Tetrahedron Letters No. 39, pp 3729 -3730. 0040-4039/79/0922-3729$02.00/0
©Pergamon Press Ltd. 1979. Printed in Great Britain.

A SUBSTITUTED 1-AZAADAMANTANE DERIVATIVE BY "ONE POT" CYCLISATION OF MONOCYCLIC MONOTERPENOIDS

A. PANCRAZI, I. KABORE, B. DELPECH and Q. KHUONG-HUU

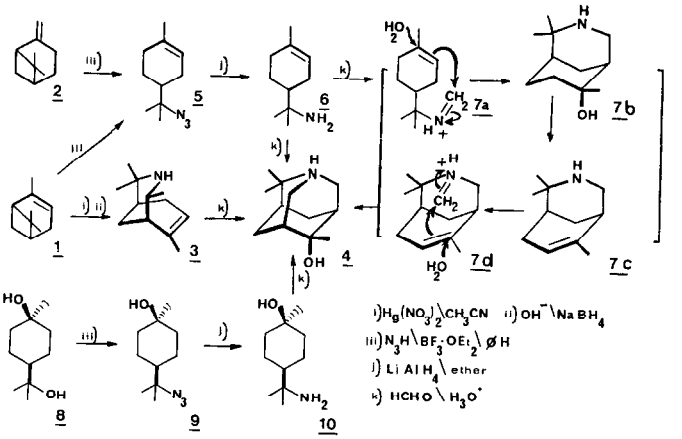
Institut de Chimie des Substances Naturelles, CNRS,

91190 Gif sur Yvette, France

Summary : Cyclisation of monocyclic amines via iminium intermediates provides a facile synthesis of a substituted 1-azaadamantane derivative.

The synthesis of 1-azaadamantane derivatives has generally involved long multistep sequences[1-3]. The synthesis of 1-azaadamantane 4 from 3-azabicyclo [3.3.1] non-6-ene 3 has recently been described by two of us[4]. The synthesis of intermediate 3, however, involved the use of a mercuric salt, which we wished to avoid for reasons of pollution. We therefore envisaged an alternative synthesis of the title compound via cyclisation of iminium salts derived from 8-amino-p-menth-1-ene 6 and 1-hydroxy-8-amino-trans-p-menthane 10

SCHEME



Treatment of α et β-pinenes 1, 2 with N_3H/BF_3-OEt_2[5] gave azide 5 which was reduced to amine 6. In a similar manner, terpine hydrate 8 led to azide 9 and amine 10.

It was gratifying to observe that addition of the remaining two carbon atoms and cyclisation to the 1-azaadamantane skeleton could be achieved directly in "one pot" by treatment with aqueous formaldehyde and acid catalysis Thus, amino-δ-olefin 6, afforded 1-azaadamantane 4, in 80% yield[6]. The proposed mechanism for the key step cyclisation is outlined in the scheme. Condensation with formaldehyde leads to the formation of the iminium intermediate 7a which undergoes cyclisation to the amino alcohol 7b and subsequent dehydration of the tertiary alcohol to yield the olefinic amine 7c. Reaction of 7c with a second molecule of formaldehyde generates the iminium intermediate 7d thus allowing cyclisation to the 1-azaadamantanol 4. Treatment of the amino-alcohol 10 with aqueous formaldehyde in acidic conditions[7] led to the same 1-azaadamantanol 4 (45%) and the starting material (45%). In this case, elimination of the tertiary alcohol of 10 is slow and formation of 4 proceeded via the olefinic amine 6.

The ready availability of terpenic azides and amines[5] and the high yield achieved in the desired iminium cyclisation thus provide a direct access to the substituted 1-azaadamantane skeleton.

References

1 - R.C. FORT, Jr. in "Adamantane. The Chemistry of Diamond Molecules", P.G. Gassman, Ed. Marcel Dekker, New-York, 1976, p. 268.

2 - W.N. SPECKAMP, J. DIJKINK and H.O. HUISMAN, Chem. Comm., 197 (1970) ; A.W.J.D. DEKKERS, W.N. SPECKAMP and H.O. HUISMAN, Tetrahedron Lett., 489 (1971) ; W.N. SPECKAMP, J. DIJKINK, A.W.J.D. DEKKERS and H.O. HUISMAN, Tetrahedron, 27, 3143 (1971).

3 - H. STETTER and W. REINARTZ, Chem. Ber., 105, 2773 (1972).

4 - B. DELPECH and Q. KHUONG-HUU, J. Org. Chem., 43, 4899 (1978).

5 - A. PANCRAZI, I. KABORE and Q. KHUONG-HUU, Bull. Soc. Chim. Fr., 162 (1977).

6 - A solution of the amine hydrochloride 6[5], (9.5 mmol., 1.8 g) in dioxane (25 ml) and 40% aqueous formaldehyde (10 ml) was treated in a steam bath for 4 h. The solution was basified by NaOH and extracted by methylene chloride. The crude product 4 was crystallized from acetone (1.5 g, 80%) m.p. 178°, identical in all aspects to the 4,8,8-trimethyl-4-hydroxy-1-azaadamantane 4[4].

7 - A solution of the hydrochloride of 10[5] (5 g, 24.1 mmol.) in dioxane (50 ml) and 40% aqueous formaldehyde (20 ml) was treated in a steam bath for 24 h. Work up as described above gave 4 (2.5 g, 45%) and 10 (2 g. 45%).

(Received in France 16 July 1979)