

SYNTHESIS OF FUNCTIONALLY SUBSTITUTED 1-AZAADAMANTANES
ANOMALOUS 1,3-DIOL FRAGMENTATION

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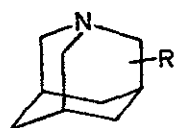
The synthesis of a number of 2- and 3-substituted 1-azaadamantanes, in which the substituent carries a functional group, is reported. Anomalous fragmentation of a 1,3-diol is described and discussed in terms of conformation.

As part of our continuing investigations of the properties of 1-azaadamantanes^{2,3} a synthesis for 2- and 3-substituted 1-azaadamantanes 1 became necessary. In view of earlier experiences the transformation and ring closure of suitable azabicyclo[3,3,1]-nonanes was considered to be an attractive route.

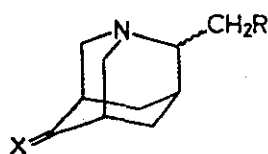
Starting materials for all amino cage compounds were the aldehydes 2a-c, which in turn were synthesized from the corresponding alcohols³ in 80-85% yield using pyridinium chlorochromate.⁴ Reaction of 2a and 2b with methylene triphenylphosphorane and subsequent acid-catalyzed cyclisation was expected to furnish the 2-methyl-1-azaadamantanes.

Two equivalents of ylid were found to be necessary in order to obtain a good yield (85% in both cases) of the products 3a and 3b: use of only 1,25 equivalent decreased the yield to 55%. This

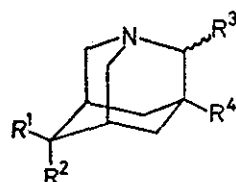
effect is probably due to partial consumption of ylid by the tosylgroup; recent investigations have indicated a similar behaviour.⁵ The C₇-substituent of 3b was shown to occupy the endo position by ring closure in HCl/acetic acid under reflux conditions to the known compound⁶ 5 in 79% yield; m.p. 76-80°C (dec); ¹H-NMR (CD₃OD) δ 1.48 (3H, d, N-CH-CH₃).



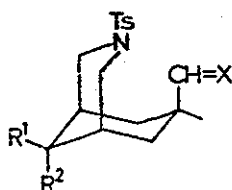
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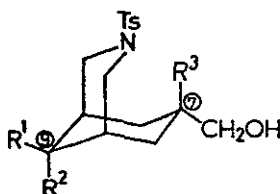
5 X=O R=H
6 X=H₂ R=OH
7 X=O R=OH



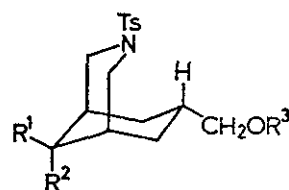
10 R¹R²=O R³=OH R⁴=CH₂OH
11 R¹R²=O R³=H R⁴=CHO
12a R¹=R²=H R³=H R⁴=CH₂OH
b R¹R²=-SCH₂CH₂S- R³=H R⁴=CH₂OH
16 R¹R²=-SCH₂CH₂S- R³=H R⁴=H



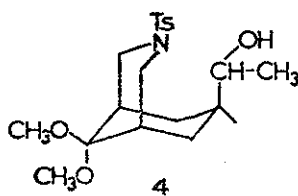
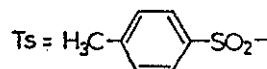
2a R¹=R²=H X=O
b R¹=R²=OCH₃ X=O
c R¹R²=-SCH₂CH₂S- X=O
3a R¹=R²=H X=CH₂
b R¹=R²=OCH₃ X=CH₂



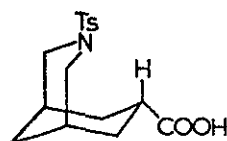
8a R¹=R²=H R³=CHO
b R¹=R²=OCH₃ R³=CHO
c R¹R²=-SCH₂CH₂S- R³=CHO
9a R¹=R²=H R³=CH₂OH
b R¹=R²=OCH₃ R³=CH₂OH
c R¹R²=-SCH₂CH₂S- R³=CH₂OH



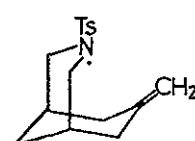
13a R¹=R²=H R³=C(=O)CH₃
b R¹R²=-SCH₂CH₂S- R³=C(=O)CH₃
15 R¹=R²=R³=H



4



14



17

Figure 1

Treatment of the alkenes 3a and 3b with 1 equivalent of *m*-chloroperbenzoic acid gave directly the ringclosed products 6 and 7. Data for 6: m.p. 106-110°C (dec); $^1\text{H-NMR}$ (D_2O) δ 4.35 (1H, t, $\text{N-CH-CH}_2\text{OH}$); 4.1 and 3.7 (4H, 2x N-CH_2); 3.9 (2H, CH_2OH); 2.50 and 2.00 (9H, other cage protons). For 7: m.p. 80-85°C (dec); $^1\text{H-NMR}$ (D_2O) 4.40 (1H, 2 x d, $\text{N-CH-CH}_2\text{OH}$); 2.25 (2H, broad s, 2 x CH-C=O). A related case of olefin epoxidation with concomitant ring closure by attack of a neighbouring group leading to 2-azaadamantanes was recently reported.⁷

Condensation of the aldehydes 2a-c with formaldehyde under basic conditions in a two-layer system (water-dichloromethane) gave the aldols 8a-c. The relative C_7 -configuration of the aldehyde and alcohol functions in 8b was shown to be as depicted by its ring closure to 10 in 72% yield; $^1\text{H-NMR}$ (D_2O) δ 3.55 and 3.25 (2H, CH_2OH); 2.50 (2H, broad s, 2 x CH-C=O); m.p. 155-159°C (dec). No trace of the bridgehead aldehyde 11, corresponding to the reversed C_7 -configuration in 8b, was found. Reduction of the aldols 8a-c with NaBH_4 afforded the diols 9a-c in nearly quantitative yield.

To obtain the desired functionally C_3 -substituted 1-azaadamantane derivative 12a, the diol 9a was submitted to cyclisation conditions similar to those used before in the preparation of 1-azaadamantane.^{2a} Quite unexpectedly, the only product isolated from the reaction mixture (in 94% yield) was the acetate 13a; m.p. 118-120°C; IR (KBr) 1710 cm^{-1} (C=O); $^1\text{H-NMR}$ (CDCl_3) δ 3.82 (2H, d, $\text{CH-CH}_2\text{OAc}$); 2.90 (1H, m, $\text{CH-CH}_2\text{OAc}$); 2.05 (3H, s, OOC-CH_3). Further evidence for this structure assignment was obtained from an independent synthesis: the known³ acid 14 was converted with LiAlH_4 to the alcohol 15 (yield: 91%); acetylation of 15 with acetic anhydride gave a single product, identical with 13a.

When, however, the diol 9c was submitted to the same reaction conditions a 70% yield of the ringclosed product 12b was obtained, together with a small amount of the acetate 13b. Data for 12b: $^1\text{H-NMR}$ ($\text{C}_5\text{D}_5\text{N}$): 3.75 and 3.30 (4H, $2 \times \text{N-CH}_2$); 3.40 (s, 6H, $-\text{SCH}_2\text{CH}_2-\text{S}$ and CH_2OH); 3.22 (s, 2H, N-CH_2); 2.40 and 1.98 (4H, $2 \times \text{cage -CH}_2$); 1.92 (2H, $2 \times \text{-C-H}$ (cage)); m.p. 146-149°C.

The $^1\text{H-NMR}$ -spectrum could be interpreted by comparison with the spectrum of 16, the thioketal of 1-azaadamantan-4-one.^{2b}

A possible explanation for this striking difference in behaviour might be the following: protonation of the endo-CH₂OH can lead to ringclosed product only if the N-Ts group is in the vicinity of the intermediate carbenium intermediate; because of a diminished steric hindrance at C_9 the distance between N-Ts and endo-CH₂OH is considerably larger in 9a than in 9c, 9a most probably possessing a chair-boat conformation. In the latter molecule cyclisation is therefore hindered and fragmentation occurs as an undesired side reaction. A difference in conformation between 9a and 9c is also indicated by $^{13}\text{C-NMR}$ analysis.⁸

Originally an explanation for the formation of the acetates 13a-b was formulated as follows⁹: fragmentation of the 1,3-diol would give the intermediate alkene 17, which could add acetic acid in an anti-Markovnikov manner, giving the acetate. This explanation, however, is incorrect as is discussed in the sequel.

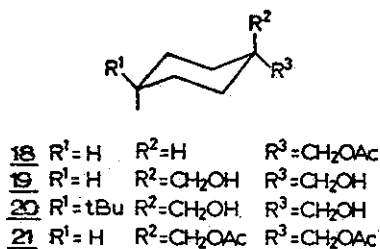
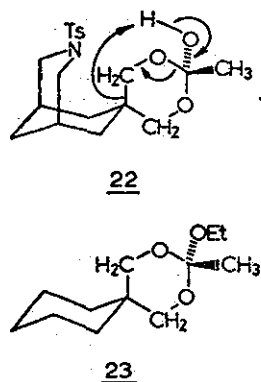


Figure 2



Although it proved not possible to prepare the alkene 17 under a variety of conditions¹⁰, indirect information on the reaction course was obtained from the following experiments. Firstly, the reaction of methylenecyclohexane with acetic acid-hydrochloric acid did not yield any of the expected acetate 18. In view of the known sluggish behaviour of olefins in analogous type of reactions¹¹ this result is not surprising. Secondly and of even more significance reactions of 1,1 bis(hydroxymethyl)cyclohexanes 19 and 20 gave similar fragmentation results. Treatment of 19 in HOAc-HCl gave mainly the acetate 18 (45% yield).¹² Analogous reaction of 20 gave a mixture of two acetate epimers (ratio 1:1). Thus the two experiments establish the general character of the 1,3 diol fragmentation in cyclohexane-like compounds while the latter result seems to indicate the more or less equivalence of both hydroxymethyl groups. A plausible reaction path would be the following: after formation of a monoacetate it might be anticipated that the cyclic ortho-ester 22 arises as a transient intermediate.¹³ Next to a reversible process leading to starting material the irreversible proton transfer - presumably via a cyclic transition state - and concomitant expulsion of formaldehyde gives rise to generation of the acetate.¹⁴ This to the best of our knowledge unprecedented process is apparently a fairly general reaction for 1,3 diols if other pathways are not available and it also accounts for the formation of 13a. In the latter example the preferential loss of the endo hydroxymethyl presumably arises from the steric hindrance exerted by the sulfonamide substituent.

Finally, the compound 12a could be obtained from 12b by desulphurisation with Raney-Nickel, in 70% yield. Data: ¹H-NMR (CD₃OD) δ 3.35 (2H, s, CH₂)OH; 2.20-1.80 (8H, cage protons).

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