162. *Calciferol and its Relatives. Part III.* Partial Synthesis of Calciferol and of* epi*Calciferol.*[1]

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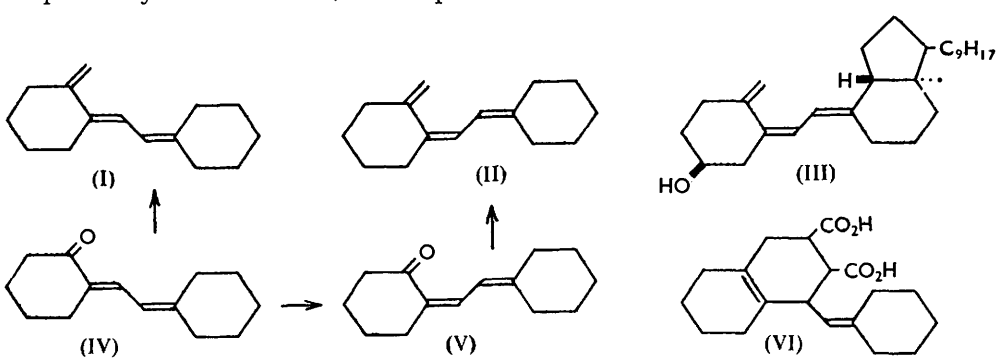
The *cis*-triene (II), a simple model for calciferol, has been prepared from the *cis*-dienone (V), obtained by photoisomerisation of the *trans*-dienone (IV). By extending the method, calciferol and *epi*calciferol have been obtained in a partial synthesis from the aldehyde (VII).

Two main difficulties impede synthesis of calciferol; they arise from the semicyclic disposition of the three conjugated double bonds and from the *cis*-configuration of the central member. We have attempted in this series to overcome these difficulties separately in model synthetic work, aiming first at the trisemicyclic *trans*-triene (I), and later at the *cis*-isomer (II) which contains essentially the same conjugated system as calciferol (III). If these model studies were successful it seemed unlikely that their extension to provide for the special features of the vitamin (hydroxyl group and bicyclic CD-system) would meet major difficulties.

Completion of experiments leading to the *trans*-triene (I) has been reported.[2,*] The triene was first * obtained by established elimination methods of forming the double bonds, but the advent of Wittig and Schöllkopf's [3] reaction provided an alternative method of constructing semicyclic double bonds which was clearly to be of great value in the present field. We applied this reaction to construct the central double bond of the triene (I) in a synthesis [2] using 2-dimethylaminomethyl*cyclo*hexanone as the ketonic starting material, and also to construct the terminal methylene double bond in a further synthesis using the *trans*-dienone (IV) as the ketonic component. The last is the most effective of the three available methods. Inhoffen and his associates [4] have also used the Wittig reaction independently in related work, some aspects of which are referred to below.



The above methods give exclusively trienes with the *trans*-configuration; the problem of securing a central *cis*-double bond remained for study. We have obtained solutions by two very different methods, which are reported in this and the following paper. The present paper describes the simpler of the two methods in its application to a synthesis of the *cis*-triene (II) and also to a partial synthesis of calciferol.

The most desirable intermediate for a synthesis of the *cis*-triene (II) was clearly the *cis*-dienone (V). Few chemical methods for the preparation of *cis*-αβ-unsaturated ketones have been reported in the literature. The semihydrogenation of acetylenic ketones, used

* Part II, Lythgoe, Trippett, and Watkins, *J.*, 1956, 4060.

[1] A preliminary report appeared in *Proc.*, 1957, 261.
[2] Harrison, Lythgoe, and Trippett, *Chem. and Ind.*, 1955, 507; *J.*, 1955, 4016.
[3] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.
[4] Inhoffen, Kath, Sticherling, and Brückner, *Annalen*, 1957, **603**, 25; cf. *Angew. Chem.*, 1955, **67**, 276.

recently by Schinz and his colleagues,[5] is inapplicable to the present case. On a few occasions a *cis*-αβ-unsaturated ketone has been obtained as the product of an aldol condensation; an example is the formation of a *cis*-*p*-methoxybenzylidene derivative from 6-methoxy-1-tetralone.[6] Reaction [7] of *cyclo*hexanone and *cyclo*hexylideneacetaldehyde gives the *trans*-dienone (IV), its *trans*-nature being shown by its conversion into the *trans*-triene (I); we varied the conditions of the aldol condensation in attempts to isolate some *cis*-dienone, but without success.

On the other hand, *cis*-αβ-unsaturated ketones have long been known as irradiation products of the *trans*-isomers. Paal and Schulze [8] recorded an early example in the quantitative isomerisation of dibenzoylethylene to its *cis*-isomer by sunlight, and more recently Lutz and Jordan [9] found that irradiation of *trans*-benzylideneacetophenone gave an equilibrium mixture in which the *cis*-form predominated (74%). Büchi and Yang [10] have shown that the *trans*-dienones crotonylideneacetone and β-ionone also undergo the reaction, although the geometric inversion of β-ionone is complicated by cyclisation of the *cis*-form to a pyran derivative. We therefore attempted the photochemical isomerisation of the *trans*-dienone (IV).

The less stable *cis*-forms of αβ-unsaturated ketones are usually, although not invariably, isomerised rapidly to the *trans*-forms when treated with mineral acids at room temperature. They are also differentiated from the *trans*-forms by their light absorption; the *cis*-form may absorb maximally at either shorter [9] or longer [5] wavelengths than the *trans*-form according to the particular structure present, but the intensity of absorption is always much lower for a *cis*-form. These criteria were used to detect isomerisation of the *trans*-dienone (IV) and later to determine its extent under different conditions. Sunlight and ultraviolet light from an unshielded mercury-vapour lamp decomposed the dienone; the observed spectral changes were incompletely reversed by the addition of acid to the solutions. The most suitable light source was a shielded lamp with main emission near 365 mμ. Solutions of the dienone (IV) showed absorption of slightly reduced wavelength and of very much reduced intensity after exposure to this source; moreover under favourable conditions these changes were almost completely reversed by acids, consistently with the presence of the required *cis*-isomer. The equilibrium concentration of the latter in the irradiated solution was found to increase with increase in dilution and with decrease in temperature; it was also dependent upon the nature of the solvent. In very dilute (*ca.* 10^{-5}M) benzene solution at room temperature about 50% of the dienone was isomerised, and values of 67% for ethanol and 80% for methanol solutions were obtained under the same conditions. In irradiated methanol solutions containing about 300 mg./l. at −60° some 90% of the dienone was present as the *cis*-isomer (V); it was obtained crystalline from such solutions after separation from the *trans*-isomer on alumina, which retained the *trans*-isomer more strongly. The *cis*-form (V) had $\lambda_{max.}$ 304—305 mμ (ε 15,200 in EtOH); the *trans*-form (IV) has $\lambda_{max.}$ 309—310 mμ (ε 22,500 in EtOH). Some *cis*-αβ-unsaturated ketones [5] give the semicarbazones of the *trans*-isomers when the normal procedure is used, free alcoholic semicarbazide being required in order to obtain the derivative of the *cis*-form, but the semicarbazone of the *cis*-dienone (V) was obtained by the normal procedure. When slowly heated it was transformed into the semicarbazone of the *trans*-isomer.

Reaction with methylenetriphenylphosphorane converted the *cis*-dienone (V) into the desired *cis*-triene (II), a rather unstable oil which decomposed in the presence of air at room temperature and also in its absence above 70°; the nature of the latter change merits investigation. The new triene required 3 mols. of hydrogen for saturation in the presence of palladium. Its $\lambda_{max.}$ 261 mμ (ε 17,000 in EtOH) differs somewhat from that of calciferol

[5] Theus, Surber, Colombi, and Schinz, *Helv. Chim. Acta*, 1955, **38**, 239.
[6] Bentley and Firth, *J.*, 1955, 2403.
[7] Dimroth, *Ber.*, 1938, **71**, 1346.
[8] Paal and Schulze, *Ber.*, 1902, **35**, 168.
[9] Lutz and Jordan, *J. Amer. Chem. Soc.*, 1950, **72**, 4090.
[10] Büchi and Yang, *J. Amer. Chem. Soc.*, 1957, **79**, 2318.

(265—266 mμ) in the same way as that of the *trans*-triene (I) (269—270 mμ) differs from that of 5 : 6-*trans*-calciferol [11] (XII) (272—273 mμ), these differences depending on the presence or absence of the bicyclic CD-system. The trisemicyclic structure of the triene (II) was shown by infrared bands near 852 (=CH), 891 ($=CH_2$), 1610, 1639, and 1653 (triene C=C) cm.$^{-1}$; similar bands occur in the spectrum of calciferol near 859, 887, 1610, 1634, and 1653 cm.$^{-1}$. The *cis*-triene, like calciferol, but unlike the *trans*-triene (I), was isomerised only slowly by dilute mineral acids. The relative speeds of reaction of the three compounds with maleic anhydride were approximately: *trans*-triene : *cis*-triene : calciferol = 6·9 : 1·3 : 1, this being the expected order of increasing steric hindrance to the reaction. The adduct so obtained from the *cis*-triene (II) was hydrolysed to the crystalline acid (VI), which is analogous to the dibasic acid similarly obtained from calciferol,[12] and stereoisomeric with that similarly obtained from the *trans*-triene [2] (I). These reactions demonstrate the *cis*-configuration of the new triene (II).

Means for extending the above work to a partial synthesis of calciferol were to hand. The bicyclic analogue (VII) of *cyclo*hexylideneacetaldehyde was first obtained by Heilbron, Spring, and their co-workers [13] in their degradation of the vitamin by chromic acid, and it is now readily obtained by Windaus and Riemann's method.[14] Inhoffen *et al.*[15] condensed this aldehyde with 4-acetoxy*cyclo*hexanone in the presence of sodium ethoxide and obtained a mixture, m. p. 141° (138°), of the $C_{(3)}$-epimers * of the conjugated dienone (VIII). They were aware of the possibility that the base might cause a change at $C_{(14)}$ to the more stable β(H)-configuration, and they obtained evidence [4] against it. We have repeated their preparation of the conjugated dienones (VIII) and our results confirm theirs in this respect. The product obtained by Inhoffen *et al.* may, however, have represented a different mixture of $C_{(3)}$-epimer from ours; they cite no optical rotation for their material. Our material (VIII) had m. p. 145°, $[\alpha]_D$ +165° (in C_6H_6), and proved later to contain an excess (*ca.* 3 : 1) of the 3α-epimer.

Whereas in the model dienone (IV) the symmetry of the terminal quaternary carbon atom of the unsaturated system confines geometric isomerism to the αβ-double bond, in the dienone (VIII) the βγ(or 7 : 8)-double bond may, in principle, also be isomerised. In practice, however, this bond was not affected. Irradiation of the dienone epimers (VIII) in methanol at −60° converted them virtually quantitatively, as shown by subsequent reactions, into the 5 : 6-*cis*-7 : 8-*trans*-epimers (IX) which had $\lambda_{max.}$ 310—311 mμ (ε 15,000 in EtOH); the all-*trans*-epimers (VIII) have $\lambda_{max.}$ 312—313 mμ (ε 25,000 in EtOH).

The ketonic oxygen atom in the epimers (IX) was replaced by a methylene group in a Wittig reaction; it is worth noting that such reactions are conveniently carried out without protection for the hydroxyl group. The ultraviolet absorption of the crude products was unaffected by the addition of dilute acid, showing their essential freedom from *trans*-trienoid material. Esterification with 3 : 5-dinitrobenzoyl chloride gave a readily separable mixture: after removal of the major product, which crystallised first, the minor component was isolated; it proved identical with calciferol 3 : 5-dinitrobenzoate. Hydrolysis readily gave the free crystalline vitamin (III), identified by comparison with authentic material.

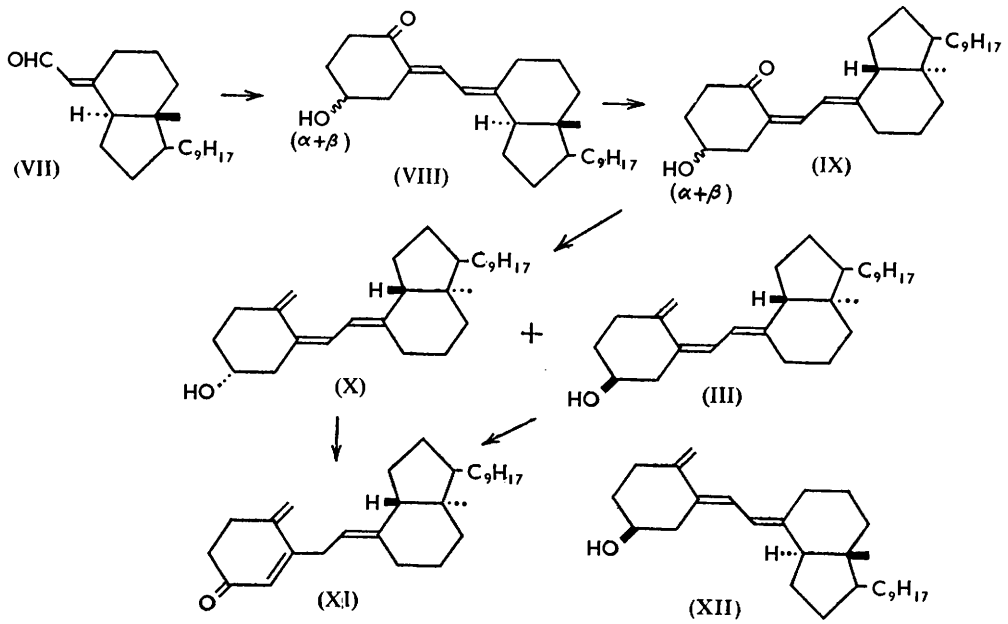
The major product was the 3 : 5-dinitrobenzoate of the hitherto unknown *epi*calciferol (X). The free hydroxy-compound, with ultraviolet absorption essentially identical with that of calciferol, was obtained by hydrolysis, but it crystallised only after some time, and in view of the relatively small amounts available and also of work in hand to obtain it by another route, its ultimate purification was not attempted. It was characterised additionally as the *p*-nitrobenzoate, and its structure was established by Oppenauer

* Steroid nomenclature is used for this and succeeding compounds.

[11] Inhoffen, Quinkert, Hess, and Erdmann, *Chem. Ber.*, 1956, **89**, 2273.
[12] Windaus and Thiele, *Annalen*, 1935, **521**, 160.
[13] Heilbron, Jones, Samant, and Spring, *J.*, 1936, 905.
[14] Windaus and Riemann, *Z. physiol. Chem.*, 1942, **274**, 206.
[15] Inhoffen, Brückner, and Gründel, *Chem. Ber.*, 1954, **87**, 1.

oxidation to the ketone (XI), characterised as the semicarbazone,[16] which was identical with material similarly obtained from calciferol.

We believe that the above experiments represent the first partial synthesis of calciferol, but, since Inhoffen and his associates [17] have recently claimed to have effected a partial synthesis, their work must now be considered. Koevoet *et al.*[18] had shown that calciferol, like other partly-*cis*-polyenes, is isomerised by iodine to the all-*trans*-isomer, and Inhoffen *et al.*[11] isolated the resulting 5 : 6-*trans*-calciferol (XII), m. p. 99—101°, $[\alpha]_D$ +223° (in C_6H_6). Inhoffen, Quinkert, and Hess [17] then showed that this compound was partially



reconverted into calciferol by irradiation. Clearly, if 5 : 6-*trans*-calciferol could be obtained synthetically the combined processes would amount to a partial synthesis of the vitamin. Inhoffen, Kath, Sticherling, and Brückner [4] have reported synthetic work to this end; they acetylated an epimer mixture (VIII), subjected the product to a Wittig reaction, and, after hydrolysis, obtained material which they refer to as " 5 : 6-*trans*-vitamin D_2 " and regard as a mixture of 5 : 6-*trans*-calciferol (XII) and its $C_{(3)}$-epimer. Their synthetic material had m. p. 125—126°, $[\alpha]_D$ +74·8° (in C_6H_6); attention is directed to these constants, which are very different from those of the authentic 5 : 6-*trans*-calciferol. The Brunswick workers' claim [17] to a partial synthesis of calciferol appears premature in that an essential link in their synthetic chain is as yet missing. If they are able to isolate authentic 5 : 6-*trans*-calciferol from their synthetic material their work will then constitute a partial synthesis of the vitamin. In view, however, of the ready separation of the 5 : 6-*cis*-epimers in our work, and also of the constants reported for " 5 : 6-*trans*-vitamin D_2 " it seems possible that the latter may be essentially homogeneous, in which case it would presumably correspond, not to 5 : 6-*trans*-calciferol, but to 5 : 6-*trans-epi*-calciferol.

Experimental

cis-2-2′-cyclo*Hexylidene-ethylidene*cyclo*hexanone* (V).—A solution of the *trans*-isomer [7] (160 mg.) in light petroleum (1 l.; b. p. 40—60°) contained under nitrogen in a quartz flask was

[16] Windaus and Buchholz, *Z. physiol. Chem.*, 1938, **256**, 273; Trippett, *J.*, 1955, 370.
[17] Inhoffen, Quinkert, and Hess, *Naturwiss.*, 1957, **44**, 11.
[18] Koevoet, Verloop, and Havinga, *Rec. Trav. chim.*, 1955, **74**, 788.

irradiated for 2 hr. with light from a Mazda No. 19 mercury-vapour lamp; the extinction measured at 309 mμ had then decreased by 17%. The solution was concentrated under reduced pressure and passed through a column of neutral alumina (Woelm; Grade II) containing 1% of fluorescent zinc oxide [19] (Leuchtfarbe K4 Grün 1, from Dr. W. Franke, Frankfurt-am-Main; we are most grateful to Dr. Franke for a sample of this material). The chromatogram was developed first with light petroleum (b. p. 60—80°) and then with the same solvent mixed with benzene (10% v/v); examination under ultraviolet light (365 mμ) then revealed two distinct zones, and as the development continued the corresponding eluates were collected separately. Evaporation of the eluate which emerged first, and crystallisation from ethanol at −40° gave the cis-*dienone* (50 mg.), m. p. 33—33·5° (mixed m. p. with the *trans*-isomer, 28—31°) (Found: C, 82·4; H, 9·85. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%). The *semicarbazone* (Found: C, 69·1; H, 9·05. $C_{15}H_{23}ON_3$ requires C, 68·9; H, 8·9%) had m. p. 175° (rapid heating); it then resolidified and remelted at 194—195°; the semicarbazone of the *trans*-isomer has m. p. 196—197°. A mixture of the semicarbazones of the *cis*- and *trans*-dienones had m. p. 157—160° (rapid heating).

Evaporation of the second eluate from the chromatogram, and crystallisation from ethanol at 0° gave the *trans*-dienone, m. p. 67°.

For preparative work an irradiation vessel constructed from two large Pyrex beakers was used. The larger outer beaker was cooled in a bath; in the inner, smaller beaker was placed the lamp, and the space between the beakers contained the solution of *trans*-dienone, which was stirred with a current of nitrogen. A typical solution of the dienone (400 mg.) in methanol (1300 c.c.) after irradiation for 1 hr. at room temperature (ice-bath) was irradiated for a further 2 hr. at −60° (−80° bath), the extinction at 309 mμ falling by 32%. The product was isolated by dilution with water and extraction with ether–light petroleum (b. p. 40—60°) (1 : 1) and chromatographed rapidly on a wide column (diam., 3·5 cm.) of alumina (75 g.; Grade II neutral), development being with light petroleum (b. p. 60—80°) containing 15% (v/v) benzene. Delay at this stage leads to isomerisation. Evaporation of the first eluate gave an oil (305 mg.) which on crystallisation as before gave the *cis*-dienone (230 mg.), m. p. 33°.

cis-1-2′-cyclo*Hexylidene*-*ethylidene*-2-*methylene*cyclo*hexane* (II).—1·0N-Ethereal butyllithium (1 equiv.) was added under nitrogen to a stirred suspension of methyltriphenylphosphonium bromide (1 g.) in dry tetrahydrofuran (30 c.c.). Stirring was continued for 30 min., after which a solution of the *cis*-dienone (V) (300 mg.) in tetrahydrofuran (1 c.c.) was added; after a further 5 min. a few drops of acetone were added to destroy the excess of phosphorane; the mixture was then kept at room temperature for 7 hr. and evaporated under reduced pressure. The residue was distributed between 50% aqueous methanol (20 c.c.) and light petroleum (75 c.c.; b. p. 40—60°), and the aqueous phase again extracted with light petroleum. The combined petroleum phases were washed with 50% aqueous methanol and with water, dried, and filtered through neutral alumina (2 g.; Grade II). The filtrate was evaporated and the residue distilled rapidly (important) at 75° (bath temp.)/6×10^{-4} mm., to give the cis-*triene* (250 mg.) as a colourless mobile oil (Found: C, 88·55; H, 10·8. $C_{15}H_{22}$ requires C, 89·0; H, 11·0%). Microhydrogenation in alcohol with palladium charcoal required 3·06 mols. of hydrogen. When the triene had been kept under nitrogen at 80° for 4 hr. it showed $\lambda_{max.}$ 240 mμ (ε 12,300 in EtOH); the original $\nu_{max.}$ 891 cm.$^{-1}$ (=CH_2) had disappeared and a new $\nu_{max.}$ 1380 cm.$^{-1}$ (–CH_3) had appeared.

Reaction of the cis-*Triene* (II) *with Maleic Anhydride*.—A solution of the *cis*-triene (135 mg.) and maleic anhydride (80 mg.) in benzene (4 c.c.) was heated under reflux for 6½ hr. The benzene was removed and the residue saponified with 6% aqueous potassium hydroxide (5 c.c.) at 100° for 45 min. The cooled and diluted solution was extracted with chloroform, the extract discarded, and the aqueous phase acidified and re-extracted. Evaporation of the extract and crystallisation from aqueous alcohol gave the dibasic *acid* (VI) (65 mg.) as a hydrate, prisms, m. p. 103° (decomp.), which could not be completely dehydrated. Anhydrous material, m. p. 179—182° (decomp.), was obtained by crystallisation from tetrahydrofuran–light petroleum (b. p. 40—60°) followed by drying at 100°/10 mm. (Found: C, 71·6; H, 8·25. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%). The isomeric dibasic acid [2] from the *trans*-triene (I) has m. p. 178—182° (decomp.); a mixture of the two had m. p. 165—170° (decomp.).

Preparation of the C_{27} trans-*Dienone Epimers* (VIII).—Solutions of 4-acetoxy*cyclo*hexanone (6 g.) and the C_{21} αβ-unsaturated aldehyde (VII) (1 g.) in ethanol (20 c.c.) and sodium ethoxide

[19] Brockmann and Beyer, *Angew. Chem.*, 1951, **63**, 133.

(140 mg. of sodium) in ethanol (20 c.c.) were cooled to −20° and mixed, and the mixture kept at −20° for 2¼ hr., then at 0° for 5 min., and next acidified with acetic acid (0·5 c.c.) in alcohol (5 c.c.). The solution was diluted with aqueous sodium hydrogen carbonate, and the product isolated with ether and dried by distillation with benzene under reduced pressure. It was adsorbed on neutral alumina (140 g.; Grade III) containing 1% of fluorescent zinc oxide, the progress of the chromatogram being observed by examination under light of 365 mμ. Development with light petroleum (b. p. 60—80°) containing 10% (v/v) of benzene removed a light-absorbing band which contained an oil (250 mg.) whose absorption indicated that it was the acetate of the required dienone. Development with benzene alone and then with benzene containing 6% of ether removed several small light-absorbing bands; development with benzene containing 25% of ether then eluted the main light-absorbing zone; the corresponding filtrate was collected in two fractions. That which emerged first was evaporated and the residue crystallised from light petroleum (b. p. 60—80°), providing the required epimer mixture (260 mg.) as blades, m. p. 144—145°, $[\alpha]_D^{20}$ +165° (*c* 1·4 in C_6H_6) (Found: C, 80·95; H, 10·4. Calc. for $C_{27}H_{42}O_2$: C, 81·3; H, 10·6%). We regret that the rotation was incorrectly recorded earlier [1] owing to an arithmetical error. The filtrate from the second part of the main light-absorbing zone of the chromatogram provided needles (55 mg.), m. p. 135°, $[\alpha]_D^{20}$ +120° (*c* 1·6 in C_6H_6), which were not further examined.

Reaction of Methylenetriphenylphosphorane and the Epimeric cis-*Dienones* (IX).—The above *trans*-dienone epimer mixture, $[\alpha]_D^{20}$ +165° (395 mg.), dissolved in methanol (2 l.), was irradiated at −65° for 2 hr., change in the extinction at 310 mμ having become very slow. The *cis*-dienone epimer mixture (385 mg.), $[\alpha]_D^{20}$ +55° (*c* 1·2 in C_6H_6), was isolated by dilution with water and extraction with ether and benzene; it did not crystallise. Its solution in tetrahydrofuran (5 c.c.) was added to a stirred solution of the phosphorane prepared under nitrogen from methyltriphenylphosphonium bromide (1·15 g.), suspended in tetrahydrofuran (20 c.c.), and 1·1N-ethereal butyl-lithium (2·9 c.c.). After 25 min. excess of phosphorane was destroyed with acetone, the solution was kept at room temperature for 7 hr., then treated with water (0·5 c.c.), and the solvents were removed under reduced pressure. The residue was distributed between light petroleum (100 c.c.; b. p. 40—60°) and 30% aqueous methanol (30 c.c.). The petroleum phase, after being washed with 50% aqueous methanol and then with water, was dried and evaporated under reduced pressure, giving an oil (525 mg.), $\lambda_{max.}$ 265—266 mμ ($E_{1\,cm.}^{1\%}$ 256 in EtOH); these values were not changed after treatment with dilute hydrochloric acid. The oil, dissolved in light petroleum (b. p. 40—60°), was chromatographed on neutral alumina (25 g.; Grade III), development being with light petroleum (b. p. 60—80°), then benzene (150 c.c.), and finally benzene–ether (10 : 1, 250 c.c.). The desired product was present in the benzene eluate, evaporation of which gave an oil (310 mg.), $\lambda_{max.}$ 265—266 mμ ($E_{1\,cm.}^{1\%}$ 395); rechromatographed on alumina this gave material (200 mg.), $E_{1\,cm.}^{1\%}$ 432. It was kept overnight at room temperature with 3 : 5-dinitrobenzoyl chloride (400 mg.) and pyridine (5 c.c.), and the mixture worked up in the usual way.

Crystallisation from acetone–alcohol gave a first crop (139 mg.) of crystals which were recrystallised from the same solvent, giving epi*calciferyl* 3 : 5-*dinitrobenzoate* as fine yellow needles m. p. 148—148·5°, $[\alpha]_D^{20}$ +35° (*c* 1·2 in C_6H_6) (Found: C, 71·2; H, 7·85; N, 4·9. $C_{35}H_{46}O_6N_2$ requires C, 71·1; H, 7·85; N, 4·7%). A mixture of this material and authentic calciferyl 3 : 5-dinitrobenzoate had m. p. 136—140°.

The mother-liquors when kept deposited a second crop (41 mg.) of crystals which, after recrystallisation from acetone–alcohol, afforded yellow prisms of calciferyl 3 : 5-dinitrobenzoate, m. p. 148—148·5°, $[\alpha]_D^{20}$ +56° (*c* 1·8 in C_6H_6) (Found: C, 71·05; H, 7·85%). It showed no depression on admixture with authentic calciferyl 3 : 5-dinitrobenzoate of m. p. 148—148·5°; Windaus *et al.*[20] record for this compound m. p. 148—149°, $[\alpha]_D^{20}$ +55° (in C_6H_6). For hydrolysis, the synthetic material (29 mg.) was dissolved in tetrahydrofuran (2 c.c.) and alcohol (5 c.c.), and the solution treated with potassium hydroxide (0·5 g.) in the minimum volume of water. The mixture was kept overnight, then diluted with water, and the product isolated with light petroleum (b. p. 40—60°). It crystallised from acetone at −15°, giving calciferol (14 mg.), m. p. and mixed m. p. 114—115°, $\lambda_{max.}$ 265—266 mμ (ε 18,300 in EtOH). The infrared spectra of synthetic and authentic specimens (KBr discs) were identical.

epi*Calciferyl* p-*Nitrobenzoate*.—The 3 : 5-dinitrobenzoate (100 mg.) was hydrolysed as described for the calciferyl ester, and gave a gum which when kept without solvent for some

[20] Windaus, Linsert, Lüttringhaus, and Weidlich, *Annalen*, 1932, **492**, 226.

weeks crystallised; the gum had $[\alpha]_D^{19}$ +25° (*c* 2·9 in C_6H_6), $\lambda_{max.}$ 265—266 mμ (ε 17,500 in EtOH). A portion was converted in the usual way into the p-*nitrobenzoate*, needles (from acetone–alcohol), m. p. 122—123° (Found: C, 77·1; H, 8·45. $C_{35}H_{47}O_4N$ requires C, 77·0; H, 8·7%).

Oppenauer Oxidation of epi*Calciferol.*—A portion (13 mg.) of the above crude *epi*calciferol was oxidised as recorded for calciferol,[16] and the product isolated as the semicarbazone (8 mg.). After crystallisation from alcohol it had m. p. 209—211° (decomp.) (undepressed on admixture with authentic material of the same m. p. prepared from calciferol), and $[\alpha]_D^{20}$ +25° (*c* 0·8 in $CHCl_3$). Inhoffen *et al.*[4] give for this semicarbazone, m. p. 209°, $[\alpha]_D$ +24° (in $CHCl_3$).

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Grant (to I. T. H), and we also acknowledge most gratefully gifts of calciferol from Dr. B. A. Hems of Glaxo Laboratories Limited.

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