The Chemistry of Tricarbonyliron Complexes of Precalciferol$_2$ and Tachysterol$_2$

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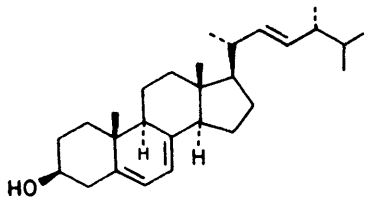
Photolysis of ergosterol in the presence of pentacarbonyliron gave (tachysterol$_2$)tricarbonyliron and (precalciferol$_2$)-tricarbonyliron as major and minor products respectively. Oxidation of these complexes with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave (5*E*,7*Z*,22*E*)-9,10-secoergosta-1(10),5,7,9(11),22-pentaen-3β-ol.

RECENTLY diene protection *via* the derived tricarbonyliron complex has been applied to ergosterol (1a) and calciferol$_2$ (2a).[1,†] As an alternative to thermal preparation from the diene and nonacarbonyldi-iron or (4-methoxybenzylideneacetone)tricarbonyliron, photolytic preparation was examined. Initially, photolysis of ergosterol (1a) in THF containing pentacarbonyliron gave a mixture of sterol complexes (t.l.c.) but (ergosterol)-tricarbonyliron (1b) did not predominate. Introduction of pentacarbonyliron slowly during photolysis resulted in formation of (α- and β-tachysterol$_2$)tricarbonyliron (3a, b) as the major products and (α- and β-precalciferol$_2$)-tricarbonyliron (4a, b) as the minor products. Predominant complexation of tachysterol$_2$ (5a) at the 6,8-diene system is consistent with the regioselectivity observed in the ready reactions with dienophiles.[2] Since precalciferol$_2$ exists predominantly in solution as conformation (6)[3] the less sterically congested α- and β-complexes (4a, b) would be most stable.

The complexes were unstable and failed to give satisfactory analyses. However, demetallation using iron(III) chloride gave respectively tachysterol$_2$ (5a) and precalciferol$_2$ (6), identified by spectral data and conversion into the known citraconic anhydride adduct[2] (7) and calciferol (2a).

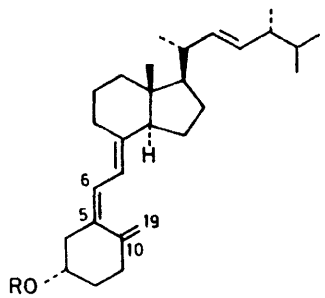
Although homogeneous on t.l.c. both complexes were separated into α- and β-isomers by esterification with benzoyl or 3,5-dinitrobenzoyl chloride and chromatography. Consideration of steric-approach control would suggest predominance of α-complexation. The hydroxy group is too distant to influence $\Delta^{6,8}$ complexation. (α-Tachysterol$_2$ 3,5-dinitrobenzoate)tricarbonyliron (3e) was obtained crystalline and analysed satisfactorily. Both the (α- and β-tachysterol$_2$ benzoate)tricarbonyliron complexes (3c, d) gave tachysterol$_2$ benzoate (5b) on reaction with iron(III) chloride.

Oxidation of either α- (3e) or β- (3f) tachysterol$_2$ 3,5-dinitrobenzoate or the α- (4c) or β- (4d) precalciferol$_2$ ester complexes with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave a single iron-free product. The



(1a)

b; α-Fe(CO)$_3$ complex



(2)

a; R=H

b; R=H; 5,6,10,19-η-Fe(CO)$_3$ complex

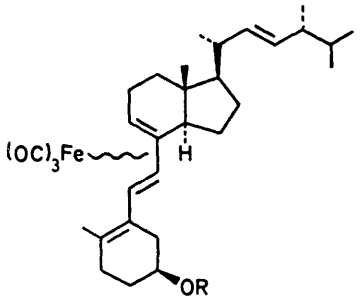
† Compounds with the ergosterol (1a) side chain are designated by the suffix 2.

[1] D. H. R. Barton, A. A. L. Gunatilaka, T. Nakanishi, H. Patin, D. A. Widdowson, and B. R. Worth, *J.C.S. Perkin I*, 1976, 821; D. H. R. Barton and H. Patin, *ibid.*, p. 829.

[2] A. Windaus, F. v. Werder, and A. Lüttringhaus, *Annalen*, 1932, **499**, 188; J. L. J. van de Vliervoet, P. Westerhof, J. A. Keverling Buisman, and E. Havinga, *Rec. Trav. chim.*, 1956, **75**, 1179.

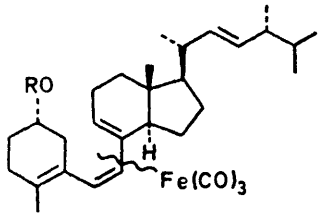
[3] G. M. Sanders, J. Pot, and E. Havinga, *Progr. Chem. Org. Natural Products*, 1969, **27**, 131; G. M. Sanders, Ph.D. Thesis, University of Leiden, 1967.

analysis and mass spectrum ($C_{35}H_{44}N_2O_6$) and spectral data {especially the u.v. spectrum [$\lambda_{max.}$ 301 (ε 31 900), 314 (42 200), and 328 nm (33 900)]} supported formulation as the pentaene (8b). The (5*E*,7*Z*)-stereochemistry was assigned by analogy with the known isocalciferol$_2$ (9).[4] Hydrolysis of (8b) gave the free sterol (8a) (structure consistent with analytical and spectral data). DDQ oxidation of the (sterol)tricarbonyliron complex (3a, b) also gave the sterol (8a).



(3)

a; R = H, α-Fe(CO)$_3$
b; R = H, β-Fe(CO)$_3$
c; R = PhCO, α-Fe(CO)$_3$
d; R = PhCO, β-Fe(CO)$_3$
e; R = 3,5-(O$_2$N)$_2$C$_6$H$_4$CO, α-Fe(CO)$_3$
f; R = 3,5-(O$_2$N)$_2$C$_6$H$_4$CO, β-Fe(CO)$_3$



(4)

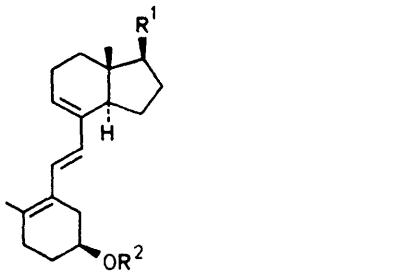
a; R = H, α-Fe(CO)$_3$
b; R = H, β-Fe(CO)$_3$
c; R = 3,5-(O$_2$N)$_2$C$_6$H$_4$CO, α-Fe(CO)$_3$
d; R = 3,5-(O$_2$N)$_2$C$_6$H$_4$CO, β-Fe(CO)$_3$

The photolytic metallation described provides the most convenient synthesis to date of tachysterol$_2$ (5a), which was previously isolated in poor yield (6—10%) *via* esterification with 4-methyl-3,5-dinitrobenzoyl chloride or retro-Diels–Alder pyrolysis of the citraconic anhydride adducts (7).[2] The pentaene (8a) should find application in the preparation of biologically important derivatives of calciferol$_2$ (2a).

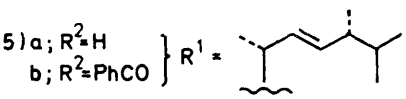
EXPERIMENTAL

Optical rotations and i.r., u.v., and n.m.r. spectra were recorded for chloroform, chloroform, ethanol, and deuteriochloroform solutions, respectively. Chromatography (eluant light petroleum–diethyl ether 1 : 0—1 : 1) was carried out on Merck Kieselgel H (silica) or neutral grade I

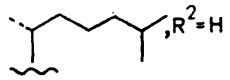
[4] H. H. Inhoffen, G. Quinkert, H. J. Hess, and H. M. Erdmann, *Chem. Ber.*, 1956, **89**, 2273.



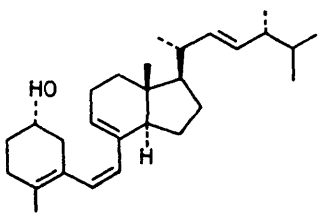
(5) a; R^2 = H
b; R^2 = PhCO
} R^1 =



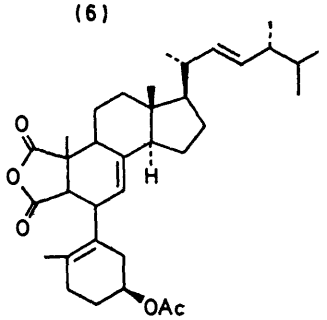
c; R^1 =



, R^2 = H



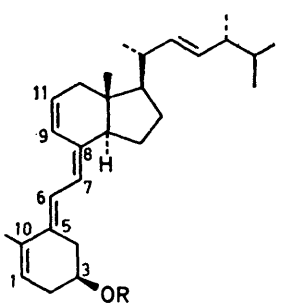
(6)



(7)

alumina; compounds are listed in order of increasing polarity. Organic extracts were dried over magnesium sulphate and evaporated *in vacuo*. All manipulations including work-up were carried out under nitrogen or carbon dioxide with degassed solvents. Petroleum refers to the redistilled fraction with b.p. 60—80 °C.

Photolysis of Ergosterol (1a) *in the Presence of Penta-*



(8) a; R = H
b; R = 3,5-(O$_2$N)$_2$C$_6$H$_4$CO

(9) 9,11-Dihydro

carbonyliron.—Ergosterol (1a) (1 g) in dry THF (120 ml) was purged with dry oxygen-free nitrogen for 10 min, and then treated with nitrogen which had been bubbled slowly through pentacarbonyliron (10 ml) in THF (50 ml) at room temperature. The solution was irradiated (cooled 200 W internal high-pressure mercury arc) for 24 h and evaporated, and the residue dissolved in petroleum and filtered through celite. Evaporation and chromatography on alumina gave (eluants diethyl ether and acetone, respectively) an orange oil and ergosterol (1a) (150 mg). Careful chromatography of the orange oil on silica gave (α- *and* β-*tachysterol*$_2$)*tricarbonyliron* (3a, b) (690 mg, 51%); $[\alpha]_D$ −40° (*c* 0.77); $\nu_{max.}$ 3 330, 2 040, 1 965, 1 955, 1 460, 1 375, 1 105, 1 040, and 975 cm^{-1}; $\lambda_{max.}$ 209 (ε 23 300) and 266 nm (13 100); τ 3.8—5.1 (5 H, m, 6-, 7-, 9-, 22-, and 23-H), 6.1 (1 H, m, $W_{1/2}$ 18 Hz, 3β-H), and 8.9, 9.0, 9.1, 9.2, and 9.3 (methyl peaks); *m/e* 536.260 2 (M^+ requires 536.258 9), 480, 452 (100%), 396, 378, 271, 269, and 253: (α- and β-*precalciferol*$_2$)-*tricarbonyliron* (4a, b) (100 mg, 7%); $[\alpha]_D$ −17° (*c* 0.63); $\nu_{max.}$ 3 400, 2 030, 1 965, 1 950, 1 450, 1 375, 1 110, and 975 cm^{-1}; $\lambda_{max.}$ 215 (ε 26 800) with inflections at 275, 287, and 300 nm; τ 4.4—5.2 (5 H, m, 6-, 7-, 9-, 22-, and 23-H), 6.1 (3 H, m, $W_{1/2}$ 20 Hz, 3β-H), and 8.9, 9.0, 9.1, and 9.2 (methyl peaks); *m/e* 536.260 2 (M^+ requires 536.258 9), 502, 480, 452 (100%), 396, 271, and 253; and, in trace amounts (ergosterol)tricarbonyliron (1b), $[\alpha]_D$ −83° (*c* 0.995), identical (t.l.c., n.m.r.) with an authentic sample.[1]

Demetallation of (α- *and* β-*Tachysterol*$_2$)*tricarbonyliron* (3a, b).—Iron(III) chloride hexahydrate (2.15 g) in ethanol (10 ml) was added to the complex (3a, b) (258 mg) in THF (10 ml). After stirring for 2 h the solution was diluted with diethyl ether, washed three times with brine, dried, and evaporated. The residual oil in diethyl ether was filtered through alumina to give on evaporation tachysterol$_2$ (5a) (183 mg, 96%); $[\alpha]_D$ −63° (*c* 0.396) (lit.,[4,5] −70°, benzene), $\lambda_{max.}$ 279 nm (ε 34 000) [lit.,[4,6] 281 (ε 24 600); tachysterol$_3$ (5c), $\lambda_{max.}$ 280 (ε 28 000) [3]]. The i.r. and n.m.r. spectra were as expected for tachysterol$_2$ (5a).

Preparation of the Tachysterol$_2$ *Acetate-Citraconic Anhydride Adduct* (7).—Citraconic anhydride (84 mg) and tachysterol$_2$ (5a) (200 mg) in dry THF (12.5 ml) were refluxed together (24 h); the solvent was evaporated off, and the residue in acetic anhydride (4 ml) was heated to 100 °C for 10 min. After cooling, evaporation (toluene azeotrope) gave an oil. This was dissolved in diethyl ether and the solution was washed with 0.25M-sodium hydroxide, dried, and evaporated. Chromatography (silica) gave the adduct (7) (61 mg, 22%), m.p. 160—161 °C (lit.,[2] 161—162 °C); $[\alpha]_D$ +73° (*c* 0.178) (lit.,[2] +75°), *m/e* 550 (M^+), 490, 438, 378 (100%), and 253.

Demetallation of (α- *and* β-*Precalciferol*$_2$)*tricarbonyliron* (4a, b).—Demetallation of the complex (4a, b) (250 mg) as described above at 0 °C (2 h) gave on rapid chromatography (silica) pre-ergocalciferol (6) (110 mg, 60%) (i.r. and n.m.r.) as an oil, $[\alpha]_D$ +36° (benzene) [lit.,[5] +43° (benzene)], $\lambda_{max.}$ 259 nm (ε 8 500) [lit.,[5] 262 (9 000)]; and as a minor product ergocalciferol (2a) (i.r. and n.m.r.), $[\alpha]_D$ +79° (*c* 0.538) (lit.,[6] +82°), $\lambda_{max.}$ 264 nm (ε 16 700) [lit.,[5] 265 (18 300)].

Preparation of (α- *and* β-*Tachysterol*$_2$ *benzoate*)*tricarbonyliron* (3c, d).—Benzoylation (benzoyl chloride–pyridine) of the tachysterol$_2$ complex (3a, b) (400 mg) followed by chromatography (alumina) gave (α-*tachysterol*$_2$ *benzoate*)-*tricarbonyliron* (3c) (221 mg, 46%), as a light orange oil, $[\alpha]_D$ −38° (*c* 0.34), $\nu_{max.}$ 2 030, 1 960, 1 717, 1 450, 1 370, 1 314, 1 270, 1 250, 1 110, 1 070, 1 025, 970, and 710 cm^{-1}; τ 1.96—2.8 (5 H, m, aryl), 4.46—5.25 (6 H, m, 3-, 6-, 7-, 9-, 22-, and 23-H), 8.26 (3 H, s, 10-Me), and 8.93, 9.02, 9.12, and 9.25 (methyl peaks); *m/e* 640.286 9 (M^+ requires 640.285 1), 584, 556 (100%), 500, 434, 432, 378, and 253: and the minor β-*isomer* (3d) (74 mg, 15%) as a dark orange oil, $[\alpha]_D$ +21° (*c* 0.21); $\nu_{max.}$ 2 030, 1 955, 1 717, 1 450, 1 370, 1 314, 1 272, 1 250, 1 112, 1 070, 1 025, 970, and 710 cm^{-1}; τ 1.8—2.67 (5 H, m, aryl), 4.4—4.88 (4 H, m, 3-, 9-, 22-, and 23-H), 4.77—5.13 (2 H, m, 6- and 7-H), 8.16 (3 H, s, 10-Me), and 8.94, 9.00, 9.11, 9.16, and 9.2 (methyl peaks); *m/e* 640.286 9 (M^+), 612, 610, 584, 556 (100%), 500, 434, 432, 378, and 253.

Demetallation of (α-*Tachysterol*$_2$ *benzoate*)*tricarbonyliron* (3c).—Demetallation of the complex (3c) gave tachysterol$_2$ benzoate (5b) (100%) as an oil, $[\alpha]_D$ +15° (*c* 0.697); $\nu_{max.}$ 1 705, 1 445, 1 310, 1 270, 1 110, 965, and 955 cm^{-1}; $\lambda_{max.}$ 280 (ε 21 500) with inflections at 273 and 290 nm; τ 1.84—2.78 (5 H, m, aryl), 3.18, 4.06 (2 H, ABq, *J* 16 Hz, 6- and 7-H), 4.35 (1 H, m, $W_{1/2}$ 7 Hz, 9-H), 4.56—5.01 (3 H, m, 3-, 22-, and 23-H), 8.18 (3 H, s, 10-Me), and 8.9, 9.02, 9.1, 9.21, and 9.3 (methyl peaks); *m/e* 500.364 7 (M^+ requires 500.365 4). Demetallation of the β-isomer (3d) gave identical ($[\alpha]_D$, u.v., i.r., n.m.r., and t.l.c.) tachysterol$_2$ benzoate (5b).

Preparation of (*Tachysterol*$_2$ 3,5-*dinitrobenzoate*)*tricarbonyliron* (3e, f).—3,5-Dinitrobenzoyl chloride (603 mg) was added to the tachysterol$_2$ complexes (3a, b) (660 mg) in dry dichloromethane (10 ml) and triethylamine (5 ml) at 0 °C. When reaction was complete (t.l.c.) the solution was diluted with diethyl ether, washed with brine, dried, and evaporated. Chromatography (silica) gave (α-*tachysterol*$_2$ 3,5-*dinitrobenzoate*)*tricarbonyliron* (3e) (300 mg, 33%) as orange-brown crystals, m.p. 124—130 °C (decomp.) (from light petroleum), $[\alpha]_D$ −72° (*c* 0.44); $\nu_{max.}$ 2 030, 1 950, 1 730, 1 630, 1 540, 1 460, 1 345, 1 280, 1 170, and 970 cm^{-1}; $\lambda_{max.}$ 210 nm (ε 35 900); τ 0.66 (3 H, m, aryl), 4.4—4.95 (6 H, m, 3-, 6-, 7-, 9-, 22-, and 23-H), 8.21 (3 H, s, 10-Me), and 8.92, 9.02, 9.10, and 9.23 (methyl peaks); *m/e* 516, 488, 460, 432 (100%), 414, 376, and 251 (Found: C, 62.3; H, 6.55; N, 3.55. $C_{38}H_{46}FeN_2O_9$ requires C, 62.4; H, 6.45; N, 3.85%): and (β-*tachysterol*$_2$ 3,5-*dinitrobenzoate*)*tricarbonyliron* (3f) (240 mg, 27%), $[\alpha]_D$ +29.3° (*c* 1.13), $\nu_{max.}$ 2 030, 1 960, 1 725, 1 630, 1 546, 1 460, 1 345, 1 280, 1 170, and 970 cm^{-1}; $\lambda_{max.}$ 210 nm (ε 54 000); τ 0.7—1.0 (3 H, m, aryl-H), 4.33—4.71 (2 H, m, 3, 9-H), 4.62—4.96 (2 H, m, 22-, and 23-H), and 8.1 (3 H, s, 10-Me); *m/e* 516, 488, 460, 432 (100%), 414, 376, and 251.

Preparation of (*Precalciferol*$_2$ 3,5-*dinitrobenzoate*)*tricarbonyliron* (4c, d).—3,5-Dinitrobenzoylation of the complex (4a, b) (450 mg) gave on repeated chromatography the major α-*isomer* (4a) as an oil, $[\alpha]_D$ +68° (*c* 1.176); $\nu_{max.}$ 2 035, 1 955, 1 725, 1 630, 1 540, 1 460, 1 340, 1 275, and 970 cm^{-1}; $\lambda_{max.}$ 211 (ε 40 000) with inflections at 278, 290, and 305 nm; τ 0.8—1.05 (3 H, m, aryl), 4.42—4.93 (6 H, m, 3-, 6-, 7-, 9-, 22-, and 23-H), and 8.76, 8.92, 9.01, 9.10, and 9.20 (methyl peaks); *m/e* 646, 616, 590, 560, 530, 488, 460, 432 (100%), 414, 375, and 251: and the minor β-*isomer* (4d) as an oil, $[\alpha]_D$ −106° (*c* 0.903); $\nu_{max.}$ 2 030, 1 955, 1 725, 1 630, 1 545, 1 343, 1 275, and 970 cm^{-1}; $\lambda_{max.}$ 209 nm

[5] A. Verloop, A. L. Koevoet, and H. Havinga, *Rec. Trav. chim.*, 1957, **76**, 689.

[6] L. Velluz, G. Amard, and A. Petit, *Bull. Soc. chim. France*, 1949, 501; H. H. Inhoffen, K. Brückner, K. Irmscher, and G. Quinkert, *Chem. Ber.*, 1955, **88**, 1424.

(ε 27 500); τ 0.73—1.0 (3 H, m, aryl), 4.4—4.73 (2 H, m, 3- and 9-H), 4.67—4.9 (2 H, m, 22- and 23-H), 4.87—5.26 (2 H, m, 6- and 7-H), and 8.48, 8.96, 9.03, 9.12, and 9.22 (methyl peaks); *m/e* 646, 590, 488, 460, 450, 448, 432 (100%), 414, 406, 404, 402, 400, 378, 376, and 251.

Oxidation of (α-*Tachysterol*$_2$ 3,5-*dinitrobenzoate*)*tricarbonyliron* (4e).—DDQ (145 mg) was added to the α-complex (4e) (200 mg) in dry benzene (8 ml). After stirring overnight ether (100 ml) was added, the solution washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated. Chromatography (alumina) gave 9,11-*didehydroisocalciferol* 3,5-*dinitrobenzoate* (8b) (107 mg, 66%) as a glass, $[\alpha]_D$ +295° (*c* 0.699); $\nu_{max.}$ 1 735, 1 630, 1 375, 1 343, 1 275, 1 171, 1 080, 985, 975, 926, 888, 765, 752, 736, and 730 cm^{-1}; $\lambda_{max.}$ 301 (ε 31 900), 314 (42 200), and 328 nm (33 900); τ 0.72—0.93 (3 H, m, aryl), 3.17—3.53 (2 H, m, 9- and 11-H), 3.9—4.64 (3 H, m, 1-, 6-, and 7-H), 4.64—4.92 (3 H, m, 3-, 22-, and 23-H), 8.06 (3 H, s, 10-Me), and 9.04, 9.12, and 9.21 (methyl peaks); *m/e* 588 (M^+), 488, 390, 376, 374, 249, and 212 (100%) (Found: C, 71.5; H, 7.6; N, 4.65. $C_{35}H_{44}N_2O_6$ requires C, 71.45; H, 7.5; N, 4.75%). DDQ oxidation of the minor β-complex (3f) or the α- (4c) or β- (4d) precalciferol$_2$ complexes gave the 9,11-didehydroester (8b), identical (t.l.c., $[\alpha]_D$, u.v., and n.m.r.) with the above sample.

Hydrolysis of the 3,5-*Dinitrobenzoate* (8b).—Potassium hydroxide in methanol (5%, 1 ml) was added to the ester (8b) (270 mg) in THF (5 ml). After 20 min diethyl ether was added and the solution washed twice with water, dried, and evaporated. Chromatography (alumina) gave 9,11-*didehydroisocalciferol*$_2$ (8a) (140 mg, 77%), m.p. 102—116 °C (from petroleum), $[\alpha]_D$ +242° (*c* 0.135); $\nu_{max.}$ 3 340, 1 450, 1 330, 1 090, 1 040, 970, 905, 875, and 730 cm^{-1}; $\lambda_{max.}$ 301 (ε 38 800), 314 (51 400), and 329 nm (41 000); τ 3.37 (2 H, m, 6- or 7-H, 9- or 11-H), 3.98 (1 H, d, *J* 12 Hz, 6- or 7-H), 4.22 (1 H, m, 9- or 11-H), 4.44 (1 H, br s, 1-H), 4.77 (2 H, m, 22- and 23-H), 5.95 (1 H, m, 3β-H), 8.10 (3 H, s, 10-Me), 8.96, 9.05, 9.14, and 9.16 (12 H, 4 d, *J* 7 Hz, side-chain methyls), and 9.40 (3 H, s, 13-Me); *m/e* 394 (M^+), 269, 251, 159, 157, 145, 137, and 131 (Found: C, 85.45; H, 10.75. $C_{28}H_{42}O$ requires C, 85.25; H, 10.65%). Reaction of (α- and β-tachysterol$_2$)tricarbonyliron (3a, b) (57 mg) with DDQ (40 mg) gave 9,11-didehydroisocalciferol$_2$ (8a), identical (t.l.c. $[\alpha]_D$, and u.v.) with the above material.

[7/2021 *Received*, 17*th November*, 1977]