HYDROGENATION OF 12-OXO-5β-CHOL-9(11)-ENATES ON PLATINUM

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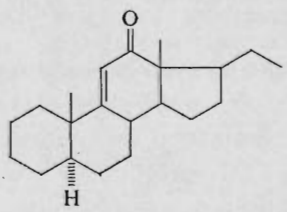
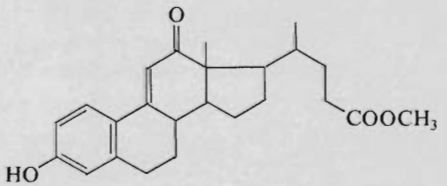
Methyl 12-oxo-5β-chol-9(11)-enates with various substituents in the position 3 were prepared and the conditions were found under which hydrogenation of the supposedly resistent double bond to 9α-cholanates takes place. Under these conditions the products of deoxygenation in the position 12, and in the case of the hydrogenation of 3-oxo derivatives the products of deoxygenation in the position 3, were isolated as side-products of this reaction. The rate of the last mentioned reaction is a function of the excess of the catalyst.

The most direct way to 9α-labelled steroids consists in the addition of deuterium to 12-oxo steroids with a double bond in the position 9(11). Thus, Djerassi and coworkers[1] achieved a smooth hydrogenation of compound *I* when using palladium on charcoal. The same conditions were employed in the hydrogenation[2] of 12-oxotetraene *II*. The 12-oxo-9(11)-unsaturated system is the easiest to obtain from the deri-



I



II

vatives of cholic acid[3] or deoxycholic acid[4], *i.e.* substances with a *cis*-annelation of the rings A and B in which, however, the double bond is very resistant to hydrogenation. Kendall and coworkers[5] found that 3α-hydroxy and 3α-acetoxy ketones *III* and *IV* are reduced merely to a mixture of 12-hydroxy derivatives *VI* and *VII* (or of corresponding acetates) which lose the 12-hydroxy group during the further reaction course without the 9(11)-double bond being saturated. The resistance toward hydrogenation in these substances was considered a consequence of the *cis*-annelation of the rings A and B which prevents access to the double bond from

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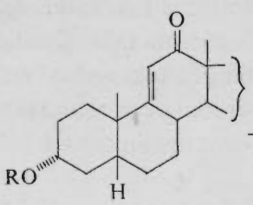
the α-side. Therefore we decided to determine whether the use of more energetic conditions could be preparatively useful for the preparation of saturated 12-ketones from unsaturated ones. We were further interested in determining whether the reduction of the 9(11)-double bond in substrates that do not contain an oxygen-containing substituent in the position 3α would not take place better than the reduction of 3α--hydroxy derivatives.

The starting substances were prepared from cholic acid[3] which was converted to methyl 3α-hydroxy-12-oxo-5β-chol-9(11)-enate (*III*) and to the corresponding methane sulfonate *V*. This substance was submitted both to solvolysis which afforded 3β-hydroxy derivative *XXV* (in addition to 3α-hydroxy derivative *III* and the corresponding 3-olefin) and to reduction with zinc in the presence of sodium iodide when it gave the 3-deoxy ester *XVIII*. For the sake of correlation the assumed products of reduction (compounds *XII*, *XIX*, *XXI*, *XXII*) were prepared using a standard procedure. In the products the configuration on the carbons 5 and 9 was guaranteed by the selection of the starting substances, *i.e.* the deoxycholic acid.

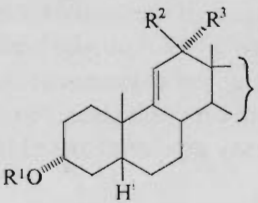
It was found that the substances differing merely in the presence or the absence of the 9(11)-double bond cannot be separated by chromatography on silica gel or silica gel with silver nitrate or alumina and therefore we determined the degree of saturation of the 9(11)-double bond from the chromatographically inseparable mixtures of 9(11)-olefins and the corresponding dihydro derivatives; in addition to the ultraviolet and the mass spectrometry ^{1}H-NMR spectrometry was also used for this purpose. The latter represents a very sensitive method for the detection of saturated 12-ketones in the presence of unsaturated ones (Table I; in the case of saturated compounds *XII*–*XIV* and *XXII* both angular methyl groups merged in a single intensive singlet).

In order to facilitate the comparison of the results of hydrogenation of various substrates we always worked up the reduction mixtures in the same manner. The product was first methanolysed with the aim of eliminating the acetoxy groups, irrespective of whether it was already present before the reduction (*IV*) or whether it was formed in the process of the reduction. Individual products were further unified by Jones's oxidation to corresponding ketones. If the crude product of reduction was not methanolysed the mixture was further complicated by the presence of the product of acetylation of corresponding intermediary 12α-hydroxy-9(11)-chol-5β-enate (for example *XXX*), especially in cases when a small amount of catalyst was used and the reaction time was long.

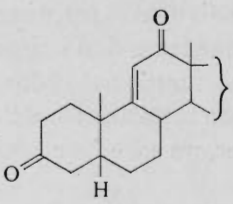
A survey of the distribution of the reduction products of individual substrates (carried out in acetic acid or [O—^{2}H]acetic acid on platinum) is given in Table II. It is evident that when more energetic conditions of hydrogenation are applied (elevated temperature and higher pressure) a partial hydrogenation of the saturated 12-ketone (after oxidation) is achieved, it is true, but at the same time the other described reaction[5] of this system is also enhanced, *i.e.* the deoxygenation in position 12. This



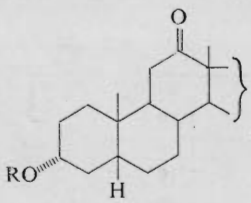
III, R = H
IV, R = Ac
V, R = Mes



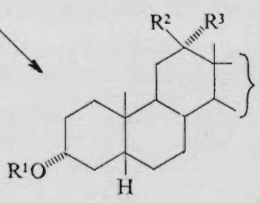
VI, $R^1 = H$, $R^2 = H$, $R^3 = OH$
VII, $R^1 = H$, $R^2 = OH$, $R^3 = H$
VIII, $R^1 = H$, $R^2 = H$, $R^3 = H$
IX, $R^1 = Ac$, $R^2 = {}^2H$, $R^3 = {}^2H$
X, $R^1 = H$, $R^2 = H$, $R^3 = AcO$



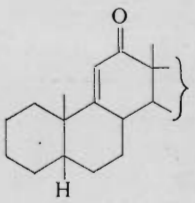
XI



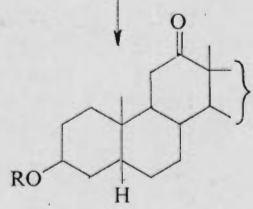
XII, R = H
XIII, R = Ac
XIV, R = Mes



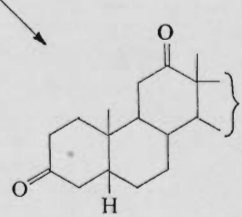
XV, $R^1 = R^2 = H$, $R^3 = OH$
XVI, $R^1 = H$, $R^2 = OH$, $R^3 = H$
XVII, $R^1 = Ac$, $R^2 = R^3 = H$



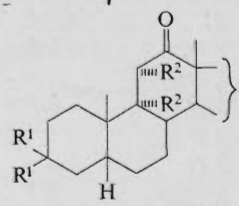
XVIII



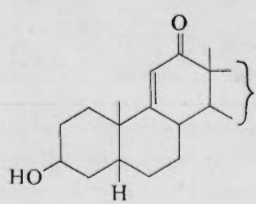
XIX, R = H
XX, R = HCO



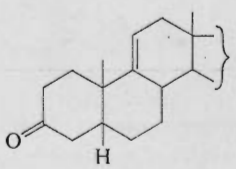
XXI



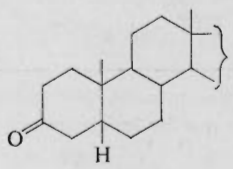
XXII, $R^1 = H$, $R^2 = H$
XXIII, $R^1 = {}^2H$, $R^2 = H$
XXIV, $R^1 = H$, $R^2 = {}^2H$



XXV



XXVI



XXVII

reaction takes place in a higher yield if the catalyst was in excess (see Fig. 1, the slope of the regression straight line $k = 5{\cdot}04$). A similar finding was also made by Kendall[5] who stated that hydrogenolysis of the oxygen atom in position 12 takes place only. when the amounts of the catalyst were as high as 5 to 150 g per mol of steroids. However, we have found that the deoxy products formed in this way contain considerable

TABLE I

Characteristic parameters of the ^{1}H-NMR spectra. The spectra were measured on a Tesla 60 intrument in deuteriochloroform (concentrations between 0·25 and 0·5 mol l^{-1}) with tetramethylsilane as internal reference, chemical shifts are given in the δ-scale (ppm)

Substance	3-H	11-H	12-H	18-H[a,b]	19-H[a,b]	Other[c]
III	3·67[d]	5·71[e]	—	0·91	1·19	—
IV	4·70[d]	5·73[e]	—	0·90	1·19	1·98[b]
V	4·87[d]	5·70[e]	—	0·89	1·18	2·97[b]
VII	3·58[d]	5·16[f]	4·08[g]	0·62	1·09	—
IX	4·70[d]	5·30[h]	—	0·56	1·04	2·00[b]
XI	—	5·85[e]	—	0·95	1·28	—
XII	3·63[d]	—	—	0·99	0·99	—
XIII	4·68[d]	—	—	1·00	1·00	1·99[d]
XIV	4·63[d]	—	—	1·00	1·00	2·97[b]
XV	3·62[d]	—	3·95[i]	0·68	0·91	—
XVII	4·72[d]	—	—	0·63	0·91	2·01[b]
XVIII	—	5·71[e]	—	0·89	1·16	—
XIX	4·08[i]	—	—	1·02	1·05	—
XX	5·20[i]	—	—	1·01	1·05	8·05[j]
XXI	—	—	—	1·05	1·11	—
XXII	—	—	—	0·99	0·99	—
XXV	4·10[i]	5·70[e]	—	0·92	1·22	—
XXVI	—	5·47[k]	—	0·61	1·07	—
XXVII	—	—	—	0·67	1·00	
XXVIII	—	—	—	0·62	0·89	—
XXIX	5·45[l]	—	—	1·02	1·02	—
XXX	—	5·81[m]	4·97[m]	0·63	1·15	2·03[b]

[a] In some cases chemical shifts of $C_{(18)}$- and $C_{(19)}$-protons have been reported (ref.[9]), our values are usually lower by 0·03 ppm; coupling constants of some 12-hydroxy compounds are discussed in ref.[18,19]; [b] singlet, 3 protons; [c] singlet of the methoxycarbonyl group (3·65 ± 0·02 ppm) was found in all the given spectra; [d] broad multiplet, $W_{1/2} = 28$ Hz; [e] doublet, $J = 2{\cdot}1$ Hz; [f] multiplet, $W_{1/2} = 5$ Hz;; [g] multiplet, $W_{1/2} = 7$ Hz; [h] multiplet, $W_{1/2} = 4$ Hz; [i] multiplet $W_{1/2}$ 6 Hz; [j] singlet, 1 proton; [k] multiplet $W_{1/2} = 9$ Hz; [l] complex multiplet of 2 vinylic protons; [m] doublet, $J_{11,12} = 6$ Hz.

amounts of saturated products (type *XXVII*), while the earlier authors described the formation of 9(11)-unsaturated 12-deoxy products of type *XXVI*.

The regression analysis of the data from Table II further shows that in the case of 3α-substituted substrates the yields of the hydrogen addition to the 9(11)-double

TABLE II

Relative yields of hydrogenations of 12-oxo-5β-chol-9(11)-enates. The hydrogenations were carried out in acetic acid, the products were separated by thin-layer chromatography after methanolysis of the acetates formed and oxidation of the hydroxy derivatives formed. The yields are calculated from the weight of the total isolated steroidal material

Substrate[a]	Time min	PtO_2: Substrate mol/mol	9α-12-one % %	3-Deoxy-compounds %	12-Deoxy-compounds %	Starting material %
III	120[b]	1·60	8	0	90	2
	155[c]	4·19	61	0	38	1
	150[c]	1·30	25	0	32	43
IV	120[c]	0·45	4	0	6	90
	60[c]	1·81	32	0	5	63
	125[c]	5·49	79	0	19	2
XI	180[c]	0·07	32	10	4	64
	30[c]	0·17	46	12	4	50
	25[c]	0·93	44	7	3	53
	10[c]	1·14	55	20	7	39
	75[c]	1·23	62	15	7	30
	10[c]	0·52	65	18	6	28
	10[c]	2·06	72	22	7	21
	90[c]	2·57	84	26	13	3
XVIII	120[c]	4·30	79	—	17	4
	30[c]	3·47	74	—	15	11
XXV	120[b]	1·64	34	0	55	11
	170[c]	2·37	86	0	13	1
	80[c]	2·65	63	0	25	2

[a] For hydrogenation 1 ml of acetic acid was used for 10 mg of substrate. For methanolysis 2 ml of 1% sodium methoxide were used for 20 mg of mixture, the solution was allowed to stand at 30°C for 18 h and then poured into 10 ml of 5% hydrochloric acid. The product was extracted with three 10 ml portions of chloroform, the extract was washed with water, dried and evaporated The residue was dissolved in ether and a diazomethane solution was added for esterification of traces of the corresponding cholanic acid present. Oxidation according to Jones was carried out at 20°C for 3 min; [b] hydrogenated in an autoclave at 100°C and 10 MPa; [c] hydrogenated in a pressureless apparatus at 20°C.

bond distinctly increase if the amount of catalyst is increased (slope $k = 29{\cdot}78$) With other substrates the relationship between the excess of the catalyst and the yield of hydrogenation is less distinct (slope of the straight line $k = 11{\cdot}3$). We succeeded in finding optimum conditions for hydrogenation of the 9(11)-double bond under preservation of the oxygen-containing function in position 12 and therefore this reaction can be of preparative importance for the synthesis of saturated 12-ketones of the 5β-series from 9(11)-unsaturated ketones: for example, on hydrogenation of substance *IV* methyl 3α-acetoxy-12-oxo-5β-cholanate[6] (*XIII*) was formed.

If substance with a 3-oxo group (*XI*) served as substrate 3-deoxy derivative *XXII* was also formed, sometimes with an admixture of 3-deoxy derivative *XVIII* if the reduction was partial. This hydrogenolysis of the oxygenated function in position 3 is not dependent on the presence of the 9(11)-double bond. In the case of the saturated diketone *XXI* it takes place still better than with diketone *XI*. The yields of the deoxy product *XXII* are directly proportional to the logarithm of the excess of the catalyst (Table III, slope of the regression straight line $k = 11{\cdot}04$, correlation coefficient $r = 0{\cdot}966$). When diketone *XXI* was reduced with deuterium 3 atoms of deuterium entered the molecule, which cannot be eliminated under the conditions of base-catalysed enolization: this result may be interpreted as a consequence of either

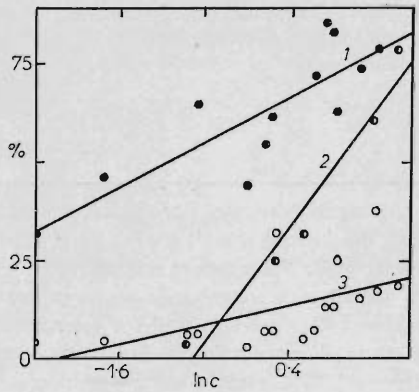
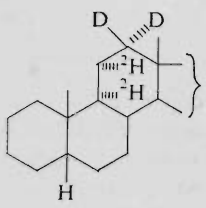


FIG. 1

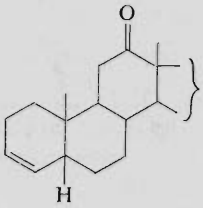
Correlation between the yields of hydrogenation of 12-oxo-5β-chol-9(11)-enates and the molar excess of the catalyst ($c = [PtO_2]/[\text{substrate}]$, mol/ml)

The straight line *1* was obtained by regression of the full points, expressing the yields of 9,11-dihydro 12-ketones obtained on hydrogenation of 3β-hydroxy, 3-oxo and 3-deoxy derivatives under a pressureless arrangement, $y = 62{\cdot}14 + 11{\cdot}3 \ln (c)$, $r = 0{\cdot}84$. The straight line *2* was obtained by regression of the half-full points and it expresses the yields of 9,11-dihydro 12-ketones obtained from 3α-substituted derivatives *III* and *IV*, $y = 21{\cdot}36 + 29{\cdot}32 \ln (c)$, $r = 0{\cdot}95$. The straight line *3* was obtained from empty points which express the yields of deoxygenation in position 12 after hydrogenation of 12-oxo-5β-chol-9(11)-enates *III*, *IV*, *XI*, *XVIII* and *XXV*. $x = 11{\cdot}62 + 5{\cdot}04 \ln (c)$, $r = 0{\cdot}57$. The graph expresses the data given in Table II.

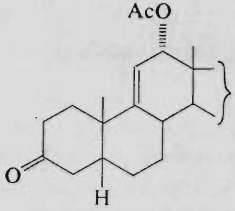
a preliminary deuteration of the 3-ketone under the effect of the deuterated acetic acid or – more probably – of a reduction to the 3-deuterio-3-alcohol which is dehydrated under the conditions of the reduction and which then adds a further molecule of deuterium[7].



XXVIII



XXIX



XXX

Ac = CH_3CO, Mes = CH_3SO_2

Experiences with the addition of hydrogen to the mentioned conjugated ketones were exploited in the additions of deuterium in [O—^{2}H]acetic acid to the unsaturated ketone *XVIII*. The product was oxidized according to Jones and separated on silica gel to the non-polar [9α,11α,12α,12β-$^2H_4$]-deoxy derivative *XXVIII* and the more polar component – [9α,11α-$^2H_2$]-ketone *XXIV*. The mass spectrum of compound *XXIV* also displays a significant peak of $[M-{}^1H^2HO]^+$ the presence of which agrees with Djerassi's finding[1] that the 12-ketones of the 5α but also of the 5β series lose water on mass spectrometry, to the detriment of the hydrogen atom in the position 9α.

TABLE III

Dependence of the yields of 3-deoxygenation on the excess of the catalyst

PtO_2: substance *XXI*[a] mol/mol	0·084	0·148	0·594	1·037	1·824	2·257	25·655
Yield of the substance *XXII* %	1·45	1·70	17·12	17·33	23·08	28·57	67·62

[a] Hydrogenations were carried out for 10 min in acetic acid (1 ml per 20 mg of substrate), the product was oxidized according to Jones and separated by chromatography on thin layers. The yields are calculated per weight of the products isolated and they can be correlated with the natural logarithm of the molar excess of the catalyst. The slope of the regression straight line is $k = 11{\cdot}34$, the correlation coefficient $r = 0{\cdot}966$.

The explanation of the dependence of the degree of reduction of the unsaturated ketone on the excess of the catalyst could consist – as we see it – in the fact that in the presence of an excess of the catalyst the back-decomposition of the reversible step[8,9] of the addition of hydrogen and the catalyst to the unsaturated ketone is suppressed.

EXPERIMENTAL

The melting points were measured on a Kofler block and they are not corrected. The samples for analysis were dried over phosphorus pentoxide at 1 kPa. Optical rotations and the infrared spectra were measured in chloroform, unless stated otherwise. The mixtures after hydrogenation were diluted with 5 volumes of acetic acid and the catalyst was filtered off on a paper filter wetted with the same solvent. The filtrate was concentrated on a rotary evaporator at 45°C bath temperature. The crude products of hydrogenation were methanolysed by standing in a sodium methoxide solution in methanol (1%, 1 ml per 10 mg of mixture) and the product was extracted with chloroform. The extracts were washed with water, dried and exposed to the action of diazomethane in ether. The products were oxidized according to Jones (20°C, 3 min) and chromatographed on a thin layer of silica gel.

Methyl 12,12-$^2H_2$-3α-Acetoxy-5β-chol-9(11)-enate (*IX*)

Methyl 3α-acetoxy-12-oxo-5β-chol-9(11)-enate (*IV*, ref.[10], 995 mg) was shaken with platinum oxide (250 mg) in [O-^{2}H]-acetic acid (15 ml) under deuterium. After one hour another portion of the catalyst was added (250 mg) and the reduction was continued for another hour. The catalyst was filtered off, the filtrate evaporated and the product oxidized according to Jones. The polar component of the mixture (910 mg) was identified as acetate *IV* on the basis of its IR spectrum, while the more lipophilic component (*IX*, 60 mg) melted at 136–139°C (methanol); mass spectrum $M = 432$ m/z.

Hydrogenation of Methyl 3,12-Dioxo-5β-chol-9(11)-enate (*XI*)

Platinum oxide (37 mg) was added to a solution of 117 mg of compound *XI* (ref.[11]) in 4 ml of acetic acid and shaken with hydrogen (after previous elimination of air) for 10 min. Chromatography of the product on a thin layer gave the following fractions (in the order of increasing polarity): 21·3 mg of 3-deoxy derivatives which were oxidized to a mixture of 12-ketones *XXII* and *XVIII* (according to UV spectra in a 7 : 3 ratio), 7·6 mg of 12-deoxy derivatives which were oxidized to a mixture of 3-ketones *XXVII* and *XXVI* (7 : 3 according to mass spectra), 7·9 mg of 3β-hydroxy ketones *XIX* and *XXV* (in a 7 : 3 ratio, UV spectrum), 39·5 mg of 3α-hydroxy ketones *XII* and *III* (7 : 3); 30·2 mg of 3α,12β-diols *XVI* and *VII* and 10·7 mg of 3α,12β-diols *XV* and *VI*. The last two fraction were combined, affording a mixture of diketones *XXI* and *XI* in a 7 : 3 ratio (UV).

Methyl 3α-Acetoxy-12-oxo-5β-cholanate (*XIII*)

Unsaturated ketone *IV* (48·5 mg) was dissolved in 4 ml of warm acetic acid and, after cooling, platinum oxide (147 mg) was added to it. When air was substituted by hydrogen the mixture was shaken for 2 h and worked up as in the preceding case. The product was oxidized according to Jones and separated by thin-layer chromatography. The non-polar component (9·5 mg)

was identified as a mixture of 12-deoxy compounds *XXVII* and *XXVI* (in a 8 : 1 ratio), while the polar component was identical with the 12-ketone *XIII* (39·7 mg) according to chromatographic data; in the UV spectrum only the terminal absorption could be found, hiding maximally 1% of the unsaturated ketone *IV*. After crystallization from methanol 30 mg of compound *XIII* were obtained, m.p. 152—155°C (lit.[6] gives m.p. 153—155°C); IR spectrum (CCl_4): 1 740 and 1 245 (acetoxy group), 1 740, 1 436 and 1 171 ($COOCH_3$), and 1 710 (keto group) cm^{-1}, identical with the spectrum of the authentic compound *XIII*.

Methyl [9α,11α-$^2H_2$]-12-Oxo-5β-cholanate (*XXIV*)

Platinum oxide (110 mg) was added to a solution of 50 mg of unsaturated ketone *XVIII* (ref.[12,13]) in 3 ml of deuterio acetic acid and the mixture was shaken under deuterium for 1 h. After working up as in the preceding case the mixture was oxidized according to Jones and the product was separated by thin-layer chromatography in benzene. Elution of the main zone (detection with morine) with ether afforded 42 mg of ketone *XXIV*. After crystallization from methanol it melted at 105—108°C (lit.[14] gives 107—108°C) and had the following mass spectrum: $M^+ = 390$ *m/z* (b.p.), $[M-H_2O]^+ = 371$ *m/z* (16%).

Methyl [9α,11α,12,12-$^2H_4$]-5-Cholanate (*XXVIII*)

The zone of the non-polar substance from the preceding experiment was eluted with ether, affording 7·8 mg of a substance the polarity of which was identical with that of methyl 5β-cholanate[15]. Mass spectrum: $M^+ = 378$ *m/z*; IR spectrum (CCl_4): 1 744, 1 447, 1 169 ($COOCH_3$), 2 195, 2 175 and 2 110 (C—^{2}H) cm^{-1}.

Methyl [3,3-$^2H_2$]-12-Oxo-5β-cholanate (*XXIII*)

40 mg of 3,12-diketone *XXI* were deuterated under the above-mentioned conditions in 2 ml of [O-^{2}H]acetic acid and 55 mg of platinum oxide. After 90 min the mixture was worked up in the above described manner and the product was oxidized according to Jones. The product was separated by chromatography on thin layers of silica gel to a more polar component (25 mg of the starting substance *XXI*) and a less polar component (10 mg). The polarity of the latter was identical with that of an authentic sample of compound *XXII*. The mass spectrum demonstrated the presence of dideuterated derivative *XXIII* ($M^+ = 390$ *m/z*, 38% of the base peak), but also some trideuterated component ($M^+ = 391$ *m/z*, 17% of the base peak). The amount of the latter did not decrease after alkali catalysed exchange of active hydrogens according to ref.[1] (36 h boiling with methanolic potassium hydroxide and then reesterification with diazomethane).

Methyl 12-Oxo-3α-methanesulfonyloxy-5β-chol-9(11)-enate (*V*)

3α-Hydroxy derivative *III* (0·4 g) was exposed to the action of methanesulfonyl chloride (1 ml) in pyridine (2 ml) at room temperature. After 18 h standing the mixture was decomposed with ice, the product[16] was extracted with ether and washed with dilute hydrochloric acid, water, a solution of potassium hydrogen carbonate, then dried over sodium sulfate and evaporated *in vacuo*. The residue was crystallized from a mixture of chloroform and ether, affording a product with m.p. 127—129°C, $[\alpha]_D^{20}$ +93° (*c* 1·0); IR spectrum: 1 731, 1 174 ($COOCH_3$). 1 334, 1 174, 931 (sulfonyloxy group) and 1 678, 1 608 (keto group) cm^{-1}. For $C_{26}H_{40}O_6S$ (480·7) calculated: 64·97% C, 8·39% H; found: 64·88% C, 8·45% H.

Methyl 12-Oxo-3α-methanesulfonyloxy-5β-cholanate (*XIV*)

3α-Hydroxy derivative *XII* (0·4 g) was converted to methanesulfonate *XIV* under the conditions described above, m.p. 140—143°C (chloroform–ether), $[\alpha]_D^{20}$ +92 (*c* 1·2); IR spectrum: 1 741, 1 439, 1 172 ($COOCH_3$), 1 333, 1 172 (sulfonyloxy group), 1 703 (oxo group) cm^{-1}. For $C_{26}H_{42}O_6S$ (312·3) calculated: 64·69% C, 8·77% H; found: 64·30% C, 8·77% H.

Solvolysis of 3α-Methanesulfonate *XIV*

Methanesulfonate *XIV* (0·7 g) was heated with 12 ml of dimethylformamide at 82°C for 24 h. The mixture was evaporated and the residue separated by thin-layer chromatography (silica gel, 30% of ether in benzene). The following substances were isolated (in order of increasing polarity): 25 mg (4%) of 3α-hydroxy derivative *XII*, 82 mg (14%) of 3β-hydroxy derivative *XIX*, identical with the sample described below, 270 mg (43%) of methyl ester of 3β-formyloxy-12-oxo-5β-cholanic acid (*XX*, ref.[17]) and 162 mg (28·8%) of methyl 12-oxo-5β-chol-3-enate (*XXIX*, ref.[17]). Compound *XX* was crystallized from ether, m.p. 132—134°C, $[\alpha]_D^{20}$ +83° (*c* 1·3); IR spectrum (CCl_4): 1740, 1 438, 1 172 ($COOCH_3$), 1 728, 1 192 (formyloxy group) 1 710 (keto group) cm^{-1}. For $C_{26}H_{40}O_5$ (432·6) calculated: 72·19% C and 0·32% H; found: 72·04% C, 0·16% H.

Methyl 3β-Hydroxy-12-oxo-5β-cholanate (*XIX*)

Formate *XX* (200 mg) was reacted with potassium hydrogen carbonate (600 mg) in 10 ml of methanol and 3 mol of water for 45 min under reflux. After concentration *in vacuo* the product was precipitated with water and filtered off under suction. The precipitate was washed with water and crystallized from aqueous methanol, m.p. 95—96°C. After recrystallization from ether, m.p. 127—129°C (ref.[17] gives 126·5—127°C); $[\alpha]_D^{20}$ +82° (*c* 0·9); IR spectrum: 1 740, 1 440, 1 251, 1 175 ($COOCH_3$), 1 702, 1 695 (inflexion, oxo group), 3 615, 1 030 (HO) cm^{-1}. For $C_{25}H_{40}O_4$ (404·6) calculated: 74·21% C, 9·97% H; found: 73·95% C, 9·88% H.

Methyl 3β-Hydroxy-12-oxo-5β-chol-9(11)-enate (*XXV*)

a) *Solvolysis of methanesulfonate* V: 450 mg of methanesulfonate *V* were heated with dimethylformamide (12 ml) at 70°C for 80 h. The mixture was concentrated in a vacuum and the residue hydrolysed with hydrochloric acid (0·2 ml) in methanol (10 ml). After 20 h standing at 40°C the mixture was diluted with chloroform (50 ml), concentrated to about 10 ml volume, washed with water, dried by filtration through a layer of sodium sulfate and concentrated in a vacuum. Chromatography on silica gel gave compound *XXV* (203 mg), m.p. 113—114°C (methanol), $[\alpha]_D^{20}$ +92° (*c* 1·0); IR spectrum: 1 731, 1 440, 1 175 ($COOCH_3$), 1 674, 1 607 (keto group), 3 620, 1 035 (HO) cm^{-1}. For $C_{25}H_{38}O_4$ (402·6) calculated: 74·55% C, 9·51% H; found: 74·28% C, 9·60% H. The side-product (160 mg) was identified as a product of elimination of the methanesulfonyloxy group on the basis of identical R_F value with the related methyl 12-oxo-5β-chol-9(11)-enate (*XXIX*).

b) *Reduction of methyl* 3,12-*dioxo*-5β-*chol*-9(11)-*enate*: 5 g of diketone *XI* were reduced with 10 g tritert-butoxylithium aluminum hydride in 20 ml of tetrahydrofuran at 0°C. After 1 h standing the mixture was decomposed by pouring it onto ice and hydrochloric acid, the product was extracted with chloroform, the extract washed with a solution of potassium hydrogen carbonate, filtered and evaporated. The residue was chromatographed on a column of silica gel (250 g, 50% ether in light petroleum). Gradually the following substances were eluted: the starting diketone *XI* (2·06 g), 3β-hydroxy ketone *XXV* (155 mg, according to IR spectrum identical with the product prepared as under *a*), 3α-hydroxy ketone *III* (2·35 g).

Methyl 12α-Acetoxy-3-oxo-5β-chol-9(11)-enate (*XXX*)

70 mg of compound *III* were hydrogenated in 5 ml of acetic acid, using 55 mg of platinum oxide. After 2 h the reaction was stopped and the mixture oxidized without previous methanolysis. Using thin-layer chromatography the product was separated into 3 components. The middle one (13 mg) represented a non-crystallizing oil, $[\alpha]_D^{20}$ +103° (*c* 1·0). IR spectrum (CCl_4): 1 740, 1 245, 1 019 (acetoxy group), 1 732, 1 437, 1 175 ($COOCH_3$), 1 715 (inflexion, oxo group), 1 654, 1 646, 3 060 (double bond) cm^{-1}; mass spectrum: $M^+ = 444$ *m/z*; ^{1}H-NMR spectrum: see Table I.

Hydrogenation of Compound *XI* on Palladium

Diketone *XI* (60 mg) was dissolved in methanol (8 ml) and hydrogenated on 10% palladium on calcium carbonate (200 mg). After 8 h stirring the catalyst was filtered off. The product contained (according to thin-layer chromatography) about 80% of a mixture of diol *XV* and *XVI* (in about 1 : 1 ratio) and about 20% of diketone *XXI*. The product was oxidized according to Jones and purified by thin-layer chromatography on silica gel: the main component is saturated dione *XXI* (54 mg), the IR, ^{1}H-NMR and mass spectra of which were in agreement with the proposed structure.

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