Synthesis of 3-Aza-bicyclo[3,3,1]nonanes

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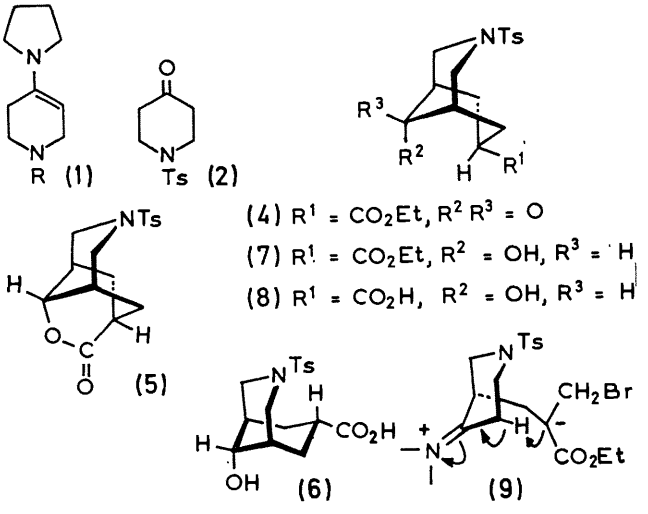
Summary 3-Aza-bicyclo[3,3,1]nonanes are synthesized *via* the reaction of the pyrrolidine enamine of *N*-toluene-*p*-sulphonylpiperidone and α-bromomethylacrylate: the stereochemistry of the adduct and some of its transformation products is discussed.

ADDITION reactions of heterocyclic enamine systems such as (**1**) have not been widely examined.[1] In view of projected investigations on aza-bicyclic systems αα′-annelation reactions of the pyrrolidine enamine of *N*-toluene-*p*-sulphonylpiperid-4-one[2] were investigated. The ketone (**2**) could be prepared on a large scale *via* the controlled acetic anhydride–pyridine cyclization[3] of *N*-toluene-*p*-sulphonyl-(ββ′-dicarboxyethyl)amine† and was converted into the enamine (**3**), m.p. 132—136°, (**1**; R = Ts) in the usual manner.‡ Reaction of diethyl ββ′-dibromoisobutyrate[4] with (**3**) in the presence of 1 equiv. of Et_3N gave the adduct (**4**), m.p. 159—161°, in 80% yield. N.m.r. ($CDCl_3$) δ 1·30 (t, $CO_2CH_2CH_3$), 2·41 (s, $ArCH_3$), 2·3—2·8 (m, 9H), 3·96 (d, N–C*H*), 4·27 (q, $CO_2CH_2CH_3$), 7·30, 7·60 (q, aromatic H). Alternatively, ethyl α-bromomethylacrylate[5] could also be used in this condensation although the yields (53%) were markedly lower.§

Attempted alkaline cleavage of the *N*-toluene-*p*-sulphonyl[6] group resulted in the formation of a lactone (**5**), m.p. 241—243°. N.m.r. ($CDCl_3$) δ 2·0—2·5 (m, 8H) (2·43 s, $ArCH_3$), 2·65 [q, –C(=O)–C*H*], 3·71 (d, N–C*H*), 4·12 (t, –O–C*H*), 7·32, 7·65 (q, aromatic H). The correspondingly formed hydroxy-acid (**6**) (no sharp m.p. because of lactone



† This compound was prepared *via* acid hydrolysis of the corresponding nitrile, which in turn was obtained upon addition of acrylonitrile to ammonia and tosylation of the subsequently formed dinitrile.

‡ The compounds described gave elemental analyses and spectral data—mass, n.m.r., and i.r.—in agreement with the assigned structures.

§ A discussion of the mechanism of this addition will be presented elsewhere.

formation upon heating) could be obtained *via* base-catalysed isomerization of the hydroxy-ester (**7**), m.p. 211—214°, the latter alcohol being isolated from the $NaBH_4$ reduction of ketone (**4**). The hydroxy-acid (**6**) was different from the hydroxy-acid (**8**), m.p. 247—251°, which resulted from the acid hydrolysis of ester (**7**). These data establish the configuration of the ester group in the adduct (**4**) as *endo*.

Contrary to earlier reports on the $NaBH_4$ reduction of 3-aza-bicyclo[3,3,1]nonanes[7] one of the two possible hydroxy-esters, *i.e.* (**7**) was formed preferentially. The relative position of the hydroxy-group follows from its lactonization on alkaline treatment. Therefore, the attack of the hydride ion has to occur from the *N*-toluene-*p*-sulphonylpiperidine half of the molecule, which evidently points to the presence of a steric barrier in the other half of the molecule with respect to additions at the carbonyl group.[8] In recent years several communications[9] have reported on the boat–chair form in bicyclo[3,3,1]nonanes, and this form is likely in our system. Further evidence for this assignment is obtained from an examination of the n.m.r. spectra of (**6**) and (**7**) in which the RO_2C–C*H* proton is separately visible. Its signal-width (*ca.* 30 Hz) corresponds closely to a similar line-shape of the C*H*OH proton in *endo*-3-hydroxybicyclo[3,3,1]nonane, a system which was shown to exist in a boat–chair conformation.[10]

One implication of this stereochemical behaviour must be mentioned. The originally determined *endo*-stereochemistry of similar adducts has been explained[11] on the basis of a preferred *exo*-protonation of the chair-like transition state of the Michael adduct. This argument need not be necesarily true for a boat-like transition state and therefore the accepted reaction sequence of the $\alpha\alpha'$-annelation *i.e.* alkylation as the first, Michael addition as the second step may also be reversed.[12] The observed stereoselectivity can then be explained *via* an exclusive internal protonation[13] of the primary Michael adduct (**9**), which is formed preferentially.

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