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RING EXPANSION OF STEROID OXETHANS INTO HIHYDROOXAZINES

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Abstract: In the case of oxethans condensed in an appropriate steric position to the sterane skeleton, the formation of six-membered dihydrooxazines has been observed with aliphatic or aromatic acid nitriles in the presence of Lewis acids, involving thus ring expansion.

Epoxides and their substituted derivatives can be converted into derivatives of 1,2-hydroxycarboxamides with acid nitriles in the presence of acids under the conditions of the Ritter reaction[1].

The reaction has been applied in the conversion of several steroid epoxides into trans-1,2-hydroxycarboxamides with acetonitrile in the presence of $HClO_4$.[2] This reaction also takes place with other aromatic and aliphatic acid nitriles on the action of a Lewis acid and the corresponding trans-1,2-hydroxycarboxamides are formed [3].

It has been found, however, that the four-membered oxethans react with ring cleavage or polymerisation[4] on the action of protic or Lewis acids. The number of reactions involving ring expansion is relatively low[5].

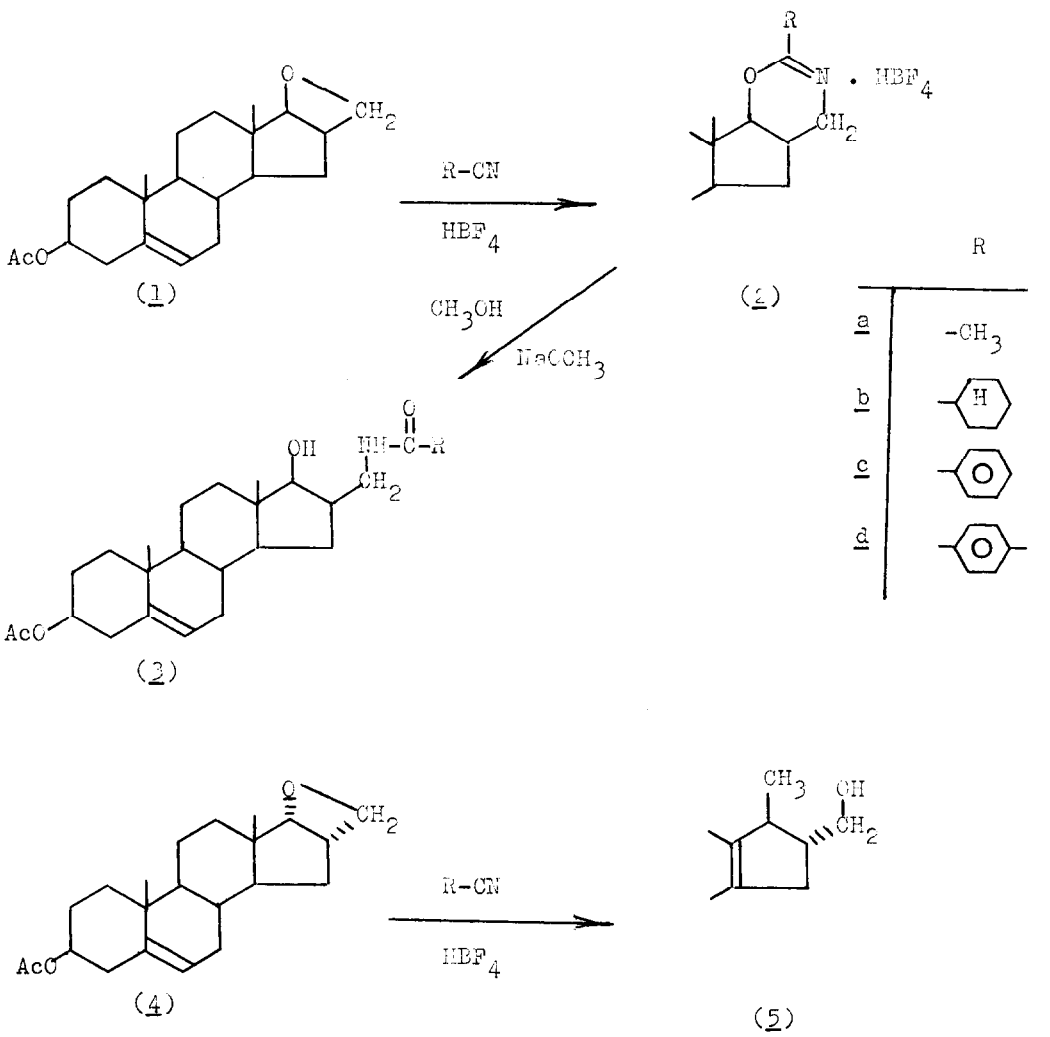
In the case of oxethans condensed in an appropriate steric position to the sterane skeleton, the formation of six-membered dihydrooxazines has been observed almost quantitatively with aliphatic or aromatic acid nitriles in the presence of Lewis acids, involving thus ring expansion.

The 3-acetoxy-16β,17β-epoxymethyleneandrost-5-ene-3β-ol (1) reacts with acetonitrile, cyclohexylnitrile, benzonitrile and p-methoxybenzonitrile in the presence of equivalent amounts of the tetrafluoroboric acid - diethyl ether complex in diethyl ether solutions at room temperature and the corresponding substituted dihydrooxazine-HBF_4 salts (2a, b, c, d)are obtained in crystalline form.

The relatively unstable base can be liberated from the salt with aqueous $NaHCO_3$.

When the salts are liberated with $NaOCH_3$ in methanol, the corresp 16β N-acylaminomethylandrost-5-ene-3β,17β -diol (3) is formed.

Under similar experimental conditions, the 3-acetoxy-16α,17α -ep methylene-androst-5-ene-3β -ol (4) suffers ring cleavage on the action lewis acid and becomes stabilized in a Wagner-Meerwein rearrangement (5) and no dihydrooxazine is formed (Scheme 1).



(Scheme 1)

Table

IR and ^{1}H NMR data of compounds 2a-d (salts and bases)

(IR spectra were recorded with a Perkin-Elmer 577 spectrometer in KBr pellets; ^{1}H-NMR spectra were obtained with a Varian EM-390 spectrometer in $CDCl_3$ solution at 90 MHz room temperature, using TMS as internal standard.)

IR frequencies (cm^{-1})						^{1}H-NMR chemical shifts (δ_{TMS} = 0 ppm					
							δCH_3 s (3H)				
Compounds	ν N⊕H band (diffuse)	ν C=O band	ν C=N band	ν C-O bands	ν B-F band (diffuse)	C-18	C-19	other	H-17 d° (1H)	NCH m● (2H)	NH× s (1H)
2a (salt)	3600-2500	1730	1685	1250 1035	1200-950	0,80	1,05	2,45▯	4,35	3,8 4,5	10,0
2a (base)	-	1730	1680	1240-20 1030	-	0,75	1,05	1,95▯	300-360 Hz ▽		-
2b (salt)	3600-2500	1740	1675	1250 1035	1200-950	0,75	1,05	-	4,40	3,5 4,0	9,9
2b (base)	-	1730	1685	1245	-	0,70	1,05	-	3,70	2,80 3,65	-
2c (salt)	3600-2500	1730	1660	1250 1035	1200-950	0,80	1,05	-	4,55	3,3 4,1	10,4
2c (base)	-	1735	1650	1250 1040-30	-	0,80	1,05		4,00	3,00 3,90	-
2d (base)	-	1735	1650	1255 1035	-	0,80	1,05	3,80	3,95	3,00 3,80	-

▯ methyl group attached to the oxazine ring;

■ t (^{5}J=1 Hz): long-range coupling with NCH_2 group;

○ J = 9Hz;

● A and B part of an ABX multiplet with $^2J_{AB} \approx$ 15Hz, $^3J_{AX}$ and $^3J_{BX} \approx$ 10 and 6 Hz, in case of salt broad signals;

× broad signal;

▽ overlapped multiplets in Hz.

The structures of the products were determined from spectral data or, where the substances are already known, on the basis of authentic synthetic samples prepared (Table).

The formation of a product with ring expansion renders probable the intermediate with carbonium cation character. The coordiantion of the Lewis acid results in the formation of an oxonium ion, this becomes attacked by the nucleophilic nitrile at the primary carbon atom, being in a sterically favourable position. A carbonium cation is formed which becomes stabilized by ring closure and the corresponding dihydrooxazine is obtained (Scheme 2).

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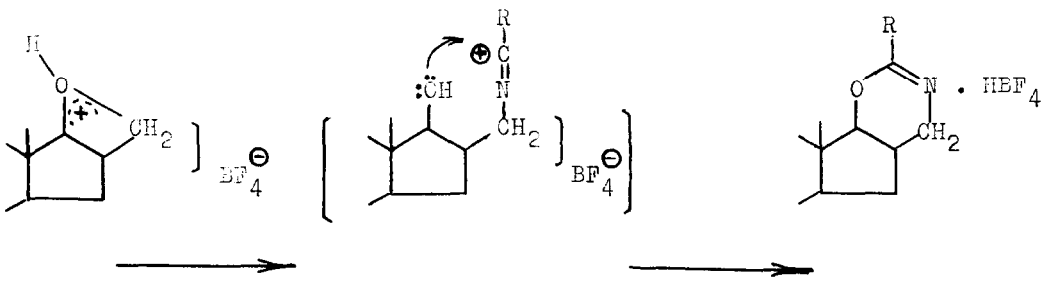

(Scheme 2)

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