UNUSUAL COURSE OF PHOTOLYSIS OF 3β-ACETOXY-28-NITROSYLOXYLUPANE. SYNTHESIS OF TRITERPENIC N-OXIDES AND HYDROXAMIC ACIDS*

J.PROTIVA, M.BUDĚŠÍNSKÝ and A.VYSTRČIL

Department of Organic Chemistry, Charles University, Albertov 2030, 128 40 Prague 2

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Photolysis of 3β-acetoxy-28-nitrosyloxylupane (*II*) gives rise to anomalous triterpenic products, N-hydroxylactam *IV* and enamine-oxide *VIII*. The structures of compounds *IV* and *VIII* were determined by spectroscopic methods (IR, UV, ^{1}H-NMR, ^{13}C-NMR, MS) and chemical conversions. Derivative *IV* was converted to the known unsaturated amide *VII*.

In preceding papers[1,2] we have demonstrated that for the functionalization of the lupane skeleton in the position 13β, 28-hydroxy group may be made use of in spite of the fact that in contrast to the usually employed skeletal axial hydroxy groups it possesses a higher conformational freedom. Photooxidations led to the 13β,28--epoxylupane system which is analogous to that of the naturally occurring 13β,28--epoxy-18β-oleanane derivatives cyclamiretin[3] A, protoprimulagenin[4] A and priverogenin B (ref.[5-7]). A similar bridging of the positions 13β,28 by an oxygen bridge in a *trans-transoid-cis* perhydroanthracene system has been performed by photolysis of the nitrite of 13β-hydroxy-18β-oleanane[8], *i.e.* by utilizing the conformationally fixed 13β-hydroxy group. Now we were interested to see whether more favourable conditions for this reaction might be found in a system with a *trans* annelated terminal cycle, *i.e.* in the photolysis of the 3β-acetoxy-28-lupanol nitrite (*II*).

The photolysis of nitrite *II*, prepared in the usual manner[9] from 3β-acetoxy--28-lupanol (*I*), afforded 30% of nitrogen-free products which were identified, using authentic samples, as isomeric 3β-acetoxy-28-norderivatives[1], 3β-acetoxylupan-28-oic acid (*III*) and the starting alcohol *I*. The more polar nitrogen-containing compounds *A* and *B* were present in 9% and 50% yields. The minor component *A*, $C_{32}H_{51}NO_4$, shows in the IR region in addition to the absorption of the acetoxyl group also absorption for the amide group (1665 cm^{-1}) and for associated hydroxyl groups (3110 cm^{-1}). In its ^{1}H-NMR spectrum signals of the AB system of the $C_{(28)}$ protons are lacking and the signals of two angular methyl groups (8β and 14α) are strongly shifted downfield (δ = 1·13 and 1·18), similarly as in 28 → 13β-lupanolide deriva-

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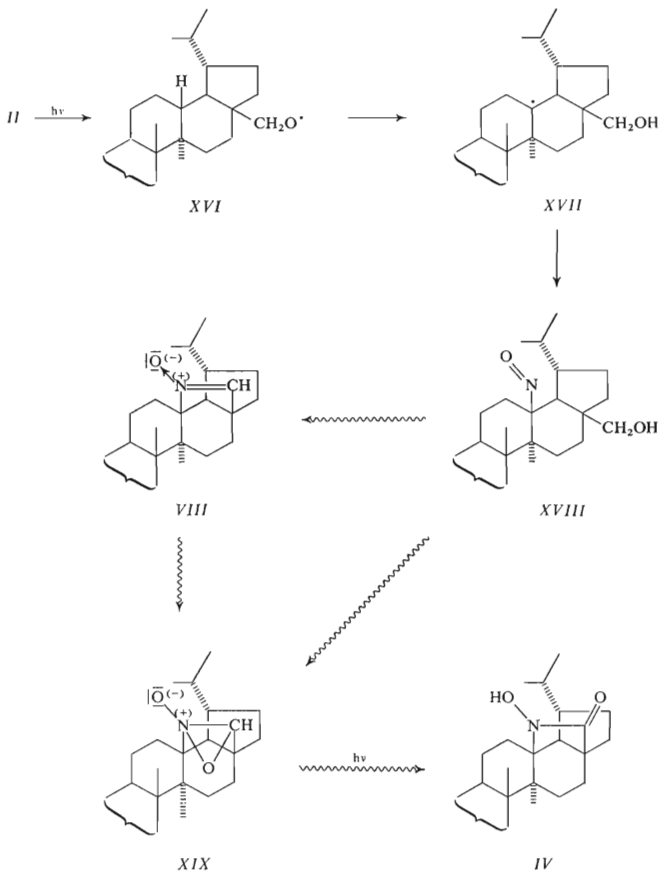
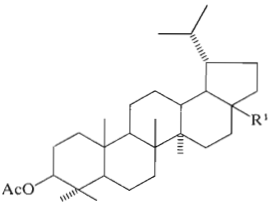
tives. The presence of the hydroxy group was further confirmed by the reaction with trichloroacetyl isocyanate[10] in the cell, under formation of N-trichloroacetylcarbamate (NH proton at $\delta = 9{\cdot}53$). As in the ^{1}H-NMR spectrum of product *A* there is no other >CH—O proton signal present in addition to that of 3α-H, the hydroxyl group must be bound either on a tertiary carbon atom or, more probably, on nitrogen. These facts are compatible with the structure of N-hydroxylactam *IV*. In order to confirm it product *A* was acetylated; the diacetate *V* formed contains two different acetoxy groups (IR: 1715, 1795 cm^{-1}, ^{1}H-NMR: $\delta = 2{\cdot}03$ and $2{\cdot}22$) and in addition to 3α-H it does not contain a hydrogen vicinal to the acetoxy group. It may be expected that on reduction of product *A* with zinc in acetic acid the expected system *IV* would give[11] lactam *VI*, which, as we have found earlier[2], is unstable. Unsaturated amide *VII* was isolated from the reaction mixture which was identical with an authentic specimen[2]. By this it was proved that the minor product *A* of the photolysis of nitrite *II* is N-hydroxylactam *IV*.

The main, more polar product *B*, $C_{32}H_{51}NO_3$, displays a hypsochromic and hyperchromic shift of the UV absorption during the passage from an unpolar (cyclohexane) to a protic (ethanol) medium ($\Delta\lambda = 8$ nm); in its IR spectrum the band at 1567 cm^{-1} is characteristic. In the ^{1}H-NMR spectrum a singlet of a single hydrogen (evidently olefinic, $\delta = 6{\cdot}68$, unexchangeable by deuterium) appears instead of an AB system of two $C_{(28)}$-protons, and the signals of 8β and 14α methyl groups are still more strongly shifted downfield ($\delta = 1{\cdot}21$ or $1{\cdot}28$, resp.) than in product *A*. The IR absorption does not exclude the presence of an enamine-oxide group[12], the UV absorption[13] and ^{1}H-NMR exclude the isomeric oxazirane structure *XIV*, while ^{1}H-NMR localizes the nitrogen function formed again between carbon atoms $C_{(28)}$ and $C_{(13)}$. From the ^{13}C-NMR spectrum of product *B* it is evident that it contains 32 carbon atoms of which 28 are within the 0–80 ppm range, four carbon atoms have their signals at lower magnetic fields, *i.e.* $CH_3\underline{C}OO$—, $\underline{C}_{(3)}$, —N=$\underline{C}_{(28)}$ and —$\underline{C}_{(13)}$—N, in agreement with the shifts of analogous systems[14,15]. The partial structure $O^{(-)}$—$N^{(+)}$=CH— is also confirmed by the mass spectrum in which the most abundant fragments $M^+ - 16$ (75%) and $M^+ - 17$ (100%) are formed by the splitting off of the oxygen and hydroxyl radicals; this fragmentation is characteristic of N-oxides[16]. For the confirmation of the assumed structure *VIII* we acetylated product *B*. The diacetate *IX* formed corresponds to the addition of acetic acid, *i.e.* in addition to the newly introduced acetoxy group (IR: 1,742 cm^{-1}, ^{1}H-NMR: $\delta = 2{\cdot}12$) it also contains an associated hydroxyl group (IR: 3485 cm^{-1}). The acetylation is accompanied by a distinct shift of the one-proton singlet to higher fields (from $\delta = 6{\cdot}68$ to $4{\cdot}66$) and a small shift of the methyl groups 8β and 14α in the same direction ($\delta = 1{\cdot}07$ and $1{\cdot}13$, resp.). The reaction of hydroxy-diacetate *IX* with trichloroacetyl isocyanate in the cell took place anomalously, under formation of two products in a 3 : 1 ratio, independent of the amount of trichloroacetyl iso-

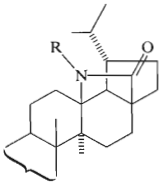


SCHEME 1

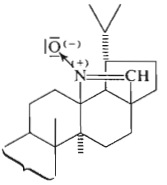
cyanate, of which neither contains N-trichloroacetylcarbamate residue. We were unable to identify the products or to isolate them. As a further proof of the assumed structure *VIII* product *B* was reduced with lithium aluminum hydride. Due to the



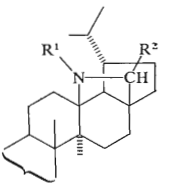
I, $R^1 = CH_2OH$
II, $R^1 = CH_2ONO$
III, $R^1 = COOH$



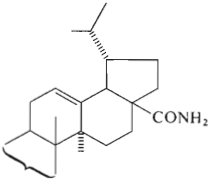
IV, R = OH
V, R = $OCOCH_3$
VI, R = H



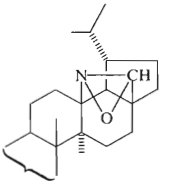
VIII



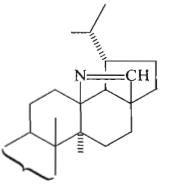
IX, $R^1 = OH$, $R^2 = OCOCH_3$
X, $R^1 = OH$, $R^2 = H$
XI, $R^1 = OCOCH_3$, $R^2 = H$
XII, $R^1 = H$, $R^2 = H$
XIII, $R^1 = COCH_3$, $R^2 = H$



VII



XIV



XV

difficulties during isolation the amino derivative *XII* obtained was acetylated under formation of N,N-disubstituted acetamide *XIII* (IR: 1 635 cm^{-1}) in the ^{1}H-NMR spectrum of which again an AB system of protons at $C_{(28)}$ appeared (δ = 3·17 d

and 3·05 d, J = 11 Hz). A milder reduction of N-oxide *VIII* with sodium borohydride led – according to analogies[12,17] – to hydroxylamine derivative *X* which is unstable and is slowly converted to the starting enamine-oxide *VIII*. Therefore the product of the reduction, *X*, was acetylated, giving rise to N-acetoxy derivative *XI*, which also contained the $-C_{(28)}H_2-N<$ grouping (δ = 2·69 and 3·50 d, J = = 13 Hz). When heated at 150°C N-acetoxy derivative *XI* eliminates spontaneously and quantitatively acetic acid under formation of enamine *XV*. The low frequency of the absorption band of the double bond (1602 cm^{-1}) and the one-proton singlet at δ = 7·39 confirm the presence of the $-\overset{|}{\underset{|}{C}}-N=CH-\overset{|}{\underset{|}{C}}-$ grouping. In all the conversions carried out it was proved that the nitrogen containing group is bound between $C_{(28)}$ and the quaternary carbon atom. As its magnetic anisotropy distinctly influences the signals of the methyl groups 8β and 14α, but only weakly the signals of the side chain methyl groups, it is practically excluded that the bond of this group is connected with the position 19β. This confirms the proposed structures *VIII*–*XIII* and *XV*.

The unusual character of the products obtained by this Barton's reaction is due to the fact that C-nitroso derivative *XVIII* is formed by the normal reaction course. This derivative cannot be stabilized neither by tautomery nor by dimerization. There are several mechanistic (speculative) possibilities for its further conversion to enamine-oxide *VIII*. The same is true of the genesis of N-hydroxy lactam *IV* by photoisomerization of oxazirane-oxide *XIX*, which is analogous to the conversion of oxaziranes to lactams [18] (see Scheme 1).

EXPERIMENTAL

The melting points were measured on a Kofler block and they are not corrected. Optical rotation was measured in chloroform on an automatic polarimeter ETL-NPL (Bendix-Ericsson) with a ±2° accuracy. The IR spectra were measured in chloroform on a UR-10, Zeiss, Jena, apparatus. The ^{1}H-NMR spectra (Table I) were recorded with a Varian HA-100 instrument, using deuteriochloroform as solvent and tetramethylsilane as internal reference. Chemical shifts are given in δ-scale with a ±0·01 ppm accuracy. The ^{13}C-NMR spectrum was measured at 15·03 MHz on a Jeol FX-60 apparatus, in deuteriochloroform, using hexamethyldisiloxane as internal standard. Chemical shifts are given in δ-scale. The mass spectra were measured on a Varian MAT 311 spectrometer, energy of ionizing electrons 70 eV, ionizing current 1 mA, ion source temperature 200°C, temperature of direct inlet system 150–190°C. The samples for analysis were dried at 100°C and 0·1 Torr over phoshorus pentoxide for 12 hours. The "conventional working up of the reaction mixture" means that it was evaporated *in vacuo*, the residue extracted with ether, the extract washed with hydrochloric acid (1 : 4 dilution), sodium sulfate solution (5%) and repeatedly with water. After drying of the solution with anhydrous sodium sulfate and filtration it was evaporated in a vacuum. Chromatographies were carried out on neutral alumina (Reanal), act. II according to Brockmann.

TABLE I

Characteristic Parameters of the ^{1}H-NMR Spectra in $CDCl_3$

Compound	4α-CH_3 [a]	4β-CH_3 [a]	10β-CH_3 [a]	8β-CH_3 [a]	14α-CH_3 [a]	20-2 CH_3 [b]	28-H	3α-H [c]	Ac [a]
IV	0·87	0·87	0·91	1·19	1·18	0·82; 0·88	—	4·49	2·05
V	0·86	0·86	0·90	1·19	1·12	0·81; 0·87	—	4·48	2·03; 2·22
VIII	0·85	0·85	0·93	1·28	1·21	0·80; 0·86	6·68 s	4·49	2·04
IX	0·85	0·85	0·85	1·13	1·07	0·79; 0·84	4·66 s	4·49	2·03; 2·12
X	0·85	0·85	0·89	1·06	1·26	0·80; 0·89	2·98 d 3·35 bd J = 12 Hz	4·49	2·04
XI	0·85	0·85	0·85	1·05	1·30	0·81; 0·88	2·69 d 3·50 d J = 13 Hz	4·47	2·01; 2·03
XIII	0·85	0·85	0·90	1·05	1·01	0·80; 0·84	3·05 d 3·17 d J = 11 Hz	4·49	2·03; 2·03
XV	0·85	0·85	0·92	1·14	1·11	0·80; 0·83	7·39 s	4·50	2·04

[a] Singlets; the assignment of the signals of 8β and 14α methyl groups can be interchanged; [b] doublets with J = 7 Hz; [c] multiplet, W = 16 Hz.

3β-Acetoxy-28-nitrosyloxylupane (*II*)

3β-Acetoxy-28-lupanol (*I*, 2 g) was dissolved in pyridine (50 ml) and gaseous nitrosyl chloride was introduced into the solution under cooling at −10°C and stirring until the orange coloration persisted. The mixture was stirred for another 15 minutes at room temperature, then poured into icy water (50 ml), and the separated nitrite *II* filtered off under suction. After washing with water it was dried *in vacuo* over phosphorous pentoxide. Thus 2 g of nitrite *II* were obtained, m.p. 233–234°C, $[\alpha]_D$ − 6° (*c*, 0·63). IR spectrum: 1028, 1245, 1725 ($OCOCH_3$), 1640 (ONO) cm^{-1}.

Photolysis of 3β-Acetoxy-28-nitrosyloxylupane (*II*)

A solution of nitrite *II* (2 g) in dry benzene (150 ml) was irradiated under nitrogen and at 10°C with a 100 W UV discharge lamp (Tesla, Sial glass) 5 hours. The mixture was evaporated and the residue chromatographed on a column of alumina (250 g). Elution with benzene gave 190 mg of mixture of isomeric 3β-acetoxy-28-nor-derivative[1], m.p. 174–176°C (ether–light petroleum), $[\alpha]_D$ + 17° (*c*, 0·65). Elution with benzene–ether 9 : 1 gave 175 mg of 3β-acetoxylupan-28-oic acid (*III*), m.p. 302–305°C, $[\alpha]_D$ − 5° (*c*, 0·68), IR spectrum: 1030, 1260, 1730 (OAc), 1700 (COOH) cm^{-1}. On further elution with benzene–ether 8 : 2 220 mg of the starting alcohol *I* were obtained. Elution with ether alone gave 180 mg of N-hydroxylactam *IV*, m.p. 321–325°C (ether), $[\alpha]_D$ − 23° (*c*, 0·43). IR spectrum: 1028, 1255, 1717 ($OCOCH_3$), 1665 (C=O), 3110 (broad, OH) cm^{-1}. Mass spectrum: *m/e* (%): M^+ 513 (4), 496 (34), 436 (9), 248 (12), 234 (14), 203 (10), 189 (40), 43 (100). For $C_{32}H_{51}NO_4$ (513·5) calculated: 74·81% C, 10·01% H, 2·73% N; found: 74·50% C, 10·01% H, 2·59% N.

Elution with methanol gave 960 mg of N-oxide *VIII*, m.p. 262–266°C (ether–methanol), $[\alpha]_D$ − 115° (*c*, 0·15), IR spectrum: 1029, 1260, 1722 (OAc), 1567 (C=N→O) cm^{-1}. UV spectrum in cyclohexane 261 nm (ε = 5151), in ethanol 254 nm (ε = 6170). ^{13}C-NMR spectrum: 0–80 ppm: 28 C atoms, 81·10 (C_3), 85·39 (C_{13}), 139·70 (C_{28}), 172·01 ($CH_3\underline{C}$=O) ppm. Mass spectrum, *m/e* (%): M^+ 497 (2), 481 (75), 480 (100), 466 (12), 438 (26), 422 (20), 218 (10), 190 (8), 189 (11). For $C_{32}H_{51}NO_3$ (497·7) calculated: 77·21% C, 10·33% H, 2·82% N; found: 76·60% C, 10·10% H, 2·95% N.

Acetylation of *IV*

A solution of N-hydroxy lactam *IV* (50 mg) in pyridine (10 ml) and acetic anhydride (8 ml) was heated at 100°C for 2 hours. After evaporation the residue was worked up in the usual manner and the product dissolved in ether and filtered through a small column of alumina. Crystallization from ether gave acetate *V* (40 mg), m.p. 265–270°C, $[\alpha]_D$ + 8° (*c*, 1·9), IR spectrum: 1026, 1251, 1725 (OAc), 1715, 1795 (C=O, $NOCOCH_3$) cm^{-1}. Mass spectrum, *m/e* (%): M^+ 555 (1), 513 (8), 496 (30), 436 (8), 248 (10), 234 (8), 203 (9), 189 (24), 43 (100).

Reduction of *IV* with Zinc in Acetic Acid

Acetic acid (10 ml) and excess zinc dust was added to a solution of N-hydroxylactam *IV* (20 mg) in benzene (10 ml) and the mixture heated on a water bath for 3 hours. The mixture was filtered and worked up in the conventional manner. After separation by thin layer chromatography on silica gel 10 mg of unsaturated amide *VII* were obtained, m.p. 260–263°C (ether), $[\alpha]_D$ + 15° (*c*, 0·65), IR spectrum: 1028, 1255, 1715 ($OCOCH_3$), 1578, 1668, 3400, 3520 ($CONH_2$) cm^{-1}.

Acetylation of N-Oxide *VIII*

A solution of N-oxide *VIII* (350 mg) in pyridine (20 ml) and acetic anhydride (15 ml) was heated at 100°C for 2 hours. After cooling the mixture was worked up in the usual manner. Yield 330 mg of crude material which was chromatographed to give 300 mg of amorphous diacetate *IX*, $[\alpha]_D$ — — 22° (*c*, 0·83), IR spectrum: 1029, 1244, 1732 ($OCOCH_3$), 3485 (OH) cm^{-1}. Mass spectrum, *m/e* (%): 539 (M — H_2O, 2%), 497 (8), 480 (16), 466 (8), 438 (14), 422 (10), 234 (9), 229 (9), 218 (12), 204 (9), 190 (14) 189 (21), 43 (100). For $C_{34}H_{55}NO_5$ (557·7) calculated: 73·21% C, 9·94% H, 2·51% N; found: 73·09% C, 10·15% H, 3·53% N.

Reduction of N-Oxide *VIII* with Sodium Borohydride

Sodium borohydride (100 mg) was added to a solution of N-oxide *VIII* (100 mg) in ethanol (10 ml) and the mixture allowed to stand at room temperature for 48 h. Water (20 ml) was added and the mixture worked up in the conventional manner. Yield, 90 mg of hydroxy derivative *X*, m.p. 243—246°C (ether–heptane), IR spectrum: 1025, 1263, 1725 ($OCOCH_3$), 3565 (OH) cm^{-1}. Mass spectrum, *m/e* (%): 499 ($C_{32}H_{53}NO_3$, 2%), 482 (27), 481 (33), 466 (23), 438 (38), 422 (35), 232 (28), 220 (41), 218 (35), 204 (15), 190 (47), 43 (100).

Acetylation of *X*

N-Oxide *VIII* (200 mg) was reduced with sodium borohydride as in the preceding case. The reaction mixture was diluted with water and evaporated *in vacuo*. The residue was dissolved in pyridine (10 ml) and acetic anhydride (10 ml) and allowed to stand at room temperature for 12 h. After working up 120 mg of N-acetoxy derivative *XI* were obtained, m.p. 136—138°C (decomp.; methanol), $[\alpha]_D$ — 15° (*c*, 0·76), IR spectrum: 1027, 1235, 1255, 1720 ($OCOCH_3$). Mass spectrum, *m/e* (%): M^+ 541 (2), 481 (27), 466 (28), 438 (54), 422 (44), 218 (23), 190 (14), 43 (100). For $C_{34}H_{55}NO_4$ (541·8) calculated: 75·37% C, 10·23% H, 2·59% N; found: 74·82% C, 10·12% H, 3·10% N.

Pyrolysis of Acetate *XI*

Diacetate *XI* (20 mg) was heated on a Kofler block at 150°C for 20 minutes. After cooling the sample was dissolved in ether and worked up in the usual manner. Olefin *XV* (15 mg) was obtained which melted at 197—200°C (ether), $[\alpha]_D$ + 44° (*c*, 0·07). IR spectrum: 1025, 1255, 1715 ($OCOCH_3$), 1605 (C=N) cm^{-1}. Mass spectrum: *m/e* (%): M^+ 481 (27), 466 (28), 438 (54), 422 (44), 218 (23), 190 (14), 43 (100).

Reduction of N-Oxide *VIII* with Lithium Aluminum Hydride

Lithium aluminum hydride (200 mg) was added to a solution of N-oxide *VIII* (130 mg) in ether (30 ml) and the mixture was refluxed for 5 h. Water was then added (0·5 ml) and the mixture evaporated. The residue was dissolved in pyridine (5 ml) and acetic anhydride (5 ml), allowed to stand at room temperature for 12 h and worked up in the conventional manner. After chromatography on thin layer of silica gel 80 mg of N-acetyl derivative *XIII* were obtained, m.p. 261—263°C (ether), $[\alpha]_D$ + 13° (*c*, 0·45). IR spectrum: 1028, 1255, 1712 ($OCOCH_3$), 1635 (C=O) cm^{-1}. Mass spectrum, *m/e* (%): M^+ 525 (21), 510 (6), 482 (12), 466 (14), 450 (8), 440 (10), 275 (38), 274 (55), 232 (48), 218 (29), 190 (26), 189 (27), 43 (100).

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