Calciferol and its Relatives. Part 24.[1] A Synthesis of Vitamin D_4

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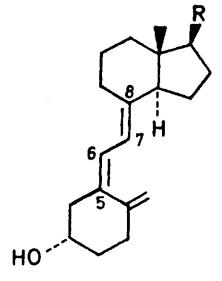
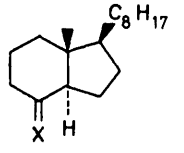
8α-Phenylsulphonyl-des-AB-ergostane (16),†,‡ prepared from des-AB-ergost-8-ene, formed a lithium derivative which reacted with the benzoyloxy-aldehyde (8) † to give, after treatment with trimethylchlorosilane, a mixture of β-silyloxy-sulphones. Reduction with lithium amalgam, followed by removal of the benzoyl group, gave vitamin D_4 (2).

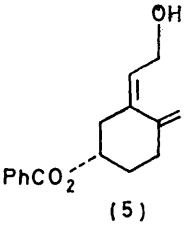
In a recent synthesis,[2] the lithium derivative of the diphenylphosphine oxide corresponding to the primary alcohol (5) † was brought into reaction with des-AB-cholestan-8-one ‡ (3) to generate the *E*-7,8-double bond of the product, vitamin D_3 (1). In parallel with that work we contemplated a related synthesis, in which the same double bond of a D-vitamin was to be generated, but with the roles of the two fragments reversed; that is, an aldehyde such as (8) would react with a bicyclic fragment activated for carbanion formation at position 8. A model experiment [3] has been carried out, in which the conjugated triene (6) was obtained by treatment of the



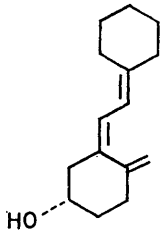
(1) R = C_8H_{17}
(2) R = C_9H_{19}



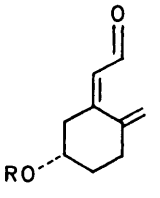
(3) X = O
(4) X = PPh_3



(5)



(6)



(7) R = H
(8) R = PhCO

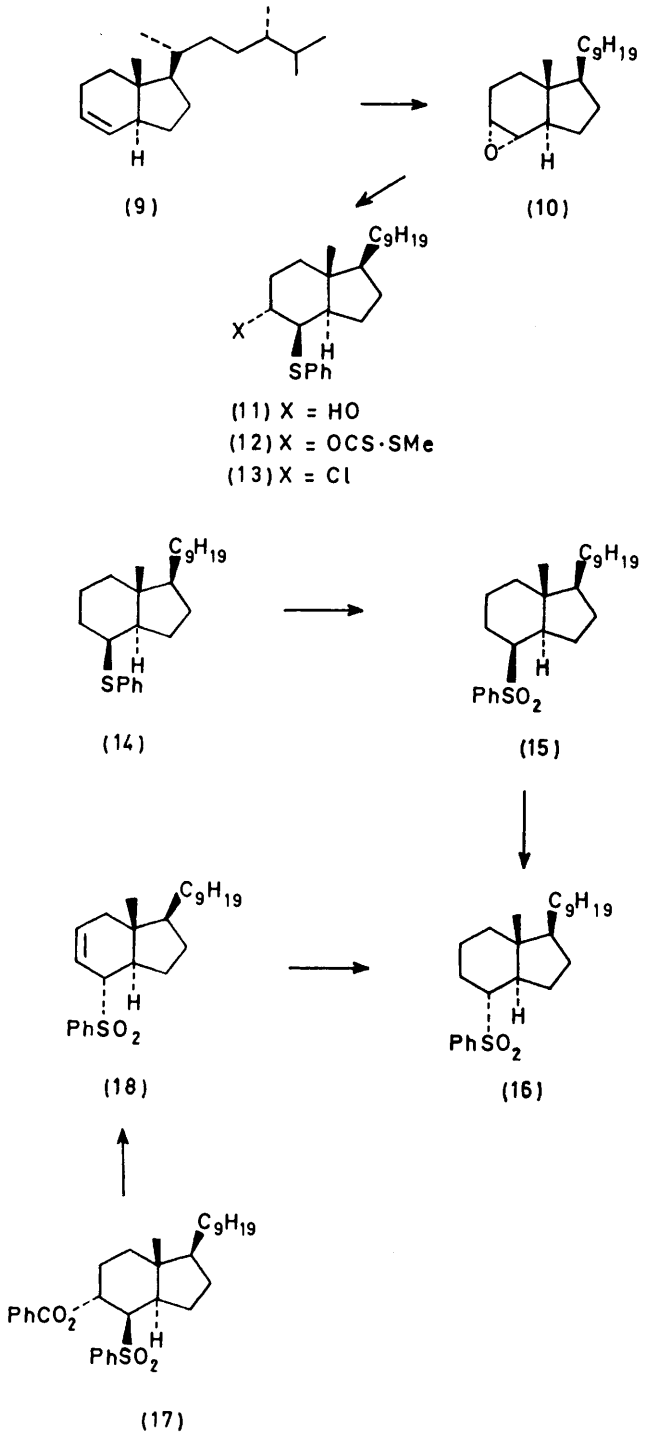
aldehyde (7) with cyclohexylidenetriphenylphosphorane, but there the main difficulty of the projected synthesis, that of securing the proper *E*-geometry of the newly generated double bond, was not confronted. It was apparent that the use of the unstabilised bicyclic phosphorane (4) might well give as the main product the *Z*-7-isomer, rather than the vitamin itself. Nevertheless, attempts [4] were made to prepare phosphonium compounds from which phosphoranes related to (4) might be obtained. These attempts were, however, unsuccessful, their outcome providing an illustration of the general difficulty of introducing a Ph_3P group into a sterically congested situation; a difficulty which is due largely to the steric size of the group, but partly also to the weak nucleophilic character of triphenylphosphine.

We next investigated carbanions stabilised by sulphur, since preliminary experiments showed that the phenylthio-group could be introduced without difficulty at position 8 in des-AB-cholestane derivative. Some initial experiments [5] on the synthesis of olefins from β-hydroxy-sulphones met with limited success. Later, in a study [6] of Julia's reductive elimination [7] of β-acyloxy-sulphones we showed for the first time that the method was well-suited for the synthesis of conjugated, as distinct from unconjugated, olefins; and further, that when used for the synthesis of internal disubstituted olefins, it was strongly *trans*-stereoselective. This suggested that when used in the synthesis of vitamin D, formation of the desired 7*E*-isomer might be favoured. We now report successful use of the method in the synthesis of vitamin D_4 (2) (the 22-dihydro-analogue of vitamin D_2), which Windaus and his colleagues [8] have already prepared by the classical irradiation method.

It was first necessary to prepare the sulphone (16), for which the starting point was des-AB-ergost-8-ene [9] (9). Oxidation with *m*-chloroperbenzoic acid gave the α-epoxide (10), which reacted readily with ethanolic sodium benzenethiolate to give the diaxial hydroxy-sulphide (11). We hoped to deoxygenate [10] this compound to the sulphide (14) by treatment of the dithiocarbonate (12) with tri-n-butyltin hydride, but the reaction took a different course, regenerating the olefin (9); applications of this interesting elimination reaction are reported elsewhere.[11] Next, the hydroxy-compound (11) was treated with methanesulphonyl chloride in pyridine, which gave, unexpectedly, the chloro-sulphide (13); presumably the methanesulphonate was formed initially, but then underwent displacement by chloride ion in a reaction assisted by participation of neighbouring phenylthio-group. The chloro-sulphide (13) reacted with lithium triethylborohydride [12] to give (*ca.* 50%) the 8β-phenylthio-compound (14). From this, the cor-

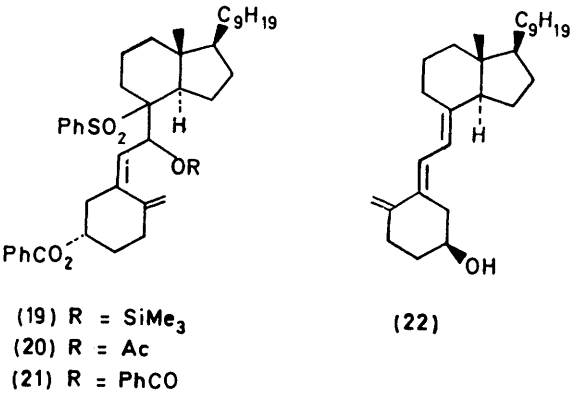
† All the structures in this paper represent absolute configurations.
‡ Steroidal numbering is used.

responding sulphone (15) was readily obtained by oxidation; in the presence of potassium t-butoxide it isomerised to give the more stable α-epimer (16).



A more convenient route to the 8α-sulphone (16) was found, commencing with the benzoylation of (11), followed by oxidation to give the benzoyloxy-sulphone (17). Treatment with potassium t-butoxide caused elimination of benzoic acid to give the Δ^8-olefin, which then underwent prototropic change to the βγ-unsaturated sulphone (18). Hydrogenation with palladium–charcoal gave the crystalline 8α-phenylsulphone (16) in excellent yield.

The ring A component (8), obtained by oxidation of the corresponding primary alcohol [2] (5) with manganese dioxide in tetrahydrofuran, proved very unstable, and had to be used immediately for the reaction with the lithium derivative of the sulphone (16). Treatment of the reaction mixture with trimethylchlorosilane gave a mixture of diastereoisomeric β-trimethylsilyloxy-sulphones (19). This was reduced at −20 °C with lithium



amalgam in methanol–tetrahydrofuran, and the product was then hydrolysed to remove the benzoyl group. The product, isolated in *ca.* 45% yield by p.l.c., had spectral characteristics which showed it to be the required vitamin (2); its m.p. and $[\alpha]_D$ were in agreement with those cited by Windaus and Güntzel [8] and the newly generated double bond had exclusively the natural *E*-configuration.

When the product of the reaction between the aldehyde (8) and the metallated sulphone (16) was treated with benzoyl chloride, a mixture of diastereoisomers (21) was formed from which a single isomer was isolated by crystallisation in *ca.* 55% yield. Surprisingly, its reductive elimination with sodium amalgam gave two compounds, which were separated by p.l.c. The major component (yield 36%) was vitamin D_4. The minor, less polar component, was obtained as an oil (yield 20%) and identified by its spectral characteristics [13] as 5-*trans*-vitamin D_4. Similar results were obtained from the reduction of the mixed diastereoisomers (21). The 5-*trans*-vitamin was not formed from the *cis*-isomer under the reaction conditions, but owes its origin to another mechanism of reductive elimination, the identification of which requires further study. Reduction of the mixture of diastereoisomeric acetates (20) proceeded normally, and gave vitamin D_4 in a yield comparable to that obtained from the silyl ethers (19). These results suggest that where, in the synthesis of a conjugated diene by the Julia method, the preservation of allylic double bond geometry is important, it may be prudent to acetylate the allylic hydroxy-group before reduction, rather than to benzoylate it.

EXPERIMENTAL

All reactions were conducted under nitrogen. Unless otherwise specified, ^{1}H n.m.r. data relate to solutions in $CDCl_3$, optical rotations to solutions in $CHCl_3$, and i.r. data to solutions in CCl_4. Light petroleum refers to the fraction having b.p. 60—80°. T.l.c. and p.l.c. were performed with Kieselgel GF_{254}.

9α-Hydroxy-8β-phenylthio-des-AB-ergostane (11).—8β-Benzoyloxy-des-AB-ergostane [9] (1.5 g) was pyrolysed at 370 °C for 3½ min. The crude pyrolysate was dissolved in ether, washed with aqueous sodium carbonate, dried, and evaporated. Chromatography on silica gel (light petroleum) gave unchanged benzoate and a mixture of olefins, which was bulb-to-bulb distilled at 140 °C (bath) and 0.25 mmHg. The combined material from the starting benzoate (4.52 g), with recycling of recovered benzoate, was an oil (2.90 g, 94%) containing (*ca.* 3 : 1) the olefin (9), τ 4.45 (s, =CH) and its $\Delta^{8(14)}$-isomer, τ 4.75 (m, =CH). This mixture was kept in methylene chloride (35 cm³) with 85% *m*-chloroperbenzoic acid (2.44 g) at 0 °C for 1½ h; ether (100 cm³) was then added, and the mixture was washed with aqueous sodium sulphite, aqueous sodium carbonate, and water, and then dried and evaporated. The residue was heated under reflux for 16 h with ethanolic sodium benzenethiolate (30 cm³) [from benzenethiol (2.42 g) and sodium (575 mg)]. The solution was diluted with water (300 cm³) and extracted with ether; the extract was washed with dilute aqueous sodium hydroxide and with water, and was then dried and evaporated. Chromatography of the oily residue (4.82 g) (silica gel; 2% ethyl acetate in benzene) gave the *hydroxy-sulphide* (11) (3.30 g, 77%), which after short-path distillation at 100 °C and 10^{-3} mmHg showed $\nu_{max.}$ (film) 995m, 1 380m, 1 468s, and 3 415s cm^{-1}, τ 5.94 (1 H, m, C*H*·OH) and 6.57 (1 H, m, C*H*·SPh), $[\alpha]_D^{25}$ +24.8° (Found: C, 77.4; H, 10.5; S, 8.5. $C_{25}H_{40}OS$ requires C, 77.3; H, 10.4; S, 8.2%). The S-*methyl dithiocarbonate* (12) formed needles (from ethanol), m.p. 105—107.5°, $\nu_{max.}$ ($CHCl_3$) 1 042s and 1 225s cm^{-1}, $[\alpha]_D^{25}$ +53.3°, τ 7.52 (3 H, s, SMe) (Found: C, 67.8; H, 8.8; S, 19.85. $C_{27}H_{42}OS_3$ requires C, 67.75; H, 8.85; S, 20.0%).

Reaction of the Dithiocarbonate (12) *with Tri-n-butyltin Hydride*.—The dithiocarbonate (12) (170 mg) in dry toluene (3 cm³) was added during 45 min to a solution of tri-n-butyltin hydride (200 mg) in boiling toluene (2 cm³), and the mixture was kept under reflux for 3 h. The solvent was then removed and the residue was chromatographed on silica gel (light petroleum), giving the olefin (9) as an oil (60 mg, 65%), $\nu_{max.}$ (film) 1 380m and 1 462m cm^{-1}, τ 4.42 (2 H, s, =CH).

8β-Phenylsulphonyl-des-AB-ergostane (15).—The hydroxy-sulphide (11) (165 mg) in pyridine (0.5 cm³) was treated at 0 °C with methanesulphonyl chloride (100 mg), and the mixture was kept at 20 °C for 16 h and then worked-up in the usual way to afford *9α-chloro-8β-phenylthio-des-AB-ergostane* (13) (146 mg, 84%) as an oil, $\nu_{max.}$ (film) 738m, 938w, 981w, 1 028w, 1 375m, and 1 585m cm^{-1}, τ 2.6—2.9 (5 H, m, ArH), 5.57 (1 H, m, CHCl), and 6.35 (1 H, m, C*H*·SPh) (Found: M^+, 406.245 3. $C_{25}H_{39}{}^{35}ClS$ requires *M*, 406.246 1).

The chloro-sulphide (13) (315 mg) was heated under reflux in tetrahydrofuran (9 cm³) with lithium triethylborohydride (424 mg) for 44 h. Water and ether were added, and the ether phase was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and was dried and evaporated. The residue contained (t.l.c.) two components; the less polar was isolated by p.l.c. (light petroleum), which gave 8β-phenylthio-des-AB-ergostane (14) as an oil (144 mg, 50%), $\nu_{max.}$ (film) 694m, 740m, 1 029w, 1 379m, and 1 587m cm^{-1}, τ 6.38br (1 H, C*H*·SPh) (Found: M^+, 372.284 2. Calc. for $C_{25}H_{40}S$: *M*, 372.285 0).

Oxidation of the phenylthio-compound (14) (176 mg) in dichloromethane (12 cm³) at 20 °C with 85% *m*-chloroperbenzoic acid (230 mg) for 1 h, with normal work-up and crystallisation of the product from light petroleum at −40 °C gave *8β-phenylsulphonyl-des-AB-ergostane* (15) as needles (173 mg, 92%), m.p. 133—135°, $[\alpha]_D^{22}$ +16.9°, $\nu_{max.}$ (Nujol) 689s, 741s, 1 131s, and 1 300s cm^{-1}, τ 6.53 (1 H, m, C*H*·SPh) and 8.87 (3 H, s, Me) (Found: C, 73.9; H, 10.2; S, 8.0. $C_{25}H_{40}O_2S$ requires C, 74.2; H, 10.0; S, 7.9%).

9α-Benzoyloxy-8β-phenylsulphonyl-des-AB-ergostane (17).—The sulphide (11) (4.55 g) was converted with benzoyl chloride and pyridine into the oily benzoate, $\nu_{max.}$ (film) 712s, 1 110s, 1 265vs, and 1 715vs cm^{-1}, τ 4.61 (1 H, m, C*H*·OBz) and 6.35br (1 H, $W_{\frac{1}{2}}$ 9 Hz, C*H*·SPh) (Found: M^+, 492.306 1. Calc. for $C_{32}H_{44}O_2S$: *M*, 492.306 2). Oxidation at 20 °C for 2 h with 85% *m*-chloroperbenzoic acid (5.68 g) in dichloromethane (50 cm³), and work-up in the usual way gave the *benzoyloxy-sulphone* (17) (from light petroleum) as needles (5.43 g, 88%), m.p. 140—143°, $[\alpha]_D^{25}$ −45.2°, $\nu_{max.}$ 1 155s, 1 260s, 1 325s, and 1 725s cm^{-1}, τ 4.62br (1 H, $W_{\frac{1}{2}}$ 6 Hz, C*H*·OBz) and 6.38 (1 H, d, *J* 5 Hz, CH·SO_2) (Found: C, 72.85; H, 8.4; S, 6.15. $C_{32}H_{44}O_4S$ requires C, 73.25; H, 8.45; S, 6.1%).

8α-Phenylsulphonyl-des-AB-ergostane (16).—A solution of the benzoyloxy-sulphone (17) (5.60 g) in tetrahydrofuran (36 cm³) was added rapidly at 20 °C to a stirred solution of potassium t-butoxide [from potassium (1.67 g) in t-butanol (36 cm³)] and tetrahydrofuran (36 cm³). A mild exothermic reaction took place and potassium benzoate was precipitated. After 3 h the mixture was poured into 0.1N-hydrochloric acid containing ice; isolation with ether gave the crude unsaturated sulphone (18) as an oil, $\nu_{max.}$ (film) 792s, 1 142s, and 1 305s cm^{-1}, τ 4.23 (2 H, m, =CH) and 6.35 (1 H, m, CH·SO_2) (Found: M^+, 402.258 1. Calc. for $C_{25}H_{38}O_2S$: *M*, 402.259 2). It was hydrogenated in ethyl acetate (125 cm³) with 10% palladium–charcoal (500 mg) at 20 °C; isolation in the usual way gave the *sulphone* (16) (3.98 g, 92%) as plates, m.p. 110—112.5° from light petroleum, $[\alpha]_D^{22}$ −3.77°, $\nu_{max.}$ 689m, 755m, 1 140s, 1 282s, and 1 305s cm^{-1}, τ 6.93 (1 H, m, CH·SO_2) (Found: C, 74.45; H, 10.3; S, 8.0. $C_{25}H_{40}O_2S$ requires C, 74.2; H, 10.0; S, 7.9%).

The Benzoyloxy-Dienal (8).—A solution of the monobenzoate (5) (563 mg) in tetrahydrofuran (30 cm³) was stirred with active manganese dioxide (7.0 g) for 20 min at 14 °C. The filtered solution was evaporated under strongly reduced pressure to give the crude aldehyde (8) (505 mg, 90%) which was used immediately for the next step. It had $\nu_{max.}$ (film) 712s, 1 110s, 1 272vs, 1 672s, and 1 715vs cm^{-1}, τ 0.15 (1 H, d, *J* 8 Hz, CH=O), 4.05 (1 H, d, *J* 8 Hz, C*H*·CHO), 4.65 (1 H, m, CH·OBz), 4.72br (1 H, $W_{\frac{1}{2}}$ 6 Hz) and 4.94br (1 H, $W_{\frac{1}{2}}$ 7 Hz) (=CH_2) (Found: M^+, 256.109 33. Calc. for $C_{16}H_{16}O_3$: *M*, 256.109 94).

The Benzoyloxy-Sulphone (21).—1.5M-n-Butyl-lithium in hexane 1.1 cm³) was added to a stirred solution of the sulphone (16) (606 mg) in tetrahydrofuran at −70 °C; after 30 min the aldehyde (8) (453 mg) in tetrahydrofuran (2 cm³) was added followed by, after a further 15 min, benzoyl chloride (420 mg). The mixture was then brought to 25 °C during 4 h, after which pyridine (2 cm³) and then

water (0.5 cm³) were added. After 30 min the mixture was poured into 1N-hydrochloric acid at 0 °C, and the product, isolated with ether, was dissolved in ether–light petroleum (6 cm³, 1 : 1) and refrigerated. The crystalline *product* (21) separated from benzene–light petroleum as plates (630 mg, 55%), m.p. 155—157°, $[\alpha]_D^{25}$ +82°, $\nu_{max.}$ 710s, 930m, 1 160s, 1 270vs, 1 305s, 1 315s, and 1 720vs cm^{-1}, τ 3.3 (1 H, d, *J* 10 Hz, CH·OBz), 4.28br (1 H, $W_{\frac{1}{2}}$ 5 Hz, =CH$_2$), 4.35 (1 H, d, *J* 10 Hz, =C*H*–CHOBz), 4.82br (1 H, $W_{\frac{1}{2}}$ 5 Hz, =CH$_2$), and 5.2br (1 H, CH·OBz) (Found: C, 75.25; H, 8.25; S, 3.95. $C_{48}H_{60}O_6S$ requires, C, 75.4; H, 7.9; S, 4.2%).

Reduction of the Benzoyloxy-Sulphone (21).—The benzoyloxy-sulphone (21) (300 mg) in tetrahydrofuran (5 cm³) and methanol (5 cm³) was stirred at −20 °C with 5.65% sodium amalgam (700 mg) for 3 h; the mixture was then brought to 25 °C and potassium hydroxide (200 mg) in water (0.5 cm³) was added. After 3 h the product was isolated with ether, and was subjected to p.l.c. (6-fold elution with methylene chloride) with rigorous exclusion of air. The more polar component (56 mg, 36%) separated from 90% aqueous methanol as fine needles, m.p. 95.5—98°, $[\alpha]_D^{25}$ +86.1° (acetone) (lit.,[8] m.p. 96—98°, $[\alpha]_D$ +85.7°), $\lambda_{max.}$ (EtOH) 267 nm (ε 17 900), $\nu_{max.}$ 895w, 910m, 940w, 960w, 1 630w, 1 645w, and 3 620w cm^{-1}, τ 3.73 and 3.97 (each 1 H, d, *J* 11 Hz, –CH=CH–), 4.95br and 5.18br (each 1 H, $W_{\frac{1}{2}}$ 5 Hz with fine splitting, =CH$_2$), 6.05 (1 H, m, C*H*·OH) and 9.46 (3 H, s, Me-18) (Found: M^+, 398.355 0. Calc. for $C_{28}H_{46}O$: *M*, 398.354 8).

The less polar component was obtained as an oil (32 mg, 20%), $\lambda_{max.}$ (EtOH) 275 nm (ε 15 900), $\nu_{max.}$ 890m, 910m, 945w, 1 620w, 1 640w, and 3 620m cm^{-1}, τ 3.42 and 4.12 (each 1 H, d, *J* 10 Hz, –CH=CH–), 5.02 and 5.30 (each 1 H, br s with fine splitting, $W_{\frac{1}{2}}$ 5 Hz, =CH$_2$), and 6.10br (1 H, C*H*·OH) (Found: M^+, 398.354 3. Calc. for $C_{28}H_{46}O$: *M*, 398.354 8). These data, together with those [13] for 5-*trans*-vitamin D$_3$, identify this compound as 5-*trans*-vitamin D$_4$ (22).

Reduction of the material present in the mother-liquor from which the crystalline benzoyloxy-sulphone (21) separated gave the same two products, (2) and (22), in the same proportions as were obtained from the crystalline compound.

Vitamin D$_4$ via *the Silyl Ether* (19).—The sulphone (16) (283 mg) was metallated and brought into reaction with the aldehyde (8) (258 mg) as described earlier, and the reaction mixture was then treated with trimethylchlorosilane (2 cm³) and kept at 20 °C for 16 h. Solvents were evaporated, and the residue was dissolved in tetrahydrofuran–methanol (6 cm³, 1 : 1) and stirred at −20 °C for 3½ h with 5.7% lithium amalgam (1.0 g). Thereafter, aqueous potassium hydroxide was added, and the mixture was worked-up as before, giving vitamin D$_4$ (125 mg, 45%), which after crystallisation from aqueous methanol had characteristics identical with those cited above. Examination of the crude reaction product by t.l.c. and n.m.r. showed the absence of any 5-*trans*-vitamin D$_4$. Similar results were obtained when the acetoxy-sulphone (20) was prepared and reduced with sodium amalgam.

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