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CLEAVAGE OF STEROIDAL EPOXIDES WITH ORGANOALUMINUM CYANIDES*

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ALTHOUGH the base catalytic cleavage of epoxides with hydrogen cyanide yielding 1,2-cyanohydrin has been long known, application of this reaction has been limited only to the simple aliphatic epoxides such as ethylene oxide (1). Bowers and his co-workers (2) at first studied the reaction of steroidal 5,6α-epoxides by the conventional method and showed reluctance of the epoxides in the complex molecules to the cleavage reaction. Thus, pregnenolone-acetate 5,6α-epoxide (I) could be cleaved with potassium cyanide only under drastic conditions giving a mixture of the various cyanated products which are isomerized and/or dehydrated products derived from the initially formed 1,2-cyanohydrin **I**. The primary compound **I** was obtained really when a relatively mild condition was used, but only in low yield (11%).

In the preceding paper, we reported a new method for conjugate addition of cyanide anion to various enones using alkylaluminums and hydrogen cyanide in aprotic solvents (3). In view of its high efficiency, it seemed highly promising to carry out cyanide fission of steroidal epoxides by this new reagent. Cholesterol 5,6α-epoxide (**II**) was at first tested by treating it with hydrogen cyanide and triethylaluminum (HCN-$AlEt_3$) (6:10 molar equiv.) in tetrahydrofuran for 4 hr. (all the experiments were carried

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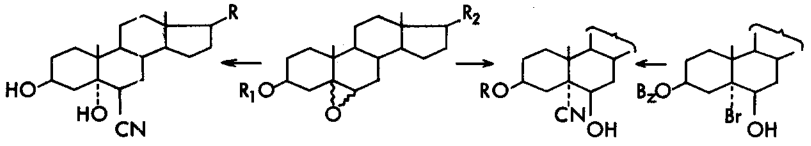
* Hydrocyanation Part **II**. (The preceding paper, W. Nagata et al., Tetrahedron Letters, No. 11, 461 (1962) should belong to this series as the Part I) A part of this work was presented at the annual lecture meeting organized by Yuki-Gosei Kyokai held at Osaka, September 1964.

out at room temperature). In contrast to the result obtained by Bowers, the reaction proceeded almost quantitatively and 3β,5-dihydroxy-6β-cyano-5α-cholestane (IV) was isolated in 90.5% yield (4). Likewise, cholesterol 5,6β-epoxide (Va) and its benzoate



III : R=Ac
IV: R=C_8H_{17}

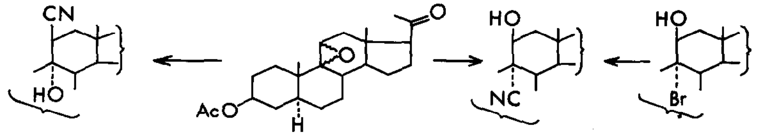
α-epoxide {I : R_1, R_2=Ac; II : R_1=H, R_2=C_8H_{17}}

β-epoxide {Va: R_1=H, R_2=C_8H_{17}; Vb: R_1=Bz, R_2=C_8H_{17}}

VIa: R=H
VIb: R=Bz

VII

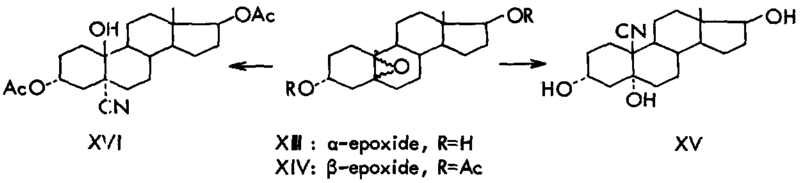
Vb were cleaved smoothly under similar conditions (HCN-AlEt$_3$; 3:5 equiv., 7 hr.) to give 3β,6β-dihydroxy-5-cyano-5α-cholestane (VIa), m.p. 220-221°, and its 3-benzoate VIb, m.p. 207-208°, in 97 and 90% yield respectively. The reaction Va→VIa was then proved to proceed more rapidly (within 2.5 hr.) when the reagent system (HCN-AlEt$_3$ in tetrahydrofuran) was replaced by diethylaluminum cyanide in toluene (5). We next examined a possibility to synthesize the 1,2-cyanohydrin VIb directly from bromohydrin VII and realized the conversion in a yield of 52.6% by treating the latter with HCN and AlEt$_3$ (7:10 equiv.) for 19 hr. In this case, intermediate formation of the 5,6β-epoxide Vb was presumed, since this was obtained in a separate experiment in which bromohydrin VII was treated with triethylaluminum alone. Confirmation of the stereochemistry of the products IV and VI and thence of diaxial cleavage of the epoxides was carried out as follows. The reasonable downfield shifts of the C$_{19}$-methyl signals due to 6β-substituents (0.33 p.p.m. in IV and 0.22 p.p.m. in VIa) in the N.M.R. spectra (6) were observed. 5α-Configuration of the cyano group in VI was substantiated by a transformation of VIb to known 3β-hydroxy-5-cyano-5α-cholestane (7) via the 6-keto derivative and its dithioketal.



XII VIII: β-epoxide IX : α-epoxide X XI

9,11-Epoxides were next examined. As expected, 3β-acetoxy-9,11β-epoxy-5α-pregnan-20-one (VIII) was cleaved smoothly by treating with HCN-AlEt$_3$ (3:5 equiv.) for 5 hr. giving the 9α-cyano-11β-hydroxy steroid X, m.p. 277-279°, in 84.5% yield. The same product was also prepared from the bromohydrin XI by direct hydrocyanation in a yield of 64%. The 11β-configuration of the hydroxyl group was confirmed by its de-shielding effect towards 19- and 18-methyl groups (0.29 and 0.18 p.p.m.) as well as its conversion to a non-ketalizable ketone. In view of the fact that steroidal 9,11α-epoxides generally resist fission by mineral acids or lithium aluminum hydride (8), it was of considerable interest to know whether the fission is effected by the new hydrocyanating agents. It was now found that diethylaluminum cyanide could attack the 9,11α-epoxide IX in toluene (30 hr.) to yield 3β-,9α-dihydroxy-11β-cyano-5α-pregnan-20-one 3-acetate (XII), m.p. 245-246°, in a yield of 43.4%. This proved the high efficiency of the new reagent. 11β-Configuration of the cyano group in XII was confirmed likewise by N.M.R. spectroscopy (shift value due to the 11β-CN for C$_{18}$- and C$_{19}$-methyl group: 0.31 and 0.38 p.p.m.) and the tertiary nature of the hydroxyl group was based on its stability against chromic acid.

In turn, the tetrasubstituted epoxides such as 5,10α-epoxide XIII and 5,10β-isomer XIV were examined. Both XIII and XIV underwent cyanid fission readily with HCN-AlEt$_3$ within a few hours and gave the corresponding 1,2-cyanohydrins XV, m.p. 247-249°, and XVI, m.p. 213-219° in a yield of 86.6 and 60% respectively. Whereas the



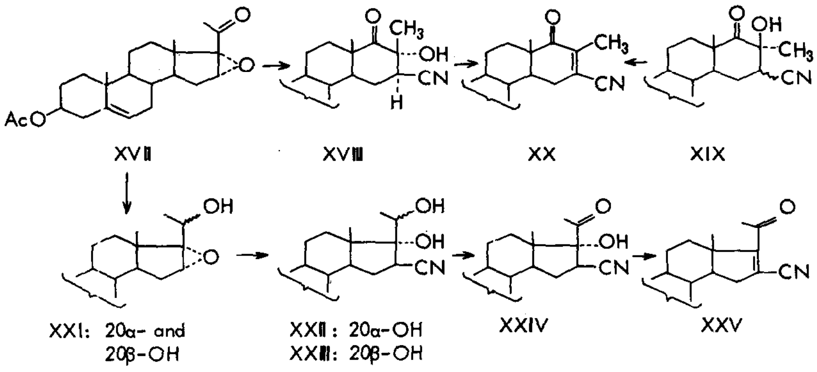
XVI

XII : α-epoxide, R=H
XIV: β-epoxide, R=Ac

XV

structure of XV was established by its conversion into known 10β-cyanoestr-4-ene-3,17-dione (9) by oxidation and subsequent dehydration, structural assignment of XVI is based on only the analogy of the other examples and thence temporarily.

When 16,17α-epoxy-20-ketosteroid XVII was treated with HCN-AlEt$_3$ similarly, a D-homo-1,2-cyanohydrin XVIII, m.p. 259-261°, was formed in 81% yield. The D-homoannulation is not unexpected because of the Lewis acid nature of the reagent. Structural assignment of the product XVIII was based upon the transformation to the known dehydration product XX (10), the axial nature of the C$_{16}$-hydrogen (d.d. at 2.82 p.p.m., J=4,12 c.p.s. at 100 MC) and the less downfield shift of the 18-angular methyl in XVIII (1.15 p.p.m.) as compared with the analogous compound XIX (10) epimeric at C$_{17}$ (1.32 p.p.m.) (11,12). The assignment of the 17β-methyl is reasonable in view of the fact that the D-homoannulation caused by Lewis acids gives generally 17β-methyl compounds (13).



XVII XVIII XX XIX

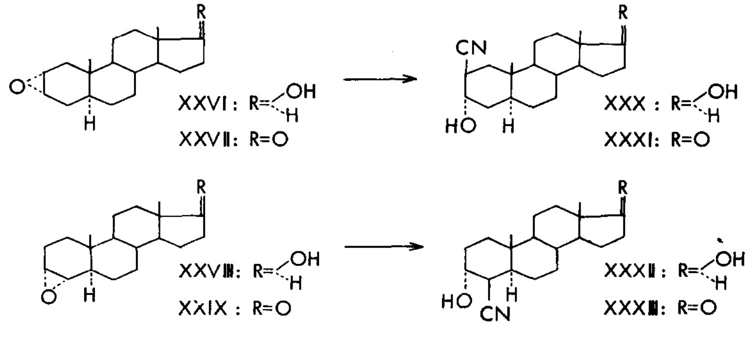
XXI: 20α- and 20β-OH

XXII : 20α-OH
XXIII: 20β-OH

XXIV XXV

However, the synthesis of the non-isomerized 1,2-cyanohydrin XXIV was accomplished by following the route depicted in the figure. Thus, a mixture of 20α- and 20β-hydroxy-16,17α-epoxide XXI derived from XVII was treated with HCN-AlEt$_3$ to give 37% of the 3β,20α,17α-trihydroxy-16β-cyanopregn-4-ene 3-acetate (XXII), m.p. 255-256°, ($[M]_D$=-217.9) and 45.5% of the 20β-epimer XXIII, m.p. 205-206° ($[M]_D$= -161.7). The latter was then converted into the desired product XXIV, m.p. 256-258°, in 61.3% yield by chromic acid oxidation in pyridine. That no rearrangement had occurred during the conversions was substantiated by transformation of XXIV to the known dehydrated compound XXV (14). The 16β-configuration of the cyano group was again based upon the N.M.R.-spectroscopic study on the hydrogen at C_{16} (d.d. at 3.33 p.p.m., J=8 and 7 c.p.s. at 100 MC) and the analogy of the other examples, in which diaxial cleavage principle is well borne out (15).

Finally some disubstituted epoxides XXVI-XXIX were tested (16). 2,3α-Epoxides XXVI and XXVII gave by treatment with HCN-AlEt$_3$ under similar conditions 2β-cyano-3α-hydroxy compounds XXX, m.p. 275-276.5°, and XXXI, m.p. 211.5-212.0° in a yield of 66.4 and 57.3% respectively. Likewise, 3,4α-epoxides XXVIII and XXIX afforded the corresponding 1,2-cyanohydrins XXXII, m.p. 258.5-261.5°, and XXXIII, m.p. 235.5-238.0° in 73.6 and 48.1% yields. The 2β- and 4β-configurations of the cyano groups



in these products were verified by their deshielding effect towards the 19-methyl group (0.3 p.p.m.). The relatively lower yield in this series was unexpected. This is probably due to high sensibility of the less substituted epoxides to the reagents leading to other unidentifiable products.

As illustrated above, the characteristic feature of this method is that the epoxides can be cleaved cleanly with the newly developed reagent under very mild conditions to afford the primary product in a high yield and that the diaxial fission principle holds through all the cases so far examined. From this point of view, the new method will be of great preparative value in synthetic organic chemistry, since the both angular and non-angular cyano groups thus introduced are readily convertible into a variety of other carbon substituents.

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4. All compounds gave satisfactory analysis and show reasonable infrared spectra.
5. The reacting species in this reagents system are considered to be both a complex acid, $H^+[R_3AlCN]^-$, and alkylaluminum cyanide, R_2AlCN, when tetrahydrofuran is used as a solvent. Organoaluminum cyanides such as Me_2AlCN, Et_2AlCN, $(Bu^i)_2AlCN$ and EtAlClCN were prepared separately and were proved to be the most efficient hydrocyanating agents. The work will be published soon.
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