Tetrahedron Letters,Vol.26,No.6,pp 801-802,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION - VII[1]
PREPARATION OF ISOQUINUCLIDINES

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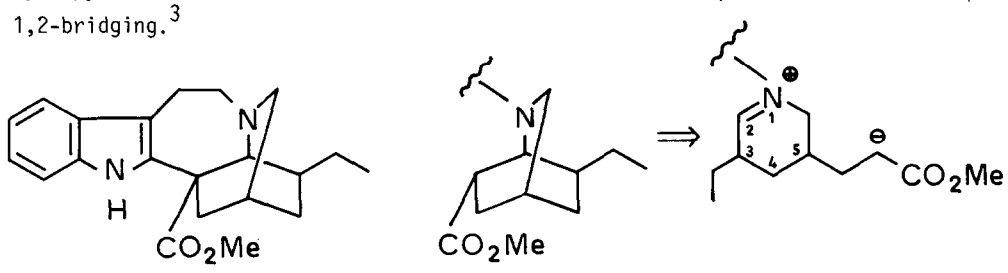
Summary: The first successful preparations of the biochemically important isoquinuclidine ring system by the modified Polonovski reaction are described.

A vexing problem in the Iboga alkaloid series (e.g. coronaridine 1) has been the preparation of the necessary isoquinuclidine (2-azabicyclo[2.2.2]octane) ring system.[2] One approach to this crucial problem would be to develop a general method for the 5,2-bridging of appropriately substituted 3,4,5,6-tetrahydropyridine (1-piperideine) units (or their equivalents, e.g. 2-cyanopiperidines). In the past, however, the 5,2-bridging of a 3,4,5,6-tetrahydropyridine unit has been considered a much less facile process than the frequently used 1,2-bridging.[3]



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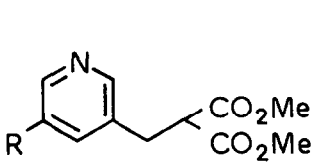
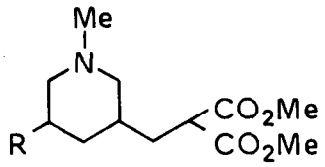
During recent years the modified Polonovski reaction has proven to be a versatile synthetic tool.[4] In the present communication we report the first successful use of this reaction for the preparation of the biochemically important isoquinuclidine ring system.

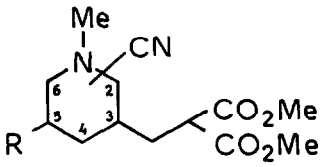
Malonic ester synthesis of 3-bromomethylpyridine and dimethylmalonate gave diester 2a, which was transformed to the corresponding methyl salt. Catalytic hydrogenation of the salt (PtO_2, 24 h) furnished the N-methylpiperidine 3a. The corresponding N-methylpiperidine N-oxide (H_2O_2) was subjected to the modified Polonovski reaction conditions (TFAA, CH_2Cl_2, 0^oC, 1 h), and the intermediate iminium salt was reacted with KCN (pH 4, two phase system) to give the α-aminonitriles 4a and 5a (in approximately 1:2 ratio) in 75% yield. It turned out to be more economical to carry out the cyclization step without prior separation of the isomers. Treatment of the mixture of 4a and 5a with $AgBF_4$ induced the desired 5,2-bridging and afforded the isoquinuclidine 6a in 20% yield.[5-6]



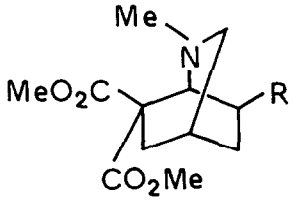
2a
2b



3a
3b



4a C(6)-CN; 5a C(2)-CN
4b C(6)-CN; 5b C(2)-CN



6a
6b

2a-6a R = H
2b-6b R = Et

In a similar fashion a mixture of α-aminonitriles 4b and 5b (in approximately 1:1 ratio), prepared from 3-bromomethyl-5-ethylpyridine via 2b and 3b, furnished the isoquinuclidine 6b in 30% yield.[6-7] The ^{13}C NMR data of 6b (vide infra) provide strong indication that the ethyl side chain is exo, as presented in the formula.

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3. E. Wenkert, K.G. Dave, I. Dainis and G.D. Reynolds, Aust. J. Chem., 1970, 23, 73. However, cf. also ref. 2b.
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5. 6a: ir 1745, 1730, pmr 2.31 (3H, s), 3.75 (6H, s), cmr 17.04 (t), 24.71 (t), 26.65 (d), 30.84 (t), 42.30 (q), 52.58 (q), 52.70 (q), 55.76 (t), 55.97 (d), 69.22 (s), 171.49 (s) (2C), m/z 241 ($M^{+\cdot}$), 210, 182, 97, 96.
6. The relative stereochemistry of compounds 3-5 was not determined.
7. 6b: ir 1745, 1735, pmr 2.31 (3H, s), 3.76 (6H, s), cmr 11.30 (q), 26.23 (t), 26.94 (d), 29.28 (t), 29.67 (t), 29.87 (d), 43.05 (q), 52.53 (q), 52.66 (q), 54.54 (t), 60.77 (d), 67.07 (s), 170.64 (s) (2C), m/z 269 ($M^{+\cdot}$), 254, 195, 125, 96.
8. Satisfactory analytical data were obtained for all new compounds.

(Received in UK 12 October 1984)