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The Photo-Beckmann Rearrangement of A-Nor-5α-cholestan-3-one Oxime[1)]

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Synopsis. The photo-Beckmann Rearrangement of A-nor-5α-cholestan-3-one oxime affords 4-aza-5α-cholestan-3-one and 3-aza-5α-cholestan-4-one as the only lactams.

In previous papers,[2)] we reported the photo-Beckmann rearrangement of some cholestanone oximes and A-nor-5β-cholestan-3-one oxime.

In this paper, we report on an investigation of the photo-Beckmann rearrangement of A-nor-5α-cholestan-3-one oxime (**3**) which is complementary to the previous communications.[2)]

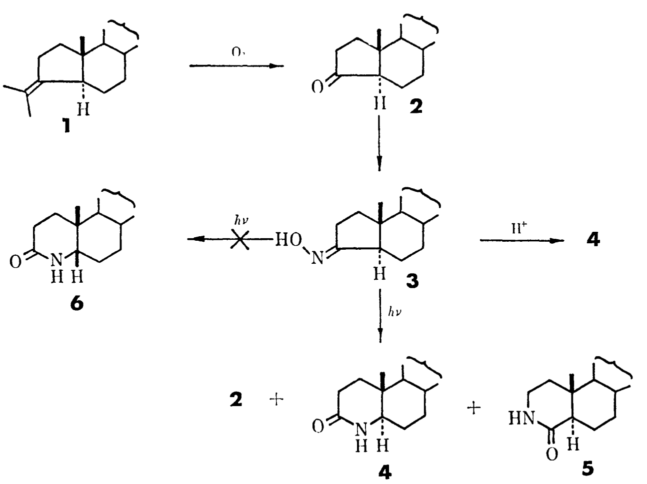
The parent ketone, A-nor-5α-cholestan-3-one (**2**),[2b,6)] has been prepared either by oxidative decarboxylation of 3-hydroxy-A-nor-5α-cholestane-3-carboxylic acid,[4)] prepared *via* three steps from cholest-4-en-3-one, with sodium bismuthate[5)] or by ozonization of 3-isopropylidene-A-nor-5α-cholestane (**1**) prepared *via* 4 steps from cholest-4-en-3-one.[6)] In the present experiment, the 3-one (**2**) was prepared by the latter method which afforded a significantly better overall yield from cholest-4-en-3-one. We have found that the reported yield for the ozonization step (12%) could be significantly improved by a modified procedure (64%, see Experimental).

The new oxime (**3**), prepared by the standard method, exhibited no deshielded proton signal due to the 2-H or the 5-αH at *ca.* τ 6.6 in the ^{1}H NMR spectrum as for the 5β-isomer.[2b)] This is expected since no proton eclipsed by the C=N bond of the hydroxyimino group is present in the oxime (**3**). The Beckmann rearrangement with thionyl chloride afforded 4-aza-5α-cholestan-3-one (**4**) as the sole product, indicating the configuration of the hydroxyimino group as depicted.

The photo-Beckmann rearrangement of the oxime (**3**) in methanol was carried out under the same procedure as for the photo-Beckmann rearrangement of cholestanone oxime previously reported.[2b)] As in the case of A-nor-5β-cholestan-3-one-oxime, irradiation of the oxime led to a mixture of products from which 4-aza-5α-cholestan-3-one (**4**) (6%) and 3-aza-5α-cholestan-4-one (**5**) (4%) were isolated as the only lactams together with A-nor-5α-cholestan-3-one (**2**) (4%) and unchanged oxime (**3**) (9%) by careful preparative TLC. Examination by TLC proved that no 5β isomers of the lactams (**4**) or (**5**) [*e.g.*,(**6**)] were formed.

Thus, it was again proved that the chirality of the migrating group in the oxime is retained during the photo-rearrangement.[2,7)]

The lactam (**5**) has been prepared by a method[3)] which involved 5 steps from 3,4-secocholest-5-ene-3,4-dioic acid. The present result may provide another route for this rather inaccessible lactam.



Scheme.

Experimental

For instruments used and general procedure see Ref. 2b. The mass spectra were taken with a Hitachi JMS-D 300 spectrometer using a direct inlet system (source temperature *ca.* 180 °C) in the Faculty of Pharmaceutical Sciences. Only fragment peaks of the relative intensities of over 20% are described. The infrared spectrum was taken with a model 260-10 Hitachi infrared spectrophotometer.

A-Nor-5α-cholestan-3-one (2).[2b,6)] This ketone was prepared either by the procedure of Camerino *et al.*[5)] or by the procedure of Biellmann and Ourisson.[6)] A modified procedure for ozonization of 3-isopropylidene-A-nor-5α-cholestane by Biellmann afforded a better yield of the ketone. Namely,

Table 1. NMR parameters (100 MHz) for the ketone, the oxime and the lactams in $CDCl_3$ solution
[Chemical shifts (τ) and splittings (Hz; in parentheses)]

Compound	18-H	19-H	$2\text{-}CH_2$	5-αH	Others
2	9.32	9.24	a)	a)	
3	9.32	9.29	a)	a)	OH 1.79 br (s)
4	9.32	9.10	7.59 (dd) (4 and 9)	6.95 (dd) (6 and 10)	NH 3.80 (s) ($W_{1/2}$ 4.8)
5	9.33	9.10	6.68 br (d) (9)	a)	

a) Unassignable.

3-isopropylidene-A-nor-5α-cholestane (2 g) in a mixed solvent of dichloromethane and methanol was ozonized at −72 °C. The temperature of the solution was raised to room temperature without adding sodium borohydride. After removal of the solvent, the residue (2.2 g) was subjected to column chromatography (silica gel, Wako C-200, 150 g). Elution with hexane afforded the starting material (41 mg). Further elutions with a 3 : 1 mixture of benzene and hexane afforded the ketone (1.21 g, 64%). This was recrystallized from methanol (1.12 g). Mp 103—106 °C (lit,[6] mp 106 °C). Biellmann[6] reports a yield of 12% for this ozonization step.

*A-Nor-5α-cholestan-3-one Oxime (**3**).* The 3-ketone (**2**) (270 mg), hydroxylamine hydrochloride (193 mg) and sodium acetate trihydrate (386 mg) in methanol (35 ml) and water (5 ml) were stirred for 3h. The solution was neutralized with 10% sodium hydrogencarbonate and was extracted with ether. The ethereal solution was worked up in usual way. The residue was recrystallized from methanol to yield the oxime (265 mg). Mp 167—168 °C; $[\alpha]^{22}_{D}$ +18.4 (*c* 1.0 $CHCl_3$); Found: C, 80.17; H, 11.87; N, 3.31%. Calcd for $C_{26}H_{45}NO$: C, 80.56; H, 11.70; N, 3.61%; IR 3288 (OH), 970, 934, and 905 cm^{-1}; MS (70 eV), *m/e* (rel. intensity), 41 (24.2), 43 (32.0), 55 (33.1), 109 (21.4), 112 (42.0), 217 (24.8), 233 (35.8), 356 (21.7), 370 (100), 371 (32.9), 372 (28.0), 387 (32.4, M^+).

*The Beckmann Rearrangement of the Oxime (**3**).* A stirred solution of the oxime (200 mg) in dioxane (6 ml) and ether (2 ml) was cooled to 5 °C. To this solution was added thionyl chloride (1 ml) and the solution was stirred for 1 min. The crystals which appeared in the solution were collected by filtration to afford the crude lactam (112 mg). The filtrate was extracted with ether-water. The ethereal solution was washed with aq sodium hydrogencarbonate solution and with water and dried (Na_2SO_4). The crude product was subjected to preparative TLC with a 4 : 1 mixture of dichloromethane and diethyl ether to afford the crude lactam (53 mg) as a least mobile fraction. The combined crude lactam (**4**) (165 mg, 83%) was recrystallized from methanol. Mp 252—255 °C (lit,[3] 253—255 °C); $[\alpha]^{22}_{D}$ +43.1 (*c*, 1.0 $CHCl_3$). MS (70 eV), *m/e* (rel. intensity), 41 (20.2), 43 (32.1), 55(28.3), 56 (40.5), 57 (24.0), 98 (37.4), 112 (26.0), 232 (82.4), 233 (50.9), 234 (23.3), 248 (21.3), 372 (24.3), 387 (100, M^+), 388 (30.2).

*The Photo-Beckmann Rearrangement of the Oxime (**3**).* The oxime (570 mg) in methanol (500 ml) was irradiated with a 15-W low pressure mercury arc in an atmosphere of nitrogen for 68 h. After removal of the solvent, the residue was extracted with ethyl acetate and the solution was worked up as usual. The TLC has shown the products to be a complex mixture. The crude photolyzate was subjected to preparative TLC (Wakogel B-5F) with a 4 : 1 mixture of dichloromethane and diethyl ether. Seven fractions A, B,C,D,E,F and G were obtained in order of decreasing mobility. The fraction A (37 mg) was the crude parent ketone and this was purified by preparative TLC (a 4 : 1 mixture of benzene and diethyl ether)followed by two recrystallizations to yield pure ketone (20 mg, 4%). The fractions B (20mg), D (28mg), E (23mg), and G (164mg) were an intractable mixture and they were not identified. The crystalline fraction C (90 mg) was recrystallized to yield the recovered oxime (50 mg, 9%). The fraction F (209 mg) was a mixture of two lactams and this was again subjected to preparative TLC with a 1 : 1 mixture of ethyl acetate and diethyl ether. Developments were made twice. The more mobile crystalline lactam (30 mg, 5%) was recrystallized from methanol to yield the lactam (**5**), (20 mg) in two crops. Mp 225 °C. (lit,[3] 225—227 °C). The less mobile crystalline lactam (34 mg, 6%) was recrystallized from methanol to yield the lactam (**4**) (25 mg). Mp 252—255 °C (lit,[3] mp 253—255 °C); $[\alpha]^{22}_{D}$ +43.1 (*c* 1.0 $CHCl_3$); MS (70 eV), *m/e* (rel. intensity). 41 (19.7), 43(27.0), 55 (28.1), 57 (20.1), 99 (25.5), 112 (42.3), 125 (42.2), 232 (78.5), 233 (34.0), 234 (23.1), 372 (21.9), 287 (100, M^+), and 388 (30.3).

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