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ADDITION OF DIETHYL 2-BROMOMESACONATE TO N-TOSYLPIPERIDONE ENAMINE[1]

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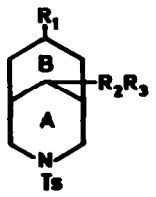
As potential precursors in the synthesis of functionalized 1-aza-adamantanes, the substituted 3-aza-bicyclo-[3,3,1]nonanes 1 are of considerable interest. A convenient preparation for the latter type of compound is the addition of 2-bromomethacrylates to enamine 2[4]. Recent work in the cyclohexanone series[5] comprises both mechanistic aspects of the addition and conformational investigations about some adducts of the bicyclo-[3,3,1]nonane type. The observation of novel mechanistic as well as conformational aspects in the piperidone series prompts us to disclose some of our results.

As described earlier[4], the addition of acrylate 3a (3, R=H) to enamine 2 occurred smoothly, yielding the ester 1a (1, R_1=$COOC_2H_5$, R_2R_3=O). However, use of the precursor of 3a, i.e. ethyl β,β'-dibromoisobutyrate[6] required 2.2 equiv. of Et_3N for optimum results[7], lesser amounts of amine resulting in the formation of α-substituted piperidones[8]. Upon use of diester 3b, (3, R=$COOC_2H_5$) experimental evidence indicated 3.3. equiv. of Et_3N being necessary for synthetically useful results; under these conditions 41% of pure 4a, m.p. 109-111°; NMR($CDCl_3$) 3.7-4.5 m (7 protons); 2.3-2.8 m (10 protons), 1.25 t (6 protons, $COOCH_2\underline{CH_3}$); IR ($CHCl_3$) 1710, 1720 cm^{-1} (C=O); was obtained. Use of lesser amounts of base gave a sharp drop in yield, and the recovery of N-Ts piperidone, while raising the Et_3N concentration leads to the formation of tarry byproducts. The observed difference between the addition of 3a and 3b is likely to find its cause in a dual reaction path. In the reaction of 3a the Michael adduct I is formed in which the carbanion acts as a proton receptor, thereby accomplishing the necessary back formation of the intermediate enamine.

In the general case, however, a preferred alkylation has to be assumed[9] leading to the imminium form II. Conformational factors, e.g. the equilibrium between imminium and enamine forms in piperidone systems, or more likely a stabilization of the imminium form by intramolecular attractive forces between relatively electron rich oxygens of the SO_2 groups[10] and the imminium moiety could oppose the establishment of an equilibrium, making necessary the use of a tertiary amine.



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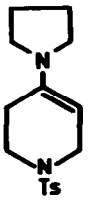

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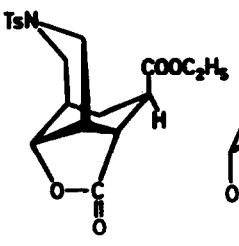

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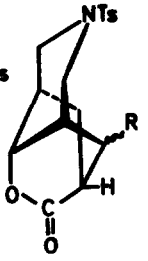
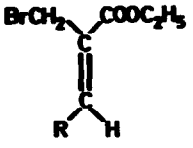


6.

a:R= endo-CH_2OH

b:R=exo-COOH



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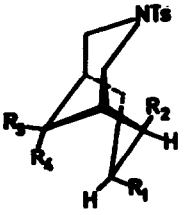

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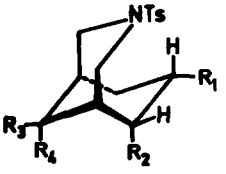
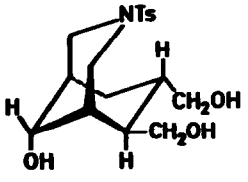


7.

a : R_1=COOEt ;	R_2=COOEt ;	R_3,R_4=O
b : R_1=COOEt ;	R_2=CH_2OH ;	R_3=H ; R_4=OH
c : R_1=COOH ;	R_2=COOH ;	R_3,R_4=O
d : R_1=CH_2OH ;	R_2=CH_2OH ;	R_3=H ; R_4=OH
e : R_1=COOEt ;	R_2=COOEt ;	R_3=H ; R_4=H
f : R_1=CH_2OH ;	R_2=CH_2OH ;	R_3=H ; R_4=H



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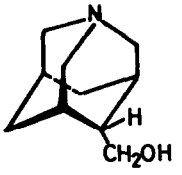

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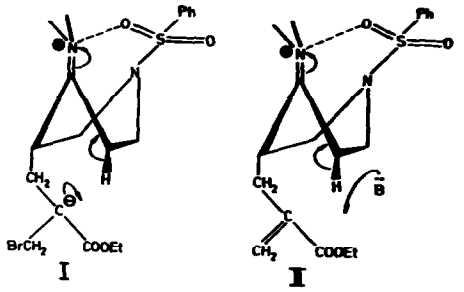

I II

The relative stereochemistry of the ester group in the adduct 4a has been assigned on the basis of the following experimental and spectral evidence: $NaBH_4$ reduction of 4a provided the diol-ester 4b, m.p. 143-145°, NMR ($CDCl_3$) δ1.25 t (3 H), the formation of which deserves some comment. The unusual course of this reduction implies the formation of a γ-lactone 5 as an intermediate, which was confirmed by its isolation from the reduction of 4a with Na-bis(2-methoxyethoxy) aluminiumhydride, m.p. 200° (dec); IR ($CHCl_3$) 1775 and 1785 cm^{-1} (O=C-O, γlactone), 1720 cm^{-1} (C=O); NMR ($CDCl_3$)[11] δ4.2-4.5, ($\underline{CH_2}CH_3$ + O=C-O-$\underline{CH}$), 4.03 and 3.75 m (N-$\underline{CH_2}$), 3.33 m ($\underline{CH}$-C=O-O) 2.75 m ($\underline{CH}$COOEt). Furthermore $NaBH_4$ reduction of 5 gave 4b as the sole product. This behaviour led to the assignment of a C_6-exo-configuration for the ester. Oxidation of 4b (Ag_2CO_3/xylene) gave also 5[12].

On treatment of 4b with Na/EtOH, a 54% yield of 6a was obtained, m.p. 162-164°, IR ($CHCl_3$) 1750 cm^{-1} (C=O); NMR ($CDCl_3$)δ4.15 t (CH-O-C=O), 3.85-3.50 m ($\underline{CH_2}$OH, $\underline{CH_2}$N); 2.7 m ($\underline{CH}$C=O). The original configuration of th C_7 ester is thus endo and the overall-stereochemistry of the ester 4a is most likely a boat-chair conformation[13]. This conclusion was further substantiated by the following series of experiments. Isomerization of 4a gave keto-diacid 7c, which was esterified (EtI/Ag_2O) to give the diester 7a, m.p. 135 - 138,5°. IR ($CHCl_3$) 1725 cm^{-1} (C=O); 1160, 1340 cm^{-1} (Ts) NMR ($CDCl_3$) δ 4.0-4.4, (5H, O$\underline{CH_2}$ + N$\underline{CH_2}$ eq + $\underline{CH_7}$); 3.69 d, J=6 c/s ($\underline{CH}$6); 2.3-3, (9H).

The low-field position of H_7 indicates a chair conformation for ring B[13].

$NaBH_4$ reduction of 7c gave directly δ-lactone acid 6b as the main product. The absence of any γ- lactone suggests, in view of the foregoing results, an endo-stereochemistry for the C_6-ester group. This was also confirmed by $LiAlH_4$ reduction of lactones 6a and 6b, in which only the position of the C_6-substituents differs. Triols 7d and 8 were obtained confirming the endo-stereochemistry for the C_6-ester group.

In both series 4 and 7 the keto-ester was converted to the methylene esters 4e and 7e via S-ketalization and Ra-Ni treatment of the resulting thioketal. The ester 4e was finally converted ($LiAlH_4$) into diol 4f, which was cyclized (HCl/AcOH) to 1-aza-adamantane 9. The synthesis of alkylsubstituted aza-adamantane thus can be achieved via this route.

Additional NMR conformational studies on the adducts as well as the chemistry of some aza-adamantanes will be reported separately.

REFERENCES

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5. J.M. McEuen, R.P. Nelson and R.G. Lawton, J. Org. Chem, 35, 690 (1970)
6. A.F. Ferris, J. Org. Chem, 20 780 (1955)
7. Contrary to the earlier report[4] in which the use of 1.0 eq of Et_3N was described, novel experimental results indicate the necessity of using 2.2 eq of Et_3N.
8. Structural proof was evidenced from spectral data:
   Mass: M^+= 365 (6%); M-Ts=210 (100%) IR ($CHCl_3$) 1710 cm^{-1} (C=O)
   NMR ($CDCl_3$) 7.5 q(ArH), 6.25 s (=CH) 5.65 s(=CH), 4.2 q(OCH_2);
   2.2-3.9 m (12H) 1.25 t (OCH_2CH_3)
   although the compound could only be obtained in an oily state.
9. For an extensive and well-documented review in the carbocyclic series see ref. 5
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11. Double irradiation experiments confirmed the assignment.
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