UNUSUAL REACTIONS OF 8β-CYANO-6,7-DIAZACHOLESTEROL

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Abstract - The synthesis of 8β-cyano-6,7-diazacholesterol (6) and attempts to convert it into azine 1 are described. The unexpected products 7, 8 and 9 are formed during reactions involving hydrogen cyanide elimination from 6.

Recent studies directed toward structural and stereochemical modifications in the vitamin D series[1] prompted us to attempt the synthesis of the 6,7-diaza-analog of provitamin D_3 1.

As a starting material for this synthesis a Diels-Alder adduct[2] of 7-dehydrocholesterol with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), 2a, was chosen, based on the synthetic strategy of using the PTAD fragment in 2a as a source of two nitrogens. We expected that the removal of C-6 and C-7 atoms, introduction of electronegative functions at 5β- and 8β-positions followed by base-catalyzed cleavage of the urazole residue with simultaneous elimination of substituents at C-5 and C-8 could afford the desired 1. Although the PTAD adduct of ergosterol has been commonly used[1a,2] to protect 5,7-diene moiety during ozonolysis of the double bond in the side chain, it is known that ring B double bond may be also cleaved with excess ozone[3].

Compound 2b (mp 155°C; $[\alpha]_D^{25}$ -79°) underwent ozonolysis smoothly to give, after reductive decomposition of the ozonides, the seco-dialdehyde 3a (a foam; $[\alpha]_D^{25}$ -50°)[4]. Since all attempts to obtain 5β,8β-diformate by Baeyer-Villiger oxidation of 3a failed, we decided to transform 3a into the dicyano derivative 4. This was realized via dioxime 3b (a foam; $[\alpha]_D^{25}$ -46°) and the thermal elimination[5] of the elements of acetic acid from its acetyl derivative 3c (a foam; $[\alpha]_D^{25}$ -23°). Dinitrile 4 (a foam; $[\alpha]_D^{25}$ -25°); ^{1}H-NMR, δ: 1.10 (s, 18-H), 1.69 (s, 19-H), 5.18 (m, $\frac{W}{2}$ = 10 Hz, 3α-H), obtained in 48% overall yield from 2b, was subjected to hydrolysis under various conditions. The best results were achieved using KOH in boiling aqueous dioxane. The first reaction product which may be isolated in about 85% yield after reflux for 1 h was partially hydrolyzed compound 5[6] (mp 206-209°C; $[\alpha]_D^{25}$ + 173°); MS, m/e: 413 (M^+-PhNCO, 56%), 386 (M^+-PhNCO-HCN, 25%), 119 (PhNCO , 100%); ^{1}H-NMR, δ: 1.12 (s, 18-H), 1.19 (s, 19-H), 3.47 (m, $\frac{W}{2}$ = 26 Hz, 3α-H), 8.58 (s, N-H). Further heating (5 h) under reflux led to the steady formation of the much more polar product 6 (mp 103-106°C;

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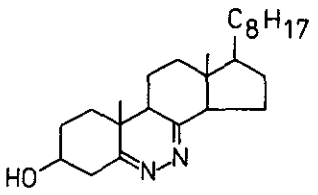

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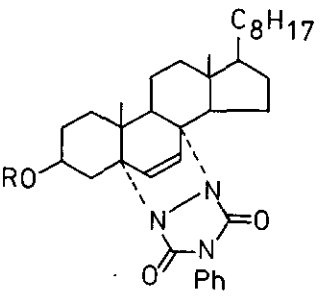
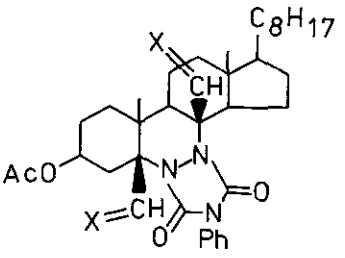
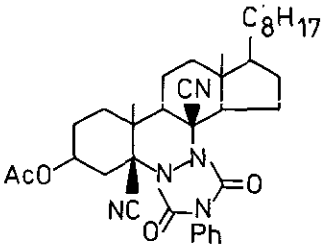


2a : R=H
b : R=Ac



3a : X=O
b : X=N–OH
c : X=N–OAc



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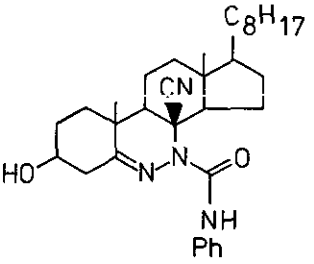

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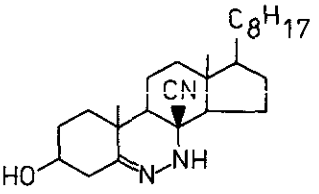

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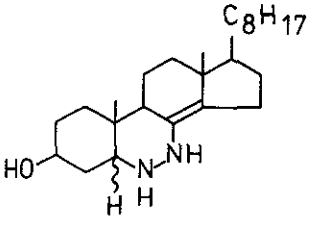
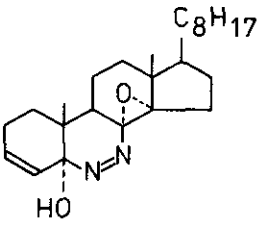


7a : 5α
b : 5β



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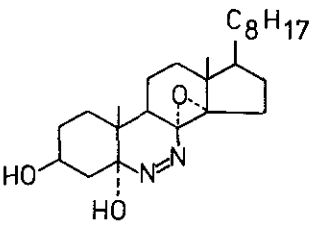

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$[\alpha]_D^{25}$ + 224°); MS, m/e: 413 (M^+, 100%), 386 (M^+-HCN, 14%), 371 (M^+-HCN-Me, 60%); ^{13}C-NMR, δ: 128.2 (-C≡N), 153.8 (>C=N-), which was obtained in 67% yield after chromatographic separation from 5 (32%). Upon prolonged heating of the reaction mixture (48 h) 8β-cyano-6,7-diazacholesterol (6) underwent further transformation to a complex mixture of many products of very similar Rf values by TLC. Based on these observations, elimination of HCN from 6 was attempted using such strong bases as NaH, LiH, $NaBH_4$, t-BuOK, LDA, but all reactions failed to afford 1 (or any of its double bond isomers). Reduction with $LiAlH_4$ (room temperature, 3 h) did result in elimination of the cyano group, and a mixture of two more polar products, 7a and 7b, was obtained. HPLC (6.2 mm x 25 cm Zorbax-SIL column) separation afforded both compunds in pure form: 7a (78% yield; mp 169-172°C; $[\alpha]_D^{25}$ +21°); MS, m/e: 388 (M^+, 100%); ^{1}H-NMR, δ: 2.71 (dd, J_1 = 4 Hz, J_2 = 12 Hz, 5α-H), 3.70 (m, $\frac{w}{2}$ = 27 Hz, 3α-H); ^{13}C-NMR, δ: 119.4 (C-14), 151.8 (C-8); 7b (16% yield; $[\alpha]_D^{25}$ +114°); MS, m/e: 388 (M^+, 100%); ^{1}H-NMR, δ: 3.06 (dd, J_1 = = 3.5 Hz, J_2 = 8 Hz, 5β-H), 4.19 (m, $\frac{w}{2}$ = 18 Hz, 3α-H). It was reasonable to assume that such an unusual elimination of hydrogen cyanide during lithium aluminum hydride reduction could be promoted by proximity of aluminum atom bonded to the neighbouring nitrogen. In order to check this hypothesis and at the same time to avoid the reduction of the carbon-nitrogen double bond compound 6 was treated with an excess of aluminum isopropoxide in refluxing benzene. This resulted in formation of single product, 8, which was isolated by HPLC in 80% yield (mp 87-89°C; $[\alpha]_D^{25}$ + 10°); MS, m/e: 400 (M^+, 7%), 384 (M^+-O, 65%), 372 (M^+-N_2, 38%), 351 (M^+-O-H_2O-Me, 100%); ^{1}H-NMR, δ: 0,96 (s, 18-H), 1.12 (s, 19-H), 5.35 (d, J = 10 Hz, 4-H), 5.73 (s, O-H), 6.07 (m, 3-H); ^{13}C-NMR, δ: 81.7 (C-5), 118.9 (C-3), 134.6 (C-4). This unusual oxidation under reductive conditions apparently involved a radical reaction with an oxygen molecule from the air.

In the next experiment the thermal elimination of HCN from 6 was attempted. A sample of 6 was melted and the temperature was slowly raised to 200°C for 10 min and then cooled for another 10 min. When the temperature exceeded 180°C an evolution of hydrogen cyanide was observed. TLC of the reaction mixture showed the presence of two main products in addition to some remaining 6. The products were separated by preparative high-performance liquid chromatography. The less polar component (45% yield) proved to be identical in all respects with the previously obtained compound 8. The second, more polar product (20% yield) with 3β-hydroxyl group intact was identified as 9 (mp 125-128°C; $[\alpha]_D^{25}$ +15°); MS, m/e: 418 (M^+, 33%), 402 (M^+-O, 11%), 390 (M^+-N_2, 37%), 375 (M^+-N_2-Me, 46%), 43 (100%); ^{1}H-NMR, δ: 0.98 (s, 18-H), 1.25 (s, 19-H), 3.89 (m, $\frac{w}{2}$ = 28 Hz, 3α-H), 5.68 (s, O-H). The mechanism of these unusual autooxidation processes observed during the pyrolysis of 6 and its reaction with aluminum isopropoxide is not clear yet in details. However, it is postulated that the same intermediate 1 or, more likely, its enamine tautomer with $C_{(8)}$ - $C_{(14)}$ double bond is initially formed in both cases. The key step of the subsequent oxidation would involve an attack of the molecular oxygen on C-14 beginning a free-radical chain process[7]. The experiments carried out under an oxygen-free atmosphere failed to afford an intermediate mentioned above proving an extreme susceptibility of such a system to oxidation.

REFERENCES AND NOTES

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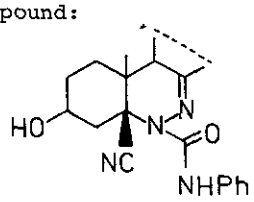
3. S. C. Eyley and D. H. Williams, J. Chem. Soc. Perkin Trans. 1, 1976, 727.
4. Satisfactory elemental analyses were obtained for all new compounds.
5. R. Kwok and M. E. Wolff, J. Org. Chem., 1963, 28, 423.
6. None of the isomeric compound:



could be detected in the reaction mixture. Evidence that the structure of the hydrolysis product was indeed 5 was derived from ^{1}H-NMR data, namely, the deshielded signal of 18-H (δ 1.12) and a broad ($\frac{w}{2}$ = 26 Hz) multiplet of 3α-H at δ 3.47 (N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964).
7. S. K. Malhotra, J. J. Hostynek and A. F. Lundin, J. Am. Chem. Soc., 1968, 90, 6565.

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