Tetrahedron Vol. 36, pp. 2263 to 2265
Pergamon Press Ltd., 1980. Printed in Great Britain

BAEYER-VILLIGER OXIDATION OF C19-NOR KETOSTEROIDS

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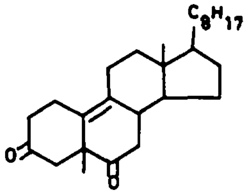
(*Received in UK 22 November 1979*)

Abstract—The Baeyer-Villiger oxidation of **1** in chloroform with perbenzoic acid yielded **3**, **4**, **5**, **7** and **8**. Similarly, the ketone **2** provided **9** and **10**. The mechanism involved in the formation of abnormal Baeyer-Villiger products has been suggested.

In continuation of our previous[1,2] studies on Baeyer-Villiger oxidation of steroidal ketones, we wish to report our work on 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione **1** and 3β-chloro-5-methyl-19-nor-5β-cholest-9(10)-en-6-one **2** with perbenzoic acid.

The ketone **1** on perbenzoic acid oxidation (*p*-toluenesulphonic acid as catalyst) afforded compounds **3** m.p. 132°, **4** m.p. 178°, **5** m.p. 170°, **7** m.p. 175° and an oil **8**. These compounds have been characterized on the basis of elemental analysis, spectral properties and chemical evidence.

The compound **3** was identified as an epoxide, m.p. and m.m.p. 132°.[3] Compound **4** melting at 178° analysed for $C_{27}H_{42}O_5$ (M^{+} 446). The elemental composition suggests that the reaction has gone beyond the normal Baeyer-Villiger stage. It is revealed by its **4** spectral properties. The UV absorption maximum at 230 nm showed the presence of an α, β-unsaturated CO chromophore. It was further supported by the IR spectrum wherein a band at 1695 cm^{-1} was observed $(C{=}C{-}\overset{\overset{O}{\|}}{C}{-})$. The IR spectrum also exhibited a band at 1770 cm^{-1}, a characteristic for the γ-lactone and



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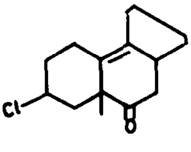

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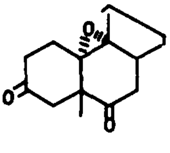

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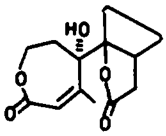

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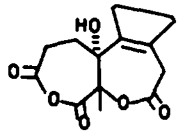

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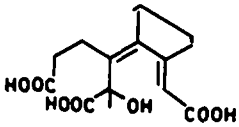

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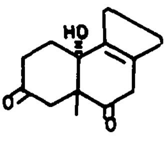

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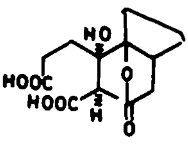

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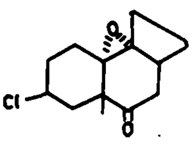

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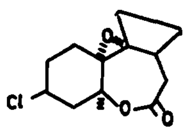

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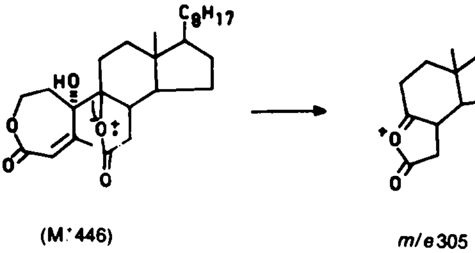
3418 cm^{-1} (OH). The NMR spectrum of the compound, m.p. 178° displayed a singlet at δ 5.2 assigned to a vinylic proton (C_{4a}-$\underline{H}$). A multiplet centred at δ 4.0 integrating for two protons is ascribable to ($C\underline{H}_2$-O-). The mass spectrum of 4 supported the assigned structure. The spectrum showed important peaks at *m/e*'s 446 (M^+), 418, 400, 388, 385, 372, 370, 358, 342, 327, 305 (base peak), 287, 263, 259, 245, 141, 123, 95, 93 and 81.

The base peak at *m/e* 305 was very useful in structure elucidation (Scheme 1).

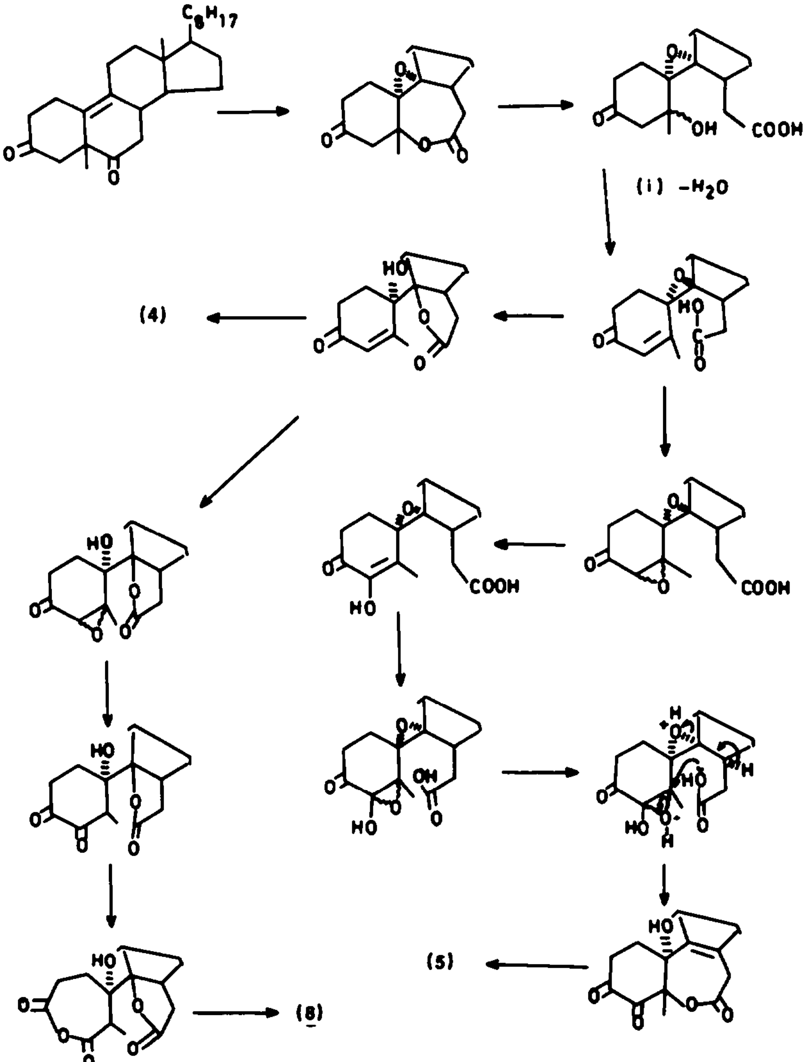
The compound 5 analysed for $C_{27}H_{40}O_6$ (M^+ 460) (+ve tetranitromethane test). The IR spectrum revealed bands at 1785 and 1750 cm^{-1}; a characteristic for acid anhydride; other bands appeared at 1705 (ε-lactone) and 3330 cm^{-1} (OH). The NMR spectrum exhibited a multiplet centred at δ 3.2 for α-keto-methylene protons (4H, C_2-$\underline{H}_2$; C_7-$\underline{H}_2$). The mass spectrum of 5 gave important peaks at *m/e*'s 460 (M^+), 418, 400 (base peak), 390, 385, 372, 358, 327, 305, 287, 277, 263, 245, 155 and 113.

Further confirmation of the structure 5 came from its hydrolysis product 6 which analysed for $C_{27}H_{42}O_7$. The IR spectrum of 6 gave bands at 3650 (Sharp; 3° OH), 3400 br ($CO\underline{OH}$), 1710 ($\underline{CO}OH$), 1660 ($-C=C-C=C-\overset{\overset{O}{\|}}{C}-OH$) and 1620 cm^{-1} (C=C). Its NMR spectrum gave a very broad signal at δ 6.7 integrating for at least four protons ($COO\underline{H}$ + $COO\underline{H}$ + $O\underline{H}$ rapidly exchanging, and C_7-$\underline{H}$ vinylic proton). A singlet at δ 6.7 for one proton was observed on D_2O shake, which can be assigned to C_7-$\underline{H}$.

The compound, 7 correctly analysed for $C_{27}H_{42}O_3$ (M^+ 414). IR spectrum exhibited bands at 3400 (Sharp, 3° OH), 1725, 1700 (carbonyls) and 1620 cm^{-1} (C=C). It gave positive tetranitromethane test. The NMR spectrum



Scheme 1.



Scheme 2.

showed no vinylic proton. The structure **7** was further supported by mass spectral studies. The spectrum showed important peaks at *m/e*'s 414 (M^{+} base peak), 396, 386, 381, 372, 354, 330, 344, 316, 301, 283, 255, 241 and 217.

The oil **8** analysed correctly for $C_{27}H_{44}O_7$. Its IR spectrum exhibited bands at 3650 (Sharp; 3° OH), 3420 (COO$\underline{H}$), 1785 (γ-lactone) and 1720 cm^{-1} ($\underline{C}$OOH). The NMR spectrum of **8** showed a broad multiplet at δ 7.45 for two protons which can be assigned to C_3- and C_4-acid protons.

The following mechanism has been proposed for the formation of **4**, **5** and **8** (Scheme 2).

Similarly the ketone **2** with perbenzoic acid furnished the compounds **9**, m.p. 138° and **10**, m.p. 105°. The compound, m.p. 138° was characterized as an epoxide of **2** on the basis of elemental and spectral studies. The compound **10** correctly analysed for $C_{27}H_{43}O_3Cl$ (M^{+} 450/452) (3:1) (+ve Beilstein test). Its IR spectrum exhibited bands at 1705 (ϵ-lactone) and 895 cm^{-1} (epoxide). The NMR spectrum showing a multiplet at δ 3.7 (1H, $W^{1/2} = 6$ Hz, C_3–$\alpha\underline{H}$) A/B ring *cis*. From this observation, it is evident that the stereochemistry of the C_5–Me has been changed during the course of the reaction. This would be in sharp contrast to the accepted mode in which stereochemistry of the migrating carbon remains unaltered.[4] The structure **10** was also supported by mass spectrum. The important mass peaks were observed at *m/e*'s 450/452 (M^{+}), 415, 414 (base peak), 386, 372, 371, 357, 342, 305, 263, 245, 109, 91 and 57.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra were determined in 95% EtOH with a Beckman DK_2 spectrophotometer. IR spectra were measured in KBr on a Perkin–Elmer 621 Grating Infrared Spectrophotometer. NMR spectra were run in $CDCl_3$ on a Varian A60 instrument with $SiMe_4$ as the internal standard. Mass spectra were measured in the Varian MAT-311(A) mass spectrometer at 70 eV using a direct insertion technique at source temperature of about 170°. Tlc plates were coated with silica gel and sprayed with a 20% soln of perchloric acid. Light petroleum refers to a fraction of b.p. 60–80°.

Reaction of 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (**1**) *with perbenzoic acid.* To a soln of **1**[5] (3 g) in $CHCl_3$ (20 ml) was added a freshly prepared $CHCl_3$ soln of perbenzoic acid (2.5 mole equiv) and a few crystals of *p*-toluenesulphonic acid monohydrate as catalyst. The mixture was allowed to stand at room temp for 3 days. The solvent was removed under reduced pressure. The residue was extracted with ether and the ethereal soln washed with water, 5% $NaHCO_3$aq and water and dried over Na_2SO_4. On removal of the solvent, the crude product (*ca* 2.9g) was chromatographed over silica gel (80 g). Elution with light petroleum:ether (4:1) gave **3** (0.55 g), m.p. 133° (reported[3] m.p. 131–132°). Further elution with light petroleum:ether (3:1) gave **7**, m.p. 175° which was recrystallized from light petroleum (0.4 g). δ 2.55 m (α-keto methylene protons), 1.05 (C_5–$C\underline{H}_3$), 0.7 (C_{13}–$C\underline{H}_3$), 0.91 and 0.83 (remaining Me protons). (Found: C, 78.35; H, 10.02. $C_{27}H_{42}O_3$ requires: C, 78.25; H, 10.14%).

Elution with light petroleum:ether (1:1) afforded a non crystallizable oil as **8** (0.3 g). δ 7.45 m (C_3- and C_4–COO$\underline{H}$), 2.65 (α-ketomethylene protons), 0.93 and 0.83 (Five Me protons). (Found: C, 67.48; H, 9.24. $C_{27}H_{44}O_7$ requires: C, 67.50; H, 9.16%).

Continued elution with light petroleum:ether (1:1) furnished **4** (0.25 g), m.p. 178° which was crystallized from light petroleum. δ 5.2 (C_{4a}–$\underline{H}$), 4.0 mc ($C\underline{H}_2$–O–), 2.56s (C_{5a}–$C\underline{H}_3$), 0.68 (C13–$C\underline{H}_3$), 0.91 and 0.83 (remaining Me protons). (Found: C, 72.58; H, 9.62. $C_{27}H_{42}O_5$ requires: C, 72.64; H, 9.41%).

Further elution with ether yielded a solid, **5** (0.30 g) m.p. 170° which was crystallized from light petroleum. δ 3.2 m (C_2–$\underline{H}_2$; C_7–$\underline{H}_2$), 1.0 (C_5–$C\underline{H}_3$), 0.7 (C13–$C\underline{H}_3$), 0.9 and 0.8 (remaining Me protons) (Found: C, 70.55; H, 8.54. $C_{27}H_{40}O_6$ requires: C, 70.43; H, 8.69%).

19-*Nor-5-methyl-5-hydroxy*-3,4,5,6-*disecocholest*-7(8), 9(10)-*dien*-2,5,7-*tricarboxylic acid* **6**. A soln of **5** (100 mg) in 50 ml methanolic NaOH (5%) was heated under reflux for 1 hr. The soln was poured into an excess water and carefully acidified with HCl. The usual work up procedure provided **6**, a non crystallizable oil (80 mg). δ 6.7 m (COO$\underline{H}$, COO$\underline{H}$, O$\underline{H}$ and C_7–$\underline{H}$), 1.26 (C_5–$C\underline{H}_3$), 0.9 and 0.8 (remaining Me protons) (Found: C, 67.90; H, 8.54. $C_{27}H_{42}O_7$ requires: C, 67.78; H, 8.78%).

Reaction of **2** *with perbenzoic acid.* The ketone **2**, m.p. 64° (prepared by the base hydrolysis and Jone's oxidation of 3β-chloro-6β-acetoxy-19-nor-5-methyl-5β-cholest-9(10)-ene)[6] (2.0 g) in $CHCl_3$ (20 ml) was treated with perbenzoic acid (2.5 mole equiv) in the usual way as described. The residue obtained on evaporation of the solvent, was chromatographed over silica gel. Elution with light petroleum:ether (17:1) gave **9** which was crystallized from light petroleum (0.75 g) m.p. 138°, 715 cm^{-1} (C–Cl). δ 4.6 m (C_3–$\alpha\underline{H}$), 1.36 (C_5–$C\underline{H}_3$), 0.75 (C13–$C\underline{H}_3$), 0.88 and 0.80 (remaining Me protons) (Found: C, 74.51; H, 10.12. $C_{27}H_{43}O_2Cl$ requires: C, 74.65; H, 9.90%).

Further elution with light petroleum:ether (16:1) afforded **10**, which was crystallized from light petroleum (0.5 g) m.p. 105°. NMR δ 3.7 m ($W^{1/2} = 6$ Hz; C_3–$\underline{H}$), 2.35 (C_{7a}–$\underline{H}_2$), 1.35 (C_5–$C\underline{H}_3$), 0.73 (C13–$C\underline{H}_3$), 0.9 and 0.8 (remaining Me protons) (Found: C, 72.20; H, 9.43. $C_{27}H_{43}O_3Cl$ requires: C, 72.0; H, 9.55%).

Acknowledgements—We are grateful to Prof. W. Rahman, Head, Department of Chemistry, Prof. M. S. Ahmad for useful discussion and CSIR (New Delhi) for financial assistance (M.A.G. and H.A.).

REFERENCES

[1] Shafiullah and E. A. Khan, *Acta. Chim. Acad. Sci. Hung.* In press.

[2] Shafiullah and M. A. Ghaffari, *J. Ind. Chem. Soc.* In press.

[3] V. A. Petrow, *J. Chem. Soc.* 999 (1939).

[4] R. B. Turner, *J. Am. Chem. Soc.* **72**, 870 (1950).

[5] H. Aebli, C. A. Crob and E. Schumacher, *Helv. Chim. Acta* **41**, 774 (1958).

[6] A. Fischer, M. J. Hardman and M. P. Hartshorn, *Tetrahedron* **23**, 159 (1967).