Tetrahedron Letters No. 31, pp. 2917-2920, 1971. Pergamon Press. Printed in Great Britain.

BICYCLIC ENAMINES III. SIGMATROPIC REARRANGEMENTS IN A QUINUCLIDINE SYSTEM [x]

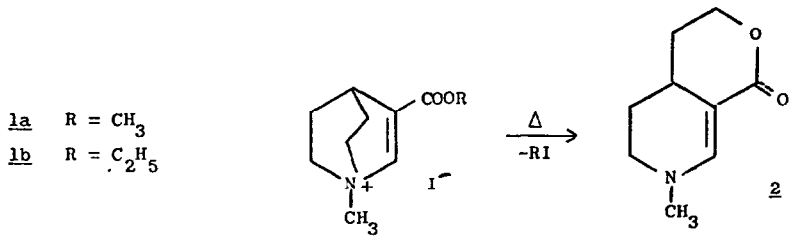
Karl-Henrik Hasselgren, Jörgen Dolby [xx] and J.L.G. Nilsson

Faculty of Pharmacy, University of Uppsala, Box 6804, S-113 86 Stockholm and

Magnus Elander

Dept. of Organic Chemistry, University of Stockholm, Box 6801, S-113 27 Stockholm

Recently, we observed (1) that when the quaternary quinuclidine-3-carboxylic acid ester 1a is heated, it rearranges to the lactone 2 under the loss of methyl iodide. We now present results indicating that the formation of 2 occurs via two consecutive suprafacial 1,3-sigmatropic rearrangements (2). This appears to be the first observation of this type of reaction.

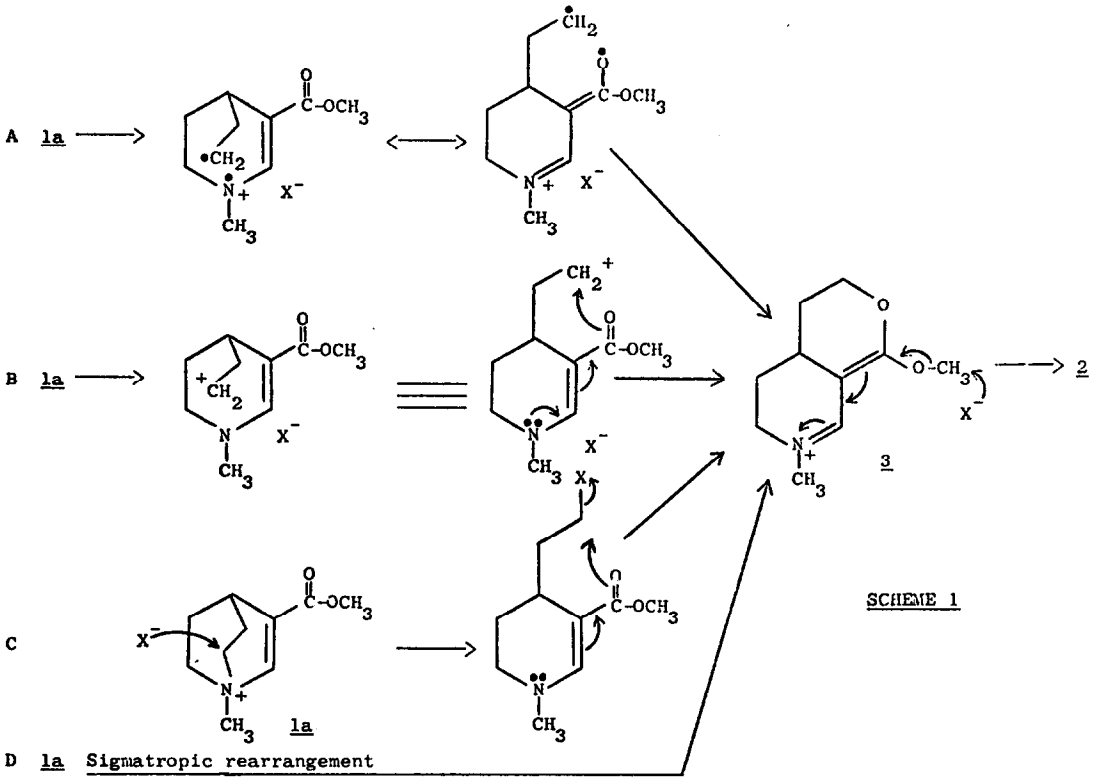


Several mechanisms can be formulated for the thermal conversion of 1a to 2. The four most probable pathways, designated A-D in Scheme 1, have a common last step, which involves the loss of an alkyl halide from the reaction intermediate 3. The postulated occurrence of 3 as an intermediate is supported by the observation that the alkyl halide formed is derived from the ester function of 1, since ethyl iodide could be isolated during the rearrangement of 1b to 2.

---

x Part II: See reference 6.

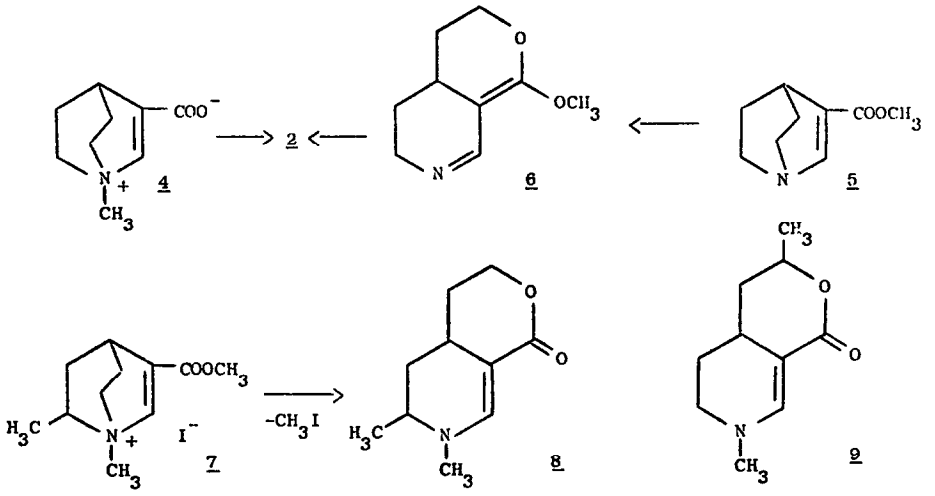
xx Present address: Farmaceutiska Centralen, Södersjukhuset, S-100 64 Stockholm 38, Sweden.



The intermediate 3 may be formed from 1a via a radical or a carbonium ion mechanism (A or B, respectively), or after attack by the counter ion as in C. Compound 3 may also be formed by a sigmatropic rearrangement of 1a (D).

The results of two different experiments indicate that the counter ion is not involved in the reaction. The betaine structure 4 (prepared from 1a (3), m.p. 260°) was smoothly rearranged to the lactone 2 when heated to its melting point for about one minute. Similarly, the base 5 (4) was converted in 75 % yield to 2 when heated for 30 min. at 200°. In this reaction, 6 may first be formed, and the methyl group may then migrate to the nitrogen.

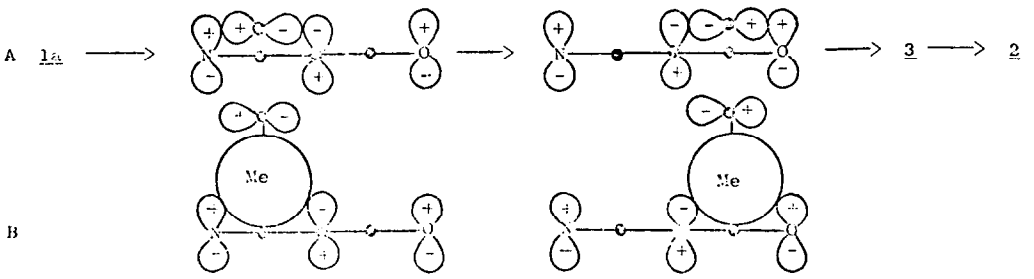
The conversion of the racemic C-methyl substituted quaternary compound 7 [prepared according to Mikhlina et al. (5) m.p. 134-135°] to the lactone 8 gave positive evidence for the sigmatropic rearrangement mechanism D. [Compound 8 was obtained in 73 % yield: M.p. 82-84°. ν_{max}(KBr) 1670 and 1590 cm^{-1}, C=C and C=O (6). NMR: ($CDCl_3$) δ = 7.55 ppm, 1H,d, J ~ 2 cps, C=C-H; 4.4-4.1 ppm, 2H,m, CH_2-O-; 2.96 ppm, 3H,s, N-CH_3 and 1.29 ppm, 3H,d, J=6.5 cps, C-CH_3. MS: m/e (rel. intensity %): 181 (100) M^+, 166 (50), 150 (11), 137 (27), 122 (33), 108 (45) and 94 (21)].



If the rearrangement of 7 had occurred via mechanism A or B, compound 9 would most probably have been the main product. The unpaired electron (mechanism A) or positive charge (mechanism B) would then be residing on a secondary carbon atom instead of on a primary one as in Scheme 1. However, compound 9 could not be detected in the reaction mixture, the only product isolated being 8.

The orbital transformations in the sigmatropic rearrangement of 7 are depicted in Scheme 2A. The net result of the reaction is a suprafacial 1,5-sigmatropic rearrangement. However, since the migrating group has to be bonded to both ends of the unsaturated system in the transition state (7,8), such a conversion is not possible in one step in quinuclidine type compounds, where the nitrogen and the ester function are trans to the double bond. We therefore propose that the reaction involves two consecutive suprafacial sigmatropic rearrangements. One-step thermal suprafacial 1,3-sigmatropic rearrangements in bicyclic systems have recently been reported (9-11).

SCHEME 2



The migrating carbon of the unsubstituted bridge of 7 undergoes two consecutive inversions when moving from the nitrogen to the carbonyl oxygen of the ester. These reactions give an intermediate compound analogous to 3, which is subsequently converted to the lactone 8. If the C-methyl substituted bridge would migrate, the size of the methyl group would effectively prevent the overlapping of the orbital lobes (9), either in the first or the second step, depending on the configuration of the reacting molecule (Scheme 2B). In analogy with this mechanism for the rearrangement of 7, we conclude that 1 is converted to 2 via two consecutive suprafacial 1,3-sigmatropic rearrangments.

Acknowledgements

We thank Professor Richard Dahlbom, Professor Bengt Lindberg and Dr. Björn Åkermark for valuable criticism and discussion.

References

1. Dolby, J., Dahlbom, R., Hasselgren, K.-H. and Nilsson, J.L.G. Acta Chem. Scand. in press 1971.
2. Woodward, R.B. and Hoffmann,R. Angew. Chem. 81, 797 (1969).
3. Kosower, E.M. and Patton, J.W. J. Org. Chem. 26, 1318 (1961).
4. Grob, C.A., Kaiser, A. and Renk, E. Helv. Chim. Acta 40, 2170 (1959).
5. Mikhlina, E.E., Vorobeva, V.Ya. and Rubtsov, M.V. Zh. Obshch. Khim. 33, 3852 (1963).
6. Dolby, J., Hasselgren, K.-H., Nilsson, J.L.G. and Elander, M. Acta Pharm. Suecica in press 1971.
7. Woodward, R.B. and Hoffmann, R. J. Amer. Chem. Soc. 87, 2511 (1965).
8. Woodward, R.B. Accounts Chem. Res. 1, 17 (1968).
9. Berson, J.A., and Nelson, G.L. J. Amer. Chem. Soc. 89, 5503 (1967).
10. Berson, J.A. Accounts Chem. Res. 1, 152 (1968).
11. Berson, J.A. and Nelson, G.J. J. Amer. Chem. Soc. 92, 1096 (1970).