REDUCTION OF TRITERPENOID KETONES BY CHLOROIRIDIC ACID AND TRIMETHYL PHOSPHITE*

Jiří PROTIVA, Eva KLINOTOVÁ, Jiří KLINOT, Miroslav KUŠIAK and Alois VYSTRČIL

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

Received December 6th, 1985

Selective reduction of keto groups on triterpenoid pentacyclic skeleton by chloroiridic acid and trimethyl phosphite (Henbest method) was studied. The 2-oxo group is stereospecifically reduced to give axial 2β-hydroxy group whereas oxo groups in positions 1, 3, 11, 12, 16, 20, 21, 22, and 28 do not react. An analogous reduction was observed with a 2-oxo steroid.

The highly specific reduction of cyclohexanones to axial alcohols with chloroiridic acid and trimethyl phosphite in boiling aqueous 2-propanol[1] represents an important method, particularly in the steroid field. This reagent reduces stereospecifically a 3-oxo group without affecting oxo groups in other positions of the steroid system[2]. The reaction is highly sensitive to the steric situation around the reaction center. An application of this method to pentacyclic triterpenoids seemed very interesting to us, since no compounds of this type had been reduced so far.

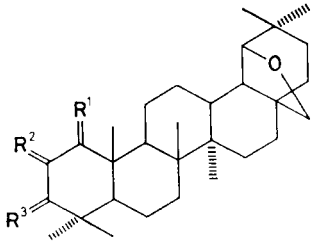
To investigate the reactivity of the individual oxo groups we used the following ketones, already prepared or isolated in our Laboratory: 19β,28-epoxy-18α-oleanan--1-one (*I*)[3], 19β,28-epoxy-18α-oleanan-2-one (*II*)[3], 19β,28-epoxy-18α-oleanan-3-one (*III*)[4], 28-acetoxylupan-3-one (*IV*; prepared by oxidation of the corresponding 3β--hydroxy derivative), methyl 3-oxo-20(29)-lupen-28-oate (*V*)[5], friedelan-3-one (*XIII*)[6], methyl 11-oxo-29,30-dinorlupan-20-oate (*VI*)[7], methyl 12-oxo-29,30-dinorlupan-20-oate (*VII*)[8], 28-norlupan-16-one (*VIII*)[9], 20,29,30-trinorlupan-21-one (*IX*)[10], 3β,28-dibenzoyloxy-18α,19βH,20ξ-ursan-21-one (*XIV*)[11], 20β,28-epoxy-18α, 19βH-ursane-3,21-dione (*XV*)[12] and 28-norlupan-22-one (*X*)[9].

Derivatives with oxo group in the side chain were represented by 3β,28-diacetoxy--30-norlupan-20-one (*XII*)[13] and 3β-acetoxy-20(29)-lupen-28-al (*XI*)[14].

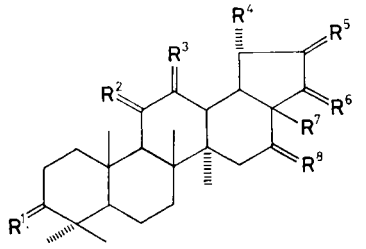
The reductions were carried out in two standard solutions. One of them was prepared according to the literature[2], the other consisted of the same components but was more concentrated. The results with the more concentrated reagent are summarized in Table I. As seen, oxo groups in the positions 1, 3, 11, 12, 16, 20, 21, 22, and 28 do not undergo the Henbest reduction. Interestingly enough, in the steroid

* Part LXXVIII in the series Triterpenes; Part LXXVII: This Journal *51*, 621 (1986).

series the reduction of 3-oxo groups is relatively facile; the unreactivity of 3-oxo triterpenoids is apparently due to the geminal 4-methyl groups hindering the approach of the iridium complex to the reaction center. Even the friedelane derivative *XIII* with only one 4-methyl group does not react.

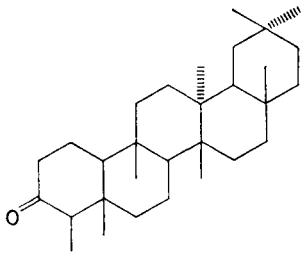


I, $R^1 = O$; $R^2 = R^3 = H_2$
II, $R^2 = O$; $R^1 = R^3 = H_2$
III, $R^3 = O$; $R^1 = R^2 = H_2$

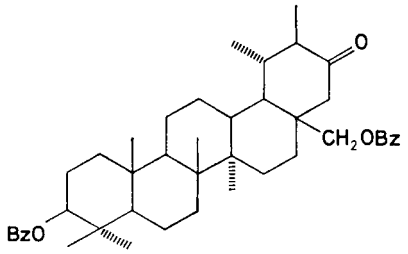


IV, $R^1 = O$; $R^2 = R^3 = R^5 = R^6 = R^8 = H_2$; $R^4 = CH(CH_3)_2$; $R^7 = CH_2OCOCH_3$
V, $R^1 = O$; $R^2 = R^3 = R^5 = R^6 = R^8 = H_2$; $R^4 = CH_3C{=}CH_2$; $R^7 = COOCH_3$
VI, $R^2 = O$; $R^1 = R^3 = R^5 = R^6 = R^8 = H_2$; $R^4 = COOCH_3$; $R^7 = CH_3$
VII, $R^3 = O$; $R^1 = R^2 = R^5 = R^6 = R^8 = H_2$; $R^4 = COOCH_3$; $R^7 = CH_3$
VIII, $R^1 = R^2 = R^3 = R^5 = R^6 = H_2$; $R^4 = CH(CH_3)_2$; $R^7 = H$; $R^8 = O$
IX, $R^1 = R^2 = R^3 = R^6 = R^8 = H_2$; $R^4 = H$; $R^5 = O$; $R^7 = CH_3$
X, $R^1 = R^2 = R^3 = R^5 = R^8 = H_2$; $R^4 = CH(CH_3)_2$; $R^6 = O$; $R^7 = H$
XI, $R^1 = \alpha H, \beta OCOCH_3$; $R^2 = R^3 = R^5 = R^6 = R^8 = H_2$; $R^4 = CH_3C{=}CH_2$; $R^7 = CHO$
XII, $R^1 = \alpha H, \beta OCOCH_3$; $R^2 = R^3 = R^5 = R^6 = R^8 = H_2$; $R^4 = COCH_3$; $R^7 = CH_2OCOCH_3$

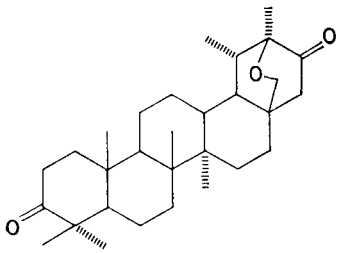
The only oxo group which is reduced stereospecifically in the Henbest reduction is that in the position 2. Whereas the originally described reagent[2] reacted extremely sluggishly, the more concentrated solution reduced quantitatively the 2-oxo derivative *II* to the OH-axial 19β,28-epoxy-18α-oleanan-2β-ol (*XVII*) in 230 hours. 2-Oxotriterpenoids can be reduced also by complex hydrides[16]; however, the reaction mixture contains predominantly the 2β-hydroxy derivative and all the oxo groups present are reduced simultaneously. The more concentrated reagent was also applied to 5α-cholestan-2-one (*XVI*) which upon heating for 110 h afforded quantitatively 5α-cholestan-2β-ol (*XVIII*).



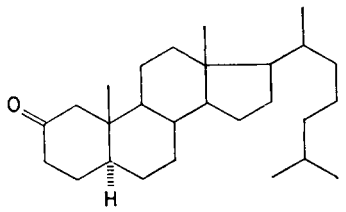
XIII



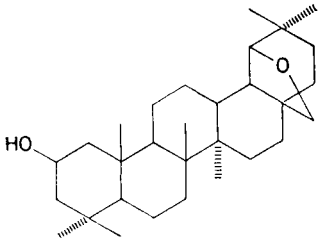
XIV, Bz = benzoyl



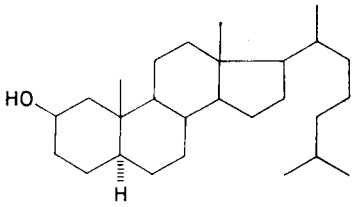
XV



XVI



XVII



XVIII

The acidic medium, arising by hydrolysis of trimethyl phosphite, hydrolysed the ester groups of the substrates. Acetates were hydrolysed most rapidly: 28-acetoxylupan-3-one (*IV*) was completely hydrolysed already after 33·5 h. The hydrolysis of methyl esters and benzoates was markedly slower.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were

measured on an ETL-NPL polarimeter (Bendix–Ericsson) in chloroform (accuracy ±2%). Mass spectra were taken on a Varian MAT 311 (electron energy 70 eV, ionizing current 1 mA, ion source temperature 200°C, direct inlet at 85—130°C). Thin-layer chromatography (TLC) was performed on Fertigplatten (Merck). 28-Acetoxylupan-3-one (*IV*) was prepared by oxidation of 3β-hydroxy derivative[14] with pyridinium chlorochromate in dichloromethane; m.p. 229 to 231°C; $[\alpha]_D$ +2° (*c* 0·59). Mass spectrum, *m/z* (%): 484 (M^+, 39), 469 (5), 466 (4), 441 (3), 399 (11), 398 (13), 381 (14), 245 (14), 229 (15), 218 (37), 205 (72), 191 (82), 95 (98), 81 (100). Chloroiridic acid was prepared from ammonium chloroiridate[15]. The reduction course was followed and identity of the samples checked by TLC. The hydrolysis products were identified also by mass spectrometry.

Reducing solutions: *a*) Normal solution: Chloroiridic acid (0·02 g) was dissolved in 2-propanol (45 ml), water (5 ml), and trimethyl phosphite (1 ml). The solution was kept in the dark at 0°C and used within 14 days. *b*) Concentrated solution: Chloroiridic acid (0·03 g) was dissolved in a mixture of 2-propanol (15 ml), water (1·6 ml), and trimethyl phosphite (1 ml).

Reduction Procedure

The oxo triterpenoid (5—20 mg) was dissolved in the normal reducing solution (5 ml) and refluxed, the reaction course being monitored by TLC. After the end of the reaction the mixture was poured in water (10 ml) and extracted with ether. The ethereal layer was washed with 5% sodium carbonate solution and dried over sodium sulfate. After evaporation of solvent the product was crystallized or chromatographed on a column of silica gel.

TABLE I
Reduction experiments

Ketone	Reaction time (h)	Products
I	150	*I*
II	230	*XVII*
III	150	*III*
IV	150	hydrolysis product
V	100	*V* + hydrolysis product (1 : 1)
VI	150	*VI* + hydrolysis product (9 : 1)
VII	150	*VII* + hydrolysis product (9 : 1)
VIII	150	*VIII*
IX	150	*IX*
X	150	*X*
XI	160	*XI* + hydrolysis product (1 : 1)
XII	150	hydrolysis product
XIII	150	*XIII*
XIV	150	*XIV* + hydrolysis product (9 : 1)
XV	170	*XV*
XVI	110	*XVIII*

2β-*Hydroxy derivative* XVII: The 2-oxo derivative *II* (5 mg) was processed in the usual manner. Crystallization from ethanol afforded 2·5 mg of 19β,28-epoxy-18α-oleanan-2β-ol (*XVII*), m.p. 260–262·5°C; $[\alpha]_D$ +83° (*c* 0·11); reported[16] m.p. 266–268°C; $[\alpha]_D$ +80°. Mass spectrum, *m/z* (%): 442 (M^+, $C_{30}H_{50}O_2$, 21), 440 (16), 424 (32), 409 (10), 399 (10), 393 (11), 371 (11), 369 (16), 353 (7), 341 (10), 323 (21), 220 (21), 207 (30), 203 (46), 189 (61), 95 (100).

5α-*Cholestan*-2β-*ol* (XVIII): The 2-oxo derivative *XVI* (5 mg) was processed in the usual manner. Crystallization from methanol gave 3 mg of *XVIII*, m.p. 150–152°C; $[\alpha]_D$ +30° (*c* 0·22); reported[17] m.p. 155°C; $[\alpha]_D$ +33° (*c* 1·0). Mass spectrum, *m/z* (%): 388 (M^+, $C_{27}H_{48}O$, 100), 386 (32), 373 (52), 355 (15), 328 (6), 315 (14), 275 (8), 262 (16), 248 (22), 234 (82), 233 (88), 215 (85), 165 (49).

REFERENCES

1. Haddad Y. M. Y., Henbest H. B., Husbands J., Mitchell T. R. B.: Proc. Chem. Soc., London *1964*, 361.
2. Browne P. A., Kirk D. N.: J. Chem. Soc., C *1969*, 1653.
3. Klinot J., Kliment M., Vystrčil A.: This Journal *39*, 3357 (1974).
4. Huneck S.: Chem. Ber. *98*, 1837 (1965).
5. Klinot J., Šumanová E., Vystrčil A.: This Journal *37*, 603 (1972).
6. Protiva J., Skorkovská H., Urban J., Vystrčil A.: This Journal *45*, 2710 (1980).
7. Řezanka T.: unpublished results.
8. Řezanka T.: *Thesis*. Charles University, Prague 1979.
9. Vystrčil A., Protiva J.: This Journal *39*, 1382 (1974).
10. Křeček V.: unpublished results.
11. Klinotová E., Škarková L., Vystrčil A.: This Journal *37*, 1748 (1972).
12. Beneš J.: unpublished results.
13. Pouzar V., Vystrčil A.: This Journal *42*, 2224 (1977).
14. Protiva J.: unpublished results.
15. Woo S. C., Yost D. M.: J. Amer. Chem. Soc. *53*, 884 (1931).
16. Nair M. R., Hilgard S., Klinot J., Waisser K., Vystrčil A.: This Journal *41*, 770 (1976).
17. Shoppee C. W., Cremlyn R. J. W., Evans D. E., Summers G. H. R.: J. Chem. Soc. *1957*, 4364.

Translated by M. Tichý.