

OXIDATIVE CLEAVAGE OF 22-HYDROXYMETHYLENE-21-KETONES OF THE 20,28 β -EPOXY-18 α ,19 β H-URSANE SERIES*

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Received January 1st, 1975

The oxidative cleavage of triterpenic 22-hydroxymethylene-21-ketones with chromium trioxide in acetic acid was found to be the most suitable way for the preparation of 21,22-secodiacids of the 20 β ,28-epoxy-18 α ,19 β H-ursane series. In this manner a series of secodiacids and of their derivatives VIII—XV were prepared from compounds III—V. In the series of compounds I, IV, X, XI and XIII the long-range coupling and the geminal coupling constants in the fragment $\cdot C_{(28)}H_2-O-$ change characteristically in dependence on the structure of the E ring. On the basis of the long-range coupling the signals were assigned to the *exo* and *endo* protons of this group.

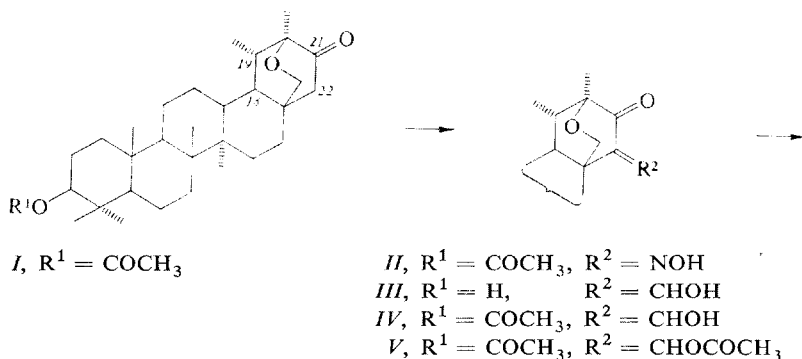
In connection with the recent finding (see^{1,2} and the references therein) that some steroidal and triterpenic carboxylic acids containing another oxygen function in the molecule possess antibacterial activity we investigated the possibility of the preparation of analogous acids by modifying the E ring in the derivatives of 18 α ,19 β H-ursane. The relatively easily accessible^{3,4} 21-oxo-20 β ,28-epoxy derivatives (for example I) represent a suitable starting material, because the $C_{(21)}-C_{(22)}$ bond in them can be cleaved selectively. Some 21,22-*seco* derivatives were prepared earlier⁵ by Beckmann rearrangement of oximino ketone II. The secodiacid VII which can be formed by oxidation of keto ether I with oxygen in alkaline medium was thus also obtained *via* nitrilic acid VI. However, as from the preparative point of view the Beckmann rearrangement of oximinoketone II is negatively affected by the presence of the epoxide ring⁵, in this paper we made use of the oxidative cleavage of 22-hydroxymethylene-21-oxo derivative III and its monoacetate IV and diacetate V for the preparation of E-*seco* derivatives.

The starting hydroxymethylene ketone III was prepared by condensation of keto ether I with ethyl formate under the effect of sodium hydride, and it was further converted to diacetate V with acetic anhydride in pyridine. The monoacetate IV was obtained on reaction of diacetate V with hydrochloric acid in acetone, during which a selective hydrolysis of the enolacetate group took place. The presence of the fragment $-CO-C=CH-OR$ in compounds III—V was confirmed by IR and UV

* Part XLIV in the series Triterpenes; Part XLIII: This Journal 40, 1758 (1975).

spectra and in the case of monoacetate *IV* also by the ^1H -NMR spectrum (the singlet of the olefinic proton at 7.10 p.p.m.).

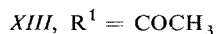
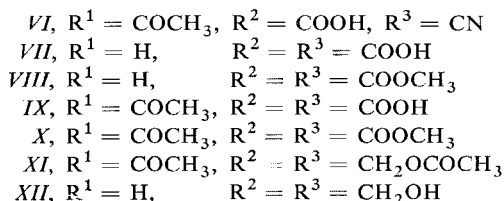
Hydroxymethylene ketone *III* was first oxidized with hydrogen peroxide in alkaline medium, which is a method often used for the preparation of steroidal and triterpenic secodioids⁶⁻⁹. As, however, this procedure gave a mixture of acids which were difficult to separate even after esterification and acetylation, we chose as another possibility for the preparation of E-seco derivatives the oxidation of hydroxymethylene ketone *III* or of its monoacetate *IV* with chromium trioxide in acetic acid. In contrast to oxidation with hydrogen peroxide this reaction gives seco derivatives in very good yields (80–90%). From hydroxymethylene ketone *III* 21,22-secodioid *XIV* was formed and from the monoacetate *IV* the analogous diacid *IX* was obtained which was isolated in the form of dimethyl ester *X*. 21,22-Secodioid *XIV* is formed as the main product even when diacetate *V* is oxidized with chromium trioxide in acetic acid, probably due to the easy hydrolysis of the enolacetate group; after oxidation at room temperature and subsequent reaction with diazomethane dimethylester *X* was isolated from the complex reaction mixture in about 25% yield; on oxidation at 80°C the yield was increased to 45%. However, the course of this reaction is always more complex than with derivatives with a non-acetylated hydroxymethylene group.



From the above results it follows that the oxidative cleavage of the $\text{O}=\text{C}-\text{C}=\text{CH}-\text{OH}$ group with chromium trioxide in acetic acid at room temperature represents the most advantageous way to the required secodioids. This procedure gives good yields under relatively mild reaction conditions in comparison with the methods which are currently used for the preparation of steroidal secoacids (see^{8,9} and the references therein).

The structure and the mutual relationships of seco derivatives obtained by oxidative cleavage of compounds *III*–*V* can be derived from the following reactions: Seco-

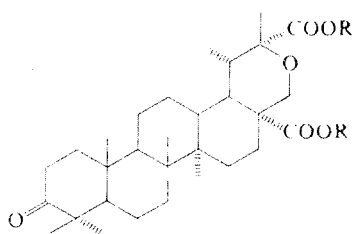
diacid *XIV* was converted with diazomethane to dimethyl ester *XV*. On reduction of the 3-oxo group of dimethyl ester *XV* with tritert-butoxy lithium aluminum hydride 3 β -hydroxy derivative *VIII* was prepared which was obtained earlier⁵ by another route. Acetylation of hydroxy derivative *VIII* gave acetyl derivative *X*, identical with the derivative obtained from the oxidative cleavage of hydroxymethylene ketones *IV* and *V*. Alkaline hydrolysis of the ester groups of compound *X* gave secodiacid *VII* which is converted even under mild acetylation conditions to anhydride⁵ *XIII*. An attempt at the preparation of monomethyl ester by methanolysis of anhydride



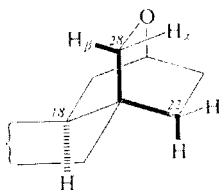
XIII led to a mixture of both monoesters which could not be separated; on reaction of this mixture with diazomethane dimethyl ester *X* was formed. For the comparison of spectral properties triacetate *XI* was prepared by reduction of anhydride *XIII* with lithium aluminum hydride and subsequent acetylation of the triol *XII* formed.

The oxidative cleavage of hydroxymethylene derivatives *III*–*V* is not accompanied by changes in their tetrahydropyran cycle, which is evident from the IR spectra of the secodiacid *XIV*. In addition to the absorption bands of the 3-oxo group and of the dimer of the carboxyl group in the position 17 strong bands at 3400 and 1780 cm⁻¹ are also present in this spectrum. These bands correspond to the carboxyl group bound by an intramolecular hydrogen bond to the ether oxygen in the position α (ref.^{5,10}) and therefore it can be assigned to the carboxyl group in the position 20. The effect of the vicinal alkoxy group also appears in the IR spectra of dimethyl esters *X* and *XV* in which the carbonyl frequency of the ester group in the position 20 is higher (1750 cm⁻¹) than that of the group in the position 17 (1730 cm⁻¹). In the ¹H—NMR spectra all signals characteristic of the tetrahydropyran ring of the 20 β ,28-epoxy-18 α ,19 β H-ursane derivatives are also present, *i.e.* the doublet of the 19 α -methyl group, the singlet of the 20 α -methyl group and two doublets of protons of the 28-methylene group.

As was observed earlier¹¹ in substances with the partial structure as in *XVI* the doublets of both protons of the $-\text{C}_{(28)}\text{H}_2-\text{O}-$ group are further split, due to the long-range coupling to the protons in the positions 18α and 22α . This splitting was observed also in all compounds^{4,12} of $20\beta,28\text{-epoxy-}18\alpha,19\beta\text{-H-ursane}$ type prepared later; in all instances a higher coupling constant ($J_{1,r.} = 2$ to 2.5 Hz) was observed for the downfield signal than for the upfield signal ($J_{1,r.} = 1$ to 1.5 Hz), but the assignment of these signals to single protons on $\text{C}_{(28)}$ is not yet possible. Hydroxymethylene derivative *IV* enables this assignment because it does not contain hydrogen atoms in the position 22; in its $^1\text{H-NMR}$ spectrum the splitting is evident only for the upfield signal ($J_{1,r.} \sim 1.5$ Hz), while the downfield signal appears as a sharp



XIV, R = H
XV, R = CH_3



XVI

doublet. Because this splitting is caused by the long-range coupling in the planar W-system formed by four single bonds¹³, the upfield signal may be assigned unambiguously to the 28α -proton which is coupled to $18\alpha\text{-H}$; the unsplit doublet at a lower field corresponds to the 28β -proton. The same character of the spectra also appears in the case of other compounds with the modified E ring, which do not have $22\alpha\text{-H}$ (ref.¹⁴). In all compounds of the mentioned type the hydrogen atom oriented to the molecule ($28\beta\text{-H}$) is shielded less in comparison with the hydrogen atom in the *exo*-position $28\alpha\text{-H}$). This assignment is also supported by the upfield shift (-0.18 p.p.m.) of the $28\alpha\text{-H}$ signal in hydroxymethylene derivative *IV* (in comparison with ketone *I*), which is caused by the anisotropy of the double bond in the position 22; the signal of the 28β -proton is affected much less (-0.05 p.p.m.). In contrast to the above mentioned compounds with a rigid oxabicyclo[2,2,2]octane system *XVI* long-range splitting is not evident for any of the $\text{C}_{(28)}\text{-H}_2$ signals in anhydride *XIII* and $21,22\text{-seco}$ derivatives *X* and *XI*. This may be due to the fact that the cleavage of the $\text{C}_{(21)}-\text{C}_{(22)}$ bond causes a change in the conformation of the ether ring and thus the loss of planarity of the W-system of bonds between $28\alpha\text{-H}$ and $18\alpha\text{-H}$.

The decreasing rigidity of the system and the corresponding change of geometry of the tetrahydropyran ring is also connected with the changes of the value of the

geminal coupling constant ($J_{28\alpha,28\beta}$), which is evident from the comparison of derivatives *I*, *IV*, *XIII*, *X* and *XI*. In compounds *I* and *IV* and in similar compounds with the partial structure *XVI* (see¹¹) in which a two-membered bridge formed by $C_{(21)}$ and $C_{(22)}$ is present the tetrahydropyran ring is rigid and lone pairs on the oxygen are eclipsed with both $C_{(28)}$ -H bonds. In these compounds the absolute value of J_{gem} is in the 8–9 Hz range. In anhydride *XIII*, where the bridge is three-membered ($C_{(21)}\text{O}-\text{O}-C_{(22)}\text{O}$), $|J|_{\text{gem}} = 11.5$ Hz and in 21,22-seco derivative *X* and *XI* it has a value of up to 13 Hz. The changes mentioned correspond¹⁵ to the dependence of J_{gem} on the ring size and especially to the mutual orientation of protons and lone pairs on the neighbouring oxygen atom.

From these results it follows that both the long-range coupling of the two protons, upfield and downfield, in the $-\text{CH}_2-\text{O}-$ group, and the magnitude of their geminal coupling constant can be very useful in the solving of structure with similar bridge systems.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured in chloroform on an automatic polarimeter ETL-NPL (Bendix-Ericsson) with a $\pm 1-3^\circ$ accuracy. The infrared spectra were measured in chloroform on a UR-20 (Zeiss, Jena) spectrophotometer, and the ultraviolet spectra in ethanol on a Unicam SP 700 spectrophotometer. The NMR spectra were measured in deuteriochloroform with tetramethylsilane as internal standard on a Varian HA-100 instrument. Samples for analysis were dried over phosphorus pentoxide at 100°C and 0.1–1 Torr for 8–20 hours.

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

A solution of keto ether *I* (0.9 g) in a mixture of benzene (25 ml) and ethyl formate (6.5 ml) was added dropwise to a suspension of sodium hydride (0.8 g) in benzene (20 ml) under nitrogen. The mixture was stirred for 14 hours at room temperature, decomposed with methanol and poured into water acidified with hydrochloric acid. The product was extracted with benzene, the benzene solution was washed with water, dried over sodium sulfate and distilled off. The hydroxymethylene-ketone *III* (0.82 g) obtained had m.p. $257-258^\circ\text{C}$ and after solidification $267-268^\circ\text{C}$ (chloroform–light petroleum), $[\alpha]_{\text{D}} + 107^\circ$ (*c* 0.71). IR spectrum: 3630, 3490 (broad), 1675, 1607 cm^{-1} . UV spectrum: λ_{max} 278 nm, $\log \epsilon$ 3.93. For $\text{C}_{31}\text{H}_{48}\text{O}_4$ (484.7) calculated: 76.81% C, 9.98% H; found: 76.60% C, 10.18% H.

Diacetate *V*: A solution of hydroxymethylene ketone *III* (0.9 g) in 20 ml of pyridine–acetic anhydride 1:1 mixture was allowed to stand at room temperature for 12 hours and then decomposed with ice. The precipitate was filtered off under suction, washed with water, dried in air, and recrystallized from a mixture of chloroform and light petroleum. Diacetate *V* (0.8 g) had m.p. $273-275^\circ\text{C}$ and after solidification $281-282^\circ\text{C}$ (under decomposition), $[\alpha]_{\text{D}} + 78^\circ$ (*c* 0.72). IR spectrum: 1785, 1730, 1638, 1260, 1030 cm^{-1} . For $\text{C}_{35}\text{H}_{52}\text{O}_6$ (568.7) calculated: 73.19% C, 9.22% H; found: 73.13% C, 9.44% H.

Monoacetate *IV*: A solution of diacetate *V* (0.25 g) in acetone (40 ml) containing a drop of 10% hydrochloric acid was allowed to stand at room temperature for 24 hours. The solvent was

partly evaporated under reduced pressure and the residue was diluted with water. The precipitate formed was filtered off and crystallized from chloroform–light petroleum. Monoacetate *IV* (0.24 g) had m.p. 317–319°C, $[\alpha]_D + 89^\circ$ (*c* 0.69). IR spectrum: 3440 (broad), 1730, 1673, 1607, 1255 cm^{-1} . UV spectrum: λ_{max} 278 nm, $\log \varepsilon$ 4.1. ^1H —NMR spectrum: 0.75 d, $J \approx 7$ Hz (19- CH_3); 0.85 (2 \times CH_3); 0.89, 0.93, 1.03, 1.22 (4 \times CH_3); 2.03 (CH_2COO); 3.18 bd, $J_{1,r} \approx 1 - 1.5$ Hz, and 4.30 d, $J_{\text{gem}} \approx 8$ Hz ($\text{C}_{(2,8)}\text{H}_2$); 4.48 m (3 α -H); 7.10 (=CH—O—). For $\text{C}_{33}\text{H}_{50}\text{O}_5$ (526.7) calculated: 74.67% C, 9.79% H; found: 74.55% C, 9.65% H.

Oxidation with Chromium Trioxide

To a solution of hydroxymethylene-ketone in acetic acid excess chromium trioxide (about 20%) in acetic acid was added at room temperature and the mixture was allowed to stand for 30 minutes. The excess chromium trioxide was reduced with methanol, the mixture diluted with water and the product extracted with ether. The ethereal layer was washed with water acidified with hydrochloric acid and dried over sodium sulfate.

a) From hydroxymethylene-ketone *III* (0.5 g) 3-oxo-20 β ,28-epoxy-21,22-seco-18 α ,19 β *H*-ursane-21,22-dioic acid (*XIV*; 0.46 g, 89%) was obtained, m.p. 279–281°C (ether), $[\alpha]_D + 100^\circ$ (*c* 0.68). IR spectrum: 3520, 3400, 3300–2800, 1780, 1710, 1415, 1348 cm^{-1} . For $\text{C}_{30}\text{H}_{46}\text{O}_6$ (502.6) calculated: 71.68% C, 9.22% H; found: 71.21% C, 9.35% H. Dimethyl ester *XV* was prepared from secodiacid *XIV* with diazomethane in ether. After crystallization from a mixture of chloroform and *n*-heptane the product had m.p. 224–226°C, $[\alpha]_D + 71^\circ$ (*c* 0.69). IR spectrum: 1750, 1730, 1712 cm^{-1} . For $\text{C}_{32}\text{H}_{50}\text{O}_6$ (530.7) calculated: 72.41% C, 9.50% H; found: 72.27% C, 9.57% H.

b) From monoacetate *IV* (0.25 g) dimethyl ester of 3 β -acetoxy-20 β ,28-epoxy-21,22-seco-18 α ,19 β *H*-ursane-21,22-dioic acid (*X*; 0.22 g, 81%) was prepared by oxidation and subsequent reaction with diazomethane. The melting point of the product was 184–186°C, and after resolidification 232–235°C (chloroform–*n*-heptane), $[\alpha]_D + 47^\circ$ (*c* 0.94). IR spectrum: 1750, 1730, 1260 cm^{-1} . ^1H —NMR spectrum: 0.79 d (19 α - CH_3); 0.83 (2 \times CH_3); 0.86, 0.95, 0.98 (3 \times CH_3); 1.56 (20- CH_3); 2.04 (CH_3COO); 3.70 (2 \times COOCH_3); 3.73 and 4.15, $J_{\text{gem}} \approx 13.5$ Hz (28- H_2); 4.48 m (3 α -H). For $\text{C}_{34}\text{H}_{54}\text{O}_7$ (574.7) calculated: 71.04% C, 9.47% H; found: 70.82% C, 9.51% H.

c) On oxidation of diacetate *V* (0.15 g) at room temperature a mixture was obtained from which acid components were separated by chromatography on silica gel, and after reaction with diazomethane dimethyl ester *X* (0.04 g, 26%) was isolated by preparative thin-layer chromatography, m.p. 180–181°C and 230–235°C (chloroform–*n*-heptane); according to its IR spectrum this sample was identical with dimethyl ester *X* prepared under *b*). Heating of a solution of diacetate *V* (0.2 g) with a 20% excess chromium trioxide at 80°C for one hour and working up as in the preceding case gave dimethyl ester *X* (0.09 g, 45%), which was according to its m.p., $[\alpha]_D$, and IR spectrum identical with the above mentioned preparation.

3 β -Hydroxy-20 β ,28-epoxy-21,22-seco-18 α ,19 β *H*-ursane-21,22-dioic Acid (*VII*)

A solution of dimethyl ester *X* (0.2 g) and potassium hydroxide (0.45 g) in 20 ml of a benzene–ethanol 1 : 1 mixture was refluxed for 2 hours, then diluted with water acidified with hydrochloric acid, and extracted with ether. After washing with an approximately 2% hydrochloric acid solution the ethereal solution was concentrated (without drying) for crystallization. Yield, 0.16 g of diacid *VII*, m.p. 335–337°C, the IR spectrum of which (in *nujol*) was identical with the spectrum of a known sample⁵.

Under the effect of a mixture of acetic anhydride and pyridine (1 : 1, 16 hours at room temperature) secodiacid *VII* (0.1 g) gave anhydride *XIII* (0.1 g), m.p. 332–335°C (under decomposition; chloroform–*n*-heptane), $[\alpha]_D^{25} + 84^\circ$ (*c* 0.79), which was identical according to its IR spectrum with a derivative obtained earlier⁵. Anhydride *XIII* (0.13 g) was refluxed in a mixture of benzene and methanol (1 : 1) for 10 hours; after evaporation of the solvents an inseparable mixture of monomethyl esters was obtained (IR spectrum: 3500, 3380, 1768, 1727, 1710 cm^{-1}) from which dimethyl ester *X* (0.12 g) was obtained by methylation with diazomethane in ether. Dimethyl ester *X* had m.p. 180–182°C and 230–232°C and it was identical according to IR spectra with the product described above.

20 β ,28-Epoxy-21,22-seco-18 α ,19 β *H*-ursane-3 β ,21,22-triol (*XII*)

Anhydride *XIII* (0.18 g) was extracted for 6.5 hours into a suspension of lithium aluminum hydride in ether. The mixture was decomposed with water and acidified with hydrochloric acid. The poorly soluble product was extracted with ethyl acetate under addition of ethanol, the solution was dried without previous washing over sodium sulfate and sodium carbonate. Crystallization from ethanol gave triol *XII* (0.15 g), m.p. 284–287°C. For $\text{C}_{30}\text{H}_{52}\text{O}_4$ (476.7). 2 $\text{C}_2\text{H}_5\text{OH}$ calculated: 71.78% C, 11.34% H; found: 72.04% C, 11.08% H.

Triacetate XI was obtained from triol *XII* by acetylation with acetic anhydride and pyridine at room temperature. 3 β ,21,22-Triacetoxo-20 β ,28-epoxy-21,22-seco-18 α ,19 β *H*-ursane (*XI*) has m.p. 237–240°C (chloroform–*n*-heptane), $[\alpha]_D^{25} + 70^\circ$ (*c* 0.61). IR spectrum: 1730, 1258 cm^{-1} . ¹H-NMR spectrum: 0.85 (2 \times CH_3); 0.88 (2 \times CH_2); 1.00 (CH_3); 1.02 d, $J \approx 7.5$ Hz (19 α - CH_3); 1.37 (CH_3); 2.04, 2.06, 2.09 (3 \times CH_3COO); 3.14 d and 3.78 d, $J_{\text{gem}} \approx 12.5$ Hz ($\text{C}_{(28)}\text{H}_2\text{—O—}$); 3.86 d and 4.06 d, $J_{\text{gem}} = 10.9$ Hz, 3.99 d and 4.17 d, $J_{\text{gem}} \approx 11.00$ Hz (2 \times $\text{—CH}_2\text{—O—CO—}$); 4.49 m (3 α -H). For $\text{C}_{36}\text{H}_{58}\text{O}_7$ (602.8) calculated: 71.72% C, 9.70% H; found: 71.69% C, 9.64% H.

Dimethyl Ester of 3 β -Hydroxy-20 β ,28-epoxy-21,22-seco-18 α ,19 β *H*-ursane-21,22-dioic Acid (*VIII*)

A mixture of dimethyl ester *XV* (0.2 g) and tritert-butoxy lithium aluminum hydride (0.4 g) in ethyl acetate (20 ml) was allowed to stand at room temperature for 2 hours, then poured into water, acidified with hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried over sodium sulfate and the residue (0.2 g) was chromatographed on silica gel. The dimethyl ester *VIII* obtained (0.18 g) melted at 254–254.5°C (chloroform–*n*-heptane), $[\alpha]_D^{25} + 45^\circ$ (*c* 0.71), and according to its IR spectrum it was identical with the preparation obtained earlier⁵.

The authors thank Mrs J. Čeřrdlová of the analytical laboratory of this Department for elemental analyses, Dr S. Hilgard of the same Department for the measurement of the IR and UV spectra, and Dr M. Buděšinský, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, for the measurement of the ¹H-NMR spectra.

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Translated by Ž. Procházka.