THE BECKMANN REARRANGEMENT OF CHOLESTA-3,5-DIEN-7-ONE OXIME*

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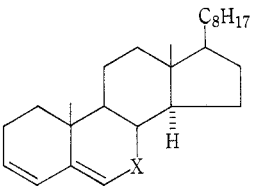
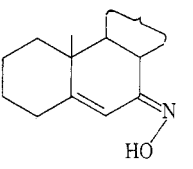
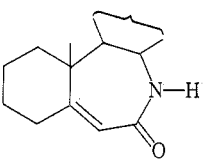
The Beckmann rearrangement of steroidal ketoximes is one of the most convenient and widely applicable methods used for obtaining aza steroids. Whereas the Beckmann rearrangement of several simple, α,β-unsaturated, and substituted ketoximes has been carried out,[1] no work has been done on the Schmidt or the Beckmann rearrangements of steroidal dienones or their oximes, respectively. Hence it was considered expedient to extend the methods to the rearrangement of some of these compounds. In this paper we describe the Beckmann rearrangement of cholesta-3,5-dien-7-one oxime (I).



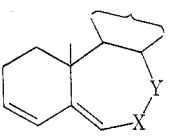


(II)
syn form

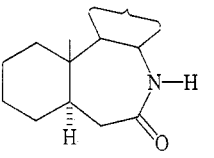


(III)

	X
(I)	C=NOH
(Ia)	C=N, HO
(Ib)	C=N, OH
(IV)	C=NOTs



	X	Y
(V)	C=O	NH
(VI)	NH	C=O



(VII)

The ketoxime (I) was obtained according to Shoppee *et al.*[2] It may exist in two forms, the *syn* form (Ia) and the *anti* form (Ib). We attempted to resolve (I) by fractional crystallization or by chromatography,[3] but there was no indication of heterogeneity of the oxime (I). Shoppee *et al.*[4] have shown that cholest-5-en-7-one

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[1] Singh, H., Parashar, V. V., and Padmanabhan, S., *J. scient. ind. Res.*, 1966, **25**, 200, and references cited therein.

[2] Shoppee, C. W., Cremlyn, R. J. W., Evans, D. E., and Summers, G. H. R., *J. chem. Soc.*, 1957, 4364.

[3] Hara, S., Oka, K., and Ike, Y., *Chemy Ind.*, 1967, 832.

[4] Shoppee, C. W., Akhtar, M. I., and Lack, R. E., *J. chem. Soc.*, 1964, 3392.

oxime (II) exists in the *syn* form and readily provided a single lactam, 7a-aza-B-homocholest-5-en-7-one (III). Further, the product of the Beckmann rearrangement of (I) is compatible with the *syn* form (Ia). However, the possibility of the presence of *anti* form (Ib) in traces cannot be completely ruled out.

The oxime (I) was treated with *p*-toluenesulphonyl chloride in pyridine. The usual work-up procedure afforded the oxime tosylate (IV) (72%), which was allowed to stand on a column of alumina.[5] Subsequent elution gave a single lactam (V) in fairly high yield (78%). It is pertinent to mention that isolation of oxime tosylate was generally observed in the case of α,β-unsaturated ketoximes.[6]

The lactam obtained may have either the structure (V) or (VI). Formulation of the lactam as (V) rather than its isomer, 7-aza-B-homocholesta-3,5-dien-7a-one (VI), was supported by (*a*) spectral data, and (*b*) chemical evidence, since on catalytic hydrogenation the lactam was converted into the known lactam, 7a-aza-B-homo-5α-cholestan-7-one (VII).

The lactam (V) was also prepared by treatment of ketoxime (I) with thionyl chloride[4] but the yield was relatively low (24%).

Experimental

All melting points are uncorrected. I.r. spectra were obtained with a Perkin–Elmer 137 Infracord and u.v. spectra in 95% EtOH with a Beckmann D.B. spectrophotometer. Light petroleum refers to fraction b.p. 60–80°.

Cholesta-3,5-dien-7-one Oxime Tosylate (IV)

Cholesta-3,5-dien-7-one oxime (I) (1·0 g, m.p. 178–180°;[2] Found: C, 81·4; H, 11·0. Calc. for $C_{27}H_{43}NO$: C, 81·55; H, 10·9%) was dissolved in pyridine (10 ml; distilled over KOH) and then mixed with *p*-toluenesulphonyl chloride (1·0 g). The reaction mixture was kept in the dark for 15 hr at 15° and then it was poured into crushed ice–water mixture. The solid material thus obtained was extracted with ether and the ether layer was washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution and water, and finally dried (sodium sulphate). Removal of the solvent provided (IV) as an oil which was crystallized from light petroleum (0·94 g; 68·1%), m.p. 138–140°, $[\alpha]_D^{25}$ −82° ($CHCl_3$). (Found: C, 73·8; H, 9·1. $C_{34}H_{49}NO_3S$ requires C, 74·05; H, 8·8%); ν_{max} (KBr) 1602, 1177, 1092, 860, 785, 772 cm^{-1}.

7a-Aza-B-homocholesta-3,5-dien-7-one (V)

(1) Cholesta-3,5-dien-7-one oxime tosylate (IV) (1·0 g) was dissolved in a light petroleum–benzene mixture and the solution was allowed to stand over a column of alumina (25 g; Brochmann grade I) for 1 hr. The eluates from light petroleum and light petroleum–benzene (2 : 1) mixture gave the unchanged oxime tosylate (IV) (20 mg), m.p. and mixed m.p. 138–140°. Further elution with benzene–ether (4 : 1 and 1 : 1) furnished the lactam (V), which was recrystallized from light petroleum–ether mixture (530 mg; 75·1%), m.p. 170–171°, $[\alpha]_D^{25}$ −153° ($CHCl_3$). (Found: C, 81·4; H, 11·1; N, 3·8. $C_{27}H_{43}NO$ requires C, 81·55; H, 10·9; N, 3·5%); ν_{max} (KBr) 3200 (NH), 1652, 1598 (C=C–C=C–CO–NH), 890 cm^{-1}; λ_{max} (EtOH) 270 mμ (log ϵ 4·3).

The mother liquor left after the separation of the oxime tosylate (IV) was evaporated to dryness on a water-bath and the residue was chromatographed over alumina as above. Elution with light petroleum and light petroleum–benzene gave the oxime tosylate (IV) (52 mg; 3·7%), m.p. and mixed m.p. 138–140°. Further elution with benzene–ether (4 : 1 and 1 : 1) provided the lactam (V) (67 mg; 6·7%), m.p. and mixed m.p. 170–171°.

[5] Craig, J. C., and Naik, A. R., *J. Am. chem. Soc.*, 1962, **84**, 3410.
[6] Kohn, F., *Chemy Ind.*, 1966, 1378.

(2) Cholesta-3,5-dien-7-one oxime (I) (500 mg) was dissolved in freshly distilled thionyl chloride (10 ml) at $-10°$ and the resulting solution was immediately poured into hot solution of potassium hydroxide (4N; 100 ml at 70°). The brownish semi-solid material was taken up in ether and worked up in the usual manner. Removal of the solvent afforded a brownish product which was chromatographed twice over alumina. Elution with benzene and benzene–ether (4 : 1) gave the lactam (V), which was recrystallized from light petroleum–ether (120 mg, 24%), m.p. and mixed m.p. 170–171°.

7a-Aza-B-homo-5a-cholestan-7-one (VII)

The lactam (V) (200 mg) was dissolved in absolute alcohol (40 ml) and the solution was shaken in an atmosphere of hydrogen for 12 hr in the presence of Pd–C catalyst (5%, 450 mg). Subsequently the catalyst was removed by filtration and the solvent removed under reduced pressure and the semi-solid substance obtained was subjected to chromatography over alumina. The eluates from benzene and benzene–ether (4 : 1) mixture provided the lactam (VII) which was recrystallized from methyl alcohol (120 mg), m.p. 90–91°, and showed no m.p. depression on admixture with an authentic sample of the lactam (VII).[4]

Acknowledgments

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