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MIGRATION OF THE SIDE CHAIN DURING THE ACID CATALYSED ISOMERISATION OF UNSATURATED 3,4-SECO DERIVATIVES

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3,4-Secotriterpenes with a double bond in the position 4 (23) undergo rearrangement in acid medium, during which the three-carbon chain migrates from $C_{(10)}$ to $C_{(5)}$ and the double bond to the position 9(10). Isomerisation of seco derivatives *I*— *V* gave 3,4-seco-1(10→5α)-abeo derivatives *VII*—*XI*, *XIX*, and *XX*, the structure and the stereochemistry of which was inferred by their transformation to unsaturated ketone *XIII*, diene *XIV*, and diphenyl derivative *XVI*, and also from their infrared, ultraviolet, and PMR spectra. The stable intermediate *XVII* was isolated and the mechanism of the rearrangement is discussed on the basis of its structure.

Triterpenic 3,4-seco-3-acids, common in nature, may be prepared by Beckmann rearrangement of 3-oximino derivatives and subsequent hydrolysis of the formed 3,4-seco-3-nitriles in basic medium (see[1] and the references therein). During an attempt in acid catalysed hydrolysis of the nitrile group of these 3,4-seco derivatives we observed that other acids are formed than in the case of alkaline hydrolysis. As according to preliminary tests it could be expected that acid catalysed hydrolysis is connected with a skeletal change, we investigated this reaction more closely. For this study a series of derivatives was chosen (*I*—*IV*) which are derived from 2,4-seco-19β,28-epoxy-18α-olean-4(23)-ene and which differ in the functional group in the position 3. Compounds *I*—*III* were prepared from allobetulonoxime in the described manner[2,3], while hydroxy derivative *IV* was obtained on reduction of methyl ester *III* with lithium aluminum hydride. In order to check the general validity of the investigated rearrangement we also comprised in our study 3,4-seco derivative *V* derived from 20(29)-lupene skeleton[1].

Isomerisation was carried out by heating with 98% formic acid. As the saturated secoester *VI* remained unchanged under these conditions, except for the hydrolysis of the ester group, the isomerisation is enabled by the presence of the double bond

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4(23). From the unsaturated nitrile *I* a mixture was obtained on reaction with formic acid, from which isomeric nitrile *VII* and products of its hydrolysis, amide *VIII* and acid *IX*, were isolated in addition to nitrile *I*. On alkaline hydrolysis of nitrile *VII* and amide *VIII* the acid *IX* was also formed, characterised as methyl ester *X*. Methyl ester *X* was obtained as the main product on isomerisation of ester *III* with formic acid or with a solution of *p*-toluene sulfonic acid in acetic acid and subsequent esterification with diazomethane. Similarly, from acid *II* isomeric acid *IX* was obtained on reaction with formic acid. The yields of these isomeric derivatives range between 55 and 75 percent; during the isomerisation small amounts of other products are formed (see below). After isomerisation of hydroxy derivative *IV* with formic acid and hydrolysis of formates the formed hydroxy derivative *XI* was isolated in 26% yield, identical with a sample prepared by reduction of methyl ester *X* with lithium aluminium hydride. In this case isomerisation was accompanied by the formation of a larger amount (43%) of polar by-products which could not be separated preparatively and identified. However, it was shown that these products are formed under the same conditions from the isomeric hydroxy derivative *XI*. Hence, it can be assumed that the rearrangement is dependent only on the presence of the double bond 4(23), that it is independent of the type of substitution in the position 3, and that the low yield of the isomeric hydroxy derivative *XI* is caused by subsequent reactions with formic acid.

From the comparison of physical properties of starting (*I*–*IV*) and isomeric (*VII*–*XI*) 3,4-seco derivatives it follows that the rearrangement is accompanied by a large shift of optical rotation to negative values ($\Delta[\Phi]_D = -533 \pm 11°$) and by the disappearance of the absorption of the terminal double bond in the infrared region. From the PMR spectra of derivatives *VII* and *IX*–*XI* (see Table I) it is evident that the double bond must be tetrasubstituted, and that one of the substituents is a methyl group (singlet ~1·50 p.p.m.). Other typical signals are due to six methyl groups of which two give doublets ($J = 6{\cdot}5-7$ Hz). In the case of nitrile *VII* it was shown by Indor experiment[4] that these doublets belong to the methyl groups of the isopropyl residue and that the methine hydrogen of the latter gives a septet. From this it follows that the isopropyl group is bound to a quaternary carbon. As derivatives *VII* and *IX*–*XI* have also preserved spectral characteristics for the 19β,28-epoxy group (singlet 19α H and the AB system of the $C_{(28)}$ H_2-group in the PMR spectra, and C—O—C frequency about 1033 cm^{-1} in the IR spectra), the data published for allobetuline derivatives[5] were used for the assignment of the other two methyl signals (0·82 and 0·94 p.p.m.); they were assigned to methyl groups at $C_{(20)}$. The remaining two signals of the methyl groups will be discussed later. From the agreement of the mentioned data between allobetuline derivatives[5], starting seco derivatives *I*, *III*, and *VI*, and the rearranged derivatives *VII*, *IX*–*XI* (Table I) it follows that the structural change taking place during the isomerisation does not extend to the proximity of the ring E. The PMR spectra of nitrile *VII*, acid *IX*, and

TABLE I

Characteristic Parameters of the PMR Spectra

Measured in deuteriochloroform, tetramethylsilane as internal standard, Varian HA-100, chemical shifts in the δ-scale, values given in parentheses are assigned tentatively and may be changed.

Compound	$COOCH_3$	$C_{(4)}(CH_3)_2$[a]		$C_{(10)}CH_3$	8β-CH_3
		Compounds with the original skeleton			
I[c]	—	—	—	(0·87)	(1·035)
III[c]	3·65	—	—	(0·85)	(1·025)
VI[c]	3·68	0·79	0·89	(0·835)	(1·00)
XVII[d]	3·64	1·00	1·00	(0·865)	(0·93)
XXI[c,e]	—	—	—	—	0·99
XXII[c,e]	—	—	—	—	0·91
		1(10 → 5α)-Abeo derivatives			
VII	—	0·67	0·85	1·51	1·08
IX	—	0·66	0·84	1·50	1·08
X	3·64	0·66	0·84	1·505	1·075
XI	—	0·66	0·84	1·49	1·085
XII	3·66	0·855	0·93	1·27	(1·055)
XIII	3·655	0·77	0·90	1·71	1·075
XIV[d]	3·64	0·72	0·89	1·625	(0·985)
XV[g]	—	0·61	0·73	1·38	1·08
XVI[d,g]	—	0·66	0·73	1·57	1·07
XIX[d]	3·64	0·66	0·85	1·51	1·095
XX	3·64	0·65	0·84	1·49	1·01

ester *X* contain further a complex multiplet of 3 to 4 protons in the 2·2–2·6 p.p.m. region which corresponds to hydrogens in the α-position to the corresponding functional group (CN, COOR) and the double bond.

The double bond of ester *X* is not split by ozonolysis to volatile fragments and, therefore, it must be a part of the cycle. It is sterically hindered, because ester *X* does not undergo hydrogenation under conventional conditions (Adams catalyst in acetic acid) and it reacts with perbenzoic acid very slowly under formation of epoxide *XII*. From the PMR spectra of epoxide *XII* it is evident that the transformation of the

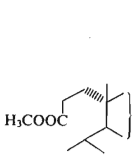
TABLE I
(*Continued*)

14α-CH_3	$C_{(20)}(CH_3)_2$		19α-H	$C_{(28)}H_2$[h]	
(0·935)	0·81	0·935	3·54	3·45	3·79
(0·94)	0·80	0·94	3·52	3·43	3·78
(0·92)	0·81	0·94	3·55	3·44	3·79
(0·93)	0·79	0·93	3·53	3·45	3·78
0·93	0·80	0·93	3·50	3·44	3·80
0·875[f]	0·95	1·025[f]	—	—	—
0·82	0·82	0·965	3·55	3·47	3·82
0·835	0·81	0·95	3·58	3·47	3·85
0·835	0·805	0·945	3·56	3·47	3·84
0·835	0·81	0·95	3·57	3·46	3·84
(1·01)	0·82	0·95	3·57	3·46	3·81
0·975	0·805	0·945	3·49	3·49	3·78
(0·74)	(0·865)	(0·915)	3·70	3·52	3·87
0·87	0·825	0·95	3·54	3·45	3·82
0·605	0·825	0·96	3·55	3·45	3·82
0·835	—	—	—	—	—
0·79	0·965	1·045	3·96	—	—

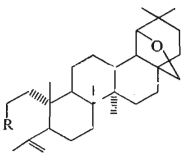
[a]Two doublets, $J = 6·5 - 7$ Hz; [b]two doublets, $J = 8$ Hz; [c]measured by Dr J. M. Lehn on a Varian HR-60 apparatus; [d]for other signals see text; [e]these values are taken from paper[5]; [f]in paper[5] these two signals are assigned in the opposite manner; the correction was made on the basis of the spectrum of compound *XX* (absence of signal in the 0·88—0·90 p.p.m. region); [g]aromatic hydrogens: 7·1—7·5 p.p.m. (10 H).

double bond to the epoxy group strongly affects the shift of isopropyl methyls (downfield shift), from which it follows that the isopropyl chain is near to the double bond. From the reaction mixture after oxidation of ester *X* with chromium trioxide the α,β-unsaturated ketone *XIII* was isolated as the main product, the spectral characteristics of which show that it has a fixed s-*cis* form with the carbonyl group in a six-membered ring[6-8].

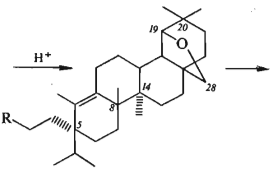
The mentioned characteristics are the low intensity of the $\pi \rightarrow \pi^*$ transition in the UV spectrum (ethanol, λ_{max} 258 nm, ε 8000) and the high difference in frequencies of the carbonyl and the



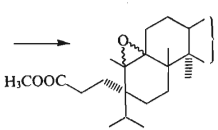
VI



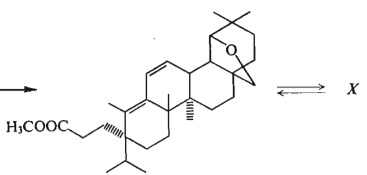
I, R = CN
II, R = COOH
III, R = $COOCH_3$
IV, R = CH_2OH



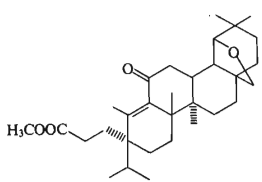
VII, R = CN
VIII, R = $CONH_2$
IX, R = COOH
X, R = $COOCH_3$
XI, R = CH_2OH
XV, R = $C(OH)(C_6H_5)_2$



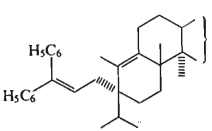
XII



XIV



XIII



XVI

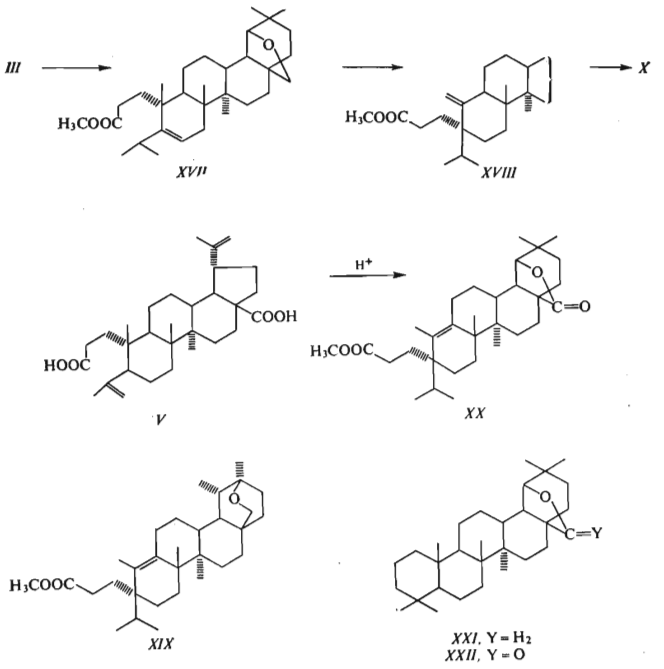
double bond in the IR spectrum ($\Delta\nu = 81\ cm^{-1}$), and the low ratio of the intensities of these bands ($r^B = 2{\cdot}7$) (see[6,8]). For ketone *XIII* in tetrachloromethane it was found: ν(C=O) 1 750 (ester), 1 687 (ketone), ν(C=C) 1 606 cm^{-1}. The band separation was carried out with a computer using the method of non-linear damped least squares[9]; $r^B = B_{(C=O)}/B_{(C=C)}$, $B = \varepsilon^{(a)} \cdot \Delta\nu_{1/2}^{(a)} \cdot \pi/2$ (see[10]).

As the unsaturated ketone *XIII* has according to its IR spectrum a methylene group in the neighbourhood of the carbonyl group, the starting ester *X* must contain the grouping $CH_3—C=C—CH_2—CH_2—$. On dehydrogenation of ester *X* with selenium dioxide diene *XIV* was prepared which was also obtained from epoxide *XII*

by reaction with hydrochloric acid. Diene *XIV*, prepared by dehydrogenation, displayed in addition to the absorption in the UV region mentioned below also additional weak absorption bands 284, 298 and 308 nm which are caused by a small content of impurities (<5%). It is probably a triene with an additional double bond in the position 13(18); an attempt to prepare it by a prolongation of the reaction time of dehydrogenation was not successful. In order to exclude the possibility of a further change of skeleton, taking place under the effect of acid medium during the preparation of diene *XIV*, we carried out its catalytic hydrogenation. As the formed dihydro derivative was identical with the starting ester *X*, the diene *XIV* must also have the same skeleton. Its absorption in the UV region (λ_{max} 245, 251, and 261 nm, log ε 4·37, 4·39, and 4·21) is characteristic of heteroanular conjugated dienes; in its position and intensity it agrees with the absorption of derivatives of 15,17(21)-hopadiene[11] (λ_{max} 245, 252, 261 nm, log ε 4·29, 4·35, 4·18). From this it can be concluded that the new double bond in diene *XIV* is in the position 11(12) and the original double bond in the position 9(10). This assumption is supported by the PMR spectrum of diene *XIV* which contains signals of two olefinic protons; both are split in a manner corresponding to a *cis*-disubstituted double bond in a six-membered ring (J = 10 Hz); one of them ($H_{(12)}$, 6·34 p.p.m.) shows an additional coupling with the neighbouring hydrogen (J_{vic} = 2·7 Hz), while the second ($H_{(11)}$, 5·45 p.p.m.) shows an allylic coupling with the same hydrogen (J_{allyl} = 1·5 Hz). The assignment of both signals was carried out by double resonance method, based on the weak long-range coupling of $H_{(11)}$ with the methyl group on the double bond, which is reflected only by a broadening of the lines. This characteristic is in full agreement with the double bond 11(12), because according to the model the neighbouring hydrogen (13β) holds an angle close to 90°C with the plane of the double bond. Identical values of chemical shifts and coupling constants were found[12] for hydrogen in the positions 11 and 12 in derivatives of 11,13(18)-oleanadiene. As an additional evidence of the position of the 11(12) double bond the downfield shift (+0·14 p.p.m.) of the 19α-H signal may be considered when compared with ester *X*. According to the molecular model this hydrogen is in diene *XIV* almost in the plane of the 11(12) double bond and it is therefore deshielded by this double bond. A weaker deshielding effect is also evident in both protons of the $C_{(28)}H_2$ group which also lie close to the plane of the double bond.

On the basis of the above mentioned data the localisation of the double bond in the position 9(10) in ester *X* may be considered as proven. In order to obtain information on the side chain, ester *X* was converted on reaction with phenylmagnesium bromide to diphenylhydroxy derivative *XV*, the dehydration of which in benzene (catalysis with iodine) gave diphenyldiene *XVI*. Its absorption in the UV region (λ_{max} 257 nm, log ε 4·18) corresponds to the chromophore $(C_6H_5)_2C{=}CH{-}$ (see[13,14]) with which the double bond 9(10) is not conjugated. The PMR spectrum of diphenyldiene *XVI* contains signals of the olefinic proton and of two non-equivalent protons

of the α-methylene group which form an isolated ABX system (δ_A 2·41, δ_B 2·23, δ_X 6·28 p.p.m.; J_{AB} = 16; J_{AX} = 9·2; J_{BX} = 6·5 Hz). Hence, the side chain of ester *X* contains three carbon atoms and it is connected with a quaternary carbon. In accordance with this the isomerisation of the double bond 9(10) does not take place in diphenyldiene *XVI*, nor in acid medium (because diphenyldiene *XVI* was also obtained on dehydration of hydroxy derivative *XV* by boiling with formic acid), nor in the presence of potassium tert-butoxide. According to the UV spectra in both instances no conjugated derivatives are formed even in a small amount. From the comparison of the PMR spectra of diphenyldiene *XVI* and ester *X* it follows that the effect of the diphenylethylene group is evident from a downfield shift of the methyl on the double bond (+0·06 p.p.m.), further by an upfield shift of one of the isopropyl group doublets (−0·11 p.p.m.), and mainly by a distinct upfield shift of the 14α-methyl



signal (−0·23 p.p.m.). From the molecular model it is evident that such an effect of the anisotropy of the diphenylethylene residue is possible only if the side chain has an α-configuration.

From all the mentioned facts it follows that structure *X* is fully satisfactory for the isomeric ester. The skeletal change during the isomerisation consists in the migration of the side chain from $C_{(10)}$ to $C_{(5)}$ under formation of 1(10 → 5α)-abeo-3,4-seco derivatives. Such a reaction course is surprising and it has not as yet been observed either in 3,4-seco derivatives, or in corresponding compounds with a closed ring A, which have the usual stereochemistry. It is possible that this is a consequence of the changed geometry of 3,4-seco derivatives, because in presently known cases[15,16] of steroidal and triterpenoidal compounds the electronic deficit created on elimination of the 5α-substituent is compensated by the migration of the antiperiplanar β-methyl group from $C_{(10)}$. Only in the case of 5α-hydroxy-9β-steroids which, however, have *cis*-connected B and C rings a migration of the 10α-substituent (*i.e.* $C_{(1)}$ to $C_{(5)}$) was observed during the elimination of the 5α-hydroxy group[17]. The formation of 3,4-seco-1(10→5α)-abeo derivatives *VII*−*XI* is evidently the result of a more complex transformation, and therefore we tried to prove some of the intermediates of this isomerisation.

On isomerisation of acid *II* with 5% sulfuric acid in acetic acid at room temperature a mixture of acids was formed from which 46% of ester *III* were isolated, having the original skeleton, further 14% of isomeric ester *X* and 18% of a new ester *XVII*. The presence of this ester was also demonstrated by thin-layer chromatography when the reaction was carried out with formic acid under mild conditions; when sulfuric acid, or formic acid was employed but under more drastic conditions, ester *XVII* could not be demonstrated. That it is an intermediary product of a rearrangement was proved by its isomerisation with boiling formic acid, leading to a sole product, ester *X*. From the IR and PMR spectra of ester *XVII* the unchanged arrangement of ring E is evident as well as the presence of a trisubstituted double bond in the neighbourhood of the methylene group (doublet of doublets at 5·62 p.p.m., $J_1 = 6{\cdot}4$ Hz, $J_2 = 2$ Hz), and of seven methyl groups of which none is on a double bond. Since both methyl groups of the isopropyl residue had the same chemical shift even when measured in different solvents, the proof of the isopropyl group was carried out by an Indor experiment. The position of the signal of the methyl groups (a six-proton doublet 1·00 p.p.m., $J = 6{\cdot}5$ Hz) and the shape of the signal of the methine hydrogen (a septet with a weak allylic coupling with the olefinic hydrogen, demonstrated by double resonance) show that the isopropyl group is bound to a double bond. Hence, this ester must have the structure *XVII*. An attempt at chemical proof of the structure by transforming it to the known ester *VI* by hydrogenation was unsuccessful. Its 5(6) double bond is evidently sterically hindered both by the isopropyl group, and by the side chain on $C_{(10)}$ and by methyl groups on $C_{(8)}$ and $C_{(10)}$. With perbenzoic acid ester *XVII* reacts under formation of a mixture of epoxides, which we were unable to separate.

Making use of intermediate *XVII* the total course of the rearrangement of 3,4-seco derivatives *I*−*IV* may now be explained in the following manner: After protonation of the double bond 4(23) either 5α-hydrogen is eliminated under formation of the exocyclic double bond 4(5) which is further isomerised to the 5(6) double bond, or this process takes place by direct 1,2-shift of the 5α-hydrogen to $C_{(4)}$ and elimination of the

axial 6β-hydrogen which is in *anti*-periplanar position with respect to the 5α-hydrogen. The intermediate *XVII* is formed in which the α-chain migrates from $C_{(10)}$ to $C_{(5)}$ after the protonation of the double bond. It is possible that at this stage the reaction takes place *via* the boat transition state of the ring B, which in contrast to the chair conformation does not have a disadvantageous synaxial interaction between 8β-, 10β-methyl groups. This boat conformation of the transition state also makes it possible to explain why it is α-substituent which migrates and not the 10β-methyl group. We consider that in a subsequent stage a direct elimination of the 9α-hydrogen which is *cis* with respect to the leaving group does not take place, but rather that the proton of the methyl group is eliminated under formation of a further intermediate *XVIII*. This derivative with an exocyclic double bond could not be proved in the reaction mixture, but according to an analogous case[18] it can be expected that under the conditions used it is immediately isomerised to a derivative with an endocyclic double bond 9(10), which is the final state proved in ester *X*. The formed 1(10 → 5α)-abeo-9-unsaturated system is evidently stable in acid medium. The same system is present in one of the side-products of isomerisation which was isolated in the form of methyl ester *XIX* (3%) after reaction of acid *II* or nitrile *I* with formic acid.

From the PMR spectra of this ester it is evident that in the arrangement of rings B, C, and D it does not differ from ester *X* (see Table I). Substantial differences are observable in signals which are due to substituents on the ring E. Such are primarily the doublet of the 19α-methyl (0·90 p.p.m., J = 7 Hz), singlet of the 20α-methyl (1·05 p.p.m.), and finally the AB system of protons of the $C_{(28)}H_2$ group, where both protons have long-range couplings (3·37 p.p.m., doublet of doublets, J_{gem} = 8·5 Hz, $J_{1,r.}$ = 1 Hz; 4·19 p.p.m. doublet of doublets, J_{gem} = 8·5 Hz, $J_{1,r.}$ = 2 Hz). Such characteristics were observed only in 20β,28-epoxytaraxastane derivatives[5], and therefore we assign this ester the structure *XIX*. In accordance with this is also the C—O—C vibration in the IR spectrum (1058 cm^{-1}) which is characteristic of six-membered ethers of this type[19]. The formation of derivative *XIX* is explicable by the migration of the ethereal bond from $C_{(19)}$ to $C_{(20)}$ under simultaneous migration of the 20α-methyl group to the position 19α. This acid-catalysed rearrangement was already observed in other derivatives of 19β,28-epoxy-18α-oleanane[20] as well.

Finally, isomerisation reaction was carried out with 3,4-seco-4-(23),20(29)-lupadiene-3,28-dioic acid (*V*). After esterification methyl ester was obtained which did not contain a terminal double bond, but a γ-lactone ring, as follows from the IR and PMR spectra (1772 cm^{-1}, 3·96 p.p.m., singlet, 19α-H). During the reaction the known[21] rearrangement took place followed by lactonisation in the ring E. From the PMR spectra (Table I) it is further evident that in this case rearrangement to 1(10 → 5α)-abeo derivative took place and that the obtained methyl ester must have the structure *XX*.

In the PMR spectra of the mentioned derivatives two signals of the methyl groups remain to be assigned (∼1·08 and ∼0·82 p.p.m.) which must correspond to 8β- and 14α-methyls, because they appear both in 19β,28-epoxy derivatives *VII*, *IX*—*XI*, and 20β,28-epoxy derivative *XIX*. On the basis of the effect of 28-oxo and 11-oxo group we propose the following assignment: 1·08 p.p.m. — 8β-CH_3, 0·82 p.p.m. — 14α-CH_3. From the comparison of the spectra of ether

XXI, lactone *XXII* (Table I) and other analogous derivatives mentioned in paper[5] it follows that the effect of the 28-oxo group is evident from the larger upfield shift of the 8β-methyl (−0·07 to −0·08 p.p.m.) than in the case of 14α-methyl (−0·04 to −0·06 p.p.m.). Comparable shifts were observed in lactone *XX* in comparison with ester *X* (8β: −0·065, 14α: −0·045 p.p.m.), which represents evidence for the proposed assignment. In agreement with this is also the downfield shift of the 14α-methyl in ketone *XIII* (+0·14 p.p.m. with respect to ester *X*), which is caused by the deshielding effect of the carbonyl group[22] in the position 11.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were measured in chloroform on an automatic polarimeter (ETL-NPL, Bendix Ericsson) with a ±1—2° error. The infrared spectra were measured using 5—8% solutions in chloroform, on spectrographs IKS-14 and model UPT ČSAV (Brno), the ultraviolet spectra on a Unicam SP-700 apparatus. Formic acid was 98%. For washing the extracts hydrochloric acid diluted in the 1 : 4 ratio was used, as well as a 5% sodium carbonate and a saturated sodium hydrogen carbonate solution. For chromatography neutral alumina (Reanal, act. II) and silica gel (Spolana) were employed. Samples for analysis were dried over phosphorus pentoxide at 100°C and 0·5—1 Torr for 8—16 hours.

Isomerisation of Nitrile *I*

A suspension of nitrile *I* (1·5 g, see[2]) in formic acid (50 ml) was refluxed for 13 hours. The formed solution was concentrated to one third of its volume, poured into water, and extracted with ether (100 ml). The extract was washed with sodium carbonate and 10% sodium hydroxide solutions. Crystalline sodium salt of acid *IX* separated which was filtered off and dissolved in warm ethanol. The solution was acidified with hydrochloric acid, and the separated acid *IX* (40 mg) was filtered off under suction, dried, and esterified with diazomethane in ether. The obtained methyl ester *X* had m.p. 144·5—146°C (methanol) undepressed on admixture of the sample mentioned below. The neutral ethereal fraction was washed with hydrochloric acid and water and dried over sodium sulfate. Ether was distilled off and the residue dissolved in benzene and chromatographed on alumina (30 g). Benzene (150 ml) eluted nitrile *VII* (0·39 g), m.p. 204—205°C (ethanol); $[\alpha]_D$ −56° (*c* 0·5). IR spectrum: 2260 (CN), 1421(α-CH_2), 1034 cm^{-1} (C—O—C). For $C_{30}H_{47}NO$ (437·7) calculated: 82·32% C, 10·82% H, 3·20% N; found: 82·18% C, 10·71% H, 3·19% N. With further 150 ml of benzene a mixture of nitriles *I* and *VII* (0·10 g) was eluted from which crystallisation from methanol gave nitrile *I* of m.p. 264—266°C. With a benzene–ether mixture (1 : 1, 300 ml) and pure ether (100 ml) an amorphous fraction (0·22 g) was eluted which was not identified. Chloroform (150 ml) eluted an amorphous product which was dissolved in methanol and filtered through a column of charcoal. On evaporation of methanol non-crystalline amide *VIII* (0·42 g) was obtained. IR spectrum: 3500, 3400, 3200, 1677, 1588 ($CONH_2$), 1033 cm^{-1} (C—O—C).

Hydrolysis of amide VIII: To a solution of amide *VIII* (0·33 g) in ethanol (5 ml) ethylene glycol (20 ml) and sodium hydroxide (2 g) were added, ethanol was evaporated, and the mixture was refluxed for 3·5 hours. It was then diluted with water and the separated salt was filtered off, washed with water and suspended in ether. The ethereal solution was washed with hydrochloric acid and water, and dried over sodium sulfate. After evaporation of ether the crude acid *IX* was methylated with diazomethane, the ester was dissolved in benzene, and chromatographed on alumina (30 g). Elution with benzene (120 ml) gave 0·16 g of methyl ester *X*, m.p. 146—147°C (methanol); $[\alpha]_D$ −52° (*c* 0·5). A mixture with a sample described below melted undepressed. For $C_{31}H_{50}O_3$ (470·7) calculated: 79·10% C, 10·71% H; found: 78·96% C, 10·80% H.

Hydrolysis of nitrile VII: A mixture of nitrile *VII* (80 mg), sodium hydroxide (1 g), and ethylene glycol (10 ml) was refluxed for 3 hours. After working up as described above ester *X* was obtained (71 mg), melting at 145—147°C (methanol).

Isomerisation of Methyl Ester *III*

a) *With formic acid*: A mixture of methyl ester *III* (0·50 g) and formic acid (20 ml) was refluxed for 8 hours, then diluted with water and extracted with ether. The ethereal extract was washed with a solution of sodium hydrogen carbonate and water and dried over sodium sulfate. The product was esterified with diazomethane, ether was distilled off and the residue was adsorbed from benzene solution on alumina (40 g). Elution with benzene (140 ml) gave ester *X* (0·33 g), m.p. 146–147°C (methanol); $[\alpha]_D$ −56° (*c* 1·2). IR spectrum: 1737, 1446, 1181 ($COOCH_3$), 1033 cm^{-1} (C—O—C). For $C_{31}H_{50}O_3$ (470·7) calculated: 79·10% C, 10·71% H; found: 78·83% C, 10·63% H. Under identical conditions the saturated methyl ester *VI* did not isomerise and after esterification it was regenerated quantitatively unchanged.

b) *With p-toluenesulfonic acid*: A solution of methyl ester *III* (0·36 g) and monohydrate of *p*-toluenesulfonic acid (0·36 g) in acetic acid (10 ml) was refluxed for 10 hours. After working up as under *a*) methyl ester *X* was obtained (0·27 g), m.p. 144–146°C (methanol); $[\alpha]_D$ −56° (*c* 1·3). A mixture with the sample prepared as under *a*) melted undepressed. Ester *X* gives a yellow coloration with tetranitromethane. After ozonisation of ester *X* (in a mixture of chloroform and ethyl acetate 3 : 7 at −75°C) and the decomposition of the ozonide with zinc in acetic acid no volatile fraction was obtained which would react with 2,4-dinitrophenylhydrazine. According to thin-layer chromatography the non-volatile fraction was a mixture of several substances which were not identified.

Isomerisation of Acid *II*

a) *With formic acid*: A mixture of acid *II* (3·62 g) and formic acid (65 ml) was refluxed for 4 hours and then concentrated under reduced pressure. The residue was diluted with methanol and the separated crystals were filtered off with suction, washed with methanol and crystallised from benzene and a mixture of chloroform and methanol. Yield 1·66 g of acid *IX*, m.p. 281–283°C; $[\alpha]_D$ −57° (*c* 0·6). IR spectrum: 3200–2500, 1706, 1415 (COOH), 1031 cm^{-1} (C—O—C). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·89% C, 10·59% H; found: 79·10% C, 10·86% H. The mother liquors after the isolation of acid *IX* were esterified with diazomethane, the product was dissolved in light petroleum and chromatographed on alumina (60 g). Elution with a mixture of light petroleum and benzene (9 : 1, 400 ml) gave 0·60 g of ester *X*; further 400 ml of the same mixture eluted methyl ester *XIX* (0·10 g), m.p. 144·5–145°C (methanol); $[\alpha]_D$ −81° (*c* 0·7). IR spectrum: 1730, 1442, 1181 ($COOCH_3$), 1058 cm^{-1} (C—O—C). For $C_{31}H_{50}O_3$ (470·7) calculated: 79·10% C, 10·71% H; found: 79·33% C, 10·99% H. Ester *XIX* was obtained in the same manner in a low yield from the products of the rearrangement of nitrile *I* with formic acid, after hydrolysis and esterification. When an attempt was made at isomerisation of acid *II* with formic acid at room temperature for 4 days, or in a mixture of chloroform and formic acid (10 : 1) at boiling point for 30 minutes, only methyl ester *III* was obtained after esterification. Heating of acid *II* (0·19) in formic acid (10 ml) on a boiling water bath for 30 minutes, esterification, and chromatography, gave esters *X* (0·10 g) and *III* (60 mg). The intermediary product *XVII* was found in traces in one of the chromatographic fractions.

b) *With sulfuric acid in acetic acid*: Acid *II* (0·50 g) was dissolved in warm acetic acid (50 ml). After cooling sulfuric acid (2·5 ml) was added dropwise and under cooling and the mixture was allowed to stand at room temperature for 20 days. After the conventional work-up and esterification with diazomethane the product was chromatographed from benzene on alumina (200 g). Benzene (90 ml) eluted ester *X* (70 mg), m.p. 146–147°C (methanol). Further 50 ml of benzene eluted methyl ester *XVII* (90 mg), m.p. 192–193°C (methanol); $[\alpha]_D$ +49° (*c* 0·3). IR spectrum: 1737, 1445, 1177 ($COOCH_3$), 1033 cm^{-1} (C—O—C). For $C_{31}H_{50}O_3$ (470·7) calculated:

79·10% C, 10·71% H; found: 79·18% C, 10·77% H. Elution with additional 500 ml of benzene gave ester *III* (0·23 g) which after crystallisation from methanol gave two crystal modifications, m.p. 146–147°C and 157–158°C (see[2]). If acid *II* (0·20 g) was allowed to stand in the presence of sulfuric acid (9 ml) and acetic acid (50 ml) for 31 hours at room temperature, methyl ester *X* (0·10 g) could be obtained in the same manner as above; esters *II* and *XVII* were not found in the mixture. On reaction of acid *II* (100 mg) with sulfuric acid (0·8 ml) in acetic acid (11 ml) at 100°C for 1·5 hours ester *X* (40 mg), m.p. 143–145°C, was obtained exclusively, $[\alpha]_D$ −56° (*c* 0·7).

Hydroxy Derivative *IV*

Methyl ester *III* (0·75) was reduced with excess lithium aluminum hydride in ether (50 ml) under 7 hours reflux. Ethyl acetate and water were added and the ethereal layer was washed with hydrochloric acid, sodium carbonate solution, and water, and dried over sodium sulfate. Ether was distilled off and the residue dissolved in benzene and chromatographed on alumina (40 g). Elution with benzene (900 ml) and crystallisation from cyclohexane afforded hydroxy derivative *IV* (0·50 g), m. p. 194–196°C; $[\alpha]_D$ +75° (*c* 2·0). IR spectrum: 3 630 (OH), 1 640, 902 (C=CH_2), 1 039 (C—O—C) cm^{-1}. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·39% C, 11·53% H.

Hydroxy Derivative *XI*

Ester *X* (0·60 g) was reduced with lithium aluminum hydride in ether (100 ml) in the same manner as above. After chromatography on alumina (30 g, elution with benzene) dimorphous hydroxy derivative *XI* (0·45 g) was obtained which after crystallisation from methanol had m.p. 168 to 170°C and, after solidification, 184–188°C. After crystallisation from cyclohexane, m.p. 187 to 188°C; $[\alpha]_D$ −45° (*c* 2·8). IR spectrum: 3631, 3440 (OH), 1036 cm^{-1} (C—O—C). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·35% C, 11·48% H.

Isomerisation of Hydroxy Derivative *IV*

A solution of hydroxy derivative *IV* (0·35 g) in formic acid (10 ml) was refluxed for 7 hours, diluted with water, and extracted with chloroform. The extract was washed with water, sodium carbonate solution, and water, and then dried over sodium sulfate. Chloroform was distilled off and the residue dissolved in methanol (15 ml). Potassium hydroxide (0·70 g) was added to the solution and the mixture was boiled for 2 hours. After dilution with water it was extracted with chloroform and the extract washed with water and dried over sodium sulfate. After filtration and evaporation of the solvent the residue was chromatographed on alumina (30 g) with benzene as eluent. Hydroxy derivative *XI* was eluted with 125 ml of benzene, yield 90 mg, m.p. 185–187°C (n-hexane); $[\alpha]_D$ −44° (*c* 0·9). In admixture with the sample described above it melted undepressed. Elution with ether (50 ml) gave a mixture of two substances (150 mg) which differ only negligibly on chromatography on a thin-layer of silica gel. IR spectrum: 3640, 3440 (OH), 1039 cm^{-1} (C—O—C). We were unable to separate these substances or obtain them in pure state. Acetylation (acetic anhydride, pyridine, room temperature) gave an amorphous mixture of acetates which also were unseparable either by chromatography or crystallisation. IR spectrum: 1725, 1367, 1253 (CH_3COO), 1033 cm^{-1} (C—O—C). Heating of hydroxy derivative *XI* (120 mg) in formic acid (5 ml) under identical conditions as above gave in addition to derivative *XI* also the mixture of the mentioned two substances (35 mg). Its IR spectrum was identical with that of the above described mixture.

Epoxide *XII*

To a solution of ester *X* (0·17 g) in chloroform (5 ml) perbenzoic acid (0·15 g) in chloroform (3 ml) was added at 0°C and the mixture allowed to stand at 0°C. The reaction course was followed by thin-layer chromatography on silica gel. After two days standing the mixture still contained approximately a half of the unreacted material, while after 6 days only traces of that material could be found. The reference 19β,28-epoxy-18α-olean-2-ene reacted quantitatively within 24 hours. After 13 days the reaction mixture was worked up in the conventional manner. Crystallisation from ethanol gave epoxide *XII* (0·12 g), m.p. 161—162°C; $[\alpha]_D$ +6° (*c* 0·7). IR spectrum: 1730, 1437, 1174 ($COOCH_3$), 1031 cm^{-1} (C—O—C). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·23% C, 10·37% H.

Unsaturated Ketone *XIII*

Ester *X* (0·50 g) was dissolved in warm acetic acid (50 ml). After cooling to 25°C a solution of chromium trioxide (0·40 g) in a mixture of water (0·5 ml) and acetic acid (20 ml) was added to it and the mixture was allowed to stand at room temperature for 24 hours. Methanol was then added and the mixture was diluted with water and extracted with ether. The extract was washed with water, sodium hydrogen carbonate solution, and water, and then dried over sodium sulfate. After evaporation of ether the residue (0·45 g) was chromatographed on alumina (40 g) with benzene. A small amount of ester *X* was eluted first, followed by epoxide *XII*, an unidentified substance, and eventually ketone *XIII* (0·18 g), m.p. 139—141°C (dilute methanol); $[\alpha]_D$ −91° (*c* 0·6). IR spectrum: 1738, 1447, 1186, 1154 ($COOCH_3$), 1032 (C—O—C) 1683, 1605 (C=C—C=O), 1425 cm^{-1} (α-CH_2). UV spectrum (ethanol): λ_{max} 258 nm (log ε 3·90). For $C_{31}H_{48}O_4$ (484·7) calculated: 76·81% C, 9·98% H; found: 76·45% C, 9·88% H. Ketone *XIII* was regenerated after an attempt at reduction with sodium borohydride (benzene–methanol, 24 hours).

Diene *XIV*

a) A mixture of epoxide *XII* (80 mg), methanol (10 ml), and conc. hydrochloric acid (1 ml) was refluxed for 1 hour, until the epoxide passed into solution. Water was added and the mixture extracted with ether. The extract was washed with sodium hydrogen carbonate solution and water, and dried over sodium sulfate. Ether was distilled off and the residue dissolved in benzene and filtered through alumina (10 g). Benzene (20 ml) eluted diene *XIV* (60 mg), m.p. 146—147°C (methanol); $[\alpha]_D$ −60° (*c* 0·7). IR spectrum: 1735, 1444, 1180 ($COOCH_3$), 1628, 1607 (C=C—C=C), 1032 cm^{-1} (C—O—C). UV spectrum (cyclohexane): λ_{max} 245 (inflexion), 251, 261 nm (inflexion) (log ε 4·37, 4·39, 4·21). For $C_{31}H_{48}O_3$ (468·7) calculated: 79·43% C, 10·32% H; found: 79·41% C, 10·55% H. With tetranitromethane it gives a brown-red coloration.

b) A solution of ester *X* (0·25 g) and selenium dioxide (0·25) in acetic acid (20 ml) was refluxed for 3 hours. After cooling ether was added and the solution was decanted from the precipitated selenium, and then washed with water, sodium hydrogen carbonate solution, and water, and dried over sodium sulfate. Ether was distilled off and the residue dissolved in benzene and filtered through alumina (25 g). On elution with benzene a fraction (0·20 g) containing derivatives *X* and *XIV* was separated from more polar components and the residue of selenium. This fraction was dissolved in n-hexane and chromatographed on silica gel containing 5% silver nitrate (20 g). Elution with n-hexane–ether mixture (9 : 1, 40 ml) gave ester *X* (140 mg), m.p. 144—145°C. Additional 80 ml of the same solvent mixture eluted diene *XIV* (50 mg), m.p. 146—147°C (methanol). In admixture with the sample described under *a*) it melted undepressed. IR spectra of both samples were identical. UV spectrum (cyclohexane): λ_{max} 245 (inflexion), 251, 261 nm (inflexion) (log ε 4·32, 4·34, 4·16) and 284, 298, 308 nm (log ε 3·01, 3·08, 3·01). When the reaction time was prolonged to 11 hours, both ester *X* and diene *XIV* disappeared from the mixture and more

polar products were formed, which could not be obtained in a pure state and identified.

Hydrogenation: Diene *XIV* (40 mg) in acetic acid (25 ml) was hydrogenated by shaking the mixture with hydrogen in the presence of platinum oxide according to Adams (100 mg) for 3 hours. After the conventional working up ester *X* was obtained as the sole product, m.p. 144—146°C (methanol); $[\alpha]_D$ —56° (*c* 0·7). The identity with an authentic sample was confirmed on the basis of mixed melting point and IR spectra.

Diphenylhydroxy Derivative *XV*

A solution of ester *X* (1·38 g) in benzene (50 ml) was added to a solution of phenylmagnesium bromide prepared from magnesium (2 g) and bromobenzene (7 ml) in ether (50 ml). The solvents were partly distilled off (up to b.p. 62°C), and the residue was refluxed for 6·5 hours. Ammonium chloride solution was added and the organic phase was washed with hydrochloric acid, a sodium carbonate solution, and water, and dried over sodium sulfate. The solvents were distilled off under reduced pressure and the residue was adsorbed on alumina (80 g) from benzene solution. Elution with benzene gave first diphenyl, then derivative *XV* (1·30 g) which after crystallisation from a chloroform–n-hexane mixture weighed 1·09 g and melted at 103—106°C; $[\alpha]_D$ —43° (*c* 2·3). IR spectrum: 3610 (OH), 1607, 1498 (aromatic character), 1039 cm^{-1} (C—O—C). UV spectrum (cyclohexane): λ_{max} 254 nm (log ε 3·07). For $C_{42}H_{58}O_2$ (594·9) calculated: 84·79% C, 9·83% H; found: 84·50% C, 9·93% H.

Diphenyldiene *XVI*

A solution of hydroxy derivative *XV* (0·35 g) and iodine (10 mg) in benzene (20 ml) was refluxed for 4 hours, then washed with a solution of sodium sulfite and water and dried by filtration through a layer of alumina. After evaporation of benzene the residue was dissolved in a mixture of light petroleum and benzene (1 : 1) and chromatographed on alumina (30 g). Elution with the same mixture gave an amorphous product (0·30 g) which was dissolved in a mixture of light petroleum–benzene (2 : 1) and rechromatographed on silica gel (20 g). Light petroleum–benzene mixture (1 : 1) eluted diene *XVI* (0·18 g) which would not crystallise, $[\alpha]_D$ —72° (*c* 0·9). IR spectrum: 1600, 1493 (aromatic character), 1032 cm^{-1} (C—O—C). UV spectrum (cyclohexane): λ_{max} 257 nm (log ε 4·18).

Attempts at dehydration of derivative *XV* by boiling in acetic anhydride or in a mixture of acetic anhydride and pyridine were unsuccessful. On dehydration of derivative *XV* (100 mg) in boiling formic acid (6 ml) for 3 hours 70 mg of diene *XVI* were obtained. IR and UV spectra were identical with those of the sample mentioned above. After the attempt at isomerisation of diene *XVI* with a 1M solution of potassium tert-butoxide in tert-butanol (3 hours reflux under nitrogen), the crude product had an UV spectrum identical with that of the starting derivative *XVI*.

Reaction of Methyl Ester *XVII*

a) *With formic acid*: A mixture of ester *XVII* (10 mg) and formic acid (3 ml) was refluxed for 5 hours. After the conventional work-up of the mixture, esterification with diazomethane, and chromatography on alumina (10 g, elution with benzene), ester *X* was obtained (6 mg), m.p. 144—146°C (methanol). According to its melting point, mixed melting point and chromatographic data (silica gel thin layer) it was identical with an authentic sample of *X*.

b) *With perbenzoic acid*: To a solution of ester *XVII* (30 mg) in chloroform (5 ml) a solution of perbenzoic acid (47 mg) in chloroform (1 ml) was added at 0°C. The mixture was allowed to stand at 0°C for 11 days and then worked up as in the case of epoxide *XII*. The residue was chromatographed from n-hexane on silica gel (7 g). Benzene–n-hexane mixture (1 : 1) eluted

a mixture of epoxides (15 mg), m.p. 138–152°C (methanol), which differ only negligibly in thin-layer chromatography on silica gel. For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·80% C, 10·50% H.

c) *Hydrogenation*: Ester *XVII* was isolated unchanged in experiments where hydrogenation was carried out in ethyl acetate, a mixture of ethyl acetate and acetic acid, or pure acetic acid, in the presence of platinum oxide according to Adams. Reaction times up to 30 hours were tested.

Isomerisation of Diacid *V*

A mixture of diacid *V* (0·21 g, see[1]) and formic acid (10 ml) was refluxed for 3 hours. After a conventional working up, esterification with diazomethane and chromatography on alumina (15 g, elution with benzene) lactone *XX* (0·1 g) was obtained, m.p. 137–139°C (aqueous methanol); $[\alpha]_D$ −42° (*c* 0·5). IR spectrum: 1738, 1443 ($COOCH_3$), 1772 cm^{-1} (lactone). For $C_{31}H_{48}O_4$ (484·7) calculated: 76·81% C, 9·98% H; found: 76·98% C, 10·23% H.

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