OXIDATION OF 21-OXO-20β,28-EPOXY-18α,19β*H*-URSANE DERIVATIVES; UNUSUAL REACTIVITY OF OXABICYCLO[2,2,1]HEPTANE SYSTEM IN RING E*

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Oxidation of keto ether *II* with oxygen in alkaline medium gives secodiacid *X* and hydroxy acid *V* in a 1 : 1 ratio. During the study of the structure of hydroxy acid *V* a series of compounds was prepared (*III*—*IX*, *XI*, *XII*, *XVI*—*XX*) with an oxabicyclo[2,2,1]heptane system in ring E; in some cases an unusual reaction course was observed in these substances: *a*) Formation of ketone *XI* by pyrolysis of α-acetoxy acid *VI*; *b*) pyrolytic or acid catalysed decarbonylation of anhydride *XV*, under formation of lactone *XIII*; *c*) formation of lactones *XIII* and *XIV* by a Baeyer–Villiger type oxidation during the reaction with lead tetraacetate; *d*) reduction of ketone *XI* to hydroxy derivative *XVI* under the coditions of alkaline hydrolysis in aqueous ethanolic medium. In most cases this reaction course may be caused by an unusual sterical strain of oxabicyclo[2,2,1]-heptane arrangement in ring E.

In connection with the preparation of E-secoacids derived from 20β,28-epoxy-18α, 19β*H*-ursane (*I*) we studied in previous papers[1,2] some oxidation reactions of its 3β-acetoxy-21-oxo derivative (keto ether *II*). It has been found that secoacids may be obtained in good yield by oxidation of 21-oxo-22-hydroxymethylene derivatives with chromium trioxide[2], while on direct oxidation of keto ether *II* with chromium trioxide the 28-methylene group is attacked only under formation of 28 → 20β lactone[3]. In this paper we study in greater detail the oxidation of keto ether *II* with oxygen in alkaline medium, the structure of the products formed, and their reactions which, in a series of cases, have a quite unusual course.

Oxidation of keto ether *II* was carried out in tert-butyl alcohol in the presence of potassium tert-butylate at 60—70°C, under constant introduction of oxygen. The reaction led to a mixture of two products in an approximately 1 : 1 ratio. One of these was secodiacid *X* which could be partly separated from the mixture by crystallization; in this manner secodiacid *X* has been obtained earlier[1]. For an easier separation of both products and mainly for the isolation of the second one the finding[1,2]

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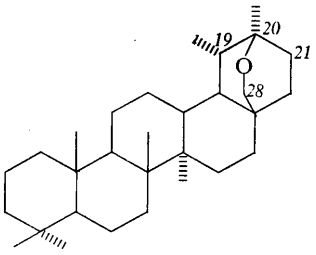
was useful that secodiacid *X* gives anhydride *XV* even under mild acetylation conditions (acetic anhydride in pyridine at room temperature). The crude mixture of oxidation products was therefore acetylated and anhydride *XV* was isolated as the less polar component by chromatography on silica gel. The structure of anhydride *XV* and secodiacid *X* was confirmed in a previous work[1,2].

The second, more polar product is an acid containing two acetoxyl groups, which can be formulated as *VI*,* as can be seen from the following reactions: Acid *VI* gives with diazomethane methyl ester *VII*; on alkaline hydrolysis of acetate groups acid *VI* gave dihydroxy acid *V*, characterized as methyl ester *VIII*. While the free dihydroxy acid *V* is acetylated under the effect of acetic anhydride in pyridine back to the starting diacetoxy acid *VI*, methyl ester *VIII* is acetylated under the same conditions at the 3β-hydroxy group only, under formation of monoacetyl derivative *IX*. Similar behaviour was also observed in model compounds *XXIV* and *XXV*, derived from 19β,28-epoxy-A-nor-18α-oleanane[5,6]: acetylation of the tertiary hydroxyl group takes place in free hydroxy acid *XXIV* only, under formation of acetyl derivative *XXVI*, while methyl ester *XXV* does not react under the same conditions. The easy acetylation of the hydroxyl group in the α-position to the carboxyl may be caused by a transitory formation of a mixed anhydride with acetic acid. The presence of the tertiary hydroxyl group in acid *V* and its derivatives follows also from the acetylation of triol *III* obtained by reduction of methyl ester *VII* with lithium aluminum hydride; this triol gives diacetyl derivative *IV* only.

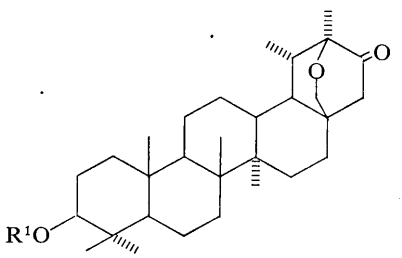
The spectral properties of derivatives of acid *V* are also in agreement with the suggested structure. Methyl ester *IX* contains a strong band of the intramolecularly bonded hydroxyl in its IR spectrum (Table I) and the total shape of the spectrum in the region of OH stretching frequencies is very similar to that of methyl ester *XXV* and further esters which have an intramolecular hydrogen bond between the ester group and the hydroxyl in the position α (ref.[7]). The intramolecular hydrogen bond was also observed in triol *III* and diacetate *IV*; the character of the spectrum found for triol *III* corresponds to derivatives of the $R^1R^2C(OH)—CH_2OH$ type with bulky substituents R^1 and R^2 (ref.[7] and the references therein).

In the ^{1}H-NMR spectrum of methyl ester *VII* all signals characteristic of tetrahydropyran fragment in the ring E of 20β,28-epoxy-18α,19β*H*-ursane derivatives are present: doublet of the 19α-methyl, singlet of the 20α-methyl, and two doublets of the $—C_{(28)}H_2—O$-group (Table II). In a previous paper[2] we demonstrated that both the value of the geminal coupling constants of protons in the position 28 and the long range coupling of the 28α-proton ($J_{28\alpha,18\alpha}$) and 28β-proton ($J_{28\beta,22\alpha}$) are characteristic of the arrangement of the bridge system in ring E. The doublet of the *endo*-proton (28β*H*) is shifted downfield and it is split in derivatives only that contain

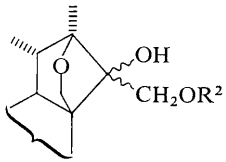
* The composition and the structure of the compounds prepared were further confirmed by mass spectra which are discussed elsewhere[4].



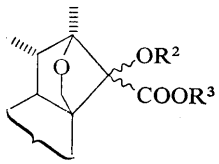
I



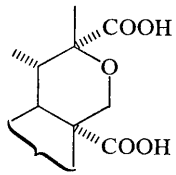
II, R¹ = CH_3CO



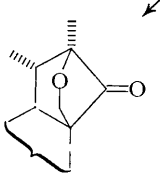
III, R¹ = R² = H
IV, R¹ = R² = CH_3CO



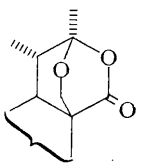
V, R¹ = R² = R³ = H
VI, R¹ = R² = CH_3CO, R³ = H
VII, R¹ = R² = CH_3CO, R³ = CH_3
VIII, R¹ = R² = H, R³ = CH_3
IX, R¹ = CH_3CO, R² = H, R³ = CH_3



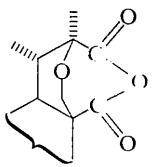
X, R¹ = H



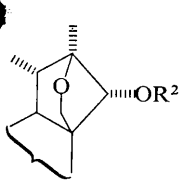
XI, R¹ = CH_3CO
XII, R¹ = H



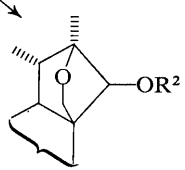
XIII, R¹ = CH_3CO
XIV, R¹ = H



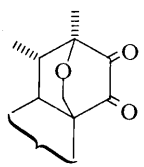
XV, R¹ = CH_3CO



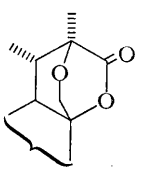
XVI, R¹ = R² = H
XVII, R¹ = R² = CH_3CO
XVIII, R¹ = CH_3CO, R² = H



XIX, R¹ = CH_3CO, R² = H
XX, R¹ = R² = CH_3CO



XXI



XXII

22α-H. The splitting of the upfield doublet, due to the proton oriented out of the molecule (28α-H), may be observed in rigid systems only, where the boat conformation of the tetrahydropyran ring is fixed by an at most two-membered bridge (in 21,22-seco derivatives and in anhydride *XV* the splitting is no longer evident[2]). In the spectrum of methyl ester *VII* the observed value for $J_{28\alpha,28\beta}$ (7·5 Hz) is lower than in derivatives *I* and *II* (~9 Hz) and the long range coupling is present for 28α-H only. These data are in agreement with the oxabicycloheptane arrangement of the E ring and they confirm that during oxidation of keto ether *II* a contraction of the ring took place.

The configuration at $C_{(22)}$ of hydroxy acid *V* and the compounds *III*–*IX* derived from it remains undetermined so far. Oxidation of ketone *II* gave a single of both

TABLE I

Wavenumbers of OH-Stretching Vibrations (cm^{-1})

Measured on a grating spectrophotometer Unicam SP 700 in a 10^{-3}M solution in tetrachloromethane.

III	*IV*	*VIII*[a]	*IX*	*XVIII*	*XIX*	*XXV*
3 636[b]	3 602	3 599	3 598	3 631	3 628[c]	3 606
3 540	3 473	3 500[d]	3 502[d]		3 584	3 535
3 554 sh[e]	3 532 sh[e]					

[a] The spectrum contains another band at 3 632 (3 622 sh) cm^{-1} corresponding to the 3β-hydroxy group; [b] superposition of the bands of the primary and the 3β-hydroxy group; [c] very weak band; [d] broad band; [e] shoulder.

TABLE II

Chemical Shifts (δ-scale, p.p.m.) and Coupling Constants (Hz) of the ^{1}H-NMR Spectra of 20β,28-Epoxy-18α,19β*H*-ursane Derivatives

Compound	—$C_{(28)}H_2$—O—					19α-CH_3[a]	20α-CH_3
	28αH	28βH	$J_{28\alpha,28\beta}$	$J_{28\alpha,18\alpha}$	$J_{28\beta,22\alpha}$		
I	3·30	4·12	9	1	1·6	0·87	1·02
II	3·36	4·35	9	1·6	2	0·77	1·13
VII	4·06	4·12	~7·5	~1	—	0·98	1·13
XI	3·72	4·39	7·6	1·4	—	0·78	1·11
XIII	3·53	4·40	9	1·3	—	0·98	1·46

[a] Doublet, $J = 6{\cdot}5-7{\cdot}2$ Hz.

possible $C_{(22)}$-isomers only; the second, if formed, may be present in the reaction mixture in negligible amount only. Hydroxy acid *V* is formed probably by benzilic rearrangement of 21,22-dioxo derivative *XXI* which, though not isolated from the reaction, may be supposed as one of the products of oxidation of ketone *II* in analogy to the results in refs[8,9]. Although the stereochemistry of the benzilic rearrangement is generally known[9,10], in the case of diketone of the type *XXI*, where both oxo groups are at the side of the boat form, the configuration of the formed products cannot be predicted. In our case it is impossible to decide unambiguously between the two possible isomers on the basis of spectral data for derivatives *III*–*IX* either. However, as in the case of ester *IX* no band appears in the OH stretching frequency region, which would correspond to the hydrogen bond of the hydroxyl group with the ether oxygen atom (the character of the spectrum is the same as in methyl ester *XXV*), the configuration with an α-hydroxyl group seems more probable; the 22β-hydroxy group in compound *XIX* is practically completely bound by an intramolecular hydrogen bond (Table I).

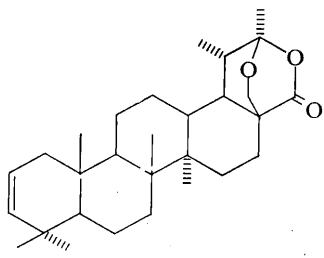
Compounds *III*–*IX* with contracted E ring are also interesting from another point of view. In experiments aimed at the checking of their structure in a chemical way we observed a number of unusual reactions:

a) *Pyrolysis of acetoxy acid* VI. On heating at melting point temperature acetoxy acid *VI* decomposes rapidly within a narrow temperature interval (approx. 2°C) while a neutral compound is formed almost quantitatively. In the IR spectrum of this compound another carbonyl band at 1780 cm^{-1} is present in addition to the acetate carbonyl. The original oxabicycloheptane arrangement of the E ring remained preserved, which is evident from the ^{1}H-NMR spectrum containing characteristic signals of 19α- and 20α-methyl groups, two doublets of the $C_{(28)}H_2$ group with long-range coupling at 28α-H only, and especially from the low geminal coupling constant ($J_{28\alpha,28\beta}$, see Table II). From all the mentioned data it follows that the product of pyrolysis has the structure of ketone *XI*; the presence of the keto group was confirmed by the preparation of oxime. The relatively high frequency of the ketone carbonyl is caused evidently by the considerable deformation of the valence angle C—CO—C in the bridge system, and it corresponds to the values found in 7-norbornanone derivatives[11]. The structure of ketone *XI* was further confirmed by its preparation from triol *III*: Oxidation of triol *III* with sodium periodate gave hydroxy ketone *XII* the acetate *XI* of which was identical with the product of pyrolysis.

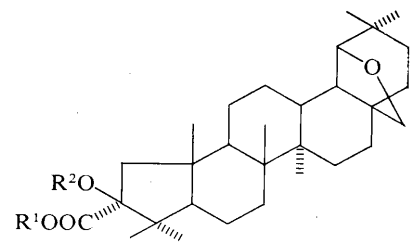
For comparison pyrolysis of acetoxy acid *XXVI* derived from A-nor oleanane was also carried out. In this case, however, the corresponding ketone *XXVIII* was detected in the pyrolysate in traces only on the basis of thin-layer chromatography. Practically the sole product was α,β-unsaturated acid *XXIX*, characterized as methyl ester *XXX*. The pyrolysis of both α-acetoxy acids *VI* and *XXVI* takes place at relatively low temperature (about 260°C) and from the preparative point of view it is remarkable for its uniformity. However, both mentioned pyrolyses do not show clearly whether the

formation of norketone takes place generally in α-acetoxy acids which have two quaternary carbon atoms in the neighbourhood of the functional groups (and therefore cannot eliminate acetic acid), or whether the presence of the ether oxygen on the neighbouring carbon atom is operative.

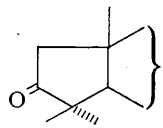
b) *Pyrolytic and acid catalysed decarbonylation of anhydride* XV. In an effort to prepare ketone *XI* by another procedure, pyrolysis of anhydride *XV* was carried out. Although the thermal decarboxylation of secoacids and their anhydrides is a common reaction for the preparation of ketones with a contracted ring[9], ketone *XI* could not be found even in traces during the pyrolysis of anhydride *XV*. The reaction took place at 330–340°C under formation of two products of which the more polar one was isolated in a 90% yield. In its IR spectrum a carbonyl band at 1760 cm^{-1} was present in addition to the absorption bands of the acetate group. This substance did not afford an oxime under the usual conditions and in contrast to the expected ketone *XI* it contained one oxygen atom more. From the ^{1}H-NMR spectrum it is evident that a formation of an oxabicyclooctane system in ring E took place; this is evident mainly from the value of the geminal coupling constant $J_{28\alpha,28\beta}$ (9 Hz), which agrees with the values found in derivatives *I* and *II* (see Table II). A long-range coupling is observable only for the 28α-H doublet; 28β-H gives a sharp doublet. On the basis of the mentioned properties this substance may be formulated as lactone



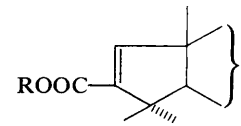
XXIII



XXIV, $R^1 = R^2 = H$
XXV, $R^1 = CH_3$, $R^2 = H$
XXVI, $R^1 = H$, $R^2 = CH_3CO$
XXVII, $R^1 = CH_3$, $R^2 = CH_3CO$



XXVIII



XXIX, R = H
XXX, $R = CH_3$

XIII or *XXII*. Presently it cannot be decided unambiguously which structure is correct, but according to the downfield shift of the 20α-methyl group (with respect to derivatives *I* and *II*) the structure *XIII* with another oxygen atom on $C_{(20)}$ seems more probable. In addition to this the chemical shift of the 20α-methyl (1·46 p.p.m.) agrees with the values given in literature[12] for an analogously situated methyl group in diterpene derivatives (1·40 – 1·43 p.p.m.). The presence of a lactone group in derivative *XIII* is also confirmed by the formation of this compound by Baeyer–Villiger oxidation of ketone *XI* with 3-chloroperbenzoic acid. In alkaline medium lactone *XIII* is hydrolysed preferentially at the acetoxyl group in the position 3, and the lactone group is hydrolysed more slowly. The formation of the acid was detected by thin-layer chromatography only, but it could not be isolated. During the working up of the reaction mixture the original lactone ring is reestablished after acidification, under formation of 3-hydroxylactone *XIV*. Its acetylation gave 3β-acetoxy derivative identical with the starting lactone *XIII*. Anhydride *XV* is also converted to lactone *XIII* during the heating in acetic anhydride in the presence of boron trifluoride etherate or *p*-toluenesulfonic acid. These reactions also support indirectly the proposed structure *XIII*, because during acid catalysed decarbonylation the elimination of the carbonyl group in the neighbourhood of the ether oxygen seems more probable.

The second, minor product of pyrolysis of anhydride *XV* was lactone *XXIII*; in this case an additional pyrolytic elimination of acetic acid from the A ring took place, as is evident from the absence of the absorption bands of the acetoxyl group in the IR spectrum. In the mass spectrum of both lactones, *XXIII* and *XIII*, the E ring has the same fragmentation pattern[4]. Both products of pyrolysis of anhydride *XV* (lactones *XIII* and *XXIII*, isolated in a total yield 96%) were formed by elimination of carbon monoxide; this decarbonylation takes place as the only reaction, instead of decarboxylation. Such a course of pyrolysis of an anhydride seems to be quite unique so far and it is evidently due to the fact that the formation of ketone *XI*, connected with the elimination of carbon dioxide, would require too great a deformation of the E ring. The easy elimination of carbon monoxide may be also observed in the mass spectrum of anhydride *XV*: the molecular ion (M^+ = 528, 0·05% of the base peak) is relatively rare and further fragmentation, beginning with the ion $M^+ - CO$, is identical with the fragmentation of lactone *XIII*, see[4].

c) *Oxidation of hydroxy acid* V *and ketone* XI *with lead tetraacetate.* In an attempt at chemical confirmation of the structure of hydroxy acid *V* by oxidation with lead tetraacetate lactone *XIV* was obtained as the sole reaction product. It seemed probable that the reaction represents a subsequent oxidation of ketone *XII* which should be formed[13] as the primary product by oxidative cleavage of α-hydroxy acid *V*. This assumption was checked in the case of acetoxy ketone *XI* which again gave lactone *XIII* as the only product on reaction with lead acetate under the same conditions. This easy oxidation of ketone to lactone is atypical for lead tetraacetate oxidation and it corresponds formally to Baeyer–Villiger oxidation.

d) *Reduction of the 22-oxo group of ketone* XI *in alkaline medium.* In an effort to prepare hydroxy ketone *XII* we submitted acetoxy ketone *XI* to alkaline hydrolysis under the usual conditions (boiling with 5% potassium hydroxide solution in benzene–ethanol 1 : 1). Two products were obtained of which the minor one was hydroxy ketone *XII*; the main reaction product was diol *XVI* which did not display carbonyl absorption in its IR spectrum, and its molecular weight was two units higher in comparison with that of ketone *XII* according to mass spectrometry. In its molecule two hydrogen atoms were exchangeable for deuterium in CH_3OD. Under the effect of acetic anhydride in pyridine diol *XVI* was converted to diacetate *XVII*. Hence, it is evident that under the conditions of alkaline hydrolysis reduction of the carbonyl group to the hydroxyl group took place.

For comparison ketone *XI* was reduced with sodium borohydride. On reduction in ethanol only one of the isomeric alcohols at $C_{(22)}$ was formed, *i.e.* hydroxy derivative *XVIII*, the acetylation of which gave a diacetate identical with the above mentioned diacetate *XVII*. In contrast to this, when pyridine was used as solvent, reduction of ketone *XI* with sodium borohydride gave a mixture of both isomeric alcohols, in which 22β-hydroxy derivative *XIX* predominated. It was further characterized as diacetate *XX*. The assignment of the configuration to both hydroxy derivatives *XVIII* and *XIX* is based on the measurement of the hydrogen bonds (Table I): 22β-hydroxy derivative *XIX* has its hydroxyl group almost completely bound by an intramolecular hydrogen bond to the ether oxygen atom, while in the case of 22α-hydroxy derivative *XVIII* only a band of a free hydroxyl group was found.

The reduction of the 22-oxo group in ketone *XI* under the effect of alkaline medium takes place reproducibly in the presence of an aliphatic alcohol as solvent (methanol, ethanol, 2-propanol). According to thin-layer chromatography 22-hydroxy derivative *XVIII* (and partly also diol *XVI*) is formed from ketone *XI* at room temperature, both in anhydrous methanol under the effect of sodium methoxide and in 96% ethanol or in a benzene–ethanol mixture under the effect of potassium hydroxide. When alkali hydroxide in boiling 96% ethanol was used diol *XVI* was obtained as the sole product; if the reaction was carried out in 2-propanol or in a benzene–ethanol mixture under reflux, the reduction product again predominated. In contrast to this, in the absence of alcohol, for example under the effect of sodium hydroxide in aqueous dioxan, reduction of the oxo group does not take place, but the acetate group in the position 3 is hydrolysed only, under formation of hydroxy ketone *XII*. Hence, the reduction of the keto group in alkaline medium takes place in the presence of alcohol only, and thus it can be considered as an extreme case of Meerwein–Ponndorf reaction which in this particular case does not require an anhydrous medium. The reason of this unusual reactivity of the 22-oxo group is evidently the unusually great tendency of $C_{(22)}$ to change in hybridization, caused by the strain of the bicycloheptane system of the E ring in ketones *XI* and *XII*. The oxo group in ketone *II* with a bicyclooctane arrangement in the E ring does not change under the same conditions.

The sterical strain of the bicyclo[2,2,1]heptanone fragment in ring E is an evident cause of anomalous reactions described in the sections *b*), *c*) and *d*). The bicycloheptanone compounds with a carbonyl bridge are generally very reactive[11,14]; the tendency to a change in hybridization on the carbonyl carbon atom is manifested by the formation of ketals and an easy reduction of the oxo group[14]; for example in reduction with sodium borohydride 7-norbornanone reacts much faster than cyclobutanone, so that the cause of the high reactivity probably does not only consist in the valence angle deformation of the C—CO—C grouping (see[11]). In the case of ketone *XI* where the bicycloheptanone fragment is a part of a larger rigid skeleton a further increase in sterical strain may be supposed. From this it follows that in the above mentioned reactions the formation of more stable compounds with a bicyclooctanone arrangement of the E ring is preferred (decarbonylation of anhydride *XV* under formation of lactone *XIII*), or also an easy expansion of the ring in the bicycloheptanone fragment to a bicyclooctanone one (oxidation of ketone *XI* to lactone *XIII*), or, finally, a change in hybridization of $C_{(22)}$ (reduction of the 22-oxo group). Especially the last mentioned reaction is probably specific for ketone *XI*, since it takes place under such mild conditions, which have no analogy in the carbonyl-bridge compounds studied so far.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotation was measured in chloroform solution on an automatic ETL-NPL (Bendix-Ericsson) polarimeter with a $\pm 2°$ accuracy. The infrared spectra were measured in chloroform with a UR-20 (Zeiss, Jena) instrument, the ^{1}H-NMR spectra were measured in deuteriochloroform, using tetramethylsilane as internal standard, on a Varian HA-100 instrument. The reaction course and the purity of the samples were controlled by thin-layer chromatography on silica gel according to Stahl (type 60). The identity of the samples was checked by thin-layer chromatography and by infrared spectra. Samples for analysis were dried over phosphorus pentoxide at 80°C and 0·1—1 Torr, for 8—16 hours. The conventional work-up means that the reaction mixture was extracted with ether, the extract washed with water, hydrochloric acid (1 : 4), sodium carbonate (5%) and water, and then dried over sodium sulfate. Methyl esters were prepared with ethereal diazomethane solution. Acetylation was carried out with acetic anhydride–pyridine mixture at room temperature, for about 12 hours.

Oxidation of Keto Ether *II*

A solution of keto ether *II* (4·75 g) in benzene (170 ml) was added dropwise and at room temperature over 10 minutes to a solution of potassium (3 g) in tert-butyl alcohol (150 ml). The mixture was heated at 60—70°C for 7 hours, under stirring and saturation with oxygen. It was then diluted with water, acidified with dilute sulfuric acid and extracted with ether. The ethereal solution was washed with water and ether was distilled off under reduced pressure without previous drying. The residue (5 g) was acetylated in the conventional manner and the mixture of acetyl derivatives (5·2 g) was separated by silica gel chromatography. Benzene eluted anhydride *XV* (2·6 g; 50%), m.p. 332—334°C (under decomp.; benzene–heptane), $[\alpha]_D$ +82° (*c* 0·78),

identical with an authentic sample[1,2]. Ether eluted 3β,22ξ-diacetoxy-21β,28-epoxy-E(21)-nor-18α,19β*H*-ursan-22ξ-carboxylic acid (*VI*; 2·1 g, 40%), m.p. 263–265°C (under decomp.; chloroform–heptane), $[\alpha]_D$ −21° (*c* 0·97). IR spectrum: 3520–2800, 1759, 1730, 1260 cm^{-1}. For $C_{34}H_{52}O_7$ (572·7) calculated: 71·27% C, 9·15% H; found: 71·13% C, 9·04% H.

Methyl ester VII: m.p. 298–300°C (chloroform–heptane), $[\alpha]_D$ −31° (0·78); IR spectrum: 1753, 1730, 1254. ^{1}H-NMR spectrum: 0·848 (2 . CH_3); 0·888, 0·897, 0·996, 1·225 (4 . CH_3); 0·980 d, $J \approx 6{\cdot}5$ Hz (19-CH_3); 2·04, 2·13 (2 . CH_3COO); 3·73 ($COOCH_3$); 4·06 d and 4·12 d, $J_{gem} \sim 7{\cdot}5$ Hz (28-H_2). For $C_{35}H_{54}O_7$ (586·8) calculated: 71·64% C, 9·28% H; found: 71·85% C, 9·45% H. Ether further eluted a mixture of acids (0·7 g), which was reacted with diazomethane and chromatographed on silica gel to give dimethyl ester *VII* (0·4 g), m.p. 297–299°C, identical with the preparation described above. As a further component dimethyl ester of 21,22-secodiacid *X* (0·1 g), m.p. 182–185°C (and 236–240°C after solidification) was obtained, identical with a sample described earlier[2].

3β,22ξ-Dihydroxy-21β,28-epoxy-E(21)-nor-18α,19β*H*-ursane-22ξ-carboxylic Acid (*V*)

A solution of diacetoxy acid *VI* (0·12 g) and potassium hydroxide (0·1 g) in a benzene–ethanol mixture (2 : 1) was refluxed for 2 hours, diluted with water, acidified with dilute sulfuric acid and extracted with ether. After washing of the ethereal extract with water the solvent was distilled off without previous drying. Crystallization from benzene–methanol gave dihydroxy acid *V* (0·06 g), m.p. 325–330°C (under decomposition). Methyl ester *VIII*; m.p. 311–314°C (methanol–benzene); IR spectrum (nujol): 3610, 3530, 1755, 1710 cm^{-1}; for $C_{31}H_{50}O_5$ (502·7). CH_3OH calculated: 71·87% C, 10·18% H; found: 71·99% C, 10·35% H. Methyl ester of 3β-acetoxy-22ξ-hydroxy-21β,28-epoxy-E(21)-nor-18α,19β*H*-ursane-22ξ-carboxylic acid (*IX*); m.p. 274 to 276°C (chloroform–methanol), $[\alpha]_D$ +5° (*c* 0·40). IR spectrum: 3600, 3530, 1729, 1261, 1388 cm^{-1}. For $C_{33}H_{52}O_6$ (544·7) calculated: 72·75% C, 9·62% H; found: 72·58% C, 9·98% H.

3β-Acetoxy-20β,28-epoxy-21-oxa-18α,19β*H*-ursan-22-one (*XIII*)

a) Anhydride *XV* (0·2 g) was heated under nitrogen at 330–345°C for 10 minutes. After cooling the product was dissolved in chloroform and filtered through a layer of alumina; after evaporation of chloroform the residue (0·18 g) was chromatographed on silica gel. Benzene eluted 22-oxo-20β,28-epoxy-21-oxa-18α,19β*H*-urs-2-en-22-one (*XXIII*; 0·01 g), m.p. 325–326°C (chloroform–heptane). IR spectrum: 1760 cm^{-1}. For $C_{29}H_{44}O_3$ (440·6) calculated: 79·04% C, 10·07% H; found: 78·89% C, 10·12% H. Benzene–ether mixture (4 : 1) eluted lactone *XIII* (0·17 g), m.p. 338–340°C (chloroform–methanol), $[\alpha]_D$ +46° (*c* 0·82). IR spectrum: 1760, 1730, 1262 cm^{-1}. ^{1}H-NMR spectrum: 0·855 (2 . CH_3); 893, 0·944, 1·019, 1·463 (4 . CH_3); 0·981 d, $J \approx 6{\cdot}5$ Hz (19-CH_3); 2·03 (CH_3COO); 3·53 bd and 4·40 d, $J_{gem} = 9{\cdot}0$ Hz, $J_{l.r.} = 1{\cdot}3$ Hz (28-H_2); 4·49 m (3α-H). For $C_{31}H_{48}O_5$ (500·7) calculated: 74·36% C, 9·65% H; found: 74,39% C, 9·65% H.

b) A solution of anhydride *XV* (0·1 g) and boron trifluoride etherate (1 ml) in acetic anhydride (20 ml) was allowed to stand at room temperature for 16 hours, then diluted with water and worked up in the conventional manner. Chromatography of the crude product on silica gel gave lactone *XIII* (0·08 g), m.p. 338–341°C (chloroform–methanol), $[\alpha]_D$ +43° (*c* 0·68), identical with the sample prepared under *a*).

c) A solution of anhydride *XV* (0·1 g) and *p*-toluenesulfonic acid (0·05 g) in acetic anhydride (15 ml) was refluxed for 10 hours. After cooling the separated crystals of lactone *XIII* (0·09 g) were filtered off under suction and washed with water, m.p. 342–344°C (chloroform–methanol), $[\alpha]_D$ +44° (*c* 0·74). The sample is identical with the preparations prepared under *a*) and *b*).

d) A solution of ketone *XI* (0·03 g) and lead tetraacetate (0·03 g) in a mixture (6 ml) of chloroform and acetic acid (1 : 3) was allowed to stand at room temperature for 20 hours. Ethylene glycol and water were then added and the mixture was worked up in the usual manner. Crystallization from chloroform–methanol gave lactone *XIII* (0·02 g), m.p. 341—343°C, which was identical with those mentioned above.

e) A solution of ketone *XI* (0·05 g) and 3-chloroperoxybenzoic acid (0·05 g) in chloroform (5 ml) was allowed to stand at room temperature for 2 hours and then worked up in the usual manner. Crystallization from a mixture of chloroform and methanol gave lactone *XIII*, m.p. 338—340°C, identical with the preceding samples.

3β-Hydroxy-20β,28-epoxy-21-oxa-18α,19β*H*-ursan-22-one (*XIV*)

a) A solution of hydroxy acid *V* (0·03 g) and lead tetraacetate (0·03 g) in 6 ml of a mixture of chloroform and acetic acid (1 : 3) was allowed to stand at room temperature for 20 hours. After addition of a drop of ethylene glycol and water the mixture was worked up in the conventional manner. Crystallization from chloroform–methanol gave lactone *XIV* (0·025 g), m.p. 326—328°C, $[\alpha]_D$ +30° (*c* 0·65). IR spectrum: 3630, 1762 cm^{-1}. For $C_{29}H_{46}O_4$ (458·7) calculated: 75·94% C, 10·11% H; found: 75·76% C, 10·28% H.

Acetate: m.p. 337—340°C (chloroform–methanol), $[\alpha]_D$ +45° (*c* 0·51), identical with acetate *XIII* mentioned above.

b) A solution of lactone *XIII* (0·04 g) and sodium hydroxide (0·06 g) in ethanol (10 ml) was refluxed for one hour. The reaction course was controlled by thin-layer chromatography: after 10 minutes the mixture contained three components: starting lactone *XIII*, 3-hydroxylactone *XIV*, and a spot on the start; after one hour only the substance on the start was present. After dilution of the reaction mixture with water and neutralization with dilute sulfuric acid and conventional work-up lactone *XIV* was obtained, m.p. 327—329°C (chloroform–methanol), identical with the sample obtained under *a*).

22ξ-Hydroxymethyl-20β,28-epoxy-E(21)-nor-18α,19β*H*-ursane-3β,22ξ-diol (*III*)

Methyl ester *VII* (0·2 g) was extracted into a suspension of lithium aluminum hydride (0·3 g) in ether (70 ml) over 7 hours. The reaction mixture was decomposed with ethyl acetate and water and worked up in the conventional manner. Triol *III* (0·15 g) had m.p. 265—266°C and, after resolidification, 273—275°C (benzene). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found: 75·64% C, 10·52% H.

Diacetate IV: m.p. 290—292°C (chloroform–heptane). IR spectrum: 3600, 3400—3550, 1729, 1255 cm^{-1}. For $C_{34}H_{54}O_6$ (558·8) calculated: 73·08% C, 9·74% H; found: 73·29% C, 9·87% H.

3β-Acetoxy-20β,28-epoxy-E(21)-nor-18α,19β*H*-ursan-22-one (*XI*)

Acetoxy acid *VI* (0·13 g) was heated at 260—270°C under nitrogen for 10 minutes. The crystalline pyrolysate was dissolved in chloroform and filtered through a small column of alumina. Crystallization from chloroform-heptane gave ketone *XI* (0·11 g), m.p. 303—309°C (decomp.), $[\alpha]_D$ +21° (*c* 0·62). IR spectrum: 1781, 1729, 1255 cm^{-1}. ^{1}H-NMR spectrum: 0·850 (2 . CH_3); 0·894, 0·910, 1·015, 1·113 (4 . CH_3); 0·783 d, J = 7·1 Hz (19-CH_3); 2·04 (CH_3COO); 4·39 d and 3·72 d, J_{gem} = 7·6 Hz, $J_{l.r.}$ = 1·4 Hz (28-H_2); 4·49 m (3α-H). For $C_{31}H_{48}O_3$ (484·7) calculated. 76·81% C, 9·98% H; found 76·99% C, 10·07% H.

Oxime. A solution of ketone *XI* and hydroxylamine hydrochloride in pyridine was heated on a water bath for 30 minutes; after the conventional work-up oxime was obtained which melted at 240—250°C and, after resolidification, at 282—290°C (chloroform–heptane). IR spectrum: 3580, 3320, 1724, 1254, 998, 975 cm^{-1}. For $C_{31}H_{49}NO_4$ (499·7) calculated. 74·51% C, 9·88% H; found: 74·30% C, 9·95% H.

3β-Hydroxy-20β,28-epoxy-E(21)-nor-18α,19β*H*-ursan-22-one (*XII*)

a) Ketone *XI* (0·07 g) was refluxed for 3 hours with sodium hydroxide (0·25 g) in a dioxan–water mixture 1 . 1 (18 ml). After addition of water the separated product was filtered under suction, dissolved in chloroform, and the solution was filtered through a layer of alumina. On crystallization from a mixture of chloroform and methanol ketone *XII* (0·05 g) was obtained, m.p. 276—278°C; IR spectrum: 3620, 1780 cm^{-1}. For $C_{29}H_{46}O_3$ (442·7) calculated: 78·68% C, 10·47% H; found: 78·57% C, 10·45% H.

b) A suspension of triol *III* (0·03 g) and sodium periodate (0·04 g) in ethanol (20 ml) was allowed to stand at room temperature for 52 hours. It was diluted with water, extracted with chloroform and worked up as usual. The residue was dissolved in benzene and filtered through a small column of silica gel. The ketone *XII* obtained (0·02 g) had m.p. 272—275°C (benzene–heptane), and it was identical with the preparation obtained under *a*).

20β,28-Epoxy-E(21)-nor-18α,19β*H*-ursane-3β,22α-diol (*XVI*)

A solution of ketone *XI* (0·1 g) and potassium hydroxide (0·2 g) in a benzene–ethanol mixture (1 : 1; 20 ml) was refluxed for 2·5 hours. After dilution with water and acidification with dilute sulfuric acid the mixture was worked up and the products separated by preparative thin-layer chromatography on silica gel, using benzene–ether 3 : 2 as developing solvent. Hydroxy ketone *XII* (0·02 g) was obtained, m.p. 276—278°C (chloroform–methanol), identical with the preparation described above; further, diol *XVI* (0·06 g) was obtained, m.p. 322—324°C (chloroform–heptane). For $C_{29}H_{46}O_3$ (444·7) calculated: 78·32% C, 10·88% H; found: 78·44% C, 10·95% H.

Diacetate XVII: m.p. 298—299°C (chloroform–heptane), $[\alpha]_D$ −7° (*c* 0·82). IR spectrum: 1730, 1258 cm^{-1}. For $C_{33}H_{52}O_5$ (528·7) calculated: 74·96% C, 9·91% H; found: 74·92% C, 10·01% H.

On boiling ketone *XI* (0·05 g) with a 5% potassium hydroxide solution in 96% ethanol (5 ml) for about one hour diol *XVI* (0·04 g) was obtained, melting at 323—324°C, the diacetate of which was identical with the diacetate *XVII* mentioned above.

A suspension of ketone *XI* in a 2% sodium methoxide in methanol was allowed to stand for 24 hours at room temperature. According to thin-layer chromatography on silica gel the reaction mixture contained ketone *XI* and hydroxy derivative *XVIII*, accompanied by traces of diol *XVI*. The presence of these components was confirmed by the IR spectrum of the crude product after the working up of the reaction mixture.

Reduction of Ketone *XI* with Sodium Borohydride

a) Sodium borohydride was added to a solution of ketone *XI* (0·04 g) in a mixture of benzene and ethanol (1 : 1; 6 ml) followed by water after five minutes reaction. After working up of the reaction mixture hydroxy derivative *XVIII* was obtained (0·04 g), m.p. 344—345°C (ether), $[\alpha]_D$ +25° (*c* 0·58). IR spectrum: 3620, 1729, 1256 cm^{-1}. For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·59% C, 10·39% H. Acetylation gave diacetate *XVII*, m.p. 299 to 301°C, identical with the preparation described above.

b) A solution of ketone *XI* (0·04 g) in pyridine was allowed to stand in the presence of sodium borohydride at room temperature for 20 minutes. After dilution with water the precipitate formed was filtered off with suction, dissolved in benzene, dried by filtration through alumina, and the product was separated by preparative thin-layer chormatography on silica gel using light petroleum–ether mixture (1 : 1) as developing solvent. Hydroxy derivative *XVIII* was obtained, melting at 344—346°C, identical with the product obtained under *a*). In addition, hydroxy derivative *XIX* (0·03 g), m.p. 335—336°C (chloroform–heptane), $[\alpha]_D$ +26° (*c* 0·61) was also obtained. IR spectrum: 3580, 1728, 1257 cm^{-1}. For $C_{31}H_{54}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·31% C, 10·28% H.

Diacetate XX: m.p. 244—246°C (chloroform–heptane), $[\alpha]_D$ +42° (*c* 0·59). IR spectrum: 1730, 1259 cm^{-1}. For $C_{33}H_{52}O_5$ (528·7) calculated: 74·96% C, 9·91% H; found: 75·01% C, 9·83% H.

3β-Acetoxy-19β,28-epoxy-A-nor-18α*H*-oleanane-3α-carboxylic Acid (*XXVI*)

Acetoxy acid *XXVI* of m.p. 263—264°C (decomp., chloroform–heptane), $[\alpha]_D$ +74° (*c* 0·81) was obtained by acetylation of hydroxy acid *XXIV* prepared according to refs[5,6]. IR spectrum: 3500—2800, 1745, 1720, 1260 cm^{-1}. For $C_{32}H_{50}O_5$ (514·7) calculated: 74·67% C, 9·79% H; found: 74·86% C, 9·77% H.

Methyl ester XXVII: m.p. 194—196°C (chloroform–methanol); IR spectrum: 1737 (broad) 1432, 1256 cm^{-1}. For $C_{33}H_{52}O_5$ (528·7) calculated: 74·96% C, 9·91% H; found: 74·75% C, 10·09% H.

Pyrolysis of acid XXVI: Acetoxy acid *XXVI* (0·07 g) was heated at 260—270°C under nitrogen for 10 minutes. Preparative chromatography on a thin layer of silica gel with light petroleum–ether 4 : 1 and crystallization from heptane gave 19β,28-epoxy-A-nor-18α-olean-2-ene-3-carboxylic acid (*XXIX*; 0·05 g), m.p. 320—322°C; IR spectrum: 3500—2800, 1697—1617 cm^{-1}. UV spectrum (cyclohexane): λ_{max} 230 nm (log ε 4·02).

Methyl ester XXX: m.p. 225—230°C (methanol), $[\alpha]_D$ +76° (*c* 0·62). UV spectrum (cyclohexane): λ_{max} 230 nm (log ε 4·04). For $C_{31}H_{48}O_3$ (468·7) calculated: 79·43% C, 10·32% H; found: 79·10% C, 10·10% H.

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