Reactive Tertiary Amide Nitrogen in Nonrigid Systems

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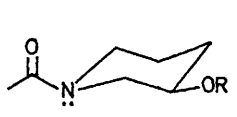
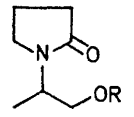
Summary Tertiary amide nitrogen participation competes significantly with amide oxygen attack in mono- and acyclic systems in substitution and elimination reactions.

ALTHOUGH a carboxamide is considered to be an ambident functional group, its reactivity has been usually associated only with the oxygen atom.[1] The reports[2] of nitrogen

participation in the rigid isoquinuclidine tertiary-amide system raise the question of how general is this phenomenon. This nitrogen effect has now been observed in the reactions of two nonrigid systems, *viz.* the monocyclic *N*-acetyl-3-piperidinol (**1a**) and the acyclic 2-(2-oxo-*N*-pyrrolidinyl)-propanol (**2a**) in displacement and elimination reactions. Together they define the general scope of this often-unnoticed property of a carboxamide.

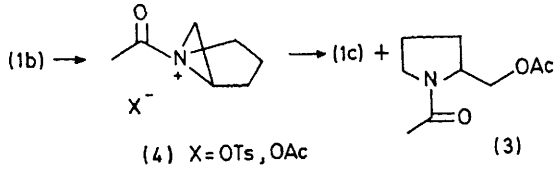


(**1**) a; R=H
b; R=Ts
c; R=Ac



(**2**) a; R=H
b; R=Ts

Solvolysis of the tosylate (**1b**) in acetic acid (0·1M, 1 equiv. NaOAc, 85°) led to the isolation of (**1c**) and the pyrrolidine (**3**) in a ratio of 1·83 : 1.† These acetates were identified by comparison with authentic synthetic materials.† Thus, both the tosylate (**1b**) and the acetate (**1c**) were prepared from the known piperidinol (**1a**)[3] by treatment with NaH–TsCl and Et_3N–Ac_2O respectively. The ring-contraction product (**3**) was prepared by reduction of proline ($LiAlH_4$) followed by acetylation.[4] Its formation in the acetolysis of (**1b**) implicates the intermediacy of the cation (**4**) as shown in Scheme 1.

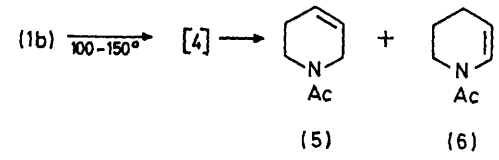


(**4**) X=OTs, OAc

SCHEME 1

For confirmation, the intermediate (**4**) was generated independently by treating 1-azabicyclo[3,1,0]hexane[5] with Ac_2O in hexane at −78°. Solvolysis of this material, as before, yielded quantitatively the acetates (**1c**) and (**3**) in a ratio of 1·86 : 1, thus confirming the amide nitrogen participation in the solvolysis of the monocyclic tosylate (**1b**).

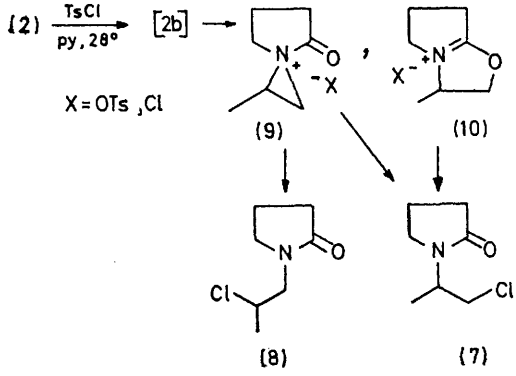
A similar nitrogen effect probably prevails in the stereospecific elimination of *p*-toluenesulphonic acid from (**1b**). Thus, heating (**1b**) neat in the range 100—150° gave rise to the piperideines (**5**) (96%)[6] and (**6**) (4%)[7] (Scheme 2), which were identified by comparison with synthetic materials. It is inconceivable why this elimination reaction should involve preferential loss of the 4-hydrogen in (**1b**). However, if prior displacement of the tosylate by the amide nitrogen to form (**4**) preceeded the hydrogen removal, the predominance of the 3-piperideine (**5**) resulting from (**4**) finds a good analogy in the stereospecific eliminations shown by some aziridinium salts.[8]



(**5**) (**6**)

SCHEME 2

In order to estimate the competitiveness of *N*- *vs.* *O*-attack in neighbouring amide participation, the acyclic propanol system (**2**) is used. 2-(2-Oxo-*N*-pyrrolidinyl)-propanol (**2**) was prepared by reacting γ-butyrolactone with α-aminopropanol[9] according to a known method.[10] Upon treatment of (**2**) with pyridine and tosyl chloride in carbon tetrachloride at 28°, the expected tosylate (**2b**) was not found. Instead, two chlorine-containing products, *viz.* the primary propyl chloride (**7**) (59·2%) and the rearranged secondary chloride (**8**) (16·7%), were isolated in a ratio of 3·56 : 1. It appears most likely that the elusive propyl tosylate (**2b**) was produced, but had reacted further with the neighbouring amide moiety to form the intermediate (**9**) and perhaps (**10**), resulting from *N*- and *O*-attack respectively (Scheme 3). Since the rearranged chloride (**8**) can be



(**8**) (**7**)

SCHEME 3

derived only from the *N*-acylaziridinium ion (**9**), the extent of the amide nitrogen involvement as manifested in the formation of (**9**) should be at least 22% of the total pyrrolidone participation.

These results reveal the high competitiveness of amide nitrogen *vs.* oxygen attack even in nonrigid systems under a variety of reaction conditions. This reactive property, hitherto unnoticed, makes the carboxamide a truly ambident function.

(*Received*, 26*th February* 1973; *Com.* 256.)

† Satisfactory elemental analysis and n.m.r. and i.r. spectra were obtained for all new compounds. Reaction products were quantitated by gas chromatography.

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