Bicyclic Enamines

VI. Synthesis of Gentianadine and the Alkaloidal
Indoloquinolizidine Skeleton*

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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

![Reaction scheme]

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,
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 occurred 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.](image)

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.

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![Scheme 2.](image)

In a previous synthesis of an indoloquinolizidine alkaloid, 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 signatropic rearrangement of the readily available dehydroquinocyclidine 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 CHCl₃-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 d₄-DMSO solution. Chemical shifts are expressed in δ 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 (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 alumina 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.

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 CO₂. The mixture was extracted with HCl (1 M, 2 ml) and the water layer was alkalinized and extracted with chloroform (3 × 4 ml), dried Na₂SO₄ and evaporated. The residue was subjected to preparative TLC on silica gel (eluted with 5 % MeOH in CHCl₃) yielding 42 mg (30%) product, m.p. 76–77° (from ether-light petroleum). Reported for gentianadine, m.p. 77–78°. A mixed m.p. with authentic material was undepressed and the spectral data for the two compounds are identical.

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Methyl N-[2-(3-indoly)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* (0.75 g; 0.0045 mol) and tryptophyl bromide* (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. Cal. for C_{19}H_{22}BrN_{2}O_{2}: C 58.3; H 6.22; N 7.16.)

4-(2-Hydroxyethyl)-N-[2-(3-indoly)ethyl]-1,4,5,6-tetrahydropicolinic 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). \( r_{\text{max}} \) (KBr) 3220 cm\(^{-1}\) (NH, indole), 1655 and 1575 cm\(^{-1}\) (C=O and C=C), \( \lambda_{\text{max}} \) (EtOH) 222 nm (\( \varepsilon = 26600 \)) and 306 nm (\( \varepsilon = 18700 \)). (Found: C 72.8; H 6.66; N 9.39. Cal. for C_{19}H_{22}N_{2}O_{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.* using 0.30 g of 7, yielding 0.18 g (60 %) of product, m.p. 224–226° (from ethanol). \( r_{\text{max}} \) (KBr) 3350, 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


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