Chemistry of the Tricarbonyliron Complexes of Calciferol and Ergosterol

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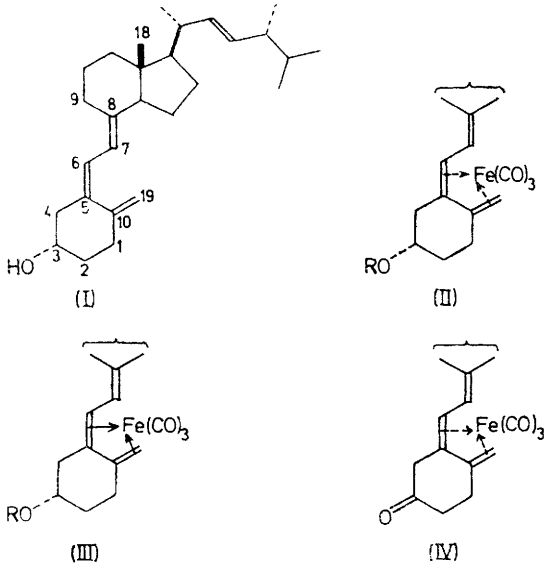
Calciferol affords α- and β-tricarbonyliron complexes in the ratio *ca.* 2:1. Oxidation of the α-complex gives the relatively stable calciferone derivative. For comparison the tricarbonyliron complex of ergosterol was likewise oxidised to the 3-ketone. This stable compound could be reduced by lithium hydrido-tri-t-butoxyaluminate to give, after decomplexing, the previously unknown epiergosterol in good yield.

THERE has been considerable interest recently in derivatives of calciferol (I) and of ergosterol with additional substituents in ring A. These compounds may show interesting biological activity. The standard method of oxidising a 3-hydroxy-steroid to a 3-ketone, and manipulation of this function, for the introduction of substituents is not generally applicable, owing to the ease of isomerisation of the β-placed olefinic system. It seemed to us that this problem might be approached more fruitfully if the triene system of calciferol (I) and the diene system of ergosterol could be strongly complexed to a metal atom. We report here a study of tricarbonyliron complexes.

Calciferol (I) reacted smoothly with nonacarbonyldiiron in toluene at 60 °C to give an almost quantitative yield of the α-complex (II; R = H) and the β-complex (III; R = H) in the ratio *ca.* 2:1 (by n.m.r.). The n.m.r. spectrum of the mixture of α- and β-complexes



showed that the 5,6- and 10,19-bonds were involved in the complexing. Thus both the C-19 protons and C-6 proton exhibited the normal upfield shift for olefinic π-complexes [1] of, respectively, 2.3 and 2.9 p.p.m. The C-7 proton signal was also moved upfield (1.6 p.p.m) but to a lesser extent.[2]

The mixture of complexes showed 13-methyl signals at τ 9.52 and 9.43 in *ca.* 2:1 ratio, the corresponding signal of calciferol itself being at τ 9.45. An identical ratio of isomeric complexes was observed from complexation with *p*-methoxybenzylideneacetone tricarbonyl iron.[3] On the other hand, complexation of calciferol acetate gave a 1:1 mixture of isomers (from the 13-methyl and the 3-acetate n.m.r. signals). Clearly in the presence of the 3-hydroxy-group complexation on the same (α) side of the molecule is favoured. There is good analogy for this in organometallic chemistry.[4]

The more abundant α-complex (II; R = H) is readily obtained by crystallisation of the mixture. Lesser amounts of the β-complex (III; R = H) can be isolated by fractional crystallisation. The α-complex (II; R = H) showed the 3-proton signal at τ 5.82 and the 13-methyl signal at τ 9.54. The β-complex (III; R = H) showed the corresponding signals at τ 5.72 and 9.44. For both compounds the 3-proton signal had $W_{\frac{1}{2}}$ *ca.* 18 Hz, characteristic of a nearly axial proton.[5] Clearly the conformational complexities seen in ring A of cholecalciferol [6] are less marked in our tricarbonyliron complexes.

The mixture of complexes (II; R = H) and (III; R = H) or the pure α-complex (II; R = H) gave back calciferol in high yield on treatment with iron(III) chloride.

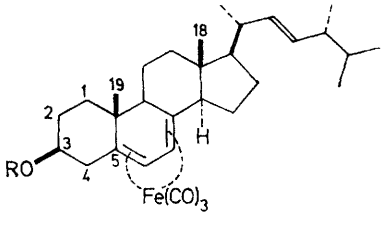
Oxidation of the complex (II; R = H) through the dimethylsulphonium salt [7] afforded the ketone complex (IV) in good yield. Although β-substituted by the tricarbonyliron-complexed triene system, this ketone is relatively stable and can be manipulated easily under neutral conditions. Reduction of the ketone (IV) with the bulky reagent lithium hydridotri-t-butoxyaluminate gave exclusively the starting alcohol (II; R = H). We attribute this stereoselectivity to the bulk of tricarbonyliron group preventing delivery of hydride from the α-side of the molecule. This evidence supports the configurations indicated in formulae (II; R = H) and (III; R = H).

Further support for these configurations was obtained as follows. Oxidation (by the dimethylsulphonium method) of the 2:1 mixture of complexes (II; R = H) and (III; R = H) affected only the α-complex (II; R = H), which afforded the ketone (IV). Since the

[1] M. L. Maddox, S. L. Stafford, and H. D. Kaesz, *Adv. Organometallic Chem.*, 1965, **3**, 47.
[2] *Cf.* R. Burton, L. Pratt, and G. Wilkinson, *J. Chem. Soc.*, 1961, 594.
[3] See 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.
[4] D. E. F. Gracey, W. R. Jackson, W. B. Jennings, and T. R. B. Mitchell, *J. Chem. Soc.* (*B*), 1969, 1204.
[5] L. M. Jackman and S. Sternhell, 'Application of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, London, 1969, p. 288.
[6] R. M. Wing, W. H. Okamura, A. Rego, M. R. Pino, and A. W. Norman, *J. Amer. Chem. Soc.*, 1975, **97**, 4980 and references cited there.
[7] E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, 1972, **94**, 7586.

hydroxy-groups in both complexes are equatorial and equally unhindered, it cannot be salt formation which is inhibited in the case of the β-complex; it must be salt fragmentation which does not occur. Clearly attack by the bulky base used (triethylamine) on the C-3 (β)-hydrogen atom is hindered by the tricarbonyliron group on the same side of the molecule.

In order to confirm these assignments of configuration we carried out a number of model experiments with ergosterol tricarbonyliron complex (V; R = H).[3,8] Oxidation as above gave the ketone (VI), characterised as its oxime. The n.m.r. spectrum of the ketone (VI) showed the expected upfield shifts for the C-6 and C-7 protons (part of the AB system is at τ 5.18, the low-field part being partly obscured by the 22- and 23-proton signals). From the oxidation mixture small amounts of the tetraenone[9] (VII) were also isolated. This compound was also formed in good yield by dehydrogenation of the complex (VI) with dicyanodichloro-1,4-benzoquinone at room temperature.



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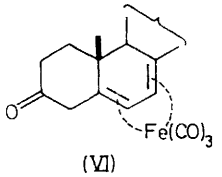

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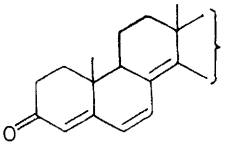

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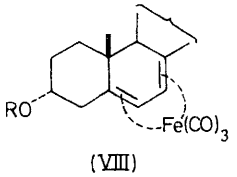

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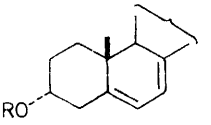

(IX)

Reduction of the ketone (VI) with lithium aluminium hydride at 0 °C gave a 1 : 1 mixture of the starting alcohol (V; R = H) and its epimer (VIII; R = H). This is in contrast to the normal reduction of a saturated *trans*-AB-3-ketone to give almost exclusively the 3β-ol, and it shows the effect of the bulky tricarbonyliron group. A much greater selectivity was achieved by using lithium hydridotri-t-butoxyaluminate, which afforded the 3α-alcohol (VIII; R = H) in 92% yield.

A further indication of the steric effect of the tricarbonyliron group was the fact that, although the complex (V; R = H) was readily acetylated at room temperature in 1 h the complex (VIII; R = H) was unchanged under these conditions and only gave 60% of the ester (VIII; R = Ac) after heating for 3 days at 50 °C.

Removal of the tricarbonyliron group from compound (VIII; R = H) in the usual way gave the previously unknown epiergesterol (IX; R = H), fully characterised by spectroscopic measurements and by acetylation.

A comparison of the n.m.r. properties of these ergosterol derivatives proved instructive (Table). Clearly compounds (V; R = H) and ergosterol have the C-3 proton axial whereas (VIII; R = H) and epiergosterol (IX; R = H) have the C-3 proton equatorial.

Comparative n.m.r. data

Compound:	(V; R = H)	(VIII; R = H)	Ergosterol	(IX; R = H)
τ (3-H)	6.40	5.94	6.50	5.95
$W_{\frac{1}{2}}$/Hz	30	10	28	9.5

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus, i.r. spectra were recorded for Nujol mulls (unless indicated to the contrary) with a Perkin-Elmer 257 spectrophotometer, u.v. spectra were recorded (unless indicated to the contrary) for solutions in ethanol with a Unicam SP 800 spectrophotometer. ^{1}H N.m.r. spectra were taken for solutions in $CDCl_3$ (Me_4Si as internal standard) with a Varian T60 spectrometer. Both thin-layer and plate chromatography were carried out on silica gel G254. Light petroleum refers to the fraction of b.p. 40—60°. Anhydrous magnesium sulphate was used for drying solutions.

Tricarbonyliron Complexes of Calciferol.—To calciferol (1.0 g) in toluene (12 ml) was added nonacarbonyldi-iron (3.0 g). The mixture was stirred at 60 °C under nitrogen for 24 h. After cooling, the solution was chromatographed over neutral alumina (grade I). Elution with light petroleum and then with ether gave the mixture of complexes (1.32 g) containing a trace (62 mg) of a less polar oil of undetermined structure, easily removed by crystallisation. Crystallisation from light petroleum gave the *α-complex* (II; R = H) (375 mg) [containing only a trace (n.m.r.) of the β-complex (III; R = H)] m.p. 134°, $[\alpha]_D$ +501° (*c* 0.58 in EtOH), $\nu_{max.}$ 3 300, 2 025, 1 970, 1 960, 1 930, 1 625, 1 050, 1 030, and 960 cm^{-1}, ν_{OH} (C_6H_{12}) 3 600 cm^{-1}, $\lambda_{max.}$ 217, 240, and 310 nm (ε 13 150, 12 000, and 6,700), τ 9.54 (13-Me), 9.25, 9.15, 9.05, and 8.95 (side chain Me's), 7.45—6.55 (=CH_2 and H-6), 5.82 (H-3, $W_{\frac{1}{2}}$ 19 Hz), 5.38 (H-7, *J* 8 Hz), and 4.84 (22- and 23-H), *m/e* 536 (M^+) and 451 (100%, M^+ − 3CO − H) (Found: C, 69.35; H, 8.5. $C_{31}H_{44}FeO_4$ requires C, 69.4; H, 8.25%).

The mother liquor was evaporated and the residue fractionally crystallised from light petroleum to give the pure *β-complex* (III; R = H) (112 mg), m.p. 152°, $[\alpha]_D$ −394° (*c* 0.574 in EtOH), $\nu_{max.}$ 3 240, 2 020, 1 975, 1 940, 1 620, 1 100, 965, and 945 cm^{-1}, ν_{OH} (C_6H_{12}) 3 600 cm^{-1}, $\lambda_{max.}$ 235 and 309 nm (ε 14 500 and 8 000), τ 9.44 (13-Me), 9.23, 9.13, 9.03, and 8.95 (Me's), 7.43 (=CH_2), 6.83 (H-6, *J* 9 Hz), 5.72 (H-3, $W_{\frac{1}{2}}$ 18 Hz), 5.42 (H-7, *J* 9 Hz), and 4.84 (22- and 23-H), *m/e* 536 (M^+) and 452 (100%, M^+ − 3CO) (Found: C, 69.2; H, 8.25%).

A mixture (65 : 35) of the α- and β-complexes (300 mg) in tetrahydrofuran (35 ml) was treated with iron(II) chloride hydrate in ethanol (35 ml) at room temperature for 90 min.

[8] H. Alper and J. T. Edward, *J. Organometallic Chem.*, 1968. **14**, 411.

[9] D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 1951, 2728.

Work-up gave calciferol (204 mg, 83%), identical with authentic material. In the same way the pure α-complex (II; R = H) gave pure calciferol (85%).

Tricarbonyliron Complexes of Calciferol Benzoate.—The mixture of α- and β-calciferol complexes (see above) (300 mg) in pyridine (0.4 ml) and benzoyl chloride (0.2 ml) was left at room temperature for 24 h (complete esterification). Work-up and crystallisation from methanol afforded the *α-complex benzoate* (II; R = PhCO), m.p. 43—45°, τ 9.53 (13-Me), 5.38 (H-7, *J* 8 Hz), and 4.50 (H-3, $W_{\frac{1}{2}}$ 19 Hz) (Found: C, 71.3; H, 7.55. $C_{38}H_{48}FeO_5$ requires C, 71.25; H, 7.55%). The β-complex benzoate (III; R = PhCO) which remained in the mother liquors could not be crystallised but it had τ 9.43 (13-Me), 6.80 (H-6, *J* 8 Hz), 5.37 (H-7, *J* 8 Hz), and 4.47 (H-3, $W_{\frac{1}{2}}$ 20 Hz).

Tricarbonyliron α-Complex (IV) *of Calciferone.*—To a stirred suspension of *N*-chlorosuccinimide (100 mg) in toluene (3 ml) was added, at 0 °C under nitrogen dimethyl sulphide (0.1 ml). After 10 min the temperature was lowered to −20 °C and the α-complex (II; R = H) (270 mg) in toluene (4 ml) was added dropwise. After 2 h at −20 °C, triethylamine (60 mg) in toluene (0.5 ml) was added and the mixture was left for 10 min. Addition of ether (10 ml), work-up in the usual way, and p.l.c. on silica gave the *ketone α-complex* (IV) (247 mg), m.p. 124—127° (from methanol), $[\alpha]_D$ +477° (*c* 0.50 in EtOH), $\nu_{max.}$ 2 010, 1 975, 1 945, 1 705, 1 625, 905, and 855 cm^{-1}, $\lambda_{max.}$ 235 and 309 nm (ε 12 100 and 7 450) τ 9.53 (13-Me), 9.25, 9.15, 9.08, and 8.95 (side chain Me's), 7.68—6.22 (=CH_2, H-2, H-4, and H-6), 5.38 (H-7, *J* 9 Hz), and 4.83 (22- and 23-H), *m/e* 534 (M^+) and 450 (100%, M^+ − 3CO) (Found: C, 69.7; H, 7.85. $C_{31}H_{42}FeO$ requires C, 69.7; H, 7.9%).

The same procedure was applied to the mixture of α- and β-complexes [(II; R = H) and (III; R = H)] (ratio 65 : 35; 3.2 g) with *N*-chlorosuccinimide (1.2 g), dimethyl sulphide (1.0 ml), and triethylamine (700 mg). P.l.c. on silica gave the ketone (IV) (90% purity; 1.57 g, 49%). The β-complex (III; R = H) was not oxidised and was recovered as unchanged alcohols (1.42 g). Recrystallisation from methanol gave the pure ketone (IV) (1.29 g).

Reduction of the Ketone α-Complex (IV).—The ketone (IV) (270 mg) in ether (20 ml) was treated at 0 °C under nitrogen with lithium hydridotri-t-butoxyaluminate (2 g), added in several portions, and left for 1 h. Work-up gave the α-complex (II; R = H) (n.m.r. comparison) (253 mg). Crystallised once this had m.p. and mixed m.p. 134°, $[\alpha]_D$ +501° (*c* 0.87 in EtOH), and all other spectroscopic data in agreement with (II; R = H).

Tricarbonyliron Complex of Ergosta-5,7,22-trien-3-one.—*N*-Chlorosuccinimide (1.9 g), suspended in toluene (50 ml), was stirred at 0 °C under nitrogen while dimethyl sulphide (1.5 ml) was added. After 10 min the temperature was lowered to −20 °C and the tricarbonyliron complex (V; R = H) of ergosterol (5.12 g) in toluene (60 ml) was added dropwise. After 2 h at −20 °C, triethylamine (1.4 g) in toluene (5 ml) was added and stirring was continued for 10 min. Addition of ether (100 ml), pouring into water, and removal of the excess of base by washing with aqueous 1% hydrochloric acid gave, on concentration to *ca.* 10 ml *in vacuo* and cooling to −10 °C, the *ketone complex* (VI) (1.58 g), m.p. 145—147° (decomp.) (from ether–light petroleum), $[\alpha]_D$ −77° (*c* 0.57 in $CHCl_3$), $\nu_{max.}$ 2 025, 1 970, 1 950, 1 715, and 975 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 252 nm (ε 10 800), M^+ 534 (Found: C, 69.7; H, 7.9. $C_{31}H_{42}FeO_4$ requires C, 69.65; H, 7.9%). More (790 mg) of this ketone was obtained on chromatography of the mother liquors. Also present was a small amount (130 mg) of the ketone (VII).

The ketone (VI) (500 mg) in pyridine (10 ml) was treated with hydroxylamine hydrochloride (3 g) at room temperature for 24 h. Work-up and crystallisation from light petroleum afforded the *oxime* (410 mg), m.p. 124—127° (decomp.) (Found: C, 67.85; H, 7.95; N, 2.2. $C_{31}H_{43}FeNO_4$ requires C, 67.75; H, 7.9; N, 2.25%).

Ergosta-4,6,8(14),22-tetraen-3-one.—The ketone complex (VI) (300 mg) in toluene (10 ml) was treated with dicyanodichloro-1,4-benzoquinone (450 mg) at room temperature for 6 h (t.l.c. control). Chromatography on silica afforded ergosta-4,6,8(14),22-tetraen-3-one (123 mg) which, after crystallisation from light petroleum, was identical with an authentic specimen.[9]

Reduction of the Ketone Complex (VI) *with Lithium Aluminium Hydride.*—The ketone complex (VI) (120 mg) in ether (20 ml) at 0 °C under nitrogen was treated slowly with lithium aluminium hydride in ether (0.1M; 30 ml). After 1 h [disappearance of (VI)] the solution was quenched with water and worked up. Chromatography afforded the known [3] ergosterol complex (V) (57 mg) and a new less polar complex (VIII; R = H) (52 mg) (see further below).

Reduction of the Ketone Complex (VI) *with Lithium Hydridotri-t-butoxyaluminate.*—The complex (VI) (2.3 g) in ether (370 ml) was treated with stirring at 0 °C under nitrogen with the tri-t-butoxyaluminate (9.0 g), added in portions during 1 h. After stirring for a further 1 h at 0 °C the reaction was quenched with water. Chromatography gave the more polar ergosterol complex (V; R = H) (180 mg) and the less polar *epiergosterol complex* (VIII; R = H) (2.05 g), m.p. (from light petroleum) 120°, $[\alpha]_D$ −137° (*c* 0.85 in EtOH), $\nu_{max.}$ 3 615, 3 570, 2 015, 1 970, 1 955, and 980 cm^{-1}, $\lambda_{max.}$ 215 and 238 nm (ε 17 000 and 18 650), M^+ 536 (Found: C, 69.35; H, 8.3. $C_{31}H_{44}FeO_4$ requires C, 69.4; H, 8.25%).

The complexes (V; R = H) and (VIII; R = H) (150 mg each) were separately treated with pyridine (6 ml) and acetic anhydride (3 ml) at room temperature. After 1 h the complex (V; R = H) had been completely acetylated,[3] whereas the complex (VIII; R = H) was unaffected. The solution of the latter was kept at 50 °C for 4 days but even then the extent of acetylation (to a non-crystalline product) was only 60%.

Epiergosterol (IX; R = H) *and its Derivatives.*—The complex (VIII; R = H) (2.0 g) in tetrahydrofuran (15 ml) was treated slowly with saturated iron(III) chloride hydrate in ethanol (25 ml) and stirred for 90 min. Work-up, followed by filtration in ether through a short column of neutral alumina (grade I) gave *epiergosterol* (IX; R = H) (1.28 g), m.p. (from ether) 152—154°, $[\alpha]_D$ −88° (*c* 0.416 in $CHCl_3$), $\nu_{max.}$ 3 280, 1 650, 1 590, 970, and 825 cm^{-1}, $\lambda_{max.}$ 261, 270, 281, and 292 nm (ε 8 000, 11 350, 12 150, and 7 000) (Found: C, 84.6; H, 11.15. $C_{28}H_{44}O$ requires C, 84.8; H, 11.2%).

Treatment of epiergosterol with an excess of pyridine–acetic anhydride overnight at room temperature gave the *acetate* (IX; R = Ac), m.p. 124° (from ether), $[\alpha]_D$ −49° (*c* 0.56 in $CHCl_3$), $\nu_{max.}$ 1 740, 1 650, 1 600, 1 240, and 970 cm^{-1}, $\lambda_{max.}$ 281 nm (ε 15 500) (Found: C, 82.1; H, 10.4. $C_{30}H_{46}O_2$ requires C, 82.15; H, 10.55%).

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