ACTA CHEMICA SCANDINAVICA 26 (1972) 2469–2472

# Bicyclic Enamines

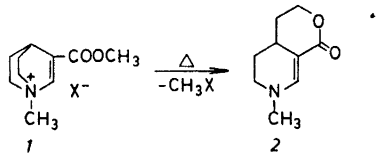
## VI. Synthesis of Gentianadine and the Alkaloidal Indoloquinolizidine Skeleton*

JÖRGEN DOLBY,** KARL-HENRIK HASSELGREN, STAFFAN CASTENSSON and J. L. G. NILSSON

*Department of Organic Chemistry, Faculty of Pharmacy, University of Uppsala, Box 6804, S-113 86 Stockholm, Sweden*

The alkaloid gentianadine (*5*) and the pentacyclic indoloquinolizidine skeleton (*8* and *9*) have been synthesized by reactions involving thermal rearrangements of quaternary 2-dehydroquinuclidine acid esters (*4* and *6*, respectively). This new reaction opens a convenient method for the preparation of tetrahydronicotinic acid lactones of type *2*.

We have previously reported that the quaternary 2-dehydroquinuclidine-3-carboxylic acid ester *1*, when heated, rearranges to the tetrahydronicotinic acid lactone *2 via* two consecutive suprafacial 1,3-sigmatropic rearrangements.[1]



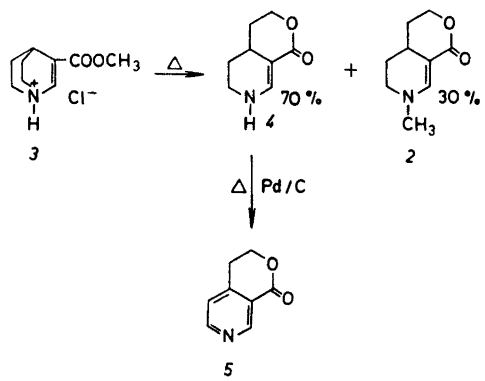

To demonstrate the usefulness of this new reaction we have synthesized the alkaloid gentianadiene (*5*) and the indoloquinolizidine skeleton (*8*), a structural fragment of many indole alkaloids.

*Synthesis of gentianadine.* Gentianadine is an alkaloid of *Gentiana turkestanorum* Gand. It was isolated by Samatov *et al.*[2] and the structure was verified by a total synthesis.[3] The synthesis was carried out in seven steps,

** Present address: Farmacevtiska centralen, Södersjukhuset, S-100 64 Stockholm 38.

* Part V, see Ref. 9. A preliminary account of the present work has been published previously.[1]

starting from 3-cyano-4-methylpyridine, as part of the work designed to elucidate structure *2*, which was isolated as a rearrangement product of *1*. Subsequent investigations on the conversion of *1* to *2* showed that this reaction ocurred *via* two consecutive 1,3-sigmatropic rearrangements.[1] We have now used this new reaction to synthesize gentianadine (*5*) by a two step procedure, as indicated in Scheme 1.



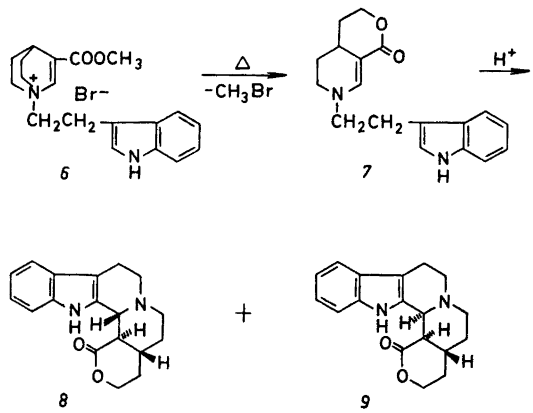

*Scheme 1.*

Heating the hydrochloride *3* to its melting point yielded two products which were separated by column chromatography and identified as *2* and *4*. The mechanism for formation of *2* in this reaction is under further investigation. Dehydrogenation of *4* using palladium on carbon yielded compound *5*, identified by comparison with authentic material.

*Synthesis of the indoloquinolizidine structure.* The pentacyclic skeleton in Scheme 2 has been obtained previously by Wenkert *et al.*[4] *via* a multistep synthesis, the last step of which involves the acid-catalyzed cyclization of a lactone of type *7*. A number of related cyclizations have been reported and have been extensively used by Wenkert *et al.* in their syntheses of indole alkaloids.[4,5]

Compound *6* was obtained from the corresponding methyl 2-dehydroquinuclidine-3-carboxylate by treatment with tryptophyl bromide. Heating the product to its melting point for about 1 min converted it in high yield to the lactone *7* which subsequently was cyclized according to Wenkert *et al.*[4]

Gas-liquid chromatography of the material obtained after cyclization indicated a mixture of two components, formed in equal amounts. Infrared studies using standard sequential dilution techniques showed a strong intramolecular hydrogen bonding. This can only occur between the NH of the indole moiety and the carbonyl group of the lactone. This was also apparent in the NMR-spectrum which shows a one-proton singlet at 10.40 ppm. Molecular models of the cyclized structure indicate that internal hydrogen bonding can occur only in the two racemic pairs *8* and *9* and these structures are therefore assigned to the two compounds obtained in the cyclization.




*Scheme 2.*

In a previous synthesis of an indoloquinolizidine alkaloid [4] the main object was to obtain an enaminolactone of type *2*. This synthesis involved about ten steps starting from a 3-cyano-4-methylpyridine derivative. By the sigmatropic rearrangement of the readily available dehydroquinuclidine ester *6* the lactone *7* is now obtained in excellent yield in a short synthetic operation.

## EXPERIMENTAL

Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. IR-spectra were recorded using a Perkin-Elmer 457 spectrophotometer and UV-spectrum was measured on a Perkin-Elmer 402 spectrophotometer. In the sequential dilution study, the IR-spectra were recorded using $CHCl_3$-solutions in a cell with variable thickness. GLC was carried out with a Varian Associates Model 1700 (FID) using a 150 cm × 3 mm i.d. steel column packed with 3 % SE 30 on 100/120 mesh Varaport. NMR-spectrum was measured with a Varian A 60 instrument using $d_6$-DMSO solution. Chemical shifts are expressed in $\delta$ ppm relative to tetramethylsilane. Mass spectrum was obtained using an LKB 9000 instrument at 70 eV.

*4-(2-Hydroxyethyl)-1,4,5,6-tetrahydronicotinic acid lactone (4) and 4-(2-hydroxyethyl)-1,4,5,6-tetrahydro-1-methylnicotinic acid lactone (2).* Methyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate hydrochloride [6] (1.0 g) was heated for 4 min at 185°. The material was then dissolved in 2 ml of chloroform and applied to a column of aluminium oxide (20 g) which was eluted with chloroform. Compound *2* was eluted with the first 25 ml of eluate, affording 0.25 g (30 %). The compound crystallized with half a mol of water. Compound *4* (0.38 g; 46 % yield) was eluted with a further 200 ml of chloroform. GLC of the crude reaction mixture indicated that compounds *2* and *4* were formed in the ratio of 3:7. The two compounds were identified by m.p. and spectral comparison with authentic material.[3]

*4-(2-Hydroxyethyl)nicotinic acid lactone (5), gentianadine.* A mixture of compound *4* (153 mg; 1 mmol) and 10 % Pd on carbon (30 mg) in *p*-cymene (3 ml) was refluxed for 6 h under a continuous stream of $CO_2$. The mixture was extracted with HCl (1 M, 2 ml) and the water layer was alkalized and extracted with chloroform (3 × 4 ml), dried ($Na_2SO_4$) and evaporated. The residue was subjected to preparative TLC on silica gel (eluted with 5 % MeOH in $CHCl_3$) yielding 42 mg (30 %) product, m.p. 76–77° (from ether–light petroleum). Reported for gentianadine,[2] m.p. 77–78°. A mixed m.p. with authentic material [3] was undepressed and the spectral data for the two compounds are identical.

*Methyl N-[2-(3-indolyl)ethyl]-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate bromide (6).* A solution of methyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate [6] (0.75 g; 0.0045 mol) and tryptophyl bromide [7] (1.0 g; 0.0045 mol) in acetone (15 ml) was left to stand at room temperature for 24 h. Addition of ether precipitated the quaternary product (1.25 g of crude material; 71 % yield) which was used in the next step without further purification. A small sample was crystallized from acetone for analysis, m.p. 132 – 133° (dec.). (Found. C 58.4; H 6.13; N 7.18. Calc. for $C_{19}H_{23}BrN_2O_2$: C 58.3; H 5.92; N 7.16.)

*4-(2-Hydroxyethyl)-N-[2-(3-indolyl)ethyl]-1,4,5,6-tetrahydronicotinic acid lactone (7).* Compound *6* was heated at 135° for 1 min. The product was dissolved in chloroform (2 ml) and chromatographed on aluminium oxide (20 g). Compound *7* (0.75 g; 90 % yield) was eluted with chloroform (50 ml); m.p. 178 – 180° (from benzene). $\nu_{max}$ (KBr) 3220 $cm^{-1}$ (NH, indole), 1655 and 1575 $cm^{-1}$ (C=O and C=C).[8] $\lambda_{max}$ (EtOH) 222 nm ($\varepsilon$ = 26 600) and 306 nm ($\varepsilon$ = 18 700). (Found: C 72.8; H 6.66; N 9.39. Calc. for $C_{18}H_{20}N_2O_2$: C 73.0; H 6.80; N 9.45.)

*Cyclization of 7 to the indoloquinolizidine lactones 8 and 9.* This reaction was carried out as described by Wenkert *et al.*[4] using 0.30 g of *7*, yielding 0.18 g (60 %) of product, m.p. 224 – 226° (from ethanol). $\nu_{max}$ (KBr) 3330, 3180, and 3065 $cm^{-1}$ (NH, indole), 1785 and 1765 $cm^{-1}$ (C=O). The spectra of dilute solutions (approx. 0.005 M in chloroform) showed only one NH-absorption band at 3450 $cm^{-1}$ indicating internal hydrogen bonding. NMR: $\delta$ = 10.40 ppm (s, 1 H, indole-NH, hydrogen bonded), 7.3 – 6.7 ppm (m, 4 Ar-*H*). The spectrum is otherwise consistent with structures *8* and *9*. Mass spectrum showed prominent peaks at *m/e* (rel. intensity %): 296 (100) $M^+$; 267 (32); 237 (58); 197 (51); 170 (59) and 169 (49).

## REFERENCES


1. Hasselgren, K.-H., Dolby, J., Nilsson, J. L. G. and Elander, M. *Tetrahedron Letters* **31** (1971) 2917.
2. Samatov, A., Akramov, S. T. and Yunosov, S. Yu. *Khim. Prir. Soedin.* **3** (1967) 182.
3. Dolby, J., Dahlbom, R., Hasselgren, K.-H. and Nilsson, J. L. G. *Acta Chem. Scand.* **25** (1971) 735.
4. Wenkert, E., Dave, K. G. and Haglid, F. *J. Am. Chem. Soc.* **87** (1965) 5461.
5. Wenkert, E. and Wickberg, B. *J. Am. Chem. Soc.* **87** (1965) 1580.
6. Grob, C. A. and Renk, E. *Helv. Chim. Acta* **37** (1954) 1689.
7. Hoshino, T. and Shimodaira, K. *Ann.* **520** (1935) 19.
8. Dolby, J., Hasselgren, K.-H., Nilsson, J. L. G. and Elander, M. *Acta Pharm. Suecica* **8** (1971) 97.
9. Dolby, J., Hasselgren, K.-H. and Nilsson, J. L. G. *J. Heterocycl. Chem.* **8** (1971) 663.
10. Dolby, J. and Hasselgren, K.-H. *Acta Pharm. Suecica* **8** (1971) 123.


Received November 23, 1971.