Synthesis of 1,4-Disubstituted Quinolizidines

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Dedicated to Professor Rolf Sammet on the occasion of his 60th birthday.

Two 9,11-seco-aphylline derivatives and four 4-substitutedimino-1-carbethoxyquinolizidines were synthesized. Conformational assignments of the predominant isomers were derived from spectral data.

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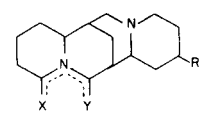
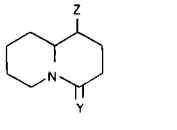
In a study to ascertain whether compounds could be generated with a favourable split between the potent blood pressure lowering properties and the toxic effects known to be displayed by bridged tetracyclic quinolizidones like the aphylline (**1a**) and lupanin (**1b**) derivatives (1), it was desired to have available for testing different compounds bearing partial structures into which the tetracyclic quinolizidines could conceptually be split. One such partial structure is the bicyclic 1,4-disubstituted quinolizidine moiety.



1a, X = H_2, Y = O, R = H
1b, X = O, Y = H_2, R = OR_1

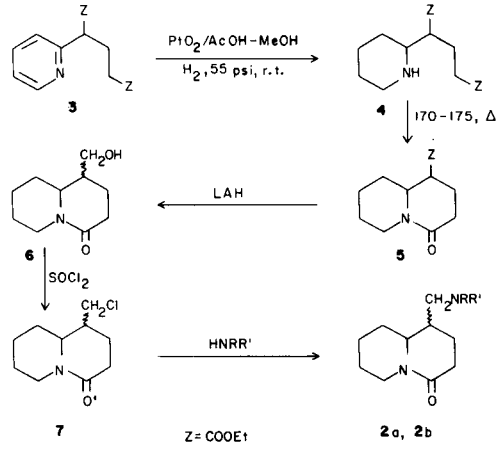


2a, Y = O, Z = CH_2N–OH
2b, Y = O, Z = CH_2–N–O
2c–f, Y = NR, Z = $COOC_2H_5$

In this report we describe the synthesis of two 4-keto-1-substituted-aminomethylquinolizidines (**2a-b**), which are, in fact, seco-aphylline derivatives, and four 4-imino-1-carbethoxyquinolizidines (**2c-f**). The blood pressure lowering properties of the compounds will be reported elsewhere.

Quinolizidines have been synthesized in different ways (2). The routes (Schemes I and II) envisaged by us for the synthesis of the desired compounds **2a-f** required 1-carbethoxy-4-quinolizidone (**5**) as a key intermediate. 1-Carbethoxy-4-quinolizidone was synthesized by minor modifications of the procedure of Boekelheide (3) (Scheme I). It was sufficient to employ 55 psi hydrogen pressure and ambient temperature for the catalytic reduction of diethyl α-(2-pyridyl)glutarate (**3**) over platinum oxide in acetic acid-methanol to saturate the pyridyl unit, as indicated by the disappearance of aromatic protons in the PMR spectrum of the product. The product, diethyl α-(2-piperidyl) glutarate (**4**), which already contained minor quantities of the desired cyclized intermediate **5** (broad doublet as a minor band at δ 4.8 due to C-6 Heq (4) in the pmr spectrum), was readily cyclized by heating at 170-175° to give 1-carbethoy-4-quinolizidine (**5**) in 79% yield. Compound **5** could be expected to be a mixture of diastereomers in which the predominant isomer would have the energetically most favourable *trans*-fused

Scheme I



conformation with the carbethoxy substituent equatorially oriented (5). The spectral data for compound **5** confirmed such an expectation. In the infrared spectrum, in accordance with established precedent for such a quinolizidine bearing a lactam group, no Bohlmann band in the region of 2800-2700 cm^{-1} is seen (6). In the pmr spectrum, the appearance of the C-10 proton as doublets of a triplet centered as δ 3.8 (J = 2 Hz, J = 7 Hz) established unequivocally the equatorial orientation of the carbethoxy substituent.

For the synthesis of the seco-aphylline derivatives **2a** and **2b**, the route beyond compound **5** depicted in Scheme I was followed. Compound **5** was selectively reduced with lithium aluminium hydride in ether at −15° to the corresponding keto alcohol **6** (8). Treatment of **6** with thionyl chloride at ambient temperatures provided the chloro compound **7**, which on condensation with appropriate amines in hexamethylphosphoric triamide gave the target aminomethylquinolizidones, **2a** and **2b** (Table I). As would be expected for compound **6**, obtained by lithium aluminium hydride reduction of **5** (5,8) and for compounds

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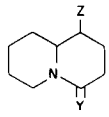
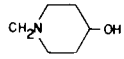
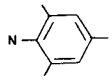
Table I

1,4-Disubstituted Quinolizidines

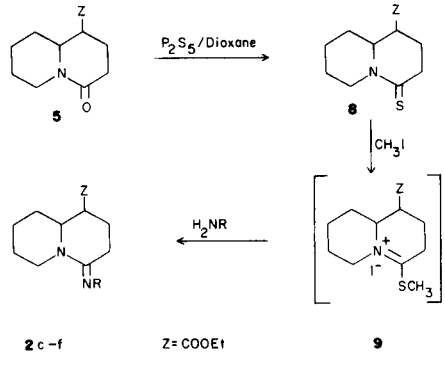


Compound No.	Y	Z	Molecular Formula	Analysis % (a) C	H	N	Cl/I
2a	O		$C_{15}H_{26}N_2O_2$ (b)				
2b	O		$C_{14}H_{24}N_2O_2$	66.26 (66.64)	9.32 (9.58)	11.42 (11.11)	
2c	NCH_2CHMe_2	COOEt	$C_{16}H_{28}N_2O_2 \cdot HI$	47.43 (47.09)	7.06 (7.158)	6.89 (6.86)	31.14 (31.09)
2d	$NCH_2CH_2NEt_2$	COOEt	$C_{18}H_{33}N_3O_2 \cdot 2HCl$	54.25 (54.54)	8.88 (9.00)	10.97 (10.60)	17.89 (17.88)
2e		COOEt	$C_{21}H_{30}N_2O_2 \cdot HCl \cdot 0.5\,H_2O$	65.35 (65.01)	8.07 (8.31)	6.94 (7.22)	9.40 (9.13)
2f	$NNMe_2$	COOEt	$C_{14}H_{25}N_3O_2 \cdot HCl \cdot 0.5\,H_2O$	54.02 (53.74)	8.63 (8.63)	13.75 (13.43)	11.17 (11.33)

(a) Values in parentheses are calculated. (b) Analysed as *O*-acetate; Calculated for $C_{17}H_{28}N_2O_3$: C, 66.16; H, 9.14; N, 9.14. Found: C, 65.99; H, 9.44; N, 9.01.

7, **2a** and **2b** derived from compound **6**, the compounds are all mixtures of C-1 epimers, as revealed once again by pmr studies. The pmr spectra of the four compounds all show a pair of doublets for the 1-substituted CH_2 protons, which are most clearly resolved in the chloromethyl compound, **7**. For compound **7**, the chemical shift of the doublet for the axially substituted 1-CH_2-Cl protons is 3.5 ppm (J = 7 Hz) and for the equatorially substituted isomer 3.6 ppm (J = 2 Hz) (7).

Scheme II



For the synthesis of the 4-iminoquinolizidines **2c-f**, the route depicted in Scheme II was followed. Compound **5** was treated with phosphorus pentasulfide in dioxane to give the corresponding thio derivative **8**. An interesting observation in the pmr spectrum of compound **8** was the considerable downfield shift of the C-6 Heq from δ 4.8 in compound **5** to δ 5.5 in compound **8**. Compound **8** was treated with methyl iodide in dioxane to provide the salt **9**, which being mositure sensitive, was reacted without isolation with different amines to give the target iminoquinolizidines **2c-f** (Table I).

EXPERIMENTAL

All melting points are uncorrected and were obtained with a Kofler hot stage apparatus. Ir spectra were obtained with a Perkin-Elmer Model 157 spectrophotometer. Nmr spectra, reported in δ units, were obtained with a Varian T-60 spectrometer, with TMS as the internal reference.

Diethyl α-(2-Piperidyl)glutarate (**4**).

Diethyl α-(2-pyridyl)glutarate (3) (13.0 g.), platinum oxide (1.30 g.), methanol (40.0 ml.) and acetic acid (40.0 ml.) was subjected to hydrogenation in a Parr hydrogenator at 55 psi for 24 hours at room temperature. The catalyst was filtered off and the solvent evaporated under reduced pressure to give 12 g. (90.22%) of the product; ir (neat): ν max 1735 (COOEt) cm^{-1}; nmr (deuteriochloroform): 1.2-1.46 (2t, 6, 2 OCH_2CH_3, J = 7 Hz), 4.25-4.44 (2q, 4, 2 OCH_2CH_3, J = 7 Hz), no aromatic protons; a broad doublet as a minor band at 4.8 was attributed to the presence of compound **5** as a contaminant (*cf.*, text).

1-Carbethoxy-4-quinolizidone (**5**).

Diethyl α-(2-piperidyl)glutarate (32.0 g.), which also contained small amounts of **5**, was heated at 170-175° for two hours, cooled and treated with cold diluted hydrochloric acid. The mixture was extracted with chloroform. The extract was washed with water, dried (sodium sulfate) and evaporated *in vacuo*. The residue was distilled under reduced pressure to give an oil, b.p. 148°/1.5 mm (3), yield 21.0 g. (79.04%), ir (neat): ν max 1740 (COOEt), 1645 (C(=O)-N-) cm^{-1}; nmr (deuteriochloroform):

1.25 (t, 3, OCH_2CH_3, J = 7 Hz), 4.2 (q, 2, OCH_2CH_3), 3.8 (d of t, 1, H-10, J = 2 Hz, J = 7 Hz), 4.8 (brd, 1, Heq-6, J = 12 Hz).

Anal. Calcd. for $C_{12}H_{19}O_3N$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.73; H, 8.84; N, 6.48.

1-Hydroxymethyl-4-quinolizidone (**6**).

To a slurry of lithium aluminium hydride (250 mg.) in dry ether (25 ml.), **5** (3) (1.0 g.) in ether (20 ml.) was added at −15° under magnetic stirring. The reaction mixture was stirred for a further 0.5 hour at −15°. The excess of lithium aluminum hydride was decomposed by careful addition of water. The organic layer was separated, washed with a minimum amount of water, dried (sodium sulfate) and evaporated *in vacuo* to dryness. The residue was chromatographed on neutral alumina, using benzene as eluent, to give 400 mg. (49.20%) of the pure alcohol (8) ir (neat): ν max 3300 (OH), 1650 (CON-) cm^{-1}; nmr (deuteriochloroform): 4.6 (brd, 1, H-6, J = 12 Hz), 3.6 (m, 2, CH_2OH) (mixture of *cis* and *trans* isomers).

1-Chloromethyl-4-quinolizidone (**7**).

A solution of **6** (8) (160 mg.) and thionyl chloride (160 mg.) in dry benzene (30.0 ml.) was stirred at room temperature for 24 hours. Benzene and the excess of thionyl chloride were distilled under reduced pressure. The residue was chromatographed over neutral alumina using benzene as eluent to give 110 mg. (62.50%) of a pale yellow oil; ir (neat): ν max absence of OH band, 1640 (CON-) cm^{-1}; nmr (deuteriochloroform): 3.5 (d, 2, CH_2Cl axial, J = 7 Hz), 3.6 (d, 2, CH_2Cl equatorial, J = 3 Hz), 4.8 (broad d, 1, H-6, J = 14 Hz).

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.57; H, 8.00; N, 6.94; Cl, 17.58. Found: C, 59.41; H, 7.82; N, 7.08; Cl, 17.61.

1-(4-Hydroxypiperidine)methyl-4-quinolizidone (**2a**).

A solution of **7** (1.0 g.), 4-hydroxypiperidine (2.50 g.) and hexamethylphosphoric triamide (30.0 ml.) was heated at 150° for 60 hours. The excess of solvent was removed under high vacuum and the residue was chromatographed over neutral alumina using petroleum ether:chloroform (1:1) as the eluent to give the desired compound as an oil, yield = 400 mg. (30.30%); ir (neat): ν max 3325 (CH), 1640 (C(=O)-N-) cm^{-1}; nmr (deuteriochloroform): shows that the compound is a mixture of C_1-epimers. Compound **2a** was converted into its acetate and analysed as a viscous syrup.

1-Morpholinomethyl 4-quinolizidone (**2b**).

Compound **2b** was prepared by a procedure analogous to that used for compound **2a**, and was isolated as a viscous liquid, 7 (1.0 g.) gave **2b** (625 mg., 50%).

1-Carbethoxy-4-quinolizidinthione (**8**).

A mixture of 1-carbethoxy-4-quinolizidone **5** (3) (500 mg.), phosphorus pentasulfide (1.75 g.) and dry dioxane (20 ml.) was refluxed for one hour. The reaction mixture was left under stirring overnight. The solvent was evaporated under reduced pressure and the residue chromatographed over neutral alumina using benzene as eluent to give 360 mg. (67.30%) of a pale yellow oil; ir (neat): ν max absence of amide band, 1740 (COOEt) cm^{-1}; nmr (deuteriochloroform): 1.15 (t, 3, CH_2CH_3, J = 7 Hz) 4.0 (q, 2, CH_2CH_3, J = 7 Hz), 5.56 (brd, 1, Heq-6, J = 12 Hz).

Anal. Calcd. for $C_{12}H_{19}NO_2S$: C, 59.73; H, 7.95; N, 5.80; S, 13.28. Found: C, 59.43; H, 7.62; N, 5.72; S, 13.01.

1-Carboethoxy-4-thiomethylquinolizidine Iodide (**9**).

A solution of 1-carbethoxy-4-quinolizidinthione, **8**, (1.0 g.) and methyl iodide (10.0 ml.) in dry tetrahydrofuran (25 ml.) was refluxed for two hours. The solvent was removed under reduced pressure to provide a pale fluffy solid (1.10 g.) (69.18%). Tlc on alumina in chloroform showed no starting material and the presence of a highly polar compound. The compound was sensitive to moisture. The product was used without further purification for subsequent reactions.

1-Carbethoxy-4-isobutyliminoquinolizidine Hydroiodide (**2c**).

Compound **8** (1.35 g.) was converted to **9** as described above and isobutylamine (40 ml.) added to the dry mass. The reaction mixture was refluxed for 40 hours. Excess of amine was removed by distillation under reduced pressure and the residue treated with dry ether to give a semisolid. Ethanol-ether crystallization provided a pure hydroiodide, 600 mg. (41.67%), m.p. 174-176°; ir (potassium bromide): ν max 1725 (COOEt), 1640 (C=N) cm^{-1}; nmr (deuteriochloroform): 1.00 (d, 6, $CHMe_2$, J = 7 Hz), 1.28 (t, 3, OCH_2CH_3, J = 7 Hz), 3.28 (m, 2, -N-CH_2-CH) 4.2 (q, 2, OCH_2CH_3, J = 7 Hz), 5.02 (brd, 1, Heq-6, J = 12 Hz).

Compounds **2d-f** were prepared in a manner analogous to that described for **2c**, except that the hydroiodides were converted to their free bases by treatment with 30% sodium hydroxide. Free bases were purified by column chromatography and converted to the corresponding hydrochlorides in the usual manner. Melting points and yields are recorded below.

Compound **2d**.

Compound **8** (2.5 g.) gave **2d** (1.44 g., 35%) as a syrup.

Compound **2e**.

Compound **8** (1.0 g.) gave **2e** (399 mg., 25%), m.p. 190-192° dec.

Compound **2f**.

Compound **8** (1.0 g.) gave **2f** (648 mg., 50%), m.p. 148-150° dec.

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