New Synthesis of Steroidal Tetrahydro-oxazin-2-ones

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Summary In dimethyl sulphoxide–$NaHCO_3$, 16α-aminomethyl- and 16α-benzylaminomethyl-3-methoxy-17β-tosyloxyestra-1,3,5(10)-triene undergo cyclisation into the corresponding tetrahydro-oxazin-2-ones instead of oxidation.

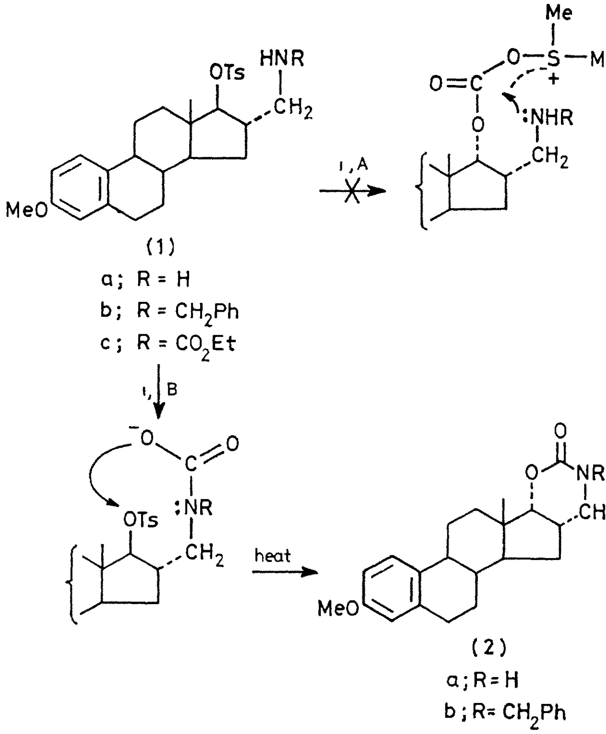
IT is well known that primary and secondary toluene-*p*-sulphonic esters can be oxidized into the corresponding carbonyl derivatives in the presence of $NaHCO_3$ in dimethyl sulphoxide (DMSO),[1] *via* a mixed carbonic acid half-ester. When a hydroxy-group is attached in a favourable steric position to the neighbouring carbon atom, a cyclic carbonate is formed and oxidation does not occur [2,3]

With primary or secondary amino-groups in appropriate steric positions near to the toluene-*p*-sulphonic ester (attached to the sterane skeleton in an αγ arrangement), in dimethyl sulphoxide–NaHCO$_3$, the formation of the tetrahydro-oxazin-2-one is again observed instead of oxidation Thus, 16α-aminomethyl-3-methoxy-17β-tosyloxyestra-1,3,5-(10)-triene (**1a**) and 16α-benzylaminomethyl-3-methoxy-17β-tosyloxyestra-1,3,5(10)-triene (**1b**) are transformed into the corresponding 16α,17α-substituted tetrahydro-oxazin-2-ones (**2a**) {m p 268—270 °C, $[\alpha]_D + 35°$ ($c = 1$, chloroform), ^{1}H n m r δ 0·83 (s, 18-Me), 4·30 (d, $J_{17,16}$ 5 Hz, 17-H), 3·53 (dd, $J_{16\,H_A,16'H_B}$ 12·5 Hz, $J_{16'H_A\,16}$ 4·5Hz, 16'-H$_A$), and 3·11 (dd, $J_{16\,H_B,16\,H_A}$ 12 5 Hz, $J_{16'H_B,16}$ 3·75 Hz, 16'-H$_A$)} and (**2b**) {m p 157—159 °C, $[\alpha]_D -23°$ ($c = 1$, chloroform), ^{1}H n m r δ 0·78 (s, 18-Me), 4·20 (d, $J_{17\,16}$ 4·5 Hz, 17-H), 3·38 (dd, $J_{16\,H_A,16'H_B}$ 4·5 Hz, $J_{16'H_A,16}$ 5 Hz, 16'-H$_A$), 2·88 (dd, $J_{16'H_B\,16\,H_A}$ 4·5 Hz, $J_{16'H_B,16}$ 4 Hz, 16'-H$_B$), and 4·68 and 4·21 (d, CH_2Ar)} in excellent yield in dimethyl sulphoxide in the presence of NaHCO$_3$ at 100 °C in 120 min

Two reaction mechanisms can be considered (Scheme) In the first mechanism (path A), the C-17 toluene-*p*-sulphonate yields, with the anion HCO$_3^-$, a carbonic acid half-ester in a nucleophilic exchange reaction stabilized by dimethyl sulphoxide This unstable intermediate and the neighbouring amino-group undergo cyclisation into the tetrahydro-oxazin-2-one However, since 3-methoxy-17β-tosyloxyestra-1,3,5(10)-triene is not oxidized under similar conditions and the C-17 toluene-*p*-sulphonic esters take part in nucleophilic exchange reactions only under vigorous conditions,[4] another mechanism was regarded as probable

It was assumed (path B) that in dimethyl sulphoxide–NaHCO$_3$ free carbamic acid was formed which yielded the tetrahydro-oxazin-2-ones in a fast cyclisation reaction involving anchimeric assistance

In order to confirm pathway B, 16α-ethoxycarbonyl-aminomethyl-3-methoxy-17β-tosyloxyestra-1,3,5(10)-tri-ene (**1c**) was prepared On heating this compound in the presence of dimethyl sulphoxide–NaOH, hydrolysis into the free carbamic acid and its conversion into (**2a**) in an intramolecular reaction occurs



Scheme i, DMSO–NaHCO$_3$

The reaction pathway agrees with the formation of oxazolidones[5] from αβ-halogenamines in dimethyl sulphoxide–Na$_2$CO$_3$ The system examined by us is an extension of this latter reaction to *p*-tolylsulphonyloxyamine systems having the αγ-arrangement

A fast cyclisation process yielding a homogeneous product is typical of neighbouring group participation, these reactions can be classified as (RNH–COO$^-$-6) according to the notation introduced by Winstein [6]

We thank the Chemical Works of Gedeon Richter Ltd , Budapest, for support

(*Received*, 11*th April* 1980, *Com* 380)

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