SYNTHESIS OF KETO DERIVATIVES OF LANOSTANE-24-CARBOXYLIC ACID

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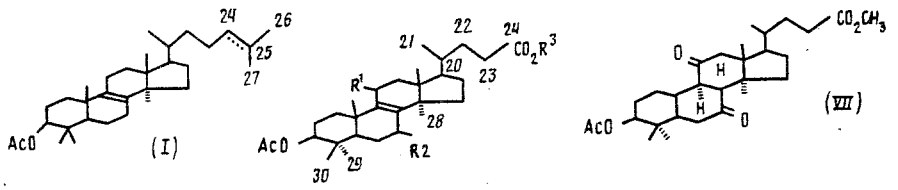
The oxidation of lanosterol by potassium permanganate and sodium periodate is a complex reaction with involvement of both the 24(25)-double bond and allylic positions (C^7 and C^{11}), leading to the formation of the corresponding ketoacids.

The chemical transformations of triterpenoids in order to obtain biologically active compounds have not been extensively developed. Lanosterol (I), which is a rather available and inexpensive starting reagent for the synthesis of such natural products as ganoderic acids [1], seychellogenin [2], and steroid antibiotics [2], has most commonly used for such purposes.

We undertook the use of (I) for the synthesis of triterpenoid analogs of ecdysones, corticoids, and other physiologically active compounds. This requires the development of a method for the reconstruction of the side chain of (I). The stepwise degradation of this side chain has been studied by many workers [3, 4]. Habermehl and Volkwein [3] have reported that the oxidation of the Δ^{24}-bond by $KMnO_4$ and $NaIO_4$ regioselectively leads to 24-acid (II) without affecting the skeleton. However, upon repeating the reaction conditions described, we discovered the formation of a complex mixture of acids, which could not be readily separated. Since chromatography on alumina, silica gel, and $AgNO_3$-impregnated silica gel proved ineffective, this acid mixture was converted to methyl esters and separated by chromatography on silica gel to give esters (III)-(V). The hydrolysis of (III) and (IV) and subsequent acetylation led to acids (II) and (VI). We also obtained diketoacid (VI) and its methyl ester (IV) upon the oxidation of (I) by chromium trioxide in aqueous acetic acid [5]. Facile functionalization of the allylic positions, C^7 and C^{11}, in (II) was discovered upon the radical oxidation of (II) using $CuCl_2$–$Na_2S_2O_8$ [6], which also led to diketoacid (VI). The sterically hindered, internal 8,9-double bond in (II) and (III) does not undergo reduction even upon ionic hydrogenation [7] with $(C_2H_5)_3SiH$ in CF_3CO_2H, but is reduced to give diketones (IV) and (VI) by action of zinc in acetic acid [5].



$R^1 = R^2 = R^3 = H$ (II), $R^1 = R^2 = H$, $R^3 = CH_3$ (III); $R^1 = R^2 = O$, $R^3 = CH_3$ (IV);
$R^1 = H$, $R^2 = O$, $R^3 = CH_3$ (V); $R^1 = R^2 = O$, $R^3 = H$ (VI)

The structures of these acids and their esters were demonstrated by mass spectrometry using their molecular ion and $[M - 15]^+$ peaks and UV and IR spectroscopy. The UV spectra show characteristic absorption for cross-conjugated diketones at 273 nm ($\varepsilon \sim 10{,}000$) ((IV) and (VI)) and α,β-unsaturated ketones at 253 nm ($\varepsilon \sim 9000$). The IR spectra have bands at 1670 cm^{-1} characteristic for cross-conjugated ketones and at 1670 and 1580 cm^{-1} for α,β-unsaturated ketones.

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TABLE 1. Spectral Indices of Products with the Lanostane Skeleton

Compound	PMR spectrum (CH_3) δ, ppm						Mass spectrum	IR spectrum, ν, cm^{-1}	UV spectrum λ^{i}_{max} (ε)
	C^{18}	C^{29}	$5C^{30}$	C^{21}	C^{19}	C^{28}			
(II)	0,74	0,9	0,94 (9H)		0,99	0,99	458(M) 443(M–15)	1740 1700	–
(III)	0,67	0,86			0,99	0,99	472(M) 457(M–15)	1740	–
(IV)	0,78	0,86	0,88	0,93	1,31	1,15	500(M) 440(M–60) 3888	1735 1675	270 (7670)
(V)	0,65	0,88	0,89	0,90	0,95	1,18	486(M) 471(M–15) 439(M–15–32)	1740 1670 1580	253 10 000
(VI)	0,8	0,9	0,91	0,96	1,32	1,18	486(M)	1740	273
(VII)	0,69	0,83	0,89		1,28	1,19	502(M) 487(M–15) 442(M–60)	1745 1716 1200	–

TABLE 2. ^{13}C NMR Spectra of Products (δ, ppm)

Atom	(II)	(III)	(IV)	(VI)	(VII)
C^1	35,35	35,32	33,78	33,82	35,76
C^2	24,25	24,22	23,95	24,00	23,69
C^3	81,08	80,94	79,29	79,40	79,98
C^4	37,00	36,94	39,61	39,67	38,25
C^5	50,33	50,28	48,92	48,98	52,51[1] *
C^6	18,20	18,17	36,24	36,29	39,15
C^7	28,17	28,13	202,26[1]	202,22[1]	209,35[2]
C^8	134,45[1]	134,39[1]	150,64	150,61	53,09[1]
C^9	134,52[1]	134,55[1]	151,80	151,83	60,46
C^{10}	37,91	37,85	37,83	37,79	36,78
C^{11}	21,08	21,04	201,67[1]	201,87[1]	208,90[2]
C^{12}	26,46	26,43	51,60	51,64	52,54
C^{13}	44,64	44,57	47,47	47,53	46,52
C^{14}	49,92	49,88	49,02	49,08	49,09
C^{15}	31,11[2]	31,30	31,00[2]	30,80[2]	31,10
C^{16}	31,31[2]	31,30	31,10[2]	31,11[2]	31,10
C^{17}	50,60	50,56	50,18	50,21	48,51
C^{18}	16,62	16,58	16,54	16,58	16,22
C^{19}	18,36	18,35	17,58	17,64	13,79
C^{20}	36,10	36,11	35,74	35,76	35,46
C^{21}	19,24	19,30	18,19	18,22	18,06
C^{22}	30,88[2]	30,84[2]	32,16	32,20	33,10
C^{23}	31,05[2]	30,02[2]	27,24	27,26	28,54
C^{28}	24,32	24,27	25,89	25,95	17,61
C^{29}	28,01	27,97	27,83	27,87	27,73
C^{30}	15,87	15,82	16,82	16,89	16,05
COOMe	174,88	180,38	174,49	179,63	174,52
	–	51,51	51,54	–	51,57
OCOMe	171,26	171,11	170,66	170,91	170,87
	21,44	21,37	21,23	21,26	21,26

*Chemical shifts 1 and 2 are interchangeable due to their similar values.

The signals of the angular methyl groups in the PMR spectra of the mono- and diketo derivatives, which are in the 1,3-positions relative to the carbonyl groups at C^{19} and C^{28}, are shifted downfield relative to the signals of the same groups in Δ^8-compounds (Table 1).

Analysis of the ^{13}C NMR spectra of these products (Table 2) indicated the presence of the Δ^8-bond and 7- and 11-carbonyl groups as well as the substituents at C^3, C^4, C^{14}, and C^{17}. The signal for C^{12} in monoketone (V) is shifted significantly upfield, indicating the lack of a carbonyl group at C^{11}. This is also indicated by the chemical shift for the protons at C^{19}. The C^{12} signal in diketones (IV), (VI), and (VII) is markedly shifted downfield due to the β-effect of the 11-ketone oxygen.

EXPERIMENTAL

The melting points of the samples were taken on a Koeffler block after recrystallization from ethyl acetate. The IR spectra were taken on a UR-20 spectrometer in KBr. The UV spectra were taken on a Unicam SP-700 spectrometer in chloroform. The mass spectra were taken on a Varian MAT 311A mass spectrometer with direct sample inlet into the ion source at 70 eV. The PMR spectra were taken on a Bruker WM-250 spectrometer and ^{13}C NMR on a Bruker AM-300 spectrometer at 300 MHz. The chemical shifts with error ±0.03 ppm were measured relative to TMS. The assignment of the signals in the ^{13}C NMR spectra was based on the chemical shifts, coupling constants, and multiplicity in comparison with previous data [1, 8, 9]. The thin-layer chromatography was carried out on silica gel 5/40 μm (+13% gypsum) or Silufol UV-254. The plates were developed with 2% $Ce(SO_4)_2$ in 2 N H_2SO_4 with heating and with UV light. The separation of the mixtures was carried out on columns packed with silica gel 40/100 μm in a nitrogen atmosphere.

Oxidation of Lanosterol Acetate by Potassium Permanganate and Sodium Periodate. A solution of 0.7 g $KMnO_4$ and 12 g $NaIO_4$ in 400 ml water heated to 60°C was added to a solution of 5 g lanosterol acetate (obtained by the acetylation of lanosterol, PMR spectroscopy indicated ~50% in the sterol mixture) in 500 ml tert-butyl alcohol and 5 g K_2CO_3 at 60°C. The reaction mixture was left to cool to 20°C and stirred at this temperature for 15 h. Then, excess hyposulfite and water were added until the solution was decolored. Butyl alcohol was evaporated and the residue was acidified with 2% hydrochloric acid, extracted with chloroform, dried over $MgSO_4$, and evaporated. The residue was subjected to chromatography on silica gel. Elution with heptane or hexane gave 2.5 g dihydrolanosterol acetate. The remaining portion was eluted with chloroform. The solvent was evaporated. The mixture of acids obtained (2.5 g) was methylated with diazomethane prepared from 4.3 g nitrosomethylurea in 150 ml ether and 15 ml 40% KOH at 0°C. After maintenance of the reaction mixture for 24 h at 20°C, ether was evaporated. The residue was subjected to chromatography on silica gel using ether–hexane as the eluent (from 10 to 100% ether). Elution gave: 1) 1.0 g methyl ester of 3β-acetoxy-25,26,27trinorlanost-8-ene-24-carboxylic acid (III), $C_{30}H_{48}O_4$, mp 226-227°C; the saponification and acetylation of this product by acetic anhydride in pyridine gave 3β-acetoxy-25,26,27-trinorlanost-8-ene-24-carboxylic acid (II), $C_{29}H_{46}O_4$, mp 249-250°C, 2) 0.75 g methyl ester of 3β-acetoxy-25,26,27-trinorlanost-8-ene-7,11-dione-24-carboxylic acid (IV), $C_{30}H_{44}O_6$, mp 178-179°C; the saponification and acetylation of this product gave 3β-acetoxy-25,26,27-trinorlanost-8-ene-7,11-dione-24-carboxylic acid (VI), $C_{29}H_{42}O_6$, mp 255-256°C, and 3) 0.25 g methyl ester of 3β-acetoxy-25,26,27-trinorlanost-8-en-7-one-24-carboxylic acid (V), $C_{30}H_{46}O_5$, mp 255-258°C.

Reduction of (IV). A sample of 1 g zinc dust was added in portions to a solution of 400 mg (IV) in 25 ml acetic acid at reflux over 1.5 h. Heating at reflux was continued for an additional 1 h. The mixture was cooled. Zinc was filtered off and washed with hot acetic acid. The filtrate was evaporated. The residue was extracted with ether. The extract was washed with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel with ether–petroleum ether as the eluent to give 100 mg methyl ester of 3β-acetoxy-25,26,27-trinorlanostane-7,11-dione-24-carboxylic acid (VII), $C_{30}H_{46}O_6$, mp 260-265°C.

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