Es konnte noch 1 μg Hg neben 150 μg eines Gemisches vieler Kationen mit einer Genauigkeit von ±4% bestimmt werden. Erfassungsgrenze und Fehlerbreite waren weitgehend durch den Neutronenfluss des zur Verfügung stehenden Kernreaktors des Physikalischen Instituts der Universität Basel gegeben.

Experimentelles. – Schicht: Kieselgel MN S–HR. – Auftragelösungen: a) Gemisch der Ionen von Pb, Bi, Cu, Cd, Co, Ni, Zn, Mn, Fe, Cr, Al, Ba, Sr, Ca, Mg, K, Na, Li, mit und ohne Hg, je 0,1M in 3M HNO_3; b) 0,1M $Hg(NO_3)_2$ in 3M HNO_3. Es wurde jeweils 1 μl aufgetragen. – Fliessmittel: 80 ml *n*-Butanol und 20 ml 4N HNO_3. – Nachweisreagens: 2-proz. Diphenylcarbazid in Methanol/Äthanol 1:1; Hg: violett, Bi: rosarot.

Wir danken dem *Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung* für die Unterstützung dieser Arbeit.

LITERATURVERZEICHNIS

[1] *J. Bäumler & S. Rippstein,* Mitt. Lebensmitt. Hyg. *54,* 57 (1963).

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222. Allylic Oxidation of some 5,6-Unsaturated Steroids with Lead Tetraacetate

Communication XXII on Reactions with Lead Tetraacetate[1])

by **M. Stefanović, A. Jokić, Z. Maksimović, Lj. Lorenc** and **M. Lj. Mihailović**[2])

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(31. VIII. 70)

Summary. Oxidation of cholesteryl acetate and diosgenyl acetate with lead tetraacetate in benzene or glacial acetic acid solution results in allylic acetoxylation in the C-7 position. These reactions are nonstereospecific, and in both solvents mixtures of the corresponding 7β- and 7α-epimeric acetoxy derivatives are formed. On the basis of the results, the mechanism of this oxidation reaction is discussed.

The importance of introducing the hydroxy function in the C-7 position of cholesterol (and other Δ^5-steroids), particularly in the less stable axial 7α-position suitable for *trans*-diaxial elimination and obtention of the precursor of vitamin D_3, has been widely discussed and different aspects of this problem have been envisaged [2]. On the other hand it is known that cyclic olefins may undergo allylic oxidation when treated with metal acetates [3] [4]. Having this in mind, we have now investigated the action of lead tetraacetate on some Δ^5-steroids[3]), namely on cholesteryl acetate (I) and diosgenyl acetate (IV), in view of exploring the possibility of a one-step introduction of the acetoxy function in the allylic 7β- and/or 7α-position.

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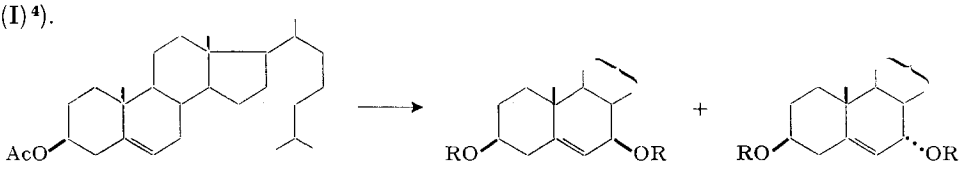
[1]) Communication XXI: s. reference [1].

[2]) Address for correspondence: Department of Chemistry, Faculty of Sciences, Studentski trg 16, P.O. Box 550, Belgrade, Yugoslavia.

[3]) The lead tetraacetate (+iodine) allylic acetoxylation of a Δ^5-steroid system has been reported previously only as a trace reaction [5].

Treatment of cholesteryl acetate (I) with two molar equivalents of lead tetraacetate in refluxing benzene (and in the presence of anhydrous calcium carbonate) or in glacial acetic acid at 80° affords a mixture of 7β- and 7α-acetoxycholesteryl acetates (IIa and IIIa, respectively), in about 20% yield. Since 60–70% of starting cholesteryl acetate (I) can be easily recovered from the reaction mixture, the yield of 7-acetoxylated compounds (IIa + IIIa), based on reacted substrate, amounts to about 50%. An increase in the amount of lead tetraacetate (to five molar equivalents) has practically no influence on the yield of the 7-acetoxy epimers (IIa and IIIa) but lowers drastically (to about 5%) the quantity of the recovered cholesteryl acetate (I)[4].



I

IIa R = Ac
IIb R = H

IIIa R = Ac
IIIb R = H

In all experiments the mixture of the 7-acetoxylated isomers IIa and IIIa was separated from the starting material (I) and other reaction products by column chromatography on alumina[5]. Since the epimeric 7-acetoxy derivatives IIa and IIIa possess different specific rotations (7β-acetoxycholesteryl acetate (IIa) +54° and 7α-acetoxycholesteryl acetate (IIIa) −177°) [6], their relative ratios in reaction mixtures obtained in different runs could be determined by optical measurements. These measurements show that all oxidations, performed in either benzene or acetic acid solution with two or five molar equivalents of lead tetraacetate, afford mixtures containing approximately the same proportion of 7β- to 7α-isomer, *i.e.* in each case the specific rotation was near −35°, indicating a ratio of about 3:2 of 7β-O-acetate (IIa) to 7α-O-acetate (IIIa).

These data were confirmed by actual separation of the 7-epimers: the mixture of the acetates IIa and IIIa was converted into the corresponding mixture of alcohols IIb and IIIb by reduction with lithium aluminium hydride, and the 7-epimeric diols IIb and IIIb were isolated by column chromatography separation on silica gel[6], again in an approximate 3:2 molar ratio in favour of the 7β-isomer (IIb).

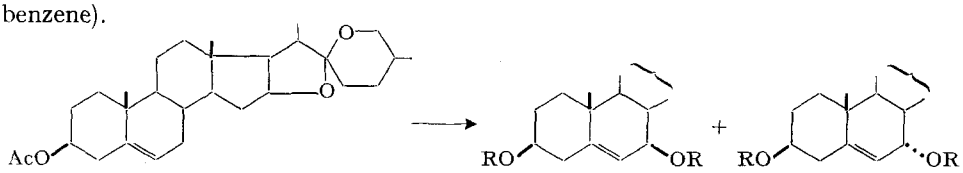
Similar results were also obtained with diosgenyl acetate (IV) as substrate, which, upon treatment with two molar equivalents of lead tetraacetate in glacial acetic acid at 80° or in refluxing benzene in the presence of calcium carbonate, is partially converted to a mixture of 7β- and 7α-acetoxydiosgenyl acetates (Va and VIa, respectively)[5], in about 15% yield. Since 57% of unreacted starting product IV could be

[4] The major part of the material isolated consists of a complex mixture of highly polar substances, out of which no well defined products could be obtained.

[5] The epimeric 7β- and 7α-acetoxycholesteryl acetates (IIa and IIIa, respectively) are indistinguishable on thin layer chromatography and are eluted upon column chromatography on alumina or silica gel as one fraction. The same is true for the epimeric 7β- and 7α-acetoxydiosgenyl acetates (Va and VIa, respectively), described later in the text.

[6] The 7-epimeric diols IIb and IIIb, and also the 7-epimeric diols Vb and VIb, appear on thin layer chromatography as two well resolved spots (the 7β-isomers having higher Rf-values) and can be readily separated by column chromatography on silica gel.

isolated from the reaction mixture when the oxidation was carried out in acetic acid, and 75% when performed in benzene, the yield of 7-acetoxylated products (Va + VIa), based on reacted substrate, amounts to about 35% (in acetic acid) and 60% (in benzene).



IV

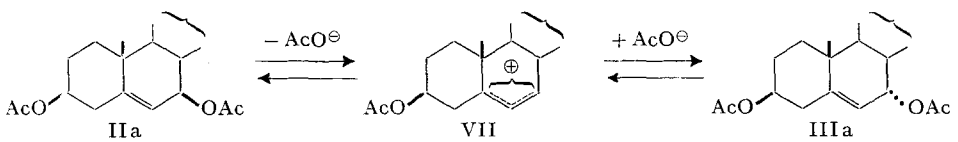
Va R = Ac
Vb R = H

VIa R = Ac
VIb R = H

The mixture of 7-acetoxydiosgenyl acetates (Va and VIa)[5]) was reduced with lithium aluminium hydride and the alcohols Vb and VIb obtained were separated on a column of silica gel[6]). In all experiments the approximate ratio of the epimeric 7β-ol (Vb) to the 7α-ol (VIb) was 3:2.

It was earlier found that 7β- (IIa) and 7α-acetoxycholesteryl acetates (IIIa) can be interconverted when refluxed in a 50% mixture of glacial acetic acid and acetic anhydride, giving a 2:1 equilibrium mixture of 7β- (IIa) to 7α-epimer (IIIa) [6]. Under these conditions, the equilibrium is most probably reached through the intermediate formation of the carbonium ion VII (Scheme 1), following an S_N1 type mechanism, although the authors [6] mention also the alternative possibility of an S_N2 type mechanism proceeding with *Walden* inversion.

Scheme 1



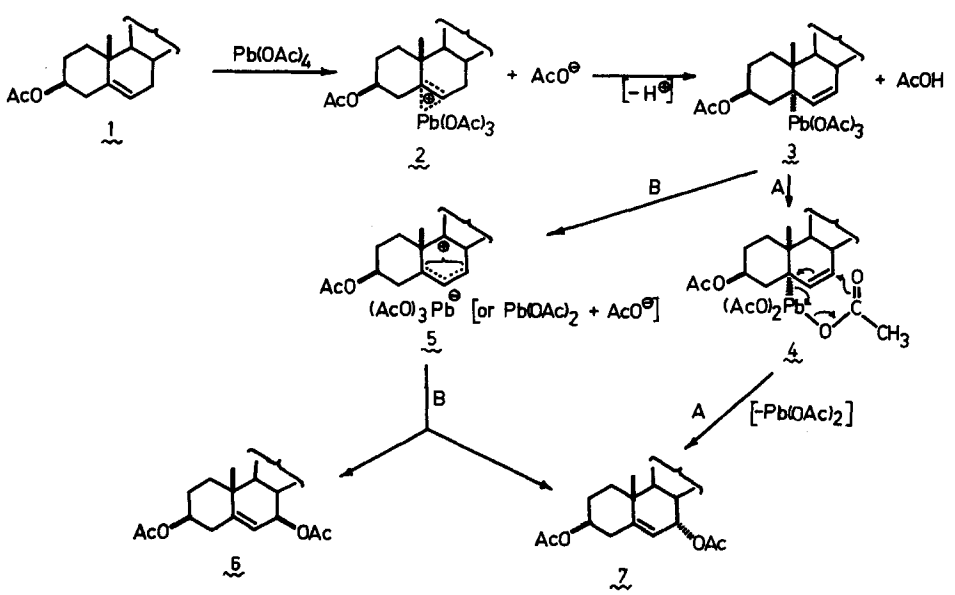
IIa VII IIIa

In the light of these results we have studied the behaviour of the 7-epimeric 7-acetoxycholesteryl acetates IIa and IIIa, and the 7-acetoxydiosgenyl acetates Va and VIa under conditions similar to those used in performing the lead tetraacetate allylic oxidations. Pure 7β- (IIa) and pure 7α-acetoxycholesteryl acetate (IIIa) were separately heated at 80° in glacial acetic acid in the presence of some lead diacetate for 2–3 hours, and after isolation their optical rotations were measured. In both cases the specific rotation changed to about $-32°$, due to isomerization and formation of an equilibrium mixture containing the same 3:2 ratio of 7β- (IIa) to 7α-epimer (IIIa), this ratio corresponding also to that found in the lead tetraacetate allylic acetoxylation of cholesteryl acetate (I) using glacial acetic acid (at 80°) as solvent (see above). The 7-epimeric 7-acetoxylated diosgenyl acetates (Va and VIa) behave similarly. Namely, both 7β-acetoxydiosgenyl acetate (Va) ($[\alpha]_D^{20} = -27°$) and 7α-acetoxydiosgenyl acetate (VIa) ($[\alpha]_D^{20} = -225°$), heated separately in glacial acetic acid at 80° for 3 hours (without or in the presence of lead diacetate), afford a mixture with practically the same specific rotation (of about $-100°$). According to these data, the approximate ratio of 7β- (Va) to 7α-isomer (VIa) is, upon equilibration, in both cases 3:2, and this corresponds to the ratio of the 7-epimeric diacetates Va and VIa obtained in the lead tetraacetate oxidation of diosgenyl acetate (IV) in glacial acetic acid solution at 80°

(see above). From these experiments in acetic acid it can only be concluded that the lead tetraacetate acetoxylation of Δ^5-steroids, using acetic acid as solvent, very probably involves, in *some stage* of the reaction course, a carbonium ion intermediate (of type VII, Scheme 1), which finally affords, as the result of thermodynamic control, an equilibrium mixture of the 7β- and 7α-epimeric O-acetates (IIa and IIIa; Va and VIa). Since in this way it was not possible to obtain a more precise picture of the actual oxidation steps in the course of the lead tetraacetate reaction, we examined the behaviour of the epimeric 7-O-acetates (IIa and IIIa; Va and VIa) in benzene solution. In equilibration experiments performed separately with pure 7β- (IIa) and pure 7α-acetoxycholesteryl acetate (IIIa) in refluxing benzene solution for 24–36 hours in the presence of two molar equivalents of lead diacetate, acetic acid and calcium carbonate (conditions similar to those existing during the lead tetraacetate oxidation of cholesteryl acetate (I) in benzene), the specific rotations of the products isolated were found to be unchanged (with respect to those of the starting compounds), *i.e.* under these conditions the 7β-acetate IIa and its 7α-epimer IIIa are stable and, once formed, do not interconvert. The same was found to be true with the 7β- (Va) and 7α-acetoxydiosgenyl acetates (VIa). Therefore, the 3:2 molar ratios of the 7β-O-acetates (IIa and Va, respectively), to the corresponding 7α-epimers (IIIa and VIa, respectively), obtained in the lead tetraacetate reaction of cholesteryl acetate (I) and diosgenyl acetate (IV), respectively, in benzene, represent the ratios in which the pairs of 7-acetoxylated stereoisomers are initially generated in the course of the actual oxidation stage.

For allylic oxidations of olefins with metal acetates, particularly lead tetraacetate, several pathways have been proposed, two of which are of special interest [3] for the present study: one proceeding through a cyclic transition state (mechanism A,

Scheme 2



Scheme 2), and the other through a mesomeric carbonium ion (mechanism B, Scheme 2), with steps 2 and 3 common to both mechanisms.

If the cyclic mechanism (A), involving transition state 4[7]), is operative in the lead tetraacetate allylic acetoxylation of Δ^5-steroids (1), it should be expected for steric reasons that only the 7α-isomer (7) is initially formed. However, the fact that both 7-epimers (6 and 7) are obtained when benzene is used as solvent (in which, as mentioned above, the 7-epimers do not interconvert), suggests that Δ^5-steroids are acetoxylated by way of mechanism B (Scheme 2) and that one of the intermediates has a delocalized distribution of positive charge involving the 7-position, *i.e.* that it is the ion pair (5) containing a resonance hybrid carbonium ion, which, as mentioned above, is also responsible (*e.g.* VII on Scheme 1) for the reversible interconversion of the 7-epimeric acetoxy derivatives (IIa ⇄ IIIa; Va ⇄ VIa) in glacial acetic acid at 80°. The further reaction course from the ion pair 5 (Scheme 2) in the lead tetraacetate oxidation in benzene would be kinetically controlled, leading to a mixture of 7β- (6) and 7α-epimer (7); probably because of similar free energies of activation for both steps 5 → 6 and 5 → 7, the ratio of the epimers 6 and 7 is the same (*i.e.* about 3:2 in favour of the 7β-epimer 6) as that produced under thermodynamically controlled conditions (equilibration in acetic acid; see above).

The authors are grateful to the *Yugoslav Federal Research Fund* and to the *Serbian Academy of Sciences and Arts* for financial support.

Experimental[8])

Melting points (uncorrected) were determined on a micro-*Kofler* hot-stage apparatus. IR. spectra were recorded on a *Perkin-Elmer* double-beam instrument, Model 221. Optical rotation. were measured in $CHCl_3$. NMR. spectra were obtained at 60 MHz with a *Varian* HA-60 spectrometer in CCl_4 solution using tetramethyl silane as internal standard (chemical shifts are reported in δ-values). Light petroleum refers to the fraction b.p. 40–60°. The separation of products was controlled by thin layer chromatography (TLC.) which was carried out on silica gel G (*Stahl*) with benzene-AcOEt (9:1) or ether-AcOEt (1:1), the detection being effected with 50% aqueous H_2SO_4.

A) Oxidations of cholesteryl acetate (I) with lead tetraacetate. – a) *Oxidation with 2 molar equivalents of $Pb(OAc)_4$ in acetic acid solution.* A solution of 5.0 g of cholesteryl acetate (I) and 10.0 g of lead tetraacetate in 150 ml of glacial acetic acid was stirred at 80°. After 2 h, the starch-iodine test for tetravalent lead was negative, indicating the end of the reaction. The mixture was poured into ice-water and extracted with ether; the ether layer was washed with water, aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue (5.23 g) was chromatographed on 150 g of neutral Al_2O_3 (activity II). With light petroleum and light petroleum-benzene (9:1 and 8:2) 3.14 g (62.8%) of cholesteryl acetate (I) was recovered (identified by m.p. and mixed m.p. determination, and comparison of IR. spectra). Elution with benzene gave a mixture (1.18 g; 20.8%) of 7β- and 7α-acetoxycholesteryl acetate (IIa+IIIa), $[\alpha]_D^{20} = -36°$ ($c = 1.6$), which on TLC. appeared as one spot. Elution with benzene-ether (in various ratios) and ether alone afforded a complex mixture which was not further investigated.

Lithium aluminium hydride reduction of 7-acetoxylated cholesteryl acetates (IIa+IIIa). The above obtained mixture (1.0 g) of IIa and IIIa was refluxed with $LiAlH_4$ (0.5 g) in dry ether for one h. After working up as usual, a mixture (750 mg; 90.6%) of 7β- and 7α-hydroxycholesterol (IIb+IIIb) was obtained, which was further chromatographed on 40 g of silica gel (0.08 mm). The

[7]) A cyclic seven-membered transition state of type 4 (Scheme 2), is structurally favourable in this case, because of the considerable length of the C-Pb bond [7].

[8]) The authors thank Mrs. *R. Tasovac* for the elemental microanalyses (which were carried out in our Microanalytical Laboratory), and Dr. *D. Jeremic* for the IR. and NMR. spectra (which were measured in our Instrumental Division).

first benzene-ether (3:2) eluates afforded 300 mg of 7β-hydroxycholesterol (IIb), which was recrystallized from methanol. M.p. 174–178°, $[\alpha]_D^{20} = +5.3°$ ($c = 2.0$) (Lit. [8]: m.p. 172–178.5°, $[\alpha]_D = +5$ to $+7.2°$)[9]). IR. spectrum (KBr): $\nu_{max} = 3320$ cm^{-1}.

$C_{27}H_{46}O_2$ (402.64) Calc. C 80.54 H 11.52% Found C 80.69 H 11.58%

Further elution with the same combination of solvents gave a mixture (96 mg) of 7β- and 7α-isomer (IIb + IIIb). Benzene-ether (1:1 and 2:3) eluates afforded 185 mg of 7α-hydroxycholesterol (IIIb), which was recrystallized from methanol. M.p. 182–184° (MeOH containing product), 155 to 156° (MeOH free), $[\alpha]_D^{20} = -86°$ ($c = 1.12$) (Lit. [8]: m.p. 184–187° (containing MeOH), 154 to 161° (MeOH free), $[\alpha]_D = -84$ to $-91°$)[9]). IR. spectrum (KBr): $\nu_{max} = 3680$, 3340 cm^{-1}.

$C_{27}H_{46}O_2$ (402.64) Calc. C 80.54 H 11.52% Found C 80.67 H 11.32%

b) *Oxidation with 5 molar equivalents of $Pb(OAc)_4$ in acetic acid solution.* A solution of I (5.0 g) in glacial acetic acid (150 ml) was treated with lead tetraacetate (25 g) at 80°, with constant stirring. After 5 h the oxidant was consumed (negative starch-iodine test). The reaction mixture was worked up and chromatographed as described in section A) a), to give unchanged I (268 mg; 5.4%), a mixture (1.04 g; 18.3%) of 7β- and 7α-acetoxylated cholesteryl acetates (IIa + IIIa), $[\alpha]_D^{20} = -35°$ ($c = 1.6$), and a complex mixture (2.5 g; about 50%) of non identified products.

Lithium aluminium hydride reduction of 7-acetoxylated cholesteryl acetates (IIa + IIIa). Reduction of the above obtained mixture (1.0 g) of IIa and IIIa with $LiAlH_4$, followed by chromatography on silica gel (as described in section A) a)) of the resulting mixture (760 mg; 92%) of 7β- and 7α-hydroxycholesterol (IIb + IIIb), afforded: 306 mg of 7β-hydroxycholesterol (IIb), m.p. 176–178° (from MeOH), $[\alpha]_D^{20} = +6.2°$ ($c = 2.4$); a mixture (80 mg) of 7β- and 7α-epimer (IIb + IIIb); 216 mg of 7α-hydroxycholesterol (IIIb), m.p. 184° (from MeOH), $[\alpha]_D^{20} = -85.8°$ ($c = 1.38$).

c) *Oxidation with 2 molar equivalents of $Pb(OAc)_4$ in benzene.* A suspension of 2.0 g of cholesteryl acetate (I), 4 g of lead tetraacetate (dried *in vacuo* over P_2O_5 and KOH) and 0.5 g of anhydrous $CaCO_3$ in 150 ml of thiophene-free benzene (dried over Na) was heated to reflux and stirred for 36 h, after which time the oxidant was completely consumed (negative starch-iodine test). The cooled mixture was diluted with ether, filtered through a Celite mat, and the insoluble precipitate thoroughly washed with ether. The combined filtrates were washed with water, aqueous $NaHCO_3$, and water, and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crystalline residue (2.21 g) was chromatographed on 60 g of neutral Al_2O_3 (activity II) to give 1.45 g (72.3%) of starting I, and a mixture (421 mg; 18.5%) of 7β- and 7α-acetoxycholesteryl acetate (IIa + IIIa), $[\alpha]_D^{20} = -34.5°$ ($c = 1.8$).

Lithium aluminium hydride reduction of 7-acetoxylated cholesteryl acetates (IIa + IIIa). Reduction of the above obtained mixture (220 mg) of IIa and IIIa with $LiAlH_4$, followed by chromatography on silica gel (as described in section A) a)) of the resulting mixture (175 mg; 96%) of 7β- and 7α-hydroxycholesterol (IIb + IIIb) afforded: 73 mg of 7β-hydroxycholesterol (IIb), m.p. 174 to 178°, $[\alpha]_D^{20} = +5.8°$ ($c = 2.3$); a mixture (21 mg) of 7β- and 7α-epimer (IIb + IIIb); and 39 mg of 7α-hydroxycholesterol (IIIb), m.p. 182–184°, $[\alpha]_D^{20} = -86°$ ($c = 1.42$).

Acetylation of 7β-hydroxycholesterol (IIb). A solution of 200 mg of IIb in pyridine (2 ml) and acetic anhydride (2 ml) was left overnight at room temperature. Methanol (5 ml) was added to the solution with external ice-cooling, and after one h the mixture was evaporated to dryness. The residue, consisting of 240 mg of 7β-acetoxycholesteryl acetate (IIa), was recrystallized from methanol. M.p. 108–110°, $[\alpha]_D^{20} = +52°$ ($c = 1.18$) (Lit. [6] [8]: m.p. 108–110°, $[\alpha]_D^{15} = +54°$)[9]). IR. spectrum (KBr): $\nu_{max} = 1745$, 1740, 1680, 1240 cm^{-1}. NMR. spectrum: $\delta = 0.65$ (CH_3-18, *s*), 0.82 (CH_3-26 and CH_3-27, *d*), 0.84 (CH_3-21, *d*), 1.04 (CH_3-19, *s*), 1.90 (CH_3COO-3 and CH_3COO-7, *s*), about 4.35 (CH-3, *m*), 4.88 (CH-7, *m*), 5.12 (=CH-6, *m*).

$C_{31}H_{50}O_4$ (486.71) Calc. C 76.50 H 10.36% Found C 76.73 H 10.43%

Acetylation of 7α-hydroxycholesterol (IIIb). The above described procedure applied to 200 mg of IIIb afforded 240 mg of 7α-acetoxycholesteryl acetate (IIIa), which was recrystallized from

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[9]) In earlier reports (*e.g.* [6a] [8a]) opposite configurations at C-7 were ascribed (erroneously) to the 7-epimeric 7-hydroxy-cholesterols and their derivatives (see [2], pp. 154–157, and [9], for correct stereochemical determinations).

acetone. M.p. 123–124°, $[\alpha]_D^{20} = -174°$ ($c = 1.32$) (Lit. [6] [8]: m.p. 123–124°, $[\alpha]_D^{14} = -175°$)[9]. IR. spectrum (KBr): $\nu_{max} = 1742, 1740, 1670, 1245\ cm^{-1}$. NMR. spectrum: $\delta = 0.66$ (CH_3-18, *s*), 0.82 (CH_3-26 and CH_3-27, *d*), 0.85 (CH_3-21, *d*), 1.01 (CH_3-19, *s*), 1.92 and 1.96 (CH_3COO-3 and CH_3COO-7, two *s*), about 4.40 (CH-3, *m*), 4.85 (CH-7, *m*), 5.52 (=CH-6, *m*).

$C_{31}H_{50}O_4$ (486.71) Calc. C 76.50 H 10.36% Found C 76.47 H 10.33%

Isomerization of 7β- (IIa) and 7α-acetoxycholesteryl acetate (IIIa). 50 mg of IIa ($[\alpha]_D^{20} = +52°$) in glacial acetic acid (2.5 ml) was heated 2 h at 80°, with stirring. The specific rotation of the isolated product was $[\alpha]_D^{20} = -32°$ ($c = 1.11$), indicating an approximate 3:2 ratio of IIa to IIIa in the resulting mixture.

50 mg of IIIa ($[\alpha]_D^{20} = -174°$) in glacial acetic acid (2.5 ml) was heated 2 h at 80°, with stirring. The specific rotation of the isolated product was $[\alpha]_D^{20} = -32°$ ($c = 1.07$), indicating the same 3:2 ratio of IIa to IIIa in the resulting mixture.

The same ratio of epimers was obtained when the isomerization experiments (either with IIa or with IIIa) were run in glacial acetic acid containing 1–2 molar equivalents of $Pb(OAc)_2$.

In contrast, in benzene solution or in benzene containing 1–2 molar equivalents of $Pb(OAc)_2$, $CaCO_3$ or AcOH, after refluxing for 24–36 h, neither IIa nor IIIa underwent any noticeable isomerization.

B) Oxidations of diosgenyl acetate (IV) with lead tetraacetate. – a) *Oxidation with 2 molar equivalents of $Pb(OAc)_4$ in acetic acid solution.* A solution of 5.0 g of diosgenyl acetate (IV) and 10.0 g of lead tetraacetate in 200 ml of glacial acetic acid was heated with stirring at 80°, until disappearance of tetravalent lead (3 h). After working up as described in section A) a), the ethereal layer was evaporated to dryness under reduced pressure. The resulting crystalline residue (5.4 g) was treated with methanol (100 ml) and the mixture left overnight at –5°, whereupon 2.83 g (56.6%) of unchanged IV separated (identified by m.p. and mixed m.p. determination, and by comparison of IR. spectra). Removal of methanol from the filtrate afforded 2.5 g of a complex mixture (according to TLC.) which was directly reduced with $LiAlH_4$ in ether in the usual manner, and the products obtained (2.1 g) were chromatographed on 100 g of silica gel (0.08 mm). Elution with ether-benzene (7:3) afforded 285 mg (6.03%) of 7β-hydroxydiosgenin (Vb), which was recrystallized from acetone. M.p. 218–220°, $[\alpha]_D^{20} = -74°$ ($c = 1.08$) (Lit. [10]: m.p. 216–219°, $[\alpha]_D^{20} = -75°$). IR. spectrum (KBr): $\nu_{max} = 3420, 3200\ cm^{-1}$.

$C_{27}H_{42}O_4$ (430.61) Calc. C 75.31 H 9.83% Found C 75.41 H 9.91%

Further ether-benzene (75:25) eluates gave a mixture (64 mg; 1.36%) of 7β- and 7α-hydroxydiosgenin (Vb + VIb), while elution with ether-benzene (4:1) yielded 197 mg (4.18%) of 7α-hydroxydiosgenin (VIb). M.p. 222–224° (from ether), $[\alpha]_D^{20} = -154°$ ($c = 0.96$) (Lit. [10]: m.p. 223–224°, $[\alpha]_D^{20} = -159°$). IR. spectrum (KBr): $\nu_{max} = 3420, 3220\ cm^{-1}$.

$C_{27}H_{42}O_4$ (430.61) Calc. C 75.31 H 9.83% Found C 75.09 H 9.68%

b) *Oxidation with 2 molar equivalents of $Pb(OAc)_4$ in benzene.* A suspension of 2.2 g of diosgenyl acetate (IV), 4.4 g of lead tetraacetate and 0.55 g of $CaCO_3$ in 110 ml of dry thiophene-free benzene was heated to reflux and stirred for 36 h, after which time the oxidation was complete. After working up as described in Section A) c) and evaporation of the solvents, the residue (2.55 g) was treated with methanol (50–60 ml), whereby 1.65 g (75%) of unreacted IV separated (identified by m.p. and mixed m.p. determination, and comparison of IR. spectra). Removal of methanol from the filtrate afforded about 900 mg of material which was chromatographed on 27 g of neutral Al_2O_3 (activity II). Light petroleum-benzene fractions (in various ratios) eluted a complex mixture (252 mg) which was not investigated. Benzene and benzene-ether (9:1) eluates gave 340 mg (15.4%) of a mixture of 7β- and 7α-acetoxydiosgenyl diacetate (Va + VIa). Since this mixture had $[\alpha]_D^{20} = -103°$ ($c = 1.12$), the approximate ratio of 7β- (Va) to 7α-epimer (VIa) was 3:2.

Lithium aluminium hydride reduction of 7-acetoxylated diosgenyl acetates (Va + VIa). Reduction of the above obtained mixture (300 mg) of Va and VIa with $LiAlH_4$, followed by chromatography on silica gel (as described in section A) a)) of the resulting products, afforded 132 mg of 7β-hydroxydiosgenin (Vb), m.p. 218° (from MeOH), and 78 mg of 7α-hydroxydiosgenin (VIb), m.p. 223° (from ether).

Acetylation of 7β-hydroxydiosgenin (Vb). Acetylation of Vb (100 mg) as described in section A) c) gave 110 mg (92%) of *7β-acetoxydiosgenyl acetate* (Va), m.p. 184° (from MeOH), $[\alpha]_D^{20} = -27°$

(c = 2.4). IR. spectrum (KBr): ν_{max} = 1740, 1735, 1690, 1240 cm^{-1}. NMR. spectrum: δ = 0.77 (CH_3-18 and CH_3-27, *d*), 0.86 (CH_3-21, *d*), 1.08 (CH_3-19, *s*), 1.92 and 1.96 (CH_3COO-3 and CH_3COO-7, two *s*), 3.28 (O–CH_2-26, *m*), about 4.30 (CH-3 and O–CH-16, *m*), 4.85 (CH-7, *m*), 5.14 (=CH-6, *m*).

$C_{31}H_{46}O_6$ (514.68) Calc. C 72.34 H 9.01% Found C 72.54 H 9.29%

Acetylation of 7α-hydroxydiosgenin (VIb). Acetylation of VIb (100 mg) in the same way afforded 110 mg (92%) of *7α-acetoxydiosgenyl acetate* (VIa), m.p. 127° (from light petroleum), $[\alpha]_D^{20}$ = −225° (c = 1.9). IR. spectrum (KBr): ν_{max} = 1745, 1740, 1670, 1240 cm^{-1}. NMR. spectrum: δ = 0.75 (CH_3-18 and CH_3-27, *d*), 0.88 (CH_3-21, *d*), 1.01 (CH_3-19, *s*), 1.90 and 1.93 (CH_3COO-3 and CH_3COO-7, two *s*), 3.26 (O–CH_2-26, *m*), about 4.34 (CH-3 and O–CH-16, *m*), 4.90 (CH-7, *m*), 5.52 (=CH-6, *m*).

$C_{31}H_{46}O_6$ (514.68) Calc. C 72.34 H 9.01% Found C 72.25 H 9.22%

Isomerization of 7β- (Va) and 7α-acetoxydiosgenyl acetate (VIa). 50 mg of Va ($[\alpha]_D^{20}$ = −27°) in glacial acetic acid (2.5 ml) was heated for 3 h at 80° with stirring. The product isolated had $[\alpha]_D^{20}$ = −100°, indicating an approximate 3:2 ratio of Va to VIa in the resulting mixture.

Isomerization of 50 mg of VIa ($[\alpha]_D^{20}$ = −225°) under identical conditions afforded a mixture ($[\alpha]_D^{20}$ = −99°) with the same (3:2) ratio of Va to VIa.

The same ratio of epimers was also obtained when isomerization experiments (either with Va or with VIa) were run in AcOH containing 1–2 molar equivalents of $Pb(OAc)_2$.

However, in benzene solution, or in benzene containing 1–2 molar equivalents of $Pb(OAc)_2$, $CaCO_3$ and/or AcOH, after refluxing for 12–24 h neither Va nor VIa underwent any noticeable epimerization.

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