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SYNTHESIS OF DI- AND TETRA-HYDROALDOSTERONE DERIVATIVES AND THE C_{19} POSITION ISOMER OF 3α,5β-TETRAHYDROALDOSTERONE

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Abstract—Crystalline 5β-dihydroaldosterone diacetate (**3b**) was prepared and converted into 3α,5β- and 3β,5β-tetrahydroaldosterone (**5a** and **4a**). 19-Oxygenated compounds were obtained by photolysis of compound *B*-3,21-diacetate-11-nitrite (**10b**).

Isolation of tetrahydro derivatives of aldosterone from human[1-4] and bullfrog[5] urine, as well as from incubation of aldosterone with rat liver homogenates,[6] has been reported.

Synthetic conversions of aldosterone into several dihydro and tetrahydro derivatives have been described.[6] We found[7] that mild palladium hydrogenation of aldosterone or its 21-acetate in ethyl acetate gives rise to 4,5-dihydro derivatives, but the 5β-dihydro compound could not be separated from the accompanying 5α-isomer; TLC studies showed that their mobilities in several solvent systems are quite similar. It has now been discovered that hydrogenation of aldosterone *di*acetate (**1b**) produces a separable mixture of the 5α and 5β diacetates **2** and **3b** (ratio about 5:3), melting at 152–3° and 186–7° (Chart 1), and having their C_{19}-Me signal at 1.10 and 1.11 ppm,[8] respectively. Since crystalline 5β-dihydroaldosterone or its esters have not been previously reported, assignment of configuration to these epimers was made by periodate degradation of **3b** to the known[3-6] 3-ketolactone **7** via the free 5β-dihydroaldosterone (**3a**). Jones oxidation of **3b** gave the lactone **9**, in analogy with a related oxidation of 3α,5α- and 3β,5β-tetrahydroaldosterone triacetates into the corresponding lactones.[4]

We have shown[7] that palladium hydrogenation of aldosterone is ethanol for 48 hr proceeds to the tetrahydro stage. The pure 5β isomer **3b** was now converted in a similar fashion into a 1:4 mixture of the oily 3α- and 3β-tetrahydro compounds **5b** and **4b**. These were laboriously separated by column chromatography and each was

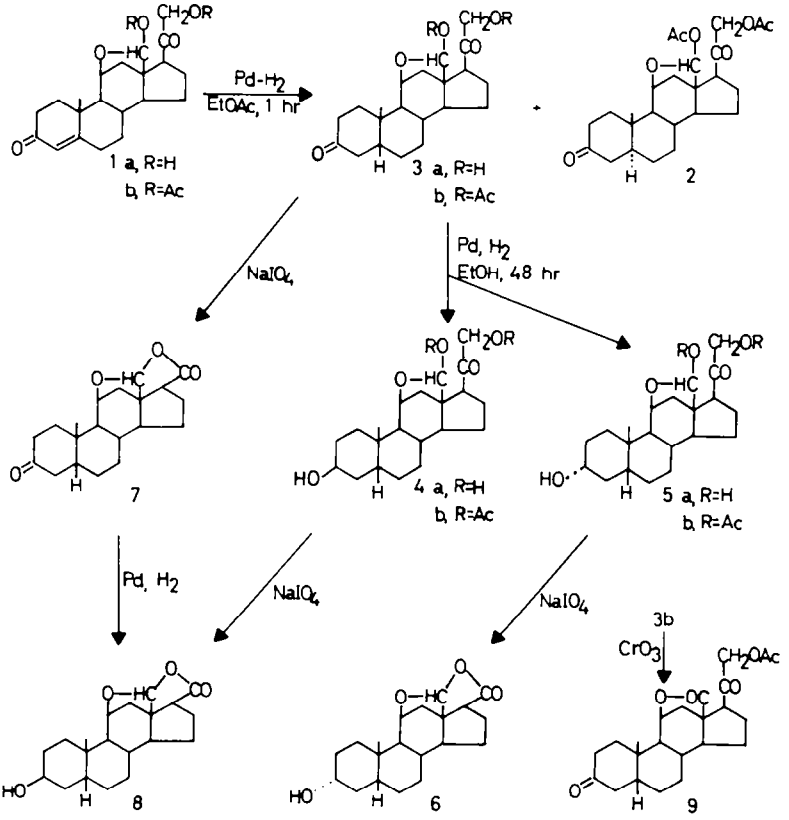

Chart 1.

hydrolyzed with potassium carbonate to give the free 3α- and 3β-tetrahydroaldosterone, **5a** and **4a**, as amorphous solids, which were converted with periodate into the known etiolactones **6**[3,4] and **8**.[3,7] The last compound was also obtained as the main product by palladium hydrogenation in ethanol of the etiolactone 7. Under these hydrogenation conditions, then, the formation of 3β-isomers from 3 - keto - 5β - compounds (**3b**→**4b** and **7**→**8**) is the predominating reaction.

In parallel with the above approach we investigated the possibility of applying the classical Barton synthesis[9] of aldosterone (**1a**) from corticosterone acetate to preparation of 3α,5β - tetrahydroaldosterone (**5a**) from 3α,5β - tetrahydrocorticosterone (compound **B**) diacetate (**10a**) (Chart 2). With nitrosyl chloride the nitrite **10b** could be prepared, which was irradiated with ultraviolet light, but only products resulting from the attack on the C_{19}- and not the C_{18}-Me group could be isolated. From the complicated oily mixture two oximes were obtained: the more polar retained both angular Me groups (NMR) and therefore cannot be the desired product. The less polar oxime **11** resulted from the intramolecular attack on the C_{19}-Me group, and due to absence of the 4,5-olefinic bond no further rearrangement involving C_4[9] took place. On treatment with nitrous acid **11** furnished the C_{19}-aldehydo compound **12b** of m.p. 173–5°, exhibiting two C_{18}-Me signals at 0.78 and 0.86 ppm[8] due to equilibrium in deuteriochloroform with the hemiacetal form,† but no C_{19}-Me signal. This splitting of the C_{18}-Me signal disappeared on Jones oxidation of **12b** into the lactone **13**, which showed a signal at 0.79 ppm. Additional support for this formulation was obtained by mild hydrolysis of **12b** into the free 21-ol **12a**, also exhibiting two C_{18}-Me signals at 0.78 and 0.83 ppm (ratio 1:4). Periodate oxidation of **12a** gave the etioacid **14**, also existing in the hemiacetal and uncyclized forms, in roughly equal amounts.† Jones oxidation of **14** gave the lactone **15a**, while hydrolysis of **14** with sodium hydroxide produced the hydroxyacid **16a** whose methyl ester **16b** was oxidized to the ketolactone **17**.

†The Referee has proposed that the presence of the two C_{18}-Me signals may be due to an equilibrium mixture of the two possible hemiacetal forms with only a small proportion of the free aldehyde present. Indeed, upon his recommendation we found the presence of only about 10% of the aldehyde form in **12a**, **12b** and **14** by integrating the CHO proton signal at 10.12 ppm, confirming the Referee's suggestion.

EXPERIMENTAL

M.ps are uncorrected. NMR spectra were recorded on a Varian Associates A-60 instrument in $CDCl_3$, using TMS as internal standard. Mass spectra were determined at 70 eV and 120–130° on an Atlas CH4 spectrometer equipped with a TO-4 source, using a direct inlet system. High resolution mass measurements were performed on a Varian MAT 731 spectrometer. Optical rotations were measured in dioxane with a Perkin–Elmer 141 polarimeter. Determinations of identity and purity were done with aid of IR, NMR and mass spectrometry, as well as the consistent use of TLC (Merck A. G. silica gel plates F-254, with EtOAc–cyclohexane,

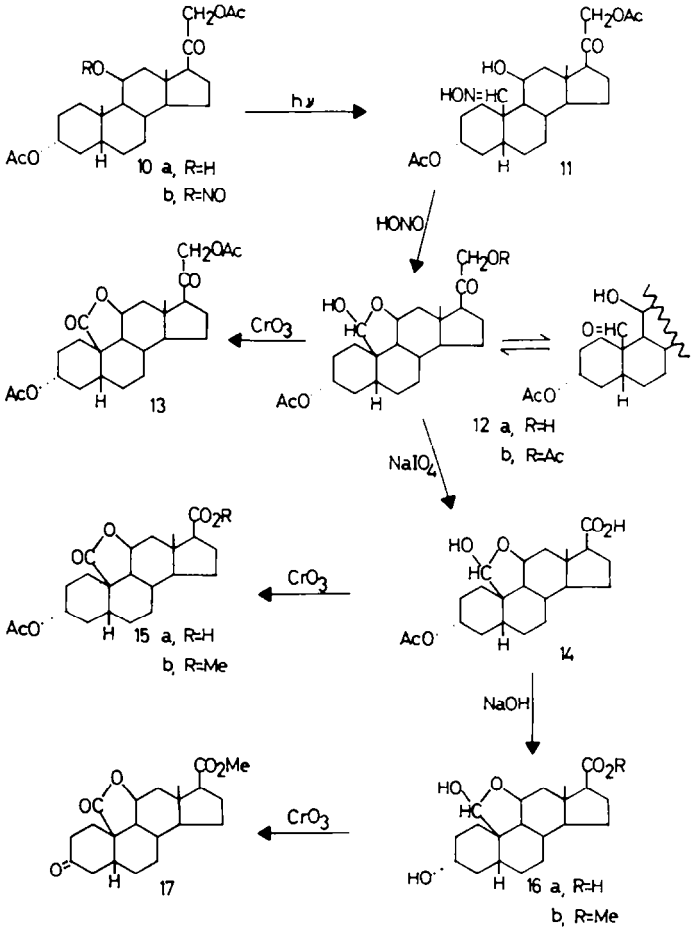

Chart 2.

EtOAc–benzene and acetone–benzene mixtures; visualization of spots with phosphomolybdic acid followed by a sulfuric acid spray. All column chromatography separations were carried out on silica gel (Merck A. G., "60"), using the "dry" method.

5α-Dihydroaldosterone diacetate (**2**) *and 5β-dihydroaldosterone diacetate* (**3b**). A soln of **1b** (10.1 g; m.p. 150–3°) in 1 l. of EtOAc was rapidly stirred under H_2 for 1 hr at atmospheric pressure with 3 g of 5% Pd–C. The oily product, whose TLC showed the presence of equal amounts of **2** and **3b**, and traces of tetrahydro compounds, was chromatographed on 900 g of silica gel using benzene–EtOAc 2:1, whereby a partial separation of **2** and **3b** was achieved, the 5α-moving faster than the 5β-isomer. In order to achieve full separation three additional column chromatographies were carried out. Finally **2** was recrystallized from acetone–ether, 5.2 g, m.p. 152–3°; found m.w. 446.2316; λ_{max}^{KBr} 5.71–5.80 and 5.86 μ; NMR δ 1.10 (s, 3H, 19-CH$_3$), 1.95 (s, 3H, 21-CH$_3$COO-), 2.09 (s, 3H, 18-CH$_3$COO-), 4.80 (s, 2H, 21-CH$_2$-) and 5.96 (s, 1H, 18-CH-); $[\alpha]_D^{25}$ + 144.5° (c, 1.0). (Found: C, 67.42; H, 7.79. Calc. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68%).

Isomer **3b** was recrystallized from acetone–ether, 3.6 g, m.p. 186–7°; M^{++}, *m/e* 446; λ_{max}^{KBr} 5.71–5.80 and 5.86 μ; NMR δ 1.11 (s, 3H, 19-CH$_3$), 1.96 (s, 3H, 21-CH$_3$–COO–), 2.17 (s, 3H, 18-CH$_3$COO–), 4.82 (s, 2H, 21-CH$_2$) and 5.99 (s, 1H, 18-CH-); $[\alpha]_D^{25}$ + 138.5° (c, 1.0). (Found: C, 67.01; H, 7.99. Calc. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68%).

3α,5β - Tetrahydroaldosterone - 18,21 - *diacetate* (**5b**) *and 3β,5β - tetrahydroaldosterone* - 18,21 - *diacetate* (**4b**). A suspension of **3b** (3.6 g) in 350 ml abs EtOH was hydrogenated at 45 psi for 48 hr in the presence of 4 g of 5% Pd–C. The catalyst was filtered off, washed well with CH_2Cl_2 and the combined filtrates were taken to dryness *in vacuo*. The gum was chromatographed over 330 g of silica gel (benzene–acetone 2:1), the 3β,5β isomer **4b** being followed by the 3α,5β compound **5b**; the separation was incomplete and necessitated three additional chromatographies to afford 1.87 g of the oily **4b** (about 90% pure in TLC), 0.560 g of the oily **5b** (about 70% pure) and 0.58 g of a 1:1 mixture of both.

At this stage it was best to hydrolyze the crude **5b** (560 mg) thus obtained with K_2CO_3, as described below for the conversion of **12b** into **12a**. The resulting *3α,5β - tetrahydroaldosterone* (**5a**) was purified by column chromatography, using benzene–acetone 1:1, to yield 230 mg of a glass (90% pure). Sodium metaperiodate oxidation of **5a**, carried out as described below for the conversion of **3a** into **7**, gave *3α,5β - tetrahydroaldosterone - γ - etiolactone* (**6**), m.p. 246–8° (EtOAc) (reported 242–4°;[3] 252–4°;[2] 254–5°;[4] 260–5°),[6] whose IR spectrum was identical with that reported.[3]

Also **4b** was hydrolyzed as above. The resulting *3β,5β - tetrahydroaldosterone* (**4a**) could be oxidized with periodate[1,6] to the corresponding *γ-etiolactone* **8**, m.p. 261–7°, identical with a sample obtained by hydrogenation of **7**, as described below.

11β,21 - Dihydroxy - 5β - pregnane - 3,20 - dione - 18 - oic acid - 21 - acetate - (18→11) - lactone (**9**). A soln of **3b** (54 mg) in 2 ml acetone was treated with 0.1 ml of the Jones reagent at 0°. After 5 min a drop of MeOH was added, followed by 20 ml water. The product was isolated with EtOAc in the usual manner and recrystallized from acetone–ether to afford 25 mg, m.p. 193–200°; λ_{max}^{KBr} 5.65, 5.72 (sh) and 5.83 μ; NMR δ 1.12 (s, 3H, 19-CH$_3$), 2.16 (s, 3H, 21-CH$_3$COO-) and 4.80 (s, 2H, 21-CH$_2$-). (Found: C, 68.90; H, 7.80. Calc. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51%).

Conversion of 5β - dihydroaldosterone diacetate (**3b**) *into 5β - dihydroaldosterone - γ - etiolactone* (**7**) *and 3β,5β - tetrahydroaldosterone - γ - etiolactone* (**8**). Hydrolysis of **3b** (177 mg) into **3a** was carried out as described below for **12b**. The oily product was purified by column chromatography, using benzene–acetone 1:1. The resulting glassy acid **3a** (93 mg) was dissolved in 7.7 ml MeOH and treated with a soln of sodium metaperiodate (500 mg) in 11 ml water. After 2 hr the precipitated crystals were collected and washed with water to furnish **7** (40 mg), m.p. 255–9° (reported 233–5.5°;[3] 249–251°;[4] 250–5°;[6] 249–251°)[5]. Its IR spectrum was identical with that reported.[3]

A suspension of **7** (40 mg) in 20 ml EtOAc was *hydrogenated* at 40 psi with 5% Pd–C (200 mg) for 48 hr. Recrystallization of the product from acetone–ether furnished needles of **8** (28 mg), m.p. 262–270° (reported[4] 277–280°), whose IR spectrum was identical with that reported.[3]

3α,5β - Tetrahydrocorticosterone - 3,21 - diacetate - 11 - nitrite (**10b**). Over a vigorously stirred, ice-cooled soln of **10a** (32 g) in 160 ml dry pyridine was passed a rapid stream of nitrosyl chloride gas for 10 min. The dark mixture was cautiously poured into 5 l. of a stirred mixture of ice and water. The half-solid product was taken up in 1 l. of ether, which was then washed 3 times with water and dried over Na_2SO_4. Gradual substitution of ether by petroleum ether furnished in 3 crops a total of 28 g of the nitrite **10b**, m.p. 120–5°. The pure sample had m.p. 122–4°, λ_{max}^{KBr} 5.73 and 5.80 μ. (Found: C, 64.42; H, 8.28; N, 3.32. Calc. for $C_{25}H_{37}NO_7$: C, 64.77; H, 80.5; N, 3.02%).

3α,5β - Tetrahydrocorticosterone - 3,21 - diacetate - 19 - aldoxime (**11**) *and 19 - oxo - 3α,5β - tetrahydrocorticosterone - 3,21 - diacetate* (**12b**). A magnetically stirred soln of **10b** (12 g) in 600 ml dry toluene, through which a stream of N_2 was passed, was irradiated at 32° for 90 min with a 200 Watt Hanovia high-pressure mercury lamp. After evaporation of the solvent *in vacuo*, TLC (benzene–EtOAc 1:1) of the residual oil exhibited a complicated pattern. Laborious column chromatography (1.12 kg of silica gel, same solvents, 100 ml fractions) gave in flasks 20–25 the oxime **11** as an oil (2.83 g), about 80% pure (TLC), which by scratching with petroleum ether could be made to solidify as a powder; λ_{max}^{KBr} 2.95 and 5.70–5.80 μ; M^{++}, *m/e* 463. Further elution gave a variety of oily materials whose further conversion products did not have the desired spectral properties.

The oxime **11** (4.2 g) was dissolved at 10° in a mixture of 67 ml of AcOH and 33 ml water containing 1.79 g of $NaNO_2$. After keeping for 10 min at that temp., the soln was poured into a stirred mixture of 780 ml of water, 145 g of solid $NaHCO_3$ and 560 ml of CH_2Cl_2. The oily product (4 g) was isolated by evaporation of CH_2Cl_2 and chromatography on 400 g of silica gel, using benzene–EtOAc 1:1. The eluted 19-oxo derivative **12b** was crystallized from CH_2Cl_2–ether to give 826 mg, m.p. 173–5°, and 203 mg, m.p. 165–8°; λ_{max}^{KBr} 2.92, 5.73, 5.79 and 5.83 μ; NMR δ 0.78 and 0.86 (2 equal s, total 3H, 18-CH$_3$), 2.03 (s, 3H, 3-CH$_3$COO)-, 2.15 (s, 3H, 21-CH$_3$COO-) and 4.65 (s, 2H, 21-CH$_2$-); $[\alpha]_D^{20}$ + 56.9° (c, 0.304). (Found: C, 67.21; H, 7.88. Calc. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09%).

19 - Oxo - 3α,5β - tetrahydrocorticosterone - 3 - monoacetate (**12a**). To a mixture of 4.9 g of anhyd K_2CO_3 in 17 ml water and 51 ml MeOH was added a soln of 1.06 g of **12b** in 34 ml CH_2Cl_2. Stirring was maintained for 15 min, whereupon a soln of 2.8 ml of AcOH in 70 ml water was added. The oily product (1.1 g) was isolated with CH_2Cl_2, and then chromatographed on 82 g of silica gel, using benzene–acetone 2:1. At first 106 mg of the unchanged **12b** was obtained, followed by **12a**, which on recrystallization from CH_2Cl_2–ether had m.p. 150–3°, 403 mg; λ_{max}^{KBr} 3.0 and 5.80–5.87 μ; NMR δ 0.78 and 0.83 (2 s, total 3H, 18-CH$_3$) and 2.05 (s, 3H, 3-CH$_3$COO); $[\alpha]_D^{20}$ +38.5° (c, 0.338). (Found: C, 68.21; H, 8.76). Calc. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43%).

3α,5β - Tetrahydrocorticosterone - 19 - oic acid - 3,21 - diacetate - (19→11) - lactone (**13**). A soln of **12b** (79 mg) in 4 ml acetone was treated at 0° with 8 drops of Jones reagent. After 5 min 3 drops MeOH were added, followed by 10 ml water. The acetone was removed *in vacuo*, the precipitated crystals were filtered off, water-washed, dried and repeatedly recrystallized from CH_2Cl_2–ether to give a wide-melting (127–137°) product, in TLC (benzene–acetone 2:1) at least 95% pure; λ_{max}^{KBr} 5.69–5.80 μ; NMR δ 0.79 (s, 3H, 18-CH$_3$), 2.02 (s, 3H, 3-CH$_3$COO-), 2.17 (s, 3H, 21-CH$_3$COO-) and 4.60 (s, 2H, 21-CH$_2$-). (Found: C, 67.53; H, 7.62. Calc. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68%).

3α,11β - Dihydroxy - 19 - oxo - 5β - androstan - 17β - oic acid - 3 - acetate (**14**). A soln of **12a** (350 mg) in 27 ml MeOH was treated with a soln of 1.75 g of sodium metaperiodate in 40 ml water. The following day the crystals were collected and water-washed to afford 309 mg of **14**, m.p. 221–7° (dec). Recrystallization from MeOH raised the m.p. to 223–7° (dec); λ_{max}^{KBr} 3.00, 5.75 and 5.86 μ; NMR (DMSO) δ 0.73 and 0.79 (2 equal s, total 3H, 18-CH$_3$) and 1.96 (s, 3H, 3-CH$_3$COO-); $[\alpha]_D^{25}$ +13.2° (c, 0.302). (Found: C, 67.38; H, 8.48. Calc. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22%).

3α,11β - Dihydroxy - 5β - androstan - 17β,19 - dioic acid - 3 - acetate - (19→11) - lactone (**15a**). Jones oxidation of **14** (26 mg) was carried out as described above for the preparation of **13**. There was obtained 19 mg of **15a**, which was recrystallized from acetone–petroleum ether, m.p. 254–5°; M^{+}, *m/e* 390; λ_{max}^{KBr} 3.20, 5.69, 5.77

and 5.90 μ; NMR δ 0.85 (s, 3H, 18-CH$_3$) and 2.03 (s, 3H, 3-CH$_3$COO-). (Found: C, 67.82; H, 7.99. Calc. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74%).

The *methyl ester* **15b** (diazomethane) had m.p. 131–2.5° (CH_2Cl_2–petroleum ether); found m.w. 404.2192; λ_{max}^{KBr} 5.67 and 5.78 μ; NMR δ 0.77 (s, 3H, 18-CH$_3$), 2.04 (s, 3H, 3-CH$_3$COO-) and 3.72 (s, 3H, 17-COOCH$_3$). (Found: C, 67.98; H, 7.91. Calc. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97%).

3α,11β - *Dihydroxy* - 19 - *oxo* - 5β - *androstan* - 17β - *oic acid* (**16a**). A soln of **14** (502 mg) in 10 ml 5% NaOH aq was allowed to stand for 3 hr at room temp., then acidified with HCl. The product was collected, washed with water and dried to afford 424 mg of **16a**; a further 10 mg of material, also pure in TLC, was obtained from the filtrate with EtOAc. Recrystallization from MeOH–ether gave the acid of m.p. 248° (dec); λ_{max}^{KBr} 2.85, 2.95 and 5.90 μ.

The *methyl ester* **16b** (diazomethane in methanol–ether) had m.p. 173–5° (CH_2Cl_2–petroleum ether). After drying *in vacuo* at 100° for 3 hr the m.p. rose to 204–210°; M$^{\cdot\cdot}$, *m/e* 364; λ_{max}^{KBr} 3.10 and 3.76 μ; NMR δ 0.85 (s, 3H, 18-CH$_3$) and 3.68 (s, 3H, 17-COOCH$_3$); $[\alpha]_D^{25}$ +34.2° (*c*, 0.292). (Found: C, 69.00; H, 8.75. Calc. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85%).

11β - *Hydroxy* - 5β - *androstan* - 3 - *one* - 17β,19 - *dioic acid* - 17 - *methyl ester* - (19→11) - *lactone* (**17**). The crude ester **16b** dissolved in acetone was treated with the Jones reagent as above. The product was best purified by column chromatography, using EtOAc–cyclohexane 2:1. First a high-melting product was eluted, followed by the desired ketolactone **17**, which had m.p. 172–4° (CH_2Cl_2–petroleum ether); found m.w. 360.1956; λ_{max}^{KBr} 5.69, 5.78 and 5.85 μ; $[\alpha]_D^{25}$ −14.8° (*c*, 0.324); NMR δ 0.77 (s, 3H, 18-CH$_3$) and 3.72 (s, 3H, 17-COOCH$_3$). (Found: C, 70.11; H, 7.77. Calc. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83%).

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