OXIDATION OF 3β,28-LUPANEDIOL DIACETATE AND LUPANE WITH PEROXYACETIC ACID*

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Received February 25th, 1986

Lupane triterpenoids are attacked by peroxyacetic acid in position 19. 3β,28-Lupanediol diacetate (*I*) affords the 18β,19β-epoxy derivative *III* and the 19β-hydroxy derivative *V*, lupane (*II*) gives 18β,19β-epoxylupane (*IV*); however, the yields are low. Structure of the products *III* and *IV* was confirmed by independent preparation from the 20(29)-unsaturated compounds *IX* and *X*.

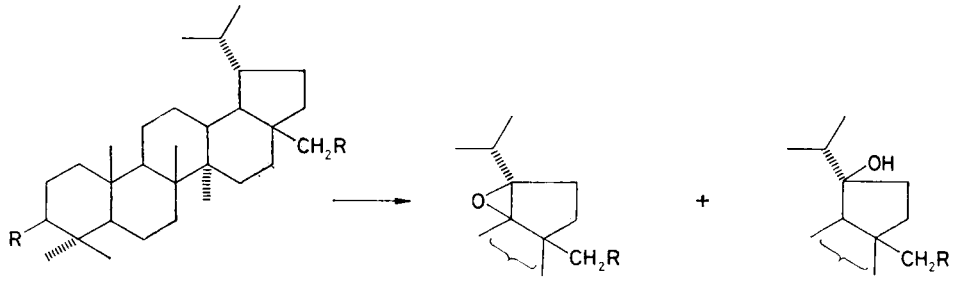
The recent preliminary communications[1,2] on hydroxylation of triterpenoids (including the lupane series) with 3-chloroperoxybenzoic acid prompted us to publish our results concerning the oxidation of 3β,28-lupanediol diacetate (*I*) and lupane (*II*) with peroxyacetic acid. This acid has been utilized for the functionalization of non-activated positions of carbon skeleton and is known to attack mainly tertiary carbon atoms[3-5].

Irradiation with UV light of a solution of diacetate *I* in acetic acid in the presence of peroxyacetic acid afforded 18β,19β-epoxy derivative *III* (4%) and 19β-hydroxy derivative *V* (5%), along with the starting diacetate *I* (54%). Because no direct epoxide formation in the functionalization of hydrocarbon skeleton with peroxy acids is known, it is probable that the reaction proceeds *via* the hydroxy derivative *V* as the primary product. The epoxide is then formed by elimination of the 19β-hydroxy group followed by epoxidation of the 18(19)-double bond in compound *VII*. Peroxyacetic acid thus attacks the $C_{(19)}$ carbon atom, similarly to ozone[6] or 3-chloroperoxybenzoic acid[2]. The total yield of compounds *III* and *V* (9%) is comparable with the yields of the 19β-hydroxy derivative *V* in the oxidation of diacetate *I* with 3-chloroperoxybenzoic acid[2] (11%) or dry ozonation[6] (10%). However, with peroxyacetic acid the conversion of the diacetate *I* is high (46%) and (similarly to steroid compounds[4]) the reaction leads, in addition to *III* and *V*, to very polar products of unidentified structure.

Reaction of the parent hydrocarbon lupane (*II*) with peroxyacetic acid afforded only minor amount (3%) of 18β,19β-epoxylupane (*IV*), a substantial portion (48%) of compound *II* being recovered. This fact is interesting in comparison with the

* Part LXXX in the series Triterpenes; Part LXXIX This Journal *51*, 2869 (1986).

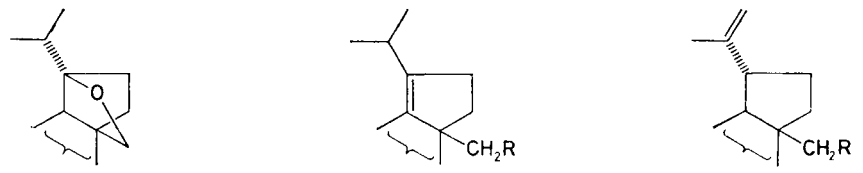
results of the Japanese authors[2] who on oxidation of 3β-lupanol acetate with 3-chloroperoxybenzoic acid obtained no products of oxidation in position 19 but only the 13β-hydroxy derivative (4%) and the 16β-hydroxy compound (1%). These authors pointed out that the presence of the 28-acetoxy group plays an important role in the oxidation in position 19. However, the formation of 18β,19β-epoxylupane (*IV*) observed by us indicates that the $C_{(19)}$-functionalization by the peroxy acid takes place also in compounds without any 28-acetoxy group.



I, R = $OCOCH_3$
II, R = H

III, R = $OCOCH_3$
IV, R = H

V, R = $OCOCH_3$



VI, R = $OCOCH_3$

VII, R = OCOCH
VIII, R = H

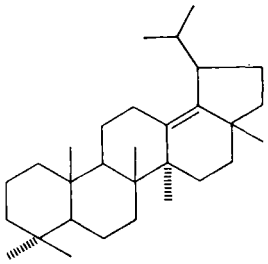
IX, R = $OCOCH_3$
X, R = H

In formula *VII* for OCOCH should read $OCOCH_3$

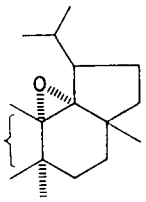
The structure of the 19β-hydroxy derivative *V* follows from agreement of its physical constants with those published in the literature[6,7] (ref.[7] erroneously assumes that the compound is the 13β-derivative; the correction in favour of the 19β-hydroxy derivative follows from refs[8,9]) and also ^{1}H NMR spectra of this compound and its 19-O-trichloroacetyl carbamate confirm the assignment. The structure was proven chemically by conversion to the ether *VI* and the unsaturated compound *VII*: on pyrolysis at 260°C the hydroxy derivative *V* lost acetic acid under formation of the 19β,28-epoxy derivative *VI*, identical with the sample prepared according to ref.[7] (in ref.[7] the compound is described as 13β,28-epoxy derivative; its structure has been corrected in refs[8,9]). Dehydration of the compound *V* with phosphorus oxychloride in pyridine afforded 18-lupene-3β,28-diol diacetate (*VII*) which, for com-

parison, was prepared by isomerization of 20(29)-lupene-3β,28-diol diacetate (*IX*) with hydrobromic acid according to ref.[10]. The epoxide *III* was identical with the compound obtained by reaction of the diacetate *VII* with 3-chloroperoxybenzoic acid[11]. The β-configuration of the epoxy group has been confirmed already by X-ray diffraction[12].

The structure of the epoxide *IV* follows from its ^{1}H NMR and mass spectra. The chemical proof of *IV* required 18-lupene (*VIII*). However, the attempted preparation of 18-lupene (*VIII*) by isomerization of 20(29)-lupene (*X*) with hydrobromic acid under the same conditions and reaction time (11 days) as in the isomerization of the diacetate *IX* was unsuccessful, the principal product being an isomeric olefin.



XI



XII

On the basis of ^{1}H NMR spectrum and analogy with the isomerization of lupeol acetate[13], we suggest that this compound is 19αH-lup-13(18)-ene (*XI*). On treatment with 3-chloroperoxybenzoic acid, compound *XI* afforded an epoxide which, by way of analogy[13], was assigned the 13α,18α-epoxide (*XII*) structure. On the other hand, when lupene *X* was isomerized with hydrobromic acid for only 12 h, the main product (44%) was the desired 18-lupene (*VIII*). The reaction mixture furnished also the olefins *X* (12%) and *XI* (8%). The structure of *VIII* follows from comparison of its ^{1}H NMR spectrum with that of the diacetate *VII*. The spectra of both compounds exhibit a characteristic septet at δ 3·1 due to the proton at $C_{(20)}$ (this septet does not occur in the spectrum of the isomeric olefin *XI*). Moreover, both doublets of the methyl groups at $C_{(20)}$ are shifted about 0·15 ppm downfield as compared with the saturated compounds *I* and *II*. Also the changes in the chemical shifts of the angular methyl groups correspond[14] to a double bond in position 18(19). Reaction of 18-lupene (*VIII*) with 3-chloroperoxybenzoic acid afforded the epoxide *IV*, identical with the epoxide obtained by reaction of lupane (*II*) with peroxyacetic acid. The epoxide *IV* was assigned the 18β,19β-configuration because the epoxidation of 18-lupene derivatives is known to proceed from the β-side even in the absence of any functional group at $C_{(28)}$ (see refs[11,13]), and because the changes of methyl shifts in going from *II* to *IV* and from *I* to *III* are the same.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined on an automatic polarimeter ETL-NPL (Bendix–Ericsson) in chloroform (*c* 0·6—1·0); accuracy ±2°. IR spectra were taken on a PE 684 (Perkin–Elmer) spectrometer in chloroform. ^{1}H NMR spectra were obtained with Tesla BS 487A (80 MHz, internal standard hexamethyldisiloxane) and Varian XL-200 (200 MHz, internal standard tetramethylsilane) instruments in deuteriochloroform. Chemical shifts are given in ppm (δ-scale). Mass spectra were measured on a Varian MAT 311 spectrometer at 70 eV. Analytical samples were dried at 100°C over phosphorus pentoxide under diminished pressure. Thin-layer chromatography was performed on silica gel G according to Stahl (Merck), column chromatography was carried out on silica gel Silpearl (Kavalier, Votice). The usual work-up procedure means dilution of the reaction mixture with ether, washing the ethereal solution with water, saturated sodium hydrogen carbonate solution and again with water, drying over sodium sulfate and evaporation of the ether. The identity of samples prepared in different ways was checked with thin-layer chromatography and IR and ^{1}H NMR spectra.

Reaction of 3β,28-Lupanediol Diacetate (*I*) with Peroxyacetic Acid

A solution of peroxyacetic acid (30%) in acetic acid (15 ml) was added to a solution of diacetate *I* (1·2 g) in acetic acid (140 ml). After introduction of nitrogen for 30 min, the mixture was irradiated in a quartz flask with a 125 W mercury lamp (type Tesla RKV; placed outside the flask) for 24 h under nitrogen. Every 8 h another portion (15 ml) of 30% peroxyacetic acid was added. The mixture was poured into water and extracted with ether. The ethereal extract was washed successively with 5% solutions of potassium iodide, sodium sulfite and sodium carbonate and with water. After drying over sodium sulfate, polar products were removed by filtration through a column of alumina (20 g), the solvent was evaporated and the residue was chromatographed on silica gel (60 g) in light petroleum–ether (8 : 1). The starting diacetate *I* was eluted first (0·65 g), followed by 18β,19β-epoxy-3β,28-lupanediol diacetate (*III*, 50 mg), m.p. 218—222°C (chloroform–methanol), $[\alpha]_D$ +23°. Ref.[10] gives m. p. 222°C; $[\alpha]_D$ +25·5°. IR spectrum: 1 725, 1 257, 1 031, 981 cm^{-1}. ^{1}H NMR spectrum: 0·85 s (2 × CH_3), 0·89 s, 1·07 s, 1·11 s, 1·03 d (J = = 7 Hz) and 1·08 d (J = 7 Hz) (5 × CH_3), 2·04 s (2 × CH_3COO), 3·89 d and 4·50 d (J = = 10·2 Hz; $C_{(28)}H_2$), 4·47 m ($C_{(3)}H$). Mass spectrum: *m/z* (%): 542 (10, M^+), 482 (9), 469 (18), 409 (7), 279 (17), 189 (30), 43 (100). Further elution with the same solvent mixture gave 61 mg of 3β,19β,23-lupanetriol 3,28-diacetate (*V*), m.p. 260—262°C, $[\alpha]_D$ +16°. Reported[6] m.p. 265°C, $[\alpha]_D$ +18°; ref.[7] gives m p. 272—273°C, $[\alpha]_D$ +19°. IR spectrum: 3 608, 1 724, 1 256, 1 030 cm^{-1}. ^{1}H NMR spectrum (200 MHz): 0·84 s, 0·85 s, 0·86 s, 0·98 s, 1·07 s, 0·87 d (J = 6·8 Hz) and 0·93 d (J = 6·6 Hz) (7 × CH_3), 2·05 s and 2·06 s (2 × CH_3COO), 4·35 dd (J = 11·6 and 1·5 Hz) and 4·45 d (J = 11·6 Hz) ($C_{(28)}H_2$), 4·48 dd (J = 10·4 and 5·8 Hz; $C_{(3)}H$). Mass spectrum; *m/z* (%): 484 (52, M^+ — 60), 441 (12), 424 (28), 409 (12), 398 (10), 381 (15), 351 (12), 249 (12), 189 (100). 3β,19β,28-Lupanetriol 3,28-diacetate, 19-trichloroacetylcarbamate (prepared *in situ*); ^{1}H NMR spectrum (200 MHz): 0·85 s (2 × CH_3), 0·89 s, 0·99 s, 1·10 s, 0·955 d (J = 6·9 Hz) and 1·00 d (J = 6·7 Hz) (5 × CH_3), 2·05 s (2 × CH_3COO), 2·63 m ($C_{(20)}H$), 2·73 ddd (J = = 16·4, 11·7 and 8·6 Hz; $C_{(21)}H$), 3·93 bd (J = 11·6 Hz) and 4·36 bd (J = 11·6 Hz) ($C_{(28)}H_2$), 4·48 m ($C_{(3)}H$), 8·14 s (NH).

Reaction of Lupane (*II*) with Peroxyacetic Acid

The reaction of lupane (*II*; 1·0 g) was carried out in a mixture of acetic acid (70 ml) and ethyl acetate (200 ml) in the same manner as described for the diacetate *I*. The product mixture was

chromatographed on a column of silica gel (50 g). Light petroleum–ether (20 : 1) eluted lupane (*II*; 0·48 g) and 18β,19β-epoxylupane (*IV*; 30 mg), m.p. 190—192°C (chloroform–methanol); $[\alpha]_D$ +21°. IR spectrum: 1 454, 1 387, 842 cm^{-1}. ^1H NMR spectrum: 0·80 s, 0·85 s, 0·86 s, 0·99 s, 1·05 s, 1·10 s, 1·03 d (J = 7 Hz) and 1·06 d (J = 7 Hz) (8 × CH_3), 2·17 septet (J = 7 Hz; $C_{(20)}H$). Mass spectrum: m/z (%): 426 (52, M^+), 411 (19), 369 (6), 221 (20), 205 (38), 191 (100). For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·48% C, 11·58% H.

19β,28-Epoxy-3β-lupanol Acetate (*VI*)

Hydroxy derivative *V* (25 mg) was heated to 260°C for 1 h. Crystallization of the melt from methanol afforded the title compound *VI* (15 mg), m.p. 276—278°C, identical with an authentic sample prepared according to ref.[7]. Reported[7] m.p. 281—282°C. ^1H NMR spectrum: 0·85 s (2 × CH_3), 0·87 s, 0·92 s and 1·01 s (3 × CH_3), 2·03 s (CH_3COO), 3·27 d (J = 7·2 Hz) and 3·95 dd (J = 7·2 and 2·0 Hz) ($C_{(28)}H_2$), 4·49 m ($C_{(3)}H$); doublets of $C_{(20)}(CH_3)_2$ are overlapped by signals of the other methyl groups.

18-Lupene-3β,28-diol Diacetate (*VII*)

A) A solution of hydroxy derivative *V* (20 mg) and phosphorus oxychloride (0·3 ml) in pyridine (2 ml) was refluxed for 20 min, cooled and poured on a mixture of ice and hydrochloric acid. The usual work-up gave 16 mg of diacetate *VII*, m.p. 214—215°C (chloroform–methanol); $[\alpha]_D$ +16°. Reported[10] m.p. 215°C, $[\alpha]_D$ +16°. ^1H NMR spectrum: 0·84 s (2 × CH_3), 0·90 s (2 × CH_3), 1·07 s, 0·91 d (J = 7 Hz) and 0·99 (J = 7 Hz) (3 × CH_3), 2·02 s and 2·03 s (2 × CH_3COO), 3·15 septet (J = 6·8 Hz; $C_{(20)}H$), 4·01 bs ($C_{(28)}H_2$), 4·49 m ($C_{(3)}H$).

B) A solution of 20(29)-lupene-3β,28-diol diacetate (*IX*, 1 g) in a mixture of benzene (35·5 ml), acetic anhydride (14·8 ml) and 34% (wt/wt) hydrogen bromide in acetic acid (20 ml; ϱ = 1·295 g . . cm^{-3}) was set aside for 14 days at room temperature, poured on ice, and the mixture was worked up in the usual manner. Crystallization from benzene–methanol afforded 0·88 g of diacetate *VII*, identical with the product obtained by procedure *A*.

18-Lupene (*VIII*)

The isomerization of 20(29)-lupene (*X*; 0·5 g) was carried out in the same manner as described for diacetate *IX* (see preparation of *VII*, procedure *B*); reaction time 12 h. The obtained mixture was chromatographed on 50 g of silica gel containing 5% of silver nitrate. Light petroleum eluted successively olefins *XI* (40 mg), *VIII* (220 mg) and *X* (60 mg). The olefin *VIII* was identical with the sample obtained[15] by hydrogenation of 18,20(29)-lupadiene; m.p. 177—180°C (ether); $[\alpha]_D$ +3°. Reported[15] m.p. 181—183°C. ^1H NMR spectrum: 0·80 s and 0·85 s (2 × CH_3), 0·87 s (2 × CH_3), 0·99 s, 1·07 s, 0·91 d (J = 7 Hz) and 0·98 d (J = 7 Hz) (4 × CH_3), 3·10 septet (J = 7 Hz; $C_{(20)}H$). Mass spectrum; m/z (%): 410 (72, M^+), 395 (31), 367 (7), 218 (27), 205 (37), 204 (100), 203 (33), 191 (59), 189 (81), 177 (62). For $C_{30}H_{50}$ (410·7) calculated: 87·73% C, 12·27% H; found: 87·73% C, 12·01% H.

19αH-Lup-13-ene (*XI*)

20(29)-lupene (*X*; 100 mg) was isomerized as described for the preparation of *VII* (procedure *B*); reaction time 11 days. The product was purified by thin-layer chromatography on silica gel (5% silver nitrate) in light petroleum, and crystallization from methanol. Yield 40 mg of *XI*, m.p. 174—176°C; $[\alpha]_D$ +6°. ^1H NMR spectrum: 0·80 s (CH_3), 0·86 s (2 × CH_3), 0·94 s, 0·995 s, 1·09 s, 0·61 d (J = 7 Hz) and 0·87 d (J = 7 Hz) (5 × CH_3). Mass spectrum; m/z (%): 410

(67, M^+), 395 (7), 367 (6), 218 (27), 205 (55), 204 (100), 203 (40), 191 (65), 189 (55). For $C_{30}H_{50}$ (410·7) calculated: 87·73% C, 12·27% H; found: 87·72% C, 12·56% H.

13α,18α-Epoxy-19αH-lupane (*XII*)

A solution of olefin *XI* (30 mg) and 3-chloroperoxybenzoic acid (60 mg) in dichloromethane (5 ml) was allowed to stand at room temperature for 14 h, diluted with ether, washed successively with 5% solutions of potassium iodide and sodium sulfite and processed as usual. Crystallization from methanol afforded epoxide *XII* (20 mg), m.p. 175–178°C; $[\alpha]_D$ +18°. Mass spectrum, *m/z* (%): 426 (15, M^+), 397 (10), 369 (8), 274 (10), 271 (7), 259 (13), 220 (14), 191 (100), 177 (55). For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·31% C, 11·75% H.

In the same way, compounds *VII* and *VIII* were converted into the respective epoxy derivatives *III* and *IV*, identical with the samples prepared above.

The authors are indebted to Dr J. Protiva for measurements of the mass spectra and to Dr M. Buděšínský, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, for measurement of the 200 MHz NMR *spectra.*

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Translated by M. Tichý.