

## Rearrangement and Reactions of Allylthioimide in the Benzoxazine Series

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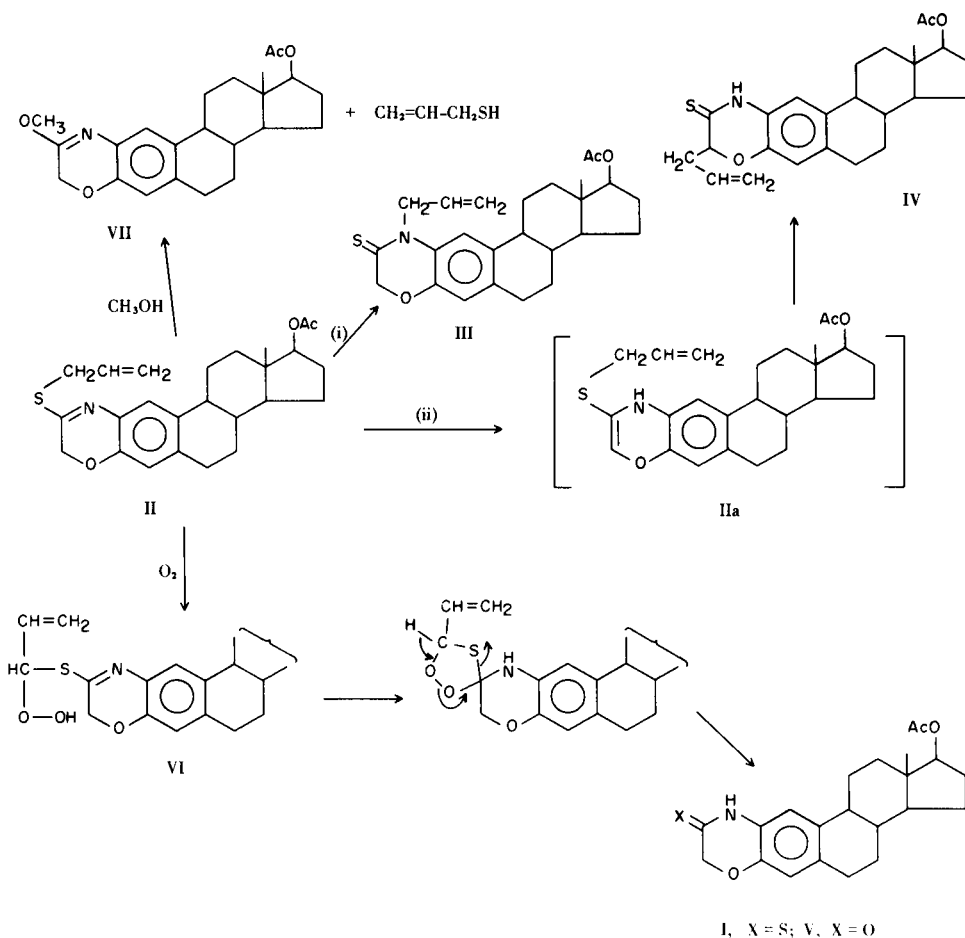
Thioclaisen rearrangements (1), in which the allyl or the propargyl group migrates from the sulfur atom to the  $\beta$ -nitrogen atom, in various heterocyclic compounds have been described. However, such rearrangements in the 1,4-benzoxazine ring system have not been reported.

The allylthioimide (II) derived from the steroidal 1,4-benzoxazine-3-thione (I) (2) could undergo thioclaisen rearrangement in two ways: (i) migration of the allyl group to nitrogen to produce III or (ii) migration of the allyl group to the  $\beta$ -carbon atom through the enamine intermediate (IIa) (3) to yield IV.

When a solution of the allylthioimide (II) in dry dimethylaniline was heated to reflux in a nitrogen atmo-

sphere, only III was produced in 44.5% yield. However, when the thermal rearrangement of II was carried out in the same solvent but in the presence of air, III could be isolated in a very low yield (1.5%) and no other products could be isolated from the intractable gum.

The reaction, however, takes an entirely different course when II was heated to reflux in dry tetralin in the presence of air when the lactam (V) (2) was produced in 85% yield and no trace of III in the reaction mixture could be detected. The formation of V can be envisaged to proceed through the generation of the allylic hydroperoxide (VI) (4) followed by intramolecular attack of the hydroperoxide ion on the C=N linkage (5). The great



susceptibility of the C=N linkage in II to nucleophilic attack is illustrated by the facile reaction of II with methanol. Thus when II was heated with methanol in the presence of charcoal, the methylimidate (VII) was produced in 85% yield with the extrusion of allyl mercaptan.

However, similar reaction of II with absolute ethanol in the presence of charcoal was sluggish and the product (71% yield) was identified as the lactam (V). The course of this transformation is not clear.

#### EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Infrared and ultraviolet spectra were determined for chloroform and methanol solutions respectively. Nmr spectra were determined for deuteriochloroform solutions using tetramethylsilane as internal standard. Solutions were dried with anhydrous sodium sulfate.

3-(Thioallyl)-17 $\beta$ -acetoxyestra-1,3,5(10)-trieno[2,3-*e*]-2'H-1',4'-oxazine (II).

A solution of the thiolactam (I) in dry acetone (100 ml.) was treated with powered potassium hydroxide (0.2 g.) and heated under reflux for 5 minutes. Allyl bromide (0.4 g.) was then added and the refluxing continued for 1.5 hours. The acetone was removed and the residue was extracted with dichloromethane (60 ml.). The solution was washed with water, dried and evaporated. The residual oil (1.05 g.) was chromatographed on silica gel (20 g.) using Skelly-B (200 ml.) and benzene (400 ml.) as eluents. Concentration of the eluates under reduced pressure gave a homogeneous oil (0.85 g.);  $uv \lambda$  max 244 ( $\epsilon$ , 18,275), 249sh (17,212), 288 (11,900), 298 (12,325), 316nm (10,200);  $ir \nu$  max 1730, 1620, 1580, 1260  $cm^{-1}$ ; nmr  $\delta$  0.83 (3H, singlet), 2.08 (3H, singlet), 3.85 (2H doublet), 4.45 (2H, singlet), 4.75 (1H, multiplet), 5-6.2 (3H, multiplet), 6.6 (1H, singlet), 7.2 (1H, singlet).

*Anal.* Calcd. for  $C_{25}H_{31}O_3SN$ : C, 70.55; H, 7.34; N, 3.29. Found: C, 70.86; H, 7.56; N, 3.10.

#### Thermal Rearrangements of II.

i). In Dimethylaniline under Nitrogen-formation of 2',4'-Dihydro-4'-allyl-17 $\beta$ -acetoxyestra-1,3,5(10)-trieno[2,3-*e*]-1',4'-oxazine-3-thione (III).

A solution of the allylthioimidate (II) (0.9 g.) in dry dimethylaniline was heated under reflux for 5 hours in a nitrogen atmosphere. The dimethylaniline was removed under reduced pressure and the residue was dissolved in chloroform (25 ml.). The solution was filtered through silica gel (10 g.) and eluted with chloroform (150 ml.). Removal of the solvent gave a brown oil which upon trituration with ether afforded (III) as a yellow solid (0.4 g.), m.p. 197-199° (44.5% yield). The analytical sample was crystallized successively from dichloromethane-methanol and acetone-methanol, m.p. 202-203°;  $uv \lambda$  max 256sh ( $\epsilon$ , 13,200), 262 (14,000), 299sh (9100), 326nm (15,420);  $ir \nu$  max 1735, 1270, 1125  $cm^{-1}$ ; nmr  $\delta$  0.85 (3H, singlet), 2.08 (3H, singlet), 4.7 (1H, multiplet), 4.86 (2H, singlet), 5.1-6.2 (4H, multiplet), 6.72 (1H, singlet), 7.08 (1H, singlet).

*Anal.* Calcd. for  $C_{25}H_{31}O_3SN$ : C, 70.55; H, 7.34; N, 3.29. Found: C, 70.36; H, 7.29; N, 3.33.

ii). In Dimethylaniline in the Presence of Air.

A solution of II (0.8 g.) in dry dimethylaniline (10 ml.) was heated to reflux in the presence of air for 5 hours. The reaction mixture was worked-up as in (i) when a dark brown oil was obtained which was dissolved in ether (30 ml.). The ether solution was diluted with Skelly-B (50 ml.) when an intractable gum separated out. The supernatant liquid was decanted and evaporated. The residual oil upon trituration with methanol gave a solid (12 mg.), m.p. 198-200° (yield, 1.5%). This was identified as (III) by comparison of infrared spectra.

iii). In Tetralin in the Presence of Air.

A solution of II (0.8 g.) in dry tetralin (10 ml.) was heated under reflux for 2 hours. The tetralin solution was diluted with Skelly-B (100 ml.) when a yellow solid separated out which after washing with ether had m.p. 253-257° dec. (0.55 g. 85% yield). One crystallization of this product from acetone gave a sample, m.p. 256-263° dec., found identical with V by comparison of infrared spectra.

Reaction of II with Methanol. Formation of 3'-(Methoxy)-17 $\beta$ -acetoxyestra-1,3,5(10)-trieno[2,3-*d*]-2'H-1',4'-oxazine (VII).

i). The allylthioimidate (II) (0.52 g.) was dissolved in anhydrous methanol (100 ml.). The solution was treated with charcoal, heated for a few minutes, filtered and concentrated when (VII) separated out as a colorless solid m.p. 172-175° (0.41 g., 85% yield). This solid was chromatographed on neutral alumina (Woelm, Grade I, 10 g.) and eluted with chloroform. Concentration of the eluate gave a solid (0.38 g.) which was crystallized from methanol to give the analytical sample, m.p. 185° dec. with softening at 172°;  $uv \lambda$  max 225sh ( $\epsilon$  23,363), 235sh (12,830), 265 (6128), 278sh (5170), 300nm (4213);  $ir \nu$  max 1727, 1650, 1260  $cm^{-1}$ ; nmr  $\delta$  0.83 (3H, singlet), 2.03 (3H, singlet), 3.9 (3H, singlet), 4.49 (2H, singlet), 4.5-4.9 (1H, multiplet), 6.6 (1H, singlet), 7.08 (1H, singlet).

*Anal.* Calcd. for  $C_{23}H_{29}O_4N$ : C, 72.03; H, 7.62; N, 3.65. Found: C, 72.44; H, 7.91; N, 3.32.

ii). In another experiment, a solution of II (1.8 g.) in anhydrous methanol (5 ml.) containing charcoal (50 mg.) was refluxed for 18 hours. The methanol solution was then distilled and the distillate was subjected to Vapor phase chromatography on a 2 meter Poropak-Q column at 160° when a peak with retention time of 12.39 minutes was obtained which corresponded with that of an authentic sample of allyl mercaptan. The residue left after distillation of the methanol was dissolved in chloroform. The solution was filtered and concentrated and the residue after one crystallization afforded light yellow needles, m.p. 171-175° dec. (1.1 g.) found identical with VII by comparison of infrared and nmr spectra.

Reaction of II with Ethanol.

A solution of II (0.5 g.) in absolute ethanol (10 ml.) containing charcoal (0.2 g.) was heated under reflux for 50 hours. The hot solution was filtered when the filtrate deposited colorless needles, m.p. 260-263° (0.31 g., 71% yield). Mixed m.p. determination and comparison of infrared spectra showed this to be the lactam (V).

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