Tetrahedron Letters No. 46, pp 4043 - 4046, 1975. Pergamon Press. Printed in Great Britain.

BIOMIMETIC HETEROCYCLISATIONS

REACTIVITY OF RIGID UNSATURATED SYSTEMS

by

J. Dijkink, H.E. Schoemaker and W.N. Speckamp*

Laboratory of Organic Chemistry, University of Amsterdam,

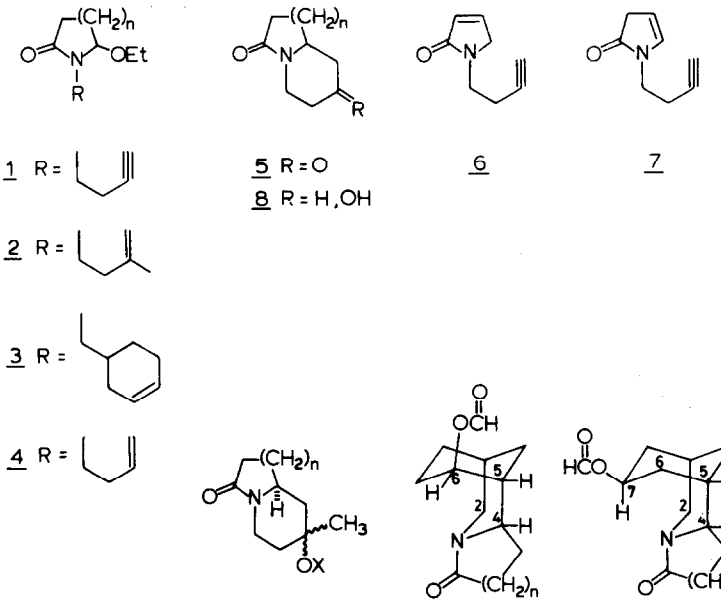
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

(Received in UK 2 September 1975; accepted for publication 29 September 1975)

In search for a general and versatile heterocyclic intermediate for achieving an adaption[1] of the well-known principle of biogenetic olefin-cyclisations[2] the cyclic acylimmonium ion has been investigated[3]. In this communication some further data on its mode of reaction are reported.

Ethoxylactams 1-3, synthesized via $NaBH_4/H^{\oplus}$-reduction of the corresponding imides, which in turn were obtained by condensing succinimide and glutarimide and the appropriate alcohol according to Mitsunobu[4] were subjected to formic acid cyclization. Reaction of 1a (HCOOH, r.t./16 hr) gave a mixture of at least three new compounds - 5a, 6 and 7 - in approximately equal ratio, in addition to starting material. Upon prolonged reaction time (HCOOH, r.t./72 hr) a 97% yield of 5a was obtained, m.p. 53-57°C (dec), IR 1710 cm^{-1} (C=O), 1680 cm^{-1} (C=O lactam); $\delta(CDCl_3)$ 4·42 (m, 1H, H_{5eq}), 3·85 (m, 1H, H_{8a}). Thus all of the intermediate compounds present after 16 hr were ultimately converted into the keto-lactam 5a. Further identification of 5a was possible by Pt/H_2/AcOH reduction giving the known[1] alcohol 8a. No trace of the other possible cyclisation product could be detected.

Similarly, the ethoxylactam 1b afforded the known[5] keto-lactam 5b (HCOOH, r.t./113 hr) in 88% yield. Again only the formation of the quinolizidine structure could be ascertained no trace of the eventually formed acetylindolizidine being found.



As compared to the cyclisation[1] of 4a a dramatic rate enhancement was noted upon HCOOH treatment of 2a. Both at r.t. and 5°C an immediate cyclisation took place to a mixture of cyclic formates while upon lowering the acidity of the soln (AcOH/r.t.) ring closure to 9a (X=Ac) is complete within 24 hr. From solvolysis experiments in different acids it was considered likely that the observed ratio of stereoisomers reflects the thermodynamic stabilities of the two isomers. In this case the cyclisation therefore may be viewed upon as proceeding via discrete steps, involving the intermediacy of a cyclic C^+ion. The data given before allow a ratio of $k^{cycl}_{2a} / k^{cycl}_{4a} > 10^3$ to be estimated which figure indicates a marked influence of the alkyl substituent on the rate of the cyclisation.

Cyclisation of 2b to 9b (X=HC=O) proceeds in a similar fashion (HCOOH, 15 mn, 8°C) affording a 1:1 mixture of formate epimers. Thus in this experiment also a marked Me-effect was noted.

Quite unexpectedly, the ring closures of 3a and 3b (HCOOH, r.t./16 hr) although proceeding quantitatively, gave mixtures of 3-aza-bicyclo[3,3,1]nonanes 10a and

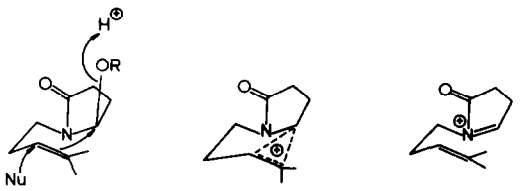
11a, 10b and 11b respectively.

In the glutarimide series the compounds 10b and 11b were formed[6] in a ratio 55:45 and could be separated via crystallization (EtOH, ether): 10b, m.p. 112-114°C (EtOH), PMR δ($CDCl_3$) 3·52 (m, 1H, H_4); 4·63 (d, 1H, H_{2eq} J=13·0 c/s; 5·36 (m, 1H, H_6, W½=7 c/s); 8·05 (S, 1H, OOCH). 11b m.p. 152-155°C (ipropether). PMR δ($CDCl_3$) 3·25-3·60 (m. 1H, H_4), 4·62 (d, 1H, H_{2eq}, J=13·5 c/s) 5·30 (m, 1H, H_7, W½=25 c/s), 7·97 (S, 1H, OOCH). The exo-position of the formate residue in 10b followed from W½ of H_6 of 7 c/s[7], while both the exo-stereochemistry and the C_7 position of the formate in 11b were indicated by the C_7-H septet possessing two diaxial (J=11·0 c/s) and two ax-eq (J=4·5 c/s) couplings[8].

The above result can be explained if a rapid [1,2]hydride shift is assumed to occur. Analogous findings have been reported in studies on classical vs non-classical carbonium ions notably in the solvolysis of medium size ring cyclo-alkenemethyl tosylates[9]. It should be noted that C_4-C_5 cis stereochemistry is imposed in view of the supposed sixmembered chairlike transition states for this type of ring closure.

With regard to the mechanism of the cyclisation the following comments are of relevance. Since the discovery[10] of this reaction type the possibility of the simultaneous occurrence of both classical and non-classical carbonium ions has been convincingly demonstrated[11]. In biogenetic cyclisations of polyolefins several pathways have been discussed[12] among which the following three are of relevance to the present work: i) a synchronous process A in which the departing OR substituent and the incoming nucleophile are both involved in the formation of the new carbon-carbon bond ii) the non-classical ion B which would explain the observed stereochemistry adequately and iii) the intermediacy of a free carbonium ion intermediate C.

POSSIBLE MECHANISMS C-C BOND FORMATION



A B C

From the results outlined above it seems likely that in the cyclisation of the derivatives 1a, 3a and 3b the occurrence of at least pathway C is ascertained while B cannot be ruled out. On the other hand, the marked accelerating Me-effect observed in cyclisations of 2a and 2b disfavors[13] the intermediacy of B. Further studies on the role of the acid used and on the eventual influence of the type of OR substituent in ω-carbinollactam cyclisations are in progress.

REFERENCES

1) J. Dijkink and W.N. Speckamp, Tetrahedron Letters, accompanying communication.

2) a. W.S. Johnson, Accounts Chem.Res., 1, 1 (1968).
b. E.E. van Tamelen, Accounts Chem.Res., 1, 111 (1968).

3) J.C. Hubert, J.B.P.A. Wijnberg, W.N. Speckamp, Tetrahedron, 31, 1437 (1975).

4) O. Mitsunobu, M. Wada, T. Sano, J.Amer.Chem.Soc., 94, 679 (1972).

5) L. Mandell, K.P. Singh, J.T. Gresham, W.J. Freeman, J.Amer.Chem.Soc., 87, 5234 (1965).

6) The ratio of 10b and 11b could be influenced to a considerable extent by variation in the type of acid used, H.E. Schoemaker, unpublished results.

7) A.C. Cope, D.L. Nealy, P. Scheiner and G. Wood, J.Amer.Chem.Soc., 87, 3130 (1965).

8) Comparison of the spectral data with those of independently prepared 3-aza-bicyclo[3,3,1]-nonanols-7 was also possible. Th. Reints Bok, results to be published.

9) M. Hanack, W. Kraus, W. Rothenwöhrer, W. Kaiser, G. Wentrup, Liebigs Ann.Chem., 703, 44 (1967).

10) G. LeNy, C.R.hebd.Séances Acad.Sci., 251, 1526 (1960).

11) a. H. Felkin, G. LeNy, C. Lion, W.D. Keith Macrosson, J. Martin, W. Parker, Tetrahedron Letters, 157 (1966).
b. W.D. Closson, G.T. Kwiatkowski, J.Amer.Chem.Soc., 86. 1887 (1964).
c. See ref. 9.

12) a. W.S. Johnson, Trans N.Y.Acad.Sci.II, 29, 1001 (1967).
b. K.E. Harding, Bio Org.Chem., 2, 248 (1973).

13) a. K.L. Servis, J.D. Roberts, J.Amer.Chem.Soc., 87, 1331 (1965).
b. J.W.T.Wu, E.R. Thornton, J.Org.Chem., 40, 1041 (1975).