Tetrahedron Letters,Vol.23,No.3,pp 349-352,1982 0040-4039/82/030349-04$03.00/0
Printed in Great Britain

NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION. A BIOMIMETIC SYNTHESIS OF QUINUCLIDINES.

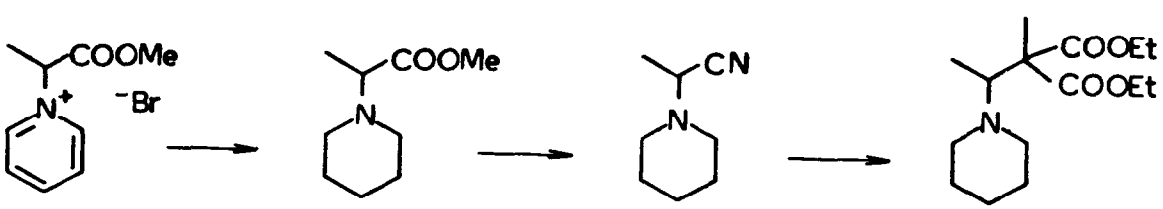
Mauri Lounasmaa* and Ari Koskinen

Technical University of Helsinki, Department of Chemistry,
SF-02150 Espoo 15, Finland

Summary: *Suitably substituted aminoesters can be transformed to the corresponding α-aminonitriles and in the case of piperidino-acetic ester derivatives, into the biochemically important quinuclidine ring system.*

In connection with our studies concerning the synthesis of sarpagine-type indole alkaloids we were able to develop an efficient biomimetic synthesis of the quinuclidine (1-azabicyclo-[2.2.2]octane) ring system.

We first examined the possibility of forming an exocyclic iminium double bond on a piperidine ring, as indicated by Potier et al.[1] Thus (scheme 1) piperidine 2 (from the pyridinium salt 1 by catalytic hydrogena-



1 2 4 5

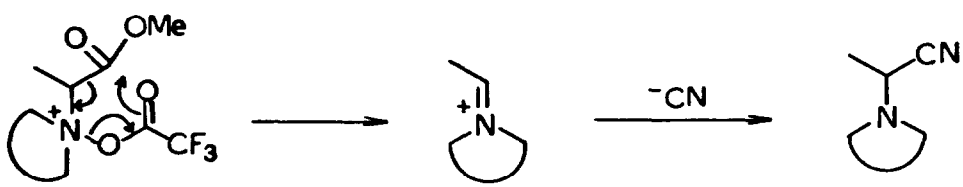
3 N-oxide

SCHEME 1

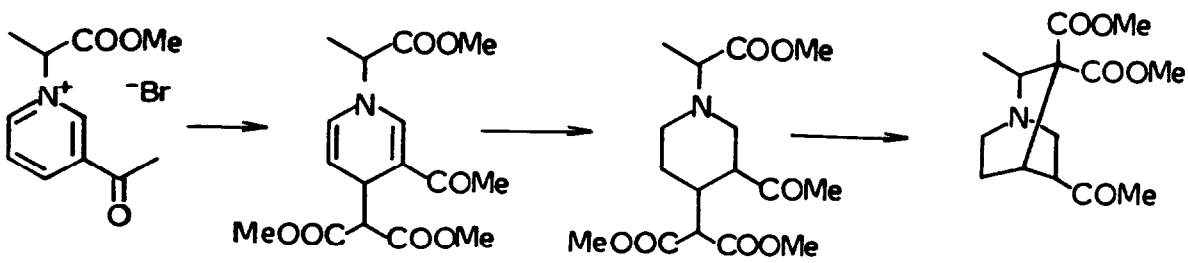
tion over 10% Pd/C in MeOH) was oxidized to the N-oxide 3 (H_2O_2,$CHCl_3$: EtOH, rfx, 24 hrs, 84%), which was subjected to the modified Polonovski reaction conditions[2] employing the cyanide ion trapping method described by Husson[3] ($(CF_3CO)_2O$,CH_2Cl_2, 0^o, then KCN,pH 4, two phase system) to furnish directly the nitrile 4[4] in 25% yield (vide infra).

Treating the nitrile 4 with sodio diethyl methylmalonate in the presence of silver trifluoroacetate[5] furnished the malonic ester 5[6] in 49% yield.

The unprecedented formation of the nitrile 4 directly from the N-oxide can be rationalized through the assistance of the $\overset{+}{N}$-$OCOCF_3$ grouping in the acid catalyzed elimination step leading to intramolecular elimination reaction:



The synthesis of the quinuclidine system 10, exhibiting clear structural similarity to several sarpagine type indole alkaloids, proceeded as follows (scheme 2). The pyridinium salt 6 was alkylated following the Kröhnke procedure[7] modified by Wenkert[8]. Without isolation, the labile[8]



6 7 8 10

9 N-oxide

SCHEME 2

dihydropyridine intermediate 7 was hydrogenated to the triester 8 (6% overall yield from 6). The triester 8 was oxidized to the N-oxide 9 (H_2O_2, $CHCl_3$: EtOH, rfx, 30 hrs, 98%) and the N-oxide 9 subjected to the above mentioned modified Polonovski reaction conditions (TFAA, CH_2Cl_2, 0^o, 1 hr, then KCN, pH 4, two phase system). To our astonishment the cyclized quinuclidine 10[9] was directly obtained (yield 20%). This clearly supports the postulate of van Tamelen[10] on the biogenesis of the sarpagine type alkaloids.

Work on the applications of this method to the synthesis of sarpagine type alkaloids is in progress.

REFERENCES AND NOTES

1. L. Chevolot, A. Husson, C. Kan-Fan, H.-P. Husson and P. Potier, Bull. Soc. Chim. Fr., 1976, 1222.

2. A. Cavé, C. Kan-Fan, P. Potier and J. Le Men, Tetrahedron 23 (1967) 4681.

3. D.S. Grierson, M. Harris and H.-P. Husson, J. Am. Chem. Soc. 102 (1980) 1064.

4. Compound 4: IR: 2220w. ^{1}H NMR ($CDCl_3$, δ): 1.45 3H d 7.3 Hz, 1.4-1.95 6H m, 2.51 4H m, 3.63 1H q 7.3 Hz. ^{13}C NMR ($CDCl_3$, δ): 17.0 q, 23.9 t, 25.5 2C t, 50.5 2C t, 52.8 d, 117.4 s. MS: 138 ($M^{+\cdot}$), 123 (100%), 111, 110, 96, 82, 69, 55.

5. D.E. Janssen and C.V. Wilson, Org. Syn. Coll. Vol. 4 (1963) 547.

6. Compound 5: IR: 1735 s. ^{1}H NMR ($CDCl_3$, δ): 1.27 6H t 7 Hz, 1.41 3H d 7 Hz, 1.60 3H s, 1.3-2.1 6H m, 2.60 4H m, 3.15 1H q 7 Hz, 4.20 4H q 7 Hz. ^{13}C NMR ($CDCl_3$, δ): 13.8 2C q, 16.8 q, 19.0 q, 21.4 t, 24.7 2C t, 46.5 d, 48.6 d, 50.4 t, 51.0 s, 61.6 2C t, 170.6 2C s. MS: 285 ($M^{+\cdot}$), 240, 212, 198, 173, 154, 127 (100%), 99.

7. F. Kröhnke, K. Ellegast and E. Bertram, Justus Liebigs Ann. Chem. 600 (1956) 176.

8. E. Wenkert, C.-J. Chang, H.P.S. Chawla, D.W. Cochran, E.N. Hagaman, J.C. King and K. Orito, J. Am. Chem. Soc. 98 (1976) 3645.

9. Compound 10: IR: 1740 s, 1715 s. ^{1}H NMR ($CDCl_3$, δ): 1.30 3H d 7 Hz, 2.16 3H s, 3.35 1H q 7 Hz, 3.70, 3.75 3H s each. ^{13}C NMR: 14.3, 14.7 q each (both isomers) 25.0 q, 26.8 t, 28.3 d, 49.2 d, 50.1 q, 50.6 t, 51.4 q, 52.2 s, 52.7 d, 62.9 t, 168.9 s, 173,4 s, 210.0 s. MS: 283 ($M^{+\cdot}$), 252, 240, 191, 165 (100%), 154, 136.

10. E.E. van Tamelen, V.B. Haarstad and R.L. Orvis, Tetrahedron 24 (1968) 687. Cf. also J. Stöckigt, Tetrahedron Letters 1979 2615.

(Received in UK 27 October 1981)