Thermolysis and Photolysis of 3β-Lanostenyl Azidocarbonate: Functionalization of the 4α-Methyl Group

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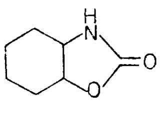
Summary The thermolysis and photolysis of 3β-lanost-8-enyl azidocarbonate leads to the functionalization in moderate yields of the C-2 methylene group and the C-4α methyl group.

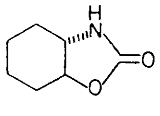
FUNCTIONALIZATION of the 4,4-dimethyl groups of lanostane derivatives has considerable synthetic and biosynthetic application.[1,2] We report a procedure for the selective functionalization of the 4α-methyl group of lanostane derivatives having a 3β-hydroxy-group. Functionalization of the 4β-methyl group has been reported recently *via* nitroxide photolysis.[2]

Our interest in the modification of aminoglycoside antibiotics[3] led us to investigate the synthetic potential of the insertion reactions of *O*-acyl nitrenes to provide vicinal aminoalcohol groups. This reaction has been rarely utilized in synthesis because of the poor yields commonly encountered. One source of side-products is the triplet state of the nitrene which readily undergoes hydrogen extraction reactions with potential hydrogen donors. It has been shown, however, that CH_2Cl_2, which is essentially inert to C–H insertion or hydrogen extraction also stabilizes the first-formed singlet state in certain nitrenes[4] and this was chosen as an appropriate solvent for the present work.

Little was known about the cyclisations of azidocarbonate derivatives of cyclic compounds until the work of Edwards and his co-workers on the thermolysis of 3β-acetoxy-11-oxolanostan-7α-yl azidocarbonate and its C-7 epimer.[5]

As we were particularly concerned with the efficiency and selectivity of insertion reactions of azidocarbonates attached to six-membered rings, the thermolysis and photolysis of cyclohexyl azidocarbonate† (b.p. 47 °C; 8 mm Hg) were examined. Thermolysis‡ at 140 °C in CH_2Cl_2 led to the efficient conversion into a mixture of the *cis* and *trans* oxazolidinones (**1**) (m.p. 55—56 °C)[6] and (**2**) (m.p. 101—103°C) in 30 and 29% yields, respectively, after chromatography and crystallization. Photolysis of cyclohexyl azidocarbonate in CH_2Cl_2 (450 W Hanovia Hg lamp, Pyrex filter, N_2) gave a similar result, with (**1**) and (**2**) being isolated in 31 and 25% yield, respectively. There appears to be no significant preference for the formation of either isomer from the thermal or photochemical reactions in this conformationally mobile system.


(1)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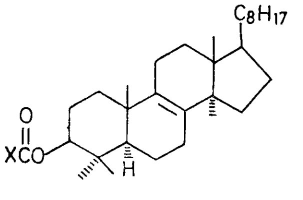
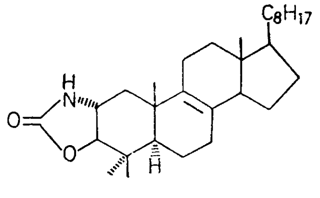

(3) X = Cl
(4) X = N_3
(5) X = NH_2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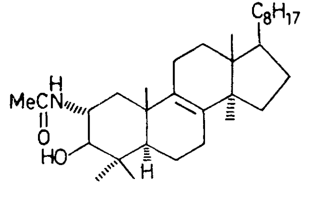
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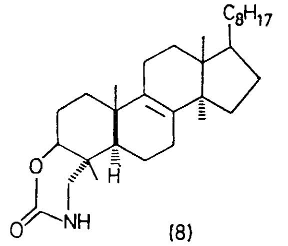
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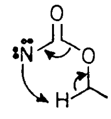
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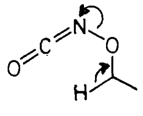
(10)

The conformationally rigid lanost-8-ene skeleton was then studied. The double-bond at the 8,9 position of the azidocarbonate (**4**) was considered to be too hindered to react with the generated nitrene at a rate comparable with intramolecular insertion, and no such side-reaction was observed. 3β-Lanost-8-enyl chloroformate (**3**) (m.p. 130—131 °C) was readily prepared from 3β-lanost-8-enol in 95% yield with phosgene in benzene and treated with NaN_3 in acetone to give lanost-8-enyl azidocarbonate (**4**) (m.p. 105—106 °C) in 94% yield. Thermolysis of this material gave two major products which were easily separated by chromatography on silica gel. The major component was the *trans* oxazolidinone (**6**) [m.p. 262—264 °C; i.r. (Nujol) 1770 cm^{-1}; δ ($CDCl_3$) 3·7 (2H, H-2 and H-3)], which was obtained in 55% yield. The n.m.r. spectrum was not readily amenable to analysis, so (**6**) was converted into the mono *N*-acetate (**7**) by base hydrolysis (KOH, aqueous dioxan) and *N*-acetylation. (**7**) had m.p. 277—279 °C; δ [$CDCl_3$ + $(CD_3)_2SO$] 3·9 (1H, dt, $J_{2,3}$ 11 Hz $J_{1,2}$ 11 and 5 Hz, H-2) and 2·95 (1H, d, $J_{2,3}$ 11 Hz, H-3). The coupling constant of 11 Hz for $J_{2,3}$ establishes the *trans* nature of the substituents at positions 2 and 3 in (**7**) and therefore of the oxazolidinone ring in (**6**).

Also isolated, in 25% yield, was the product of insertion (**8**) into the 4α-methyl group, which crystallized from acetone–methanol [m.p. 263—266 °C; i.r. (Nujol) 1745 cm^{-1}; δ ($CDCl_3$) 2·9 (1H, d, J_{gem} 11·5 Hz, H-30a), 3·1 (1H, dd, J 3·5 and 11·5 Hz, H-30b), 3·85 (1H, dd, $J_{2,3}$ 5·5 and 9 Hz, H-3), and 6·45 (1H, d, J 3·5 Hz, N–H)]. The methylene hydrogen atoms derived from the 4α-methyl group are geminally coupled but only one of them is coupled significantly to the hydrogen attached to nitrogen. The highest field absorption (δ 15·0 p.p.m.) in the ^{13}C-n.m.r. spectrum of 3β-lanost-8-enol has been assigned by two independent groups to the 4β-methyl group;[7] the 4α-methyl group resonates at δ 27·4 p.p.m. Substitution into the 4α-methyl group would be expected to result in an upfield shift of the 4β-methyl group resonance corresponding to a γ effect[8] of 2·5—4 p.p.m. The highest field carbon resonance in the ^{13}C-n.m.r. spectrum of (**8**) occurs at δ 12·5 p.p.m. replacing the absorption at δ 15·0 p.p.m. in 3β-lanost-8-enol. This is consistent with (**8**) being the product of insertion into the 4α-, but not the 4β-methyl group.

A trace of lanost-8-en-3-one was also produced. This may be formed by the pericyclic mechanism (**9**) suggested by Edwards *et al.*[5] or by rearrangement to the alkoxyisocyanate[9] followed by the elimination of isocyanic acid (**10**).§ The combined yield of insertion products was >80%.

Photolysis of (**4**) (450 W Hg lamp, Pyrex filter, N_2) in CH_2Cl_2 gave (**6**) and (**8**) in 22 and 10% yield, respectively, together with the hydrogen extraction product (**5**) in 20% yield.

Thus although both hydrogen atoms at C-2 and both methyl groups at C-4 are available, insertion takes place almost exclusively into the α-face of the molecule. Examination of molecular models suggests that this is the result of 1,3 *syn*-periplanar nonbonded interactions which develop in the probable transition states leading to insertion into the β substituents, but which are not involved in transition states leading to insertion into the α substituents. Thus the acyl nitrene side-chain can interact with the 4β-methyl group during insertion into the C-2β hydrogen. Similarly it will experience nonbonded interaction with the C-2β hydrogen during insertion into the 4β-methyl group.

The selectivity and efficiency of the thermal insertion reactions in the presence of the 8,9 double bond increases the

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† All new compounds had i.r., n.m.r., and mass spectroscopic and analytical data in agreement with the assigned structures.

‡ Thermolyses were performed in a Paar bomb equipped with a Teflon insert.

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utility of this reaction. A similar method has recently been published.[10]

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