The Photo-Beckmann Rearrangement of 3α,5-Cyclo-5α-cholestan-6-one Oxime[1,2]

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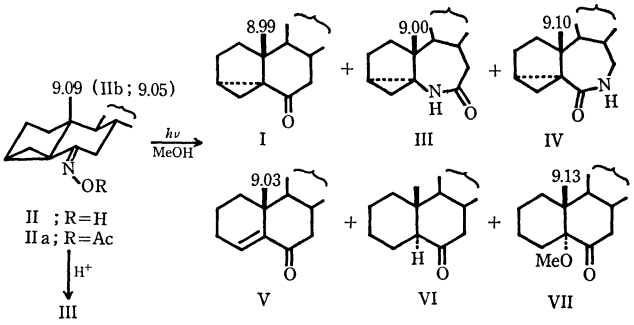
Photolysis of 3α,5-cyclo-5α-cholestan-6-one oxime affords two isomeric lactams with cyclopropane rings arising from photo-Beckmann rearrangement although the yields are poor. The result gives further support to our view on the C→N migration process in photo-Beckmann rearrangement. The major part of the products of the reaction consisted of the parent ketone and several products probably derived from it. The results are compared with those obtained in our photolysis of 5α-cholestan-6-one oxime and the isomeric 5β-cholestan-6-one oximes. The poor yields of the lactams is probably ascribable to the presence of the cyclopropane ring in this conjugated cyclopropyl ketone oxime.

Since the first paper[3] on the photochemical Beckmann rearrangement on arylaldoximes, additional results on aliphatic ketone oximes,[4] alicyclic ketone oximes[4,5,6,9] and α,β-unsaturated ketone oximes[7,8] have been reported. Mechanistic aspects of the reaction have been extensively investigated[8,9,10] and the intermediacy of oxaziridine in this reaction has been confirmed.[8,10]

We have shown[9] that in the photo-Beckmann rearrangement of 5α-cholestan-6-one oxime and the isomeric 5β-cholestan-6-one oximes the bond migration from the intermediary oxaziridines to amides proceeds in a stereospecific manner, the migration of C-5 occurring with retention of the configuration.

With regard to the effect of substituents on the migrating carbon it has been shown[11] that mono-, di-, or tri-substituted α-carbon atom migrates to yield the corresponding lactams and that the migration of the more alkyl-substituted α-carbon atom occurs predominantly, although the irradiation of a certain strained oxime with bridge-head tri-substituted α-carbon leads to the photo-Beckmann fission.[12]

In this paper, we report on the photolysis of 3α,5-cyclo-5α-cholestan-6-one oxime (II). Although the distinct difference in the mode of photolysis between conjugated cyclopropyl ketones and alkyl ketones has been clarified,[13] no investigation has so far been carried out on the photolysis of the conjugated cyclopropyl ketone oxime. Results of the photolysis of II may afford additional information on the bond migration process and also on the synthetic utility of this photochemical reaction.



Arabic numerals denote chemical shifts (τ) of 19-methyl protons.

Results

Oxime[14] of 3α,5-cyclo-5α-cholestan-6-one (I) was described by Wallis *et al.* and repetition of this work was found to give the corresponding *single* oxime (II). This revealed the π→π* band[15] at λ_{max} 197—200 nm (*n*-hexane, ε; 9440).[16] In order to confirm the configuration of the oximino group, II was submitted to the ground state Beckmann rearrangement with polyphosphoric acid.[17] This led to an amorphous single lactam III in 65% yield.[18] The structure of III should be either (III) or (IV). Compound III exhibited one-proton singlet at τ 4.18 which is exchangeable with deuterium and a single-proton quartet centered at τ 9.56. The former is ascribable to lactam NH and the chemical shift of the latter corresponds to proton attached to cyclopropane ring.[19]

On the basis of this NMR spectrum, structure III, 6-aza-3α,5-cyclo-*B*-homo-5α-cholestan-7-one, is found to be correct. The configuration of the oximino group of II is, therefore, safely assigned as an anti-

1) Photo-induced Transformations, XVIII. Part of a paper read before The 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April (1970). Abstracts of papers No. 3, p. 1291; Previous paper in this series, H. Suginome, T. Mizuguchi, and T. Masamune, *Chem. Commun.*, **1972**, 376.

2) In this paper, the prefix photo- is used in accordance with the usage recommended by Pitts *et al.* (J. N. Pitts, Jr., F. Wilkinson, and G. S. Hammond, "Advances in Photochemistry," ed. by W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Wiley-Interscience, New York, (1963), vol. 1, p. 20).

3) J. H. Amin and P. de Mayo, *Tetrahedron Lett.*, **1963**, 1585.

4) R. T. Taylor, M. Douek, and G. Just, *ibid.*, **1966**, 4143.

5) T. Sasaki, S. Eguchi, and T. Toru, *Chem. Commun.*, **1970**, 1239.

6) B. L. Fox and H. M. Rosenberg, *ibid.*, **1969**, 1115.

7) G. Just and C. Pace-Asciak, *Tetrahedron*, **22**, 1069 (1966).

8) T. Oine and T. Mukai, *Tetrahedron Lett.*, **1969**, 157.

9) H. Suginome and H. Takahashi, *ibid.*, **1970**, 5119.

10) H. Izawa, P. de Mayo, and T. Tabata, *Can. J. Chem.*, **47**, 51 (1969).

11) G. Just and L. S. Ng, *Can. J. Chem.*, **46**, 3381 (1968).

12) T. Sato and H. Obase, *Tetrahedron Lett.*, **1967**, 1633.

13) For leading reference see W. G. Dauben, G. W. Shaffer, and E. J. Deviny, *J. Amer. Chem. Soc.*, **92**, 6273 (1970).

14) E. S. Wallis, E. Fernholz, and F. T. Gephart, *ibid.*, **59**, 137 (1937).

15) P. J. Orenski and W. D. Closson, *Tetrahedron Lett.*, **1967**, 3629.

16) We are grateful to Professor H. Baba and Mr. I. Yamazaki, of the Research Institute of Applied Electricity, Hokkaido University, for the measurement of UV spectra.

17) E. C. Horning, V. L. Stromberg, and H. A. Lloyed, *J. Amer. Chem. Soc.*, **74**, 5153 (1952).

18) Subsequent to the completion of this work, the ground state Beckmann rearrangement of II was reported by Ahmad *et al.* (M. S. Ahmad, Shafiullah, and M. Mushfiq, *Tetrahedron Lett.*, **1970**, 2739).

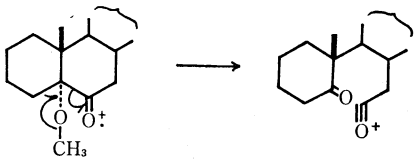
19) F. A. Bovey, "NMR Data Tables for Organic Compounds," Interscience, New York, (1967) Vol. 1, p. 102.

C_5C_6 bond. This assignment is conclusive since it is extremely unlikely that in the ground state Beckmann rearrangement of II, a complete isomerization from *syn* to *anti* takes place before the rearrangement. Hydrogen atoms attached to carbon α to oximino group are known to appear downfield[20] in the NMR spectrum of saturated oximes. 100 MHz NMR spectrum of II revealed a double doublet at τ 6.70 with J=12.2 Hz and 2.3 Hz and the coupling constant requires that the singnal should be assignable to 7α-equatorial hydrogen deshielded by OH of the oximino group. The acetyl derivative IIa (mp 99—101°C) of II showed only a doublet due to 7α-hydrogen at τ 6.76 with J=10.9 Hz.

Compound II (5g) in dry methanol (300 m*l*) was irradiated for 31 hr with a 150-W low pressure mercury arc lamp. Since further irradiation caused transformation of the initial products, it was stopped at this stage. Extensive column chromatography and the preparative tlc of a complex mixture of the products led to the isolation of six products, besides recovery of the starting oxime (31%).[21] They were 3α,5-cyclo-5α-cholestan-6-one (I)[22] (8%), amorphous III (3%), amorphous IV (2%), cholest-4-en-6-one (V)[23] (1%), 5α-cholestan-6-one (VI)[24] (1%), and compound (VII), mp 134—138°C (2%).

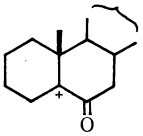
Compound III proved to be identical with lactam III obtained by the ground state Beckmann rearrangement of II. The mass spectrum of IV (the molecular ion at 399) and elemental analysis disclosed that it was isomeric with II having the molecular formula $C_{27}H_{45}ON$. The infrared spectrum of IV demonstrated typical lactam carbonyl bands at 1635 cm^{-1}. While the NMR spectrum of III revealed a signal due to lactam as a singlet, that of IV showed the corresponding signal as a triplet at τ 3.93 (J=5.9 Hz). Moreover, two single-proton double doublets appeared at τ 6.4 (J=5.9 Hz and 14.9 Hz) and at τ 7.06 (J=5.9 Hz and 14.9 Hz). These two protons are ascribable to CH_2 protons α to the lactam nitrogen. On addition of D_2O, the two double doublets coalesced into two doublets centered at the same position (J=14.9 Hz) and the NH signal vanished. It is therefore, evident that the smaller splitting is due to a coupling between CH_2 protons and a proton attached to nitrogen. Thus, structure IV, 7-aza-3α,5-cyclo-*B*-homo-5α-cholestan-6-one is assigned to the compound. The observed two doublets are ascribable to geminal protons attached to C-7 and the magnitude of splitting (J_{AB}= 14.9 Hz) is in agreement with geminal coupling. Although these geminal protons may appear as AB part of ABX system in which X is the C-8 proton, the observed doublet signal shows $J_{AX}=J_{BX}\simeq 0$ Hz, and suggests that dihedral angles between C-7α and C-7β protons and C-8β proton are about 60° and the C-8 proton approximately bisects the angle between the C-7-methylene protons. Protons attached to the cyclopropane ring were not observable since they would be hidden in the methylene envelope.[25]

The mass spectrum (molecular ion 416) and elemental analysis of VII were in agreement with $C_{28}H_{48}O_2$. The presence of a methoxyl group in VII was proved by the NMR spectrum which showed a three-proton singlet at τ 6.64. The infrared spectrum of VII revealed a 6-membered ring ketone at 1714 cm^{-1} but no hydroxyl group. It is clear that the carbonyl group was generated from the oximino group since generation of the parent carbonyl group from the oximino group was found to be usual.[4,8,11] Thus VII might be 3-, 4- or 5-methoxycholestan-6-one formed by the addition of methanol[26] to either I or V. Since in the NMR spectrum of VII we could find no signal attributable to a proton attached to a carbon atom with a OCH_3 group, the methoxyl group should be located at the carbon bearing no hydrogen. Therefore, VII is 5-methoxycholestan-6-one. Since a comparison of chemical shifts of 19-methyl protons of VI (τ 9.25) and VII (τ 9.31) reveals no deshielding of 19-methyl protons in VII by the newly introduced methoxyl group, the structure of VII should be 5α-methoxycholestan-6-one (VII). The mass spectrum of VII showed the base peak at *m/e* 401 and a prominent peak at *m/e* 385 (79%). It seems somewhat unusual that the expulsion of methyl group from aliphatic methyl ether gives a base peak. However, $M-CH_3$ base peak perhaps originates from the cleavage of acyl-carbon bond[27] followed by the loss of methyl unit to afford the following fragment ion A.



A: *m/e* 401 (100%)

Fragment ion 385 corresponds to fragment B.



B: *m/e* 385 (79%)

Discussion

The results we obtained demonstrate that the photo-Beckmann rearrangment can be achieved even in the conjugated cyclopropanone oxime and affords the corresponding lactams with cyclopropane ring. However, the yields of lactams were poor and the major portion of the products was the parent ketone arising

20) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958); H. Saito, K. Nukada, and M. Ohno, *Tetrahedron Lett.*, **1964**, 2124; W. F. Trager and A. C. Huitric, *ibid.*, **1966**, 825.

21) The isomeric *syn*-oxime was neither observed on tlc nor isolated.

22) A. Windaus and E. K. Dalmer, *Ber.*, **52**, 162 (1919). J. R. Bull, Sir E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, **1965**, 2601.

23) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).

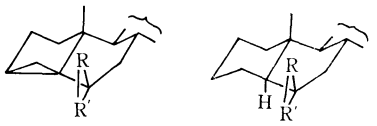
24) W. G. Dauben and E. J. Deviny, *ibid.*, **31**, 3794 (1966).

25) T. Shono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Lett.*, **1964**, 791.

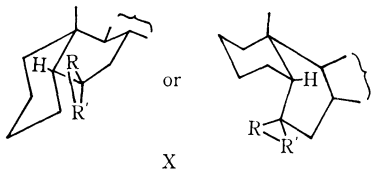
26) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964).

27) P. E. Butler, *J. Org. Chem.*, **29**, 3024 (1964).

from the elimination of the nitrogen moiety of the intermediary oxaziridine. Thus, compared with the results of the photo-Beckmann rearrangements of 5α-cholestan-6-one oxime and the isomeric 5β-cholestan-6-one oximes[9] the effects of the presence of cyclopropane ring and those of steric origin are evident.



VIII IX



X

R=O, R'=NH or R=NH, R'=O

This would imply that in the intermediate oxaziridine VIII the rearrangement into lactam becomes less easy, owing to the presence of cyclopropane ring, than in the case of oxaziridine IX, and the elimination of nitrogen as N_2, hydrazine[8] or ammonia[11] becomes dominant in the present case. Compared with the isomeric 5β-cholestan-6-one oximes (plausible conformation of the intermediate oxaziridine is depicted as is X) less easy formation of lactams from 5α-isomer is mainly attributable to the conformational factors. Formation of two lactams with cyclopropane ring gives additional support to our view[9] on the C→N migration process in the photo-Beckmann rearrangement.

With regard to the mode of formation of three ketones V, VI and VII obtained as the minor products, it is almost certain that V was derived from I since the formation of α,β-unsaturated ketone from the conjugated cyclopropyl ketone was recognized as general[13,28] and the mode of reaction was recently investigated in detail.[13,29] The other two ketones VI and VII can be derived either directly from I or through the formation of V by photo-reduction as well as photo-addition. Several investigators encountered the photo-reduction of double bond of α,β-unsaturated ketons. Addition of methanol to α,β-unsaturated carbonyl compound generally gives β-methoxy-carbonyl compound[30] and therefore the formation of VII is better understandable by the direct addition of methanol to cyclopropyl ketone (I).

Experimental

All mps were determined by a Yanagimoto type hot-stage and uncorrected. Unless otherwise stated, IR was determined in Nujol using a Jasco model IR-E spectrophotometer. Except for compound VII, all NMR spectra were determined on a Japan Electron Optics PS-100 high resolution NMR spectrometer in $CDCl_3$ solution using TMS as an internal reference. NMR spectrum of compound VII was taken with a Hitachi H-60 high resolution NMR spectrometer. Mallinckrodt silicic acid (100 mesh) was used for column chromatography and Wakogel B-5 for preparative tlc. The progress of the reactions was followed by tlc.

3α,5-Cyclo-5α-cholestan-6-one Oxime.[14] *(II).* Oximation of I by the usual procedure was found to give a single oxime, mp 125—126°C. Literature mp 143—144°C.[14] (from EtOH), $[\alpha]_D^{25}$ ($CHCl_3$) +83.3°. Mass M^+ 399. NMR: τ 9.31 (18-CH_3), τ 9.09 (19-CH_3). Acetate (IIa): *O*-acetate was prepared by the usual method. mp 99—101°C. NMR: τ 6.76 (d, J=10.9 Hz) (7αH), τ9.31 (s, 18-CH_3) τ 9.05 (s, 19-CH_3) τ 7.84 (s, O-Ac).

Beckmann Rearrangement of 3α-5-Cyclo-5α-cholestan-6-one Oxime. II (200 mg) was added to polyphosphoric acid (2 g) which was kept at *ca.* 100°C. The mixture was stirred for 10 min. After cooling the mixture was poured into 10% aqueous sodium carbonate solution. The mixture was extracted with ether. After the usual work up, tlc of the residue (200 mg) showed two spots and the major and more polar compound was purified by preparative tlc ($CHCl_3$ - ether 1 : 1). III (130 mg, 65%) was obtained in an amorphous form. (Found: C, 81.04; H, 11.60; N, 3.63%. Calcd for $C_{27}H_{45}ON$: C, 81.14; H, 11.35; N, 3.51%). IR ($CHCl_3$): 1656 cm^{-1} (CONH). NMR: τ 4.18 (s, NH), τ 9.00 (s, 19-methyl), τ 9.31 (s, 18-methyl). (τ 9.56 quartet J=8.2 and 4.8 Hz) C-4α or C-4βH (τ 7.71, broad s) C-7 methylene. Mass. M^+ 399.

Photolysis of 3α,5-Cyclo-5α-cholestan-6-one Oxime. II (5 g) in dry methanol (300 m*l*) was photolyzed for 31 hours by a 150 W low pressure Hg arc lamp under a nitrogen atmosphere. After removal of the solvent the residue was dissolved in ether (150 m*l*). The ethereal solution was washed with water, dried and evaporated. The residue was subjected to column chromatography by using 100 g of adsorbent. Elution was first made with *n*-hexane and then with a mixture of *n*-hexane and benzene with an increasing amount of benzene (*n*-hexane, 300 m*l*, hexane - benzene 9:1, 300 m*l* hexane - benzene 8:2, 300 m*l*, hexane - benzene 7 : 3, 700 m*l*, hexane - benzene 6 : 4, 600 m*l*, hexane - benzene 5 : 5, 400 m*l*), affording fraction A (1.4 g). Elution was then continued with *n*-hexane - benzene (3 : 7) (300 m*l*), pure benzene (200 m*l*) and finally benzene - $CHCl_3$ (8 : 2) (400 m*l*) to afford fraction B (1.6 g). Elution was continued with benzene - $CHCl_3$ (6 : 4) (200 m*l*), benzene - $CHCl_3$ (4 : 6) (200 m*l*) and benzene - $CHCl_3$ (2 : 8) (300 m*l*) to afford fraction C (0.24 g).

Elution was further carried out with $CHCl_3$ (200 m*l*), $CHCl_3$ - ether (8 : 2) (200 m*l*) and $CHCl_3$ - ether (6 : 4) (200 m*l*) to afford fraction D (1.3 g). Finally, elution was carried out with $CHCl_3$ - ether (4 : 6) (200 m*l*), $CHCl_3$ - ether (2 : 8) (100 m*l*), $CHCl_3$ - ether (1 : 1) (100 m*l*) and ether (200 m*l*) to give fraction E (0.9 g). Fractions A, B, C, and D were subjected to further separation as follows. Fraction A: This was again chromatographed with 26 g of adsorbent, some fractions obtained being further purified by preparative tlc to afford four products. The least polar compound was recrystallized from ethanol to afford 5α-cholestan-6-one (VI), mp 95—97°C,[31] identical with authentic specimen. (30 mg, 0.6%). The second least polar fraction (620 mg) was recrystallized from ethanol to yield 3α,5-cyclo-5α-cholestan-6-

28) C. H. Robinson, O. Gnoj, and E. E. Carlon, *Tetrahedron*, **21**, 2509 (1965). R. Beugelmans, *Bull. Soc. Chim. Fr.*, **1967**, 244.

29) B. Nann, D. Gravel, R. Schorta, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 2473 (1963). I. A. Williams and P. Bladon, *Tetrahedron Lett.*, **1964**, 257.

30) R. Stoermer and H. Stockmann, *Ber.*, **48**, 1786 (1914).

31) The literature mps for 5α-cholestan-6-one are mp 98.5—99.5°C[22] and mp 96°C (D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, **1955**, 2876.

one (I) (392 mg, 8%). The third least polar fraction (130 mg) yielded 62 mg (1.3%) of crystals mp 104—106°C, NMR: τ 3.65 (C-4H) (t, $J=3.0$ Hz), τ 9.30 (s, 18-CH_3) and τ 9.03 (s, 19-CH_3) which were identical with cholest-4-en-6-one.[23] The most polar fraction (200 mg) afforded crystals of the starting oxime (130 mg). Fraction B: This was recrystallized from ethanol to yield the starting oxime (1.4 g) which was then combined with oxime from fraction A. Total yield of pure recovered oxime was thus 31%. Fraction C: This was purified by preparative tlc ($CHCl_3$ containing a small amount of ether). Oily material obtained was recrystallized from ethanol to yield 5α-methoxycholestan-6-one, mp 134—138°C (110 mg, 2%). (Found: C, 80.70; H, 11.64%; Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61%). IR: 1714 cm^{-1} (6-membered cyclic ketone) 1090 cm^{-1} (C-O). NMR: τ 6.65 (s, OCH_3), τ 9.31 (s, 19-CH_3) τ 9.36 (s, 18-CH_3). Mass: M^+ 416. Fraction D: This was purified by column chromatography (adsorbent 26 g; solvent, benzene - chloroform). Preparative tlc of the eluates with chloroform containing a small amount of ether then afforded 300 mg of crude material which was subjected again to preparative tlc (ethyl acetate - ether - benzene 3 : 2 : 1) to afford two amorphous compounds. Less polar compound IV (100 mg; 2%) (Found: C, 81.11; H, 11.29; N, 3.55%. Calcd for $C_{27}H_{45}ON$: C, 81.14; H, 11.35; N, 3.51%). IR ($CHCl_3$): 1635 cm^{-1} (NHCO), 3420 cm^{-1} (NH). More polar compound III (160 mg; 3%) was identical with the lactam obtained by the ground-state Beckmann rearrangement.

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