

Bicyclic Enamines

I. Rearrangement of a Quaternary Quinuclidine-3-carboxylic Acid Ester and Total Synthesis of Gentianadine

JÖRGEN DOLBY, RICHARD DAHLBOM, KARL-HENRIK HASSELGREN and J. L. G. NILSSON

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

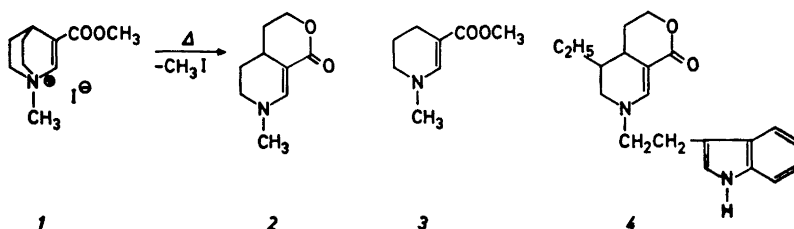
Methyl 2-dehydroquinuclidine-3-carboxylate methiodide (*I*) loses methyl iodide and is rearranged to 4-(2-hydroxyethyl)-1-methyl-1,4,5,6-tetrahydronicotinic acid lactone (*2*) when heated without solvent to its melting point. The structure of the lactone has been confirmed by an independent synthesis which also involved the total synthesis of the alkaloid gentianadine (*8*).

In two recent papers^{1,2} we have described the preparation and pharmacological properties of some amides and esters of arecaidine and quinuclidine-3-carboxylic acids. In a subsequent study, we have prepared methyl 2-dehydroquinuclidine-3-carboxylate methiodide (*I*) as a potential parasymphathomimetic agent. During this work, we discovered that the salt, which is insoluble in ether, was rapidly converted to an ether-soluble product, m.p. 119–120°, when heated to its melting point. We also observed that a gas, which was trapped and identified as methyl iodide, was evolved during the reaction.

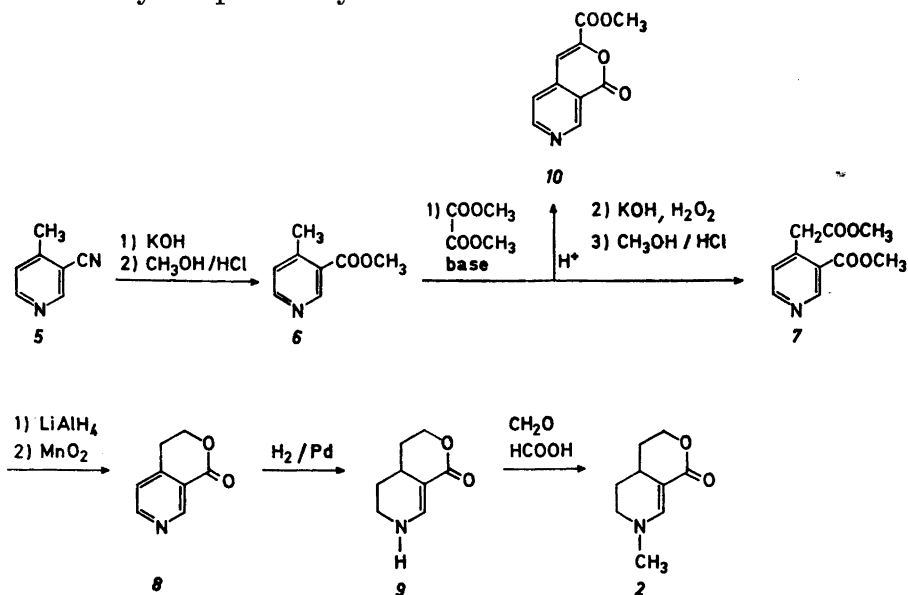
It has been shown by Grob and Renk³ that 4-cyano-1-methylquinuclidinium chloride, on heating, loses methyl chloride and is converted to 4-cyanoquinuclidine. Our new product could not be the analogously formed methyl 2-dehydroquinuclidine-3-carboxylate, since this compound is a liquid at room temperature.

When the conversion was carried out on a preparative scale, the pure new product was obtained in approximately 80 % yield. The mass spectrum shows the molecular ion at m/e 167, confirming the loss of methyl iodide from the parent quaternary compound *I*. The molecular weight of 167 was also verified by an independent determination. From this value and from the elementary analysis, the molecular formula $C_9H_{13}NO_2$ was deduced. The UV spectrum of the methiodide shows λ_{max} (EtOH) 217 nm, and the corresponding tertiary amine has λ_{max} (EtOH) 213 nm. According to Bredt's rule, the electron

pair of the nitrogen of this amine cannot be delocalized over the double bonds in the molecule, and its UV absorption is therefore typical for an α, β -unsaturated ester.⁴ The UV spectrum of the new product shows λ_{\max} (EtOH) at 303 nm, similar to the absorption of the conjugated enamino ester **3** (reported λ_{\max} (EtOH) 296 nm). Such an extended conjugated system can only be achieved if the quinuclidinic cage structure be opened with retention of the enamine to give a 1,4,5,6-tetrahydronicotinic acid derivative of type **3**. That such a transformation had occurred is also supported by the NMR spectrum, which indicates the lactone structure **2** for the new product.



Further evidence for structure **2** was obtained from the IR spectrum. This has no NH-absorption, and two strong bands appear at 1665 and 1585 cm^{-1} , which is in agreement with the spectrum of a similar lactone structure (**4**), presented by Wenkert *et al.*⁶ Structure **2** for the conversion product was finally established by independent synthesis.



Scheme 1

The synthesis of the lactone **2** was performed as depicted in Scheme 1, a reaction sequence used by Wenkert *et al.*⁶ in the synthesis of an analogous lactone. 3-Cyano-4-methylpyridine (**5**) was hydrolyzed and converted to the ester **6**. This ester was transformed in a series of steps to the diester **7**, which was reduced with LiAlH_4 to the corresponding dialcohol. Subsequent oxidation with active manganese dioxide yielded the lactone **8**, identical to the alkaloid gentianadine. Catalytic hydrogenation of **8** afforded the enamino lactone **9**, which was *N*-methylated to give a compound **2** having the same melting point and spectral data as the compound obtained by heating the methiodide **1**.

A large number of alkaloids have been isolated from plants belonging to the family Gentianaceae.⁷⁻⁹ Most of the alkaloids are pyridinal lactones of the general structure **8** with alkyl substituents in the aromatic ring. Samatov *et al.*¹⁰ have isolated a pyridine alkaloid from *G. turkestanorum*, to which they assigned the structure **8**. However, due to a confusion in the nomenclature, Samatov *et al.* compared the physical data of the alkaloid with those of 4-(1-hydroxyethyl)nicotinic acid lactone **7** and obtained poor correspondence. The physical data presented here for the lactone **8** and those presented by Samatov *et al.*¹⁰ for the isolated compound are in good agreement, thus establishing the structure **8** for gentianadine. The mechanism for the conversion of the quinuclidine derivative **1** to the lactone **2** is under investigation. A similar rearrangement has been reported by Grob and Renk³ who found that the zwitterion *N*-methylquinuclidinium-4-carboxylate is converted at high temperature to the spiro lactone of *N*-methyl-4-(2-hydroxyethyl)piperidine-4-carboxylic acid. Similar conversion of 3-substituted quinuclidine derivatives have not been reported, and it is of interest to note that the saturated analogue of **1**, methyl quinuclidine-3-carboxylate methiodide was stable on heating at its melting point.

EXPERIMENTAL

General comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. IR spectra were run on a Perkin-Elmer 457 spectrophotometer. UV spectra were measured on a Perkin-Elmer 402 spectrophotometer. NMR spectra were measured with a Varian Associated A 60 instrument, using CDCl_3 solutions. Chemical shifts are expressed in δ ppm relative to tetramethylsilane. Mass spectra were recorded, using an LKB 9000 apparatus at 70 eV. Molecular weight was determined with a Perkin-Elmer Model 115 Molecular Weight Apparatus, using benzene as solvent. Microanalyses were performed in the laboratories of Dr. A. Bernhardt, Mülheim, West Germany.

Methyl 1-azabicyclo[2,2,2]oct-2-ene-3-carboxylate methiodide (1). Methyl 1-azabicyclo[2,2,2]oct-2-ene-3-carboxylate¹¹ (1.34 g; 8 mM) in dry acetone (25 ml) was treated with methyl iodide (7.1 g; 50 mM) at room temperature for 1 h. The methiodide precipitated quantitatively, m.p. 142–143° (dec.) (from ethanol-ether). UV: λ_{max} (EtOH) 217 nm ($\epsilon = 16\,600$). IR: ν_{max} (KBr) 3005 (s), 1720 (s) and 1645 (m) cm^{-1} . (Found: C 38.9; H 5.15; N 4.42. Calc. for $\text{C}_{10}\text{H}_{16}\text{INO}_2$: C 38.8; H 5.22; N 4.53.)

Rearrangement of 1 to 4-(2-hydroxyethyl)-1-methyl-1,4,5,6-tetrahydronicotinic acid lactone (2). Compound **1** (1.60 g) was heated without solvent in a small flask at 150° in an oil bath under a stream of nitrogen for 2 min. The gas was passed through a cold trap, and the liquid collected was identified as methyl iodide by its IR spectrum and refractive index. The flask was cooled, 10 ml of water added, and the solution was extracted with chloroform (2 × 25 ml). After drying (Na_2SO_4), the solvent was removed *in vacuo*, the residue was dissolved in 2 ml of chloroform and applied to a column of aluminium oxide (20 g) which was eluted with chloroform (100 ml). Evaporation of the eluate yielded a crystalline residue (0.76 g; 81%), m.p. 119–120° (from ethyl acetate). Mol. wt.: found

169. Calc. 167.2. Titration with 0.1000 N perchloric acid in glacial acetic acid gave the equivalent weight of 167.2. The mass spectrum shows prominent peaks at m/e (rel. intensity %): 167 (92, M^+), 136 (23), 123 (89), 109 (57), 108 (63), 95 (65), 94 (100), 81 (20), 67 (22), 66 (22), 53 (21), 42 (79) and 39 (30). UV: λ_{\max} (EtOH) 303 nm ($\epsilon=21\,400$); λ_{\max} (EtOH+HCl) 306 nm ($\epsilon=26\,900$). IR: ν_{\max} (KBr) 2940 (s), 1665 (s) and 1585 (s). NMR: $\delta=7.42$ ppm (d, 1H, vinylic), 4.4–3.8 ppm (m, 2H, $-\text{CH}_2\text{O}-$), 3.3–2.8 ppm (m, 5H, $-\text{CH}_2\text{N}-$ and $-\text{NCH}_3$). A sharp signal at 2.95 ppm ($\sim 3\text{H}$) in the multiplet region is assigned to the *N*-methyl group), 2.7–0.7 ppm (m, 5H, aliphatic protons). (Found: C 64.6; H 7.90; N 8.40. Calc. for $\text{C}_9\text{H}_{13}\text{NO}_2$: C 64.6; H 7.83; N 8.38.)

Methyl 4-methylpyridine-3-carboxylate (6). 3-Cyano-4-methylpyridine¹⁸ (5) (28 g; 0.24 mol) in 20 % aqueous potassium hydroxide (300 ml) was refluxed for 3 days. After acidification with conc. HCl the solution was evaporated *in vacuo* to dryness. The residue was further dried in vacuum for 24 h. The material was suspended in methanol (500 ml), saturated with HCl-gas, and the mixture was stirred at room temperature for 36 h. The precipitated salts were filtered and the solvent was evaporated *in vacuo*. The residual oil was suspended in methylene chloride and neutralized with solid sodium bicarbonate. After filtration, drying (Na_2SO_4), and evaporation of solvent, the residue was distilled, b.p. 98°/5 mm, affording the ester 6 in 74 % yield; $n_D^{20}=1.5186$. IR: ν_{\max} (film) 1720 cm^{-1} (C=O). The ester has previously been prepared by a different route, reported¹⁸ b.p. 57–58°/1–2 mm.

Methyl 4-methoxycarbonylmethylnicotinate (7). This diester was obtained in 17 % yield from 6, following the procedure described by Wenkert *et al.*⁶ in their preparation of methyl 5-ethyl-4-methoxycarbonylmethylnicotinate, m.p. 52–53° (from ether-light petroleum). IR: ν_{\max} (KBr) = 1735 and 1720 cm^{-1} (C=O). (Found: C 57.4; H 5.35; N 6.70. Calc. for $\text{C}_{10}\text{H}_{11}\text{NO}_4$: C 57.4; H 5.30; N 6.70.)

Isolation of lactone 10. In analogy with the work by Wenkert *et al.*⁶ the intermediate lactone 10 was isolated and characterized, m.p. 182–183° (from ethanol). IR: ν_{\max} (KBr) 1735, 1720 (C=O) and 1640 cm^{-1} (C=C). (Found: C 58.4; H 3.71; N 6.91. Calc. for $\text{C}_{10}\text{H}_9\text{NO}_3$: C 58.3; H 3.44; N 6.83.)

4-(2-Hydroxyethyl)nicotinic acid lactone (8), *gentianadine*. This compound was prepared by LiAlH_4 reduction of 7 and subsequent oxidation of the dialcohol, using active manganese dioxide, essentially as described by Wenkert *et al.*⁶ The alcohol was not isolated prior to the oxidation. The lactone was obtained in 28 % overall yield, m.p. 76–77° (from ether-light petroleum) and was analyzed as its hydrochloride, m.p. 196–197° (from ethanol) IR: ν_{\max} (KBr, base) 1720 cm^{-1} (C=O). (Found: C 52.0; H 4.29; N 7.47. Calc. for $\text{C}_8\text{H}_9\text{NO}_2\cdot\text{HCl}$: C 51.8; H 4.34; N 7.55.) Reported for gentianadine,¹⁰ m.p. 77–78°; hydrochloride 195–196; ν_{\max} (KBr, base) 1730 cm^{-1} (C=O).

4-(2-Hydroxyethyl)-1,4,5,6-tetrahydronicotinic acid lactone (9). Compound 8 (150 mg) in methanol (5 ml) was hydrogenated at atmospheric pressure over 10 % Pd/C (30 mg) overnight. After filtration and evaporation of the solvent, the residue was crystallized from ether, affording 100 mg (61 %) of 9, m.p. 90–93°. The compound crystallized with half a mole of water. IR: ν_{\max} (KBr) 3270 (NH and H_2O), 1650 (C=O) and 1575 cm^{-1} (C=C and C=O).⁶ (Found: C 59.4; H 7.27; N 8.66. Calc. for $\text{C}_8\text{H}_{11}\text{NO}_3\cdot 1/2 \text{H}_2\text{O}$: C 59.2; H 7.46; N 8.64.)

4-(2-Hydroxyethyl)-1-methyl-1,4,5,6-tetrahydronicotinic acid lactone (2). To the lactone 9 (0.30 g; 1.85 mM) in formic acid (1 ml) was added paraformaldehyde (0.11 g; 2.78 mM) and the solution heated to 100° for 10 min. Water (5 ml) was added, and after neutralization with solid NaHCO_3 the water layer was extracted with chloroform (2×10 ml), dried (Na_2SO_4) and evaporated. The residue was redissolved in 1 ml of chloroform and applied to a column of Al_2O_3 (10 g) which was eluted with chloroform (50 ml). Evaporation of the eluate yielded 0.20 g (65 %) of a crystalline residue, m.p. 119–120° (from ethyl acetate). A mixed m.p. with the conversion product from the quinuclidine derivative 1 was undepressed. Spectral data of the two compounds are identical.

Attempted rearrangement of methyl quinuclidine-3-carboxylate methiodide. *Methyl quinuclidine-3-carboxylate methiodide* was prepared from methyl quinuclidine-3-carboxylate¹¹ following the procedure described for the synthesis of 1, m.p. 162–163°. IR: ν_{\max} (KBr) 1730 (s). (Found: C 39.0; H 5.90; N 4.31. Calc. for $\text{C}_{10}\text{H}_{18}\text{INO}_2$: C 38.6; H 5.83; N 4.50.)

When this compound was heated as described for methyl 1-aza-bicyclo[2,2,2]-oct-2-ene-3-carboxylate methiodide, the starting material was recovered unchanged, as shown by m.p. and IR spectrum.

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