246. Steroids and Sex Hormons

Part 263 [1]

On the Mechanism of the Reaction of 17-Hydroxyimino-steroids with Carbodiimide/Dimethylsulfoxide

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Summary

Treatment of the (*Z*)-isomers **6** and **7** of the four isomeric 16-acetoxy-17-hydroxyimino-steroids **6–9** with DCC/DMSO/CF_3COOH (*Moffat* fragmentation of oximes) yielded the *seco-α*-acetoxy-nitriles **10** and **11**, respectively, while similar treatment of both (*E*)-isomers **8** and **9** gave the formyl-carbonitrile **14**. The mechanism of these fragmentations is discussed. ^{13}C-NMR. data of oximes are presented which show the *γ-gauche* effect being associated with σ (C–H)-bond polarization.

Moffat et al. [3] have shown that 17-hydroxyimino-steroids such as **1** on treatment with dicyclohexylcarbodiimide (DCC), dimethylsulfoxide (DMSO) and trifluoroacetic acid (TFA), are converted into *seco*-nitriles such as **2** in good yields *(Scheme 1)*. In order to account for the unusually high yield of the *Beckmann*-II-reaction product (*e.g.* **2**) these authors have proposed an eightmembered ring cyclic-fragmentation mechanism (see **A**), without, however, going into the question of the effect of oxime (*E*/*Z*)-configuration on their suggested scheme.

In connection with a natural product synthesis we have had occasion to apply this fragmentation reaction to the four isomeric 16-acetoxy-17-hydroxyimino-steroids **6–9** whose configuration could be unambigously assigned[1]). Both (*Z*)-isomers **6** and **7** were found to give the *seco-α*-acetoxy-nitriles **10** and **11**, respectively, each in about 40% yield, together with the *Beckmann*-I-rearrangement products, **12** and **13**, respectively, also in about 40% yield. From the (*E*)-isomers **8** and **9** there were obtained the hydrolysis products **4** and **5**, respectively, together with the unstable formyl-carbonitrile **14** which was formed in variable amounts[2]).

[1]) Compounds **6–9** have been prepared by standard methods from **3** *via* **4** and **5** by $Pb(OAc)_4$, Ac_2O oxidation and $NH_2OH \cdot HCl$ treatment in pyridine solution, respectively (see [2] and *Table*).

[2]) The absence of product **14** from the fragmentation of **6** and of **7**, and the absence of **10–13** from the fragmentation of **8** and of **9** indicates that the starting materials are configuratively stable under the conditions employed. Moreover, configuratively unchanged starting material was isolated from the reaction mixture to the extent of 5–10%.

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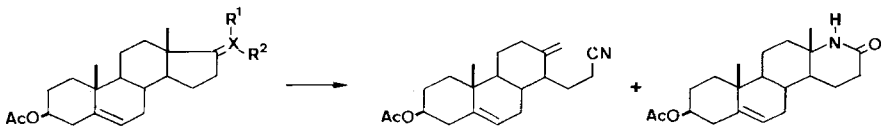
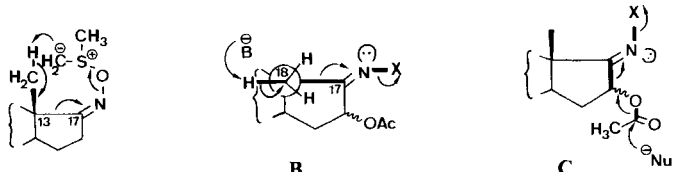
Scheme 1



1 $XR^1R^2 = \dot{N}OH$
(*E*)-**1** X = N, R^1 = lone electron pair, R^2 = OH
(*Z*)-**1** X = N, R^1 = OH, R^2 = lone electron pair
16 $XR^1R^2 = O$



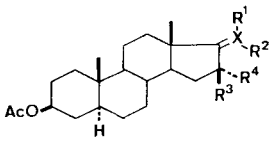
A

B
(*Z*)-O

C
(*E*)-O

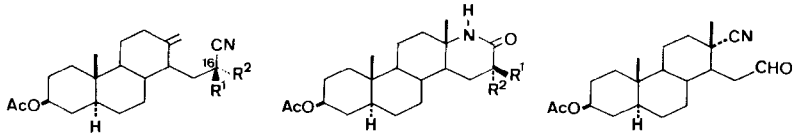
These results indicate the antiperiplanar fragmentation mechanism as shown in **B** (s. [4]) to be the more likely mode of fragmentation of 17-hydroxyimino-steroids in the presence of DCC/DMSO/TFA. This is supported by the fact that according to *Moffat*'s cyclic-fragmentation mechanism **A** no *seco*-nitriles should have resulted from the (*Z*)-isomers. On the other hand, the C(16),C(17)-bond of the (*E*)-isomers **8** and **9** appears to fragment easily (see **C**); and hence one cannot exclude the possibility that the (*E*)-isomer without a 16-acetoxy substituent could lead to a *seco*-nitrile in accord with *Moffat*'s cyclic mechanism **A**.

Scheme 2



3 $XR^1R^2 = O$, $R^3 = R^4 = H$
4 $XR^1R^2 = O$, $R^3 = H$, $R^4 = OAc$
5 $XR^1R^2 = O$, $R^3 = OAc$, $R^4 = H$
6 X = N, R^1 = lone electron pair, R^2 = OH, $R^3 = H$, $R^4 = OAc$
7 X = N, R^1 = lone electron pair, R^2 = OH, $R^3 = OAc$, $R^4 = H$
8 X = N, R^1 = OH, R^2 = lone electron pair, $R^3 = H$, $R^4 = OAc$
9 X = N, R^1 = OH, R^2 = lone electron pair, $R^3 = OAc$, $R^4 = H$

Scheme 3



10 $R^1 = H$, $R^2 = OAc$
11 $R^1 = OAc$, $R^2 = H$

12 $R^1 = H$, $R^2 = OAc$
13 $R^1 = OAc$, $R^2 = H$

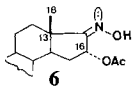
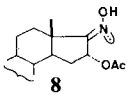
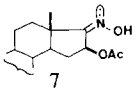
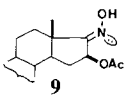
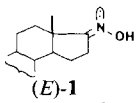
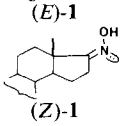
14

This question was resolved by subjecting the (*E*)-isomer (*E*)-**1** and the (*Z*)-isomer (*Z*)-**1**, both lacking a 16-acetoxy substituent, to fragmentation[3]). Under *Moffat*'s conditions (*E*)-**1** gave **2** in 34% and **15** in 44% yield, whereas, in marked contrast, (*Z*)-**1** gave the parent ketone **16** in 13% and the lactam **15** in 16% yield, and no trace of *seco*-nitrile **2**. With thionyl chloride in pyridine (*Z*)-**1** gave a 55% yield of lactam **15** together with 30% of recovered starting material which was now found to be an (*E*/*Z*)-mixture.

In conclusion it appears that an optimum yield of the seco*-nitrile is ensured by an exactly antiperiplanar arrangement of the bonds to be broken in the transition state* (s. **B**, *Scheme 1*).

*Comment on the assignment of oxime (*E/Z*)-configuration of 17-hydroxyimino-steroids.* From the ^{1}H-NMR. data given in the *Table* it can be shown that H–C(16) of **6**–**9** is *shielded* on going from the (*Z*)-series (**6** and **7**) to the (*E*)-series (**8** and **9**), a behaviour expected from the data given by *Karabatsos et al.* [5]. Consistent with [5] a *deshielding* effect, but much smaller, is found for $H_3C(18)$ on going from the (*Z*)- to the (*E*)-series.

Table

Compound	^{1}H-NMR.[a])		^{13}C-NMR.[b])			$\Delta\delta$ in ^{13}C-NMR.[c])		
	H–C(16)	$H_3C(18)$	C(13)	C(16)	C(18)	C(13)	C(16)	C(18)
 **6**	6.01 (*t*, *J* = 3)	0.89	44.1	68.8	18.3			
						+1.7	+4.3	−4.0
 **8**	5.50 (*d*×*d*, *J* = 2, *J*′ = 4)	1.00	45.8	73.1	14.3			
 **7**	5.81 (*t*, *J* = 7)	1.04	43.2	68.0	17.0			
						+1.3	+4.8	−3.0
 **9**	5.42 (*t*, *J* = 8)	1.12	44.5	72.8	14.0			
 (*E*)-**1**		0.91	43.6	25.0	16.8			
						+2.0	+3.8	−3.4
 (*Z*)-**1**		1.01	45.6	28.8	13.4			

[a]) In $CDCl_3$ on a *Varian* HA-100 spectrometer, in ppm.

[b]) In $CDCl_3$ on a *Varian* XL-100 FT. spectrometer, in ppm.

[c]) Positive value means shift to lower field on going from the first isomer to the second of the pairs, and *vice versa*.

[3]) The isomer (*Z*)-**1** was prepared in very low yield from (*E*)-**1** by treatment with $CHCl_3$/HCl and chromatographic separation.

The data given by *Roberts et al.* [6] and *Levy et al.* [7] for the ^{13}C-resonance of α-C-atoms in oximes indicate that the C-atom *trans* to the oxime-hydroxyl group is more *deshielded* than the *cis* C-atom (γ-*gauche* effect). This behaviour is true for C(16) which is always *deshielded* by about 4 ppm on going from the isomers **6**, **7** and (*E*)-**1** with OH *cis* to C(16) to the isomers **8**, **9** and (*Z*)-**1**, respectively, with OH *trans* to C(16). However, the angular quaternary C(13) of the steroid skeleton shows an anomalous behaviour. The unambigously assigned C(13)-resonances are *also deshielded* on going from the isomers **6**, **7** and (*E*)-**1** to the isomers **8**, **9** and (*Z*)-**1**, respectively. This result is in good agreement with *Grant's* theoretical prediction [8] that the γ-*gauche* effect (compression shift) is associated with the polarization of σ(C–H)-bonds. These are lacking on quaternary C-centres, and therefore the observed downfield shift of these quaternary C-atoms, on going from **a** to **b**, is due to the hydroxyl's deshielding effect.

a $R^1 - R^4 =$ alkyl **b**

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REFERENCES

[1] Part 262: *J. Pfenninger, Ch. Heuberger & W. Graf*, Helv. *63*, 2328 (1980).
[2] *J. Pfenninger & W. Graf*, Helv. *63*, 1562 (1980).
[3] *A. H. Fenselan, E. H. Hamamura & J. G. Moffat*, J. Org. Chem. *35*, 3546 (1970).
[4] *C. A. Grob & P. W. Schiess*, Angew. Chem. Int. Ed. *6*, 1 (1967).
[5] *G. J. Karabatsos & R. A. Taller*, Tetrahedron *24*, 3347 (1968).
[6] *G. E. Hawkes, K. Herwig & J. D. Roberts*, J. Org. Chem. *39*, 1017 (1974).
[7] *G. C. Levy & G. L. Nelson*, J. Am. Chem. Soc. *94*, 4897 (1972).
[8] *D. M. Grant & B. V. Cheney*, J. Am. Chem. Soc. *89*, 5315 (1967); *D. K. Dalling & D. M. Grant*, ibid. *89*, 6612 (1967).