier experiments to the diol (XII). At that time we were unable to distinguish effectively by selective esterification between the two hydroxyl groups of the diol, but later the need to do so was removed by the finding that triphenyl phosphite benzylobromide was selective

---

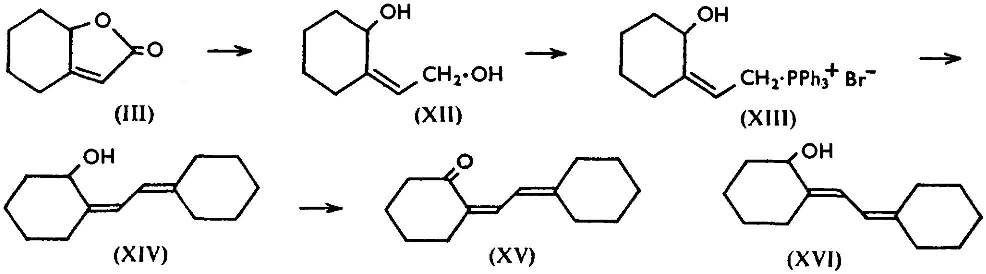
[9] Harrison, Lythgoe, and Trippett, *J.*, 1955, 4016.

[10] Faworski and Borgmann, *Ber.*, 1907, **40**, 4865.

[11] Bailey and King, *J. Amer. Chem. Soc.*, 1955, **77**, 75; Bailey, Hewitt, and King, *ibid.*, p. 357; and later papers by Bailey *et al.*

[12] Method based on the formation of ethylene in similar reactions studied by Wittig and Lohmann, *Annalen*, 1942, **550**, 260; Letsinger and Pollart, *J. Amer. Chem. Soc.*, 1956, **78**, 6079.

in its action upon alcohols. By using this reagent in the way already described, the diol (XII) was converted into the crystalline phosphonium bromide (XIII), and thence, by a Wittig reaction with *cyclo*hexanone, into the *cis*-dienol (XIV). The gross structure of this dienol was confirmed by its ultraviolet absorption, which is closely similar to that of the known *trans*-isomer (XVI);[13] since the two compounds were not identical the new dienol had the *cis*-configuration.



On oxidation with manganese dioxide the *cis*-dienol (XIV) was converted into the *cis*-dienone (XV), identical with an authentic specimen prepared by the photoisomerisation described in the preceding paper; additional evidence of the identity was provided by reducing the photochemical sample with sodium borohydride, which gave the *cis*-dienol (XIV) identical with that prepared by the chemical synthesis.

The conversion of the *cis*-dienone (XV) into the *cis*-triene (II) by means of a Wittig reaction was described in the preceding paper, so that the present work constitutes a new synthesis of the model triene by non-photochemical methods. Its extension to a synthesis of one of the vitamins D is under study.

EXPERIMENTAL

cis-*2-(2-Hydroxymethyl*cyclo*hexylidene)-ethanol* (VII).—A solution of the δ-lactone (IV) (55·5 g.) in ether (250 c.c.) was added during 30 min. to a stirred and cooled (−15°) solution of lithium aluminium hydride (13 g.) in ether (500 c.c.); stirring was continued at room temperature for a further 2 hr. Ethyl acetate (50 c.c.) in ether (100 c.c.) was then added, followed by saturated aqueous ammonium chloride (100 c.c.), after which the mixture was filtered and the residue washed with ether. The ether was removed from the united ethereal solutions and the residual viscous oil (55 g.) was dried by distillation with benzene. The p-*nitrobenzoate* separated from alcohol in small crystals, m. p. 131—132° (Found: C, 60·65; H, 5·15. $C_{23}H_{22}O_8N_2$ requires C, 60·8; H, 4·9%).

cis-*2-(2-Hydroxymethyl*cyclo*hexylidene)-ethyltriphenylphosphonium Bromide* (VIII).—Triphenyl phosphite benzylobromide was prepared from triphenyl phosphite (119 g.) and benzyl bromide (63 g.) at 170° (sealed tube; 5 hr.). A solution of the reagent in tetrahydrofuran (200 c.c.) was added during 30 min. to a stirred and cooled (0°) solution of the diol (VII) (52·5 g.) in tetrahydrofuran (700 c.c.). A solution of triphenylphosphine (88 g.) in ether (250 c.c.) was then added, and the mixture was kept overnight at room temperature. The crystalline deposit (44·5 g.) was collected, the filtrate was evaporated under reduced pressure, and the residual oil washed with ether (4 × 1 l.), the washings being discarded. Crystallisation of the residue from tetrahydrofuran gave a further crop (33 g.) of crystals. The combined crops were crystallised from hot chloroform by addition of tetrahydrofuran, giving the *phosphonium bromide* (67 g.) as prisms, m. p. 218° (Found: Br^-, 16·6. $C_{27}H_{30}OPBr$ requires Br^-, 16·6%).

cis-1-2′-cyclo*Hexylidene-ethylidene-2-hydroxymethyl*cyclo*hexane* (X).—The above phosphonium bromide (17 g.) was finely powdered and to its stirred and cooled (−25°) suspension in tetrahydrofuran (700 c.c.) under nitrogen 1·13N-ethereal butyl-lithium (59·5 c.c.) was slowly added. When the solution had become homogeneous, *cyclo*hexanone (10 c.c.) was added, and the solution was allowed to warm to 5°; the deep red colour then faded to orange. The solution was kept overnight at room temperature, the solvents were removed under reduced pressure,

---

[13] Dimroth and Jonsson, *Ber.*, 1938, **71**, 2658.

and the residue was shaken with light petroleum (250 c.c.; b. p. 40—60°) to induce crystallisation of the triphenylphosphine oxide, which was then removed. The filtrate was shaken with 66% aqueous ethanol, and the light petroleum phase evaporated, finally at 40°/0·2 mm. in order to remove any *cyclo*hexanone. The product (11 g.) was spectrophotometrically 60% pure; it was chromatographed on neutral alumina (250 g., grade III). Development with light petroleum (1 l.; b. p. 40—60°) gave a fraction (7·0 g.; 63% pure); continued development with light petroleum (1 l.; b. p. 60—80°) gave a further fraction (0·76 g.; 90% pure); development with benzene (500 c.c.) gave a further fraction (1·25 g.; 74% pure). Rechromatography of the first and the third fraction gave 4·16 g. of material *ca.* 85% pure; it was combined with the second fraction and crystallised from aqueous methanol, giving needles (3·3 g.), m. p. 68·5°. Recrystallisation from light petroleum, b. p. 40—60°, gave the pure cis-*dienol*, m. p. 70° (Found: C, 81·55; H, 10·85. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%). The 3 : 5-*dinitrobenzoate* separated from light petroleum (b. p. 60—80°) as yellow needles, m. p. 126° (Found: C, 63·85; H, 6·45; N, 7·0. $C_{22}H_{26}O_6N_2$ requires C, 63·7; H, 6·3; N, 6·8%), and had $\lambda_{max.}$ 240·5, 249, and 258 mμ (ε 43,100, 42,400, and 28,300 in EtOH).

When a portion of the above dienol of purity *ca.* 85% (*i.e.*, before crystallisation) was esterified with 3 : 5-dinitrobenzoyl chloride in pyridine it furnished a product which was separated by crystallisation into the more soluble 3 : 5-dinitrobenzoate of the above *cis*-dienol (81%) and the less soluble 3 : 5-*dinitrobenzoate* of the isomeric *trans*-dienol (4%), compact yellow needle aggregates (from alcohol), m. p. 144°, depressed to 106—110° on admixture with the *cis*-isomer (Found: C, 63·4; H, 6·45%). This had $\lambda_{max.}$ 240·5, 249, and 258 mμ (ε 44,100, 44,200, and 29,200 in EtOH). When the above dienol was prepared by a Wittig reaction at *ca.* 40°, its composition, determined by the 3 : 5-dinitrobenzoate method, was *cis*- : *trans*-dienol = 4 : 1.

A solution of the 3 : 5-dinitrobenzoate of the *cis*-dienol (30 mg.) in light petroleum (30 c.c.) containing iodine (2 mg.) was heated under reflux for 10 hr. and the product crystallised from alcohol; this gave (*a*) the ester of the *trans*-dienol (12 mg.), m. p. and mixed m. p. 143°, and (*b*) unchanged *cis*-material (8 mg.), m. p. 126°.

*Methylene*cyclo*hexane from Benzyl*cyclo*hexylmethyl Ether* (with A. Masood).—The benzyl ether (5·1 g.) and 0·76N-ethereal butyl-lithium (37 c.c.) were kept at room temperature for 10 hr., and the solution was diluted with ether, washed with water, dried, and distilled through a Vigreux column. The first portion of the ether distillate was rejected; the later fraction, collected from 70° to 90°, contained ether and methylene*cyclo*hexane, identified as the nitrosopiperidide, m. p. 126—127° (Found: C, 68·7; H, 10·5. Calc. for $C_{12}H_{22}ON_2$: C, 68·5; H, 10·5%). The yield of the hydrocarbon, determined by titration with bromine, was 60%.

cis-2-(2-*Hydroxy*cyclo*hexylidene*)-*ethanol* (XII).—Reduction of the γ-lactone (III) (15 g.) by lithium aluminium hydride as described for the δ-lactone (IV) gave the crude diol (15 g.), b. p. 117—120°/6 × 10^{-4} mm. The *di*-p-*nitrobenzoate* separated from ethyl acetate as pale yellow needles, m. p. 132° (Found: C, 60·25; H, 4·6; N, 6·55. $C_{22}H_{20}O_8N_2$ requires C, 60·0; H, 4·5; N, 6·4%).

cis-2-(2-*Hydroxy*cyclo*hexylidene*)-*ethyltriphenylphosphonium Bromide* (XIII).—Triphenyl phosphite (15·4 g.) and benzyl bromide (8·1 g.) were kept together at 120° with exclusion of moisture for 48 hr. The cooled product crystallised from tetrahydrofuran (40 c.c.), giving triphenyl phosphite benzylobromide (19 g.) as very hygroscopic prisms, m. p. 160°. A portion (15 g.) was melted in a vacuum and then dissolved whilst still warm in tetrahydrofuran (20 c.c.); the solution was added to a stirred and cooled (cold water) solution of the diol (XII) (6 g.) and triphenylphosphine (8·2 g.) in tetrahydrofuran (40 c.c.). The mixture was kept overnight, the tetrahydrofuran removed under reduced pressure, and the syrupy residue washed several times with ether, the washings being discarded. Crystallisation of the residue from tetrahydrofuran and then from alcohol–tetrahydrofuran gave the phosphonium bromide (4·02 g.) as colourless prisms, m. p. *ca.* 102—108° (gas evolution). This material was an ethanol solvate which could not be completely desolvated without decomposition. Crystallisation from water gave the *monohydrate*, m. p. 110—116° (decomp.) (Found: Br^-, 16·3. $C_{26}H_{28}OPBr,H_2O$ requires Br^-, 16·5%). This material also decomposed when complete dehydration was attempted.

cis-2-2′-cyclo*Hexylidene-ethylidene*cyclo*hexanol* (XIV).—(*a*) The above ethanol solvate (2·32 g.) was finely powdered and suspended in tetrahydrofuran (40 c.c.), and to the stirred suspension under nitrogen at −65° was added during 5 min. ethereal butyl-lithium (3 mols.). After the addition of *cyclo*hexanone (3 c.c.) the solution was allowed to attain room temperature, then kept for 18 hr. Water (5 c.c.) was added, the solvents were removed under strongly reduced pressure, and the residue was distributed in the usual manner between 50% methanol (50 c.c.) and benzene (50 c.c.). The contents of the benzene layer were chromatographed on neutral alumina (100 g.; Grade II), development being first with light petroleum (b. p. 40—60°) and later with benzene. One fraction of the benzene eluate provided an oil (0·41 g.) which crystallised from light petroleum (b. p. 40—60°), giving the cis-*dienol* (251 mg.), as needles m. p. 110—111° (Found: C, 81·5; H, 10·55. $C_{14}H_{22}O$ requires C, 81·6; H, 10·8%), $\lambda_{max.}$ 240, 247, and 256 mμ (ε 30,300, 35,200, and 23,600 in EtOH). The isomeric *trans*-dienol has m. p. 125—126° (cf. ref. 13).

(*b*) *cis*-2-2′-*cyclo*Hexylidene-ethylidene*cyclo*hexanone (230 mg.), prepared by the photoisomerisation described in Part III, was reduced in methanol (7 c.c.) and water (0·3 c.c.) by gradual addition of sodium borohydride. Dilution with water, isolation with ether, and crystallisation from light petroleum (b. p. 60—80°) gave the *cis*-dienol (210 mg.), m. p. 110—111°, undepressed on admixture with material obtained by method (*a*).

cis-2-2′-cyclo*Hexylidene-ethylidene*cyclo*hexanone* (XV).—The *cis*-dienol (100 mg.), prepared by method (*a*), was dissolved in ether (150 c.c.) and shaken with manganese dioxide (13 g. added in small portions) during 5 hr. The solution was filtered, the residue was washed thoroughly with ether, and the filtrate and washings were combined and evaporated under reduced pressure. Crystallisation of the residue from alcohol at −40° gave the *cis*-dienone (21 mg.), m. p. 32—32·5°, undepressed on admixture with material prepared as described in Part III; it had $\lambda_{max.}$ 304—305 mμ (ε 15,000 in EtOH).

We gratefully acknowledge a grant from Imperial Chemical Industries Limited. One of us (I. T. H.) thanks the Department of Scientific and Industrial Research for a Maintenance Award.

DEPARTMENT OF ORGANIC CHEMISTRY,
THE UNIVERSITY, LEEDS, 2.

[*Received, October 16th,* 1957.]