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A Synthesis of *endo*- and *exo*-1-Ethoxycarbonyl-pyrrolizidine

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endo-1-Ethoxycarbonylpyrrolizidine (VII) has been synthesised in three steps, starting from pyrrole. An improved synthesis of the intermediate ethyl 2-pyrrolylglyoxylate was worked out. Epimerisation of VII afforded *exo*-1-ethoxycarbonylpyrrolizidine.

Much interest has been devoted to syntheses of *endo*- and *exo*-1-hydroxymethylpyrrolizidine (IX and X, respectively), all four stereoisomers of which occur naturally.[1,2] Seven routes leading to either IX or X, or to a mixture of them, have previously been described.[3–9] The present paper reports the synthesis of *endo*-1-ethoxycarbonylpyrrolizidine (VII). This compound upon reduction yields *endo*-1-hydroxymethylpyrrolizidine (IX).[8,9] Epimerisation of VII by treatment with sodium methoxide in methanol and subsequent reduction affords *exo*-1-hydroxymethylpyrrolizidine (X).

Ethyl 2-pyrrolylglyoxylate (III), which had previously been synthesised [10] by reacting pyrrylmagnesium bromide with ethoxalyl chloride, was prepared by reacting pyrrole with pyridine-ethoxalyl chloride at low temperature. In the second step, the sodium salt produced from III and sodium hydride was reacted with vinyltriphenylphosphonium bromide,[11] a reagent developed by Schweitzer *et al.*[12–14] The reaction product showed in GLC-MS two peaks in the approximate ratio 99:1, corresponding to compounds having mass spectra with the same *m/e* values for the major fragments, but with different intensities. This indicates that the, according to the plausible mechanism, primarily formed 1-ethoxycarbonyl-3H-pyrrolizine (IV) was partially isomerised under the reaction conditions. (A similar pyrrolizine isomerisation has been observed [15,16] when methyl 3-(2-formyl-*N*-pyrryl)-propionate was treated with sodium methoxide in methanol. 6-Methoxycarbonyl-3H-pyrrolizine was formed as a main product, together with small amounts of 2-methoxycarbonyl-3H-pyrrolizine.) The major component is ascribed the structure V, which well accounts for the NMR spectrum of the pyrrolizine mixture. The 1H-signal centered at τ 3.56 shows a 6.0 Hz splitting, which in a 3H-pyrrolizine can only

be due to coupling between the H-1 and H-2 hydrogens,[17] and is therefore inconsistent with the structure IV. Support for structure V was also obtained from catalytic hydrogenation of the pyrrolizine mixture with 1 mol equiv. of hydrogen, which produced a compound (VI) with two hydrogens resonating in the τ 2–5 region.

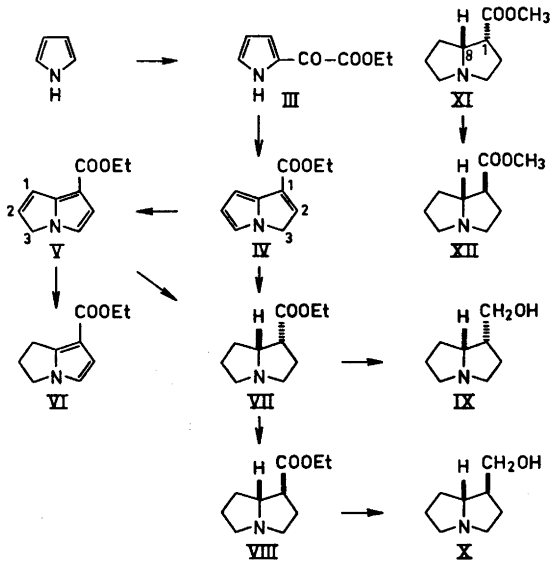

Fig. 1. Only one isomer is depicted from each of the racemates VII–X.

Finally, hydrogenation over rhodium converted the pyrrolizines to 1-ethoxycarbonylpyrrolizidine, preferentially the thermodynamically unstable *endo* isomer (VII). As we did not find any stationary phase in GLC capable of separating VII and its *exo*-isomer VIII, the exact amount of VIII in the hydrogenation product is unknown. However, the figure cannot exceed 12 %, which according to GLC is the amount of *exo*-1-acetoxymethylpyrrolizidine obtained after reduction and acetylation of the hydrogenation product. As has previously been observed,[21] the acetates give better recovery than the alcohols on GLC.

It has been reported that the alkaloid chysine, (+)-*endo*-1-methoxycarbonylpyrrolizidine (XI), in hexane shows a UV absorption band at 290 nm (ε 40),[18] which in ethanol shifts to 302 nm.[22] VII does not show any such UV absorption band, indicating that the natural material was contaminated, presumably by the corresponding $\Delta^{1,8}$ unsaturated ester.

The epimerisation from *endo*- to *exo*-ester was carried out on chysine (XI), $[\alpha]_D^{25}+64°$. Treatment of XI with sodium methoxide in methanol gave (+)-*exo*-1-methoxycarbonylpyrrolizidine (XII), $[\alpha]_D^{24}+42°$. The purity of the epimerisation product was determined by reduction and subsequent acetylation, followed by GLC analysis, which revealed the presence of less than 1 % *endo*-acetate.

EXPERIMENTAL

Melting points are corrected. The NMR spectra were measured on a Varian A-60 A, the UV spectra (in ethanol) on a Beckmann DK 2, and the IR spectra on a Perkin-Elmer 257 spectrometer. The mass spectra were measured on an LKB 9000 instrument, equipped with a GLC inlet system (2.8 m 1 % SE-30). The preparative GLC operations were carried out on a 20 % SE-52 on Chromosorb AW DMCS column (0.8 × 240 cm) with helium as carrier gas, and the analytical operations on a 20 % SE-52 on Chromosorb AW DMCS column (0.2 × 180 cm) with nitrogen as carrier gas, using a Perkin-Elmer 900 chromatograph.

Potassium ethyl oxalate (I) was prepared in a manner analogous to a preparation of potassium ethyl malonate.[19] A solution of potassium hydroxide (17.5 g) in ethanol (200 ml, 99 %) was added during 1 h to a well stirred solution of diethyl oxalate (46.0 g) in ethanol (200 ml, 99 %). The mixture was stirred overnight and then filtered. The product was dried at 120°, giving a 78 % yield of I, m.p. 228 – 230° (decomp.) (lit.[20] m.p. 222 – 225°).

Ethoxalylchloride (II) was prepared from I and sulphinyl chloride as previously described.[20]

Ethyl 2-pyrrolylglyoxylate (III). Pyridine (23.7 g, 0.30 mol) was added dropwise to a cooled (– 80°) solution of II (23.1 g, 0.17 mol) in methylene chloride (100 ml). When the addition of pyridine was complete, a similarly cooled solution of pyrrole (10.0 g, 0.145 mol) in methylene chloride (20 ml) was added dropwise (1 h). The mixture was stirred (– 80°, 3 h) and then poured on ice-dilute hydrochloric acid. The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated. After distillation through a 20 cm column, III was obtained as a pale yellow liquid (b.p. 105°/0.1 mm), which solidified in the receiver to a crystalline mass (18.0 g, 64 %), m.p. 38 – 39.5° (lit.[10] m.p. 44.5°). (Found: C 57.4; H 5.27; N 8.54; O 28.8. Calc. for $C_8H_9NO_3$: C 57.5; H 5.43; N 8.38; O 28.7.) IR σ_{max} (CCl_4): 3300(m), 1742(s) cm^{-1}. NMR ($CDCl_3$): τ –1.1 (s, 1H), τ 2.61 (m, 1H) τ 2.76 (m, 1H), τ 3.69 (m, 1H), τ 5.62 (m, 2H), τ 8.68 (t, 3H). No position isomers could be detected (GLC, NMR).

Ethoxycarbonylpyrrolizine (IV + V). III (5.22 g, 0.031 mol) was added to a mixture of dry ether (150 ml) and sodium hydride in an oil suspension (0.78 g 50 % NaH, 0.0325 mol). After stirring for 10 min at room temperature, ground vinyltriphenylphosphonium bromide[11] (11.6 g, 0.0315 mol) was added. The reaction mixture was stirred under reflux for 20 h, cooled, filtered and concentrated. The resulting solution was chromatographed on neutral alumina (5 × 24 cm). The oil in which the sodium hydride had been dispersed was eluted with hexane, and the pyrrolizines with ether. Yield: 2.35 g (43 %). GLC showed two peaks in the approximate ratio 1:99. MS major peak, *m/e* (rel. intensity): $M^+ = 177(85)$, 149(13), 148(25), 132(80), 104(100). MS minor peak: $M^+ = 177(88)$, 149(20), 148(28), 132(95), 104(100). An analytical sample, containing both isomers, was obtained by preparative GLC (190°). (Found: C 67.8; H 6.33; N 7.89; O 18.2. Calc. for $C_{10}H_{11}NO_2$: C 67.8; H 6.26; N 7.91; O 18.1.) UV λ_{max} nm (ε) 233 (12000), 258 (5600), 268 (5600), 305 (8700). IR (CCl_4): 1707 (s) cm^{-1}. NMR ($CDCl_3$): τ 2.93 – 3.22 (m, 2H), τ 3.34 (m, 1H), τ 3.56 (m, 1H), τ 4.58 (m, 2H), τ 4.71 (m, 2H), τ 8.67 (t, 3H).

Hydrogenation to VI. The mixture (0.09 g) of IV and V was hydrogenated (1 atm. 15 min) in ethanol (5 ml), using PtO_2 (10 mg). The reaction product showed in GLC a peak with the same retention time as the starting material, but with a different MS: $M^+ = 179$ (48), 150 (84), 134 (100), 106 (43). NMR ($CDCl_3$): τ 3.38 (d, 1H, $J = 3$ Hz), τ 3.48 (d, 1H, $J = 3$ Hz). IR ($CHCl_3$): 1692 (s) cm^{-1}.

endo-*1-Ethoxycarbonylpyrrolizidine* (VII). The pyrrolizine mixture (0.095 g, 0.54 mmol) was hydrogenated (1 atm, 70 min) in acetic acid (14 ml) over 5 % Rh on alumina (0.12 g). The product was indistinguishable from a sample of transesterified chysine[18] (GLC, MS). MS: $M^+ = 183$ (18), 154 (16), 138 (21), 110 (9), 108 (6), 83 (100), 82 (40), 55 (22). For the measurement of the UV spectrum of VII, the hydrogenation was prolonged to 4 h, and 70 mg of the picrate (m.p. 121 – 122.5°, from ethanol, lit. m.p.[8,9] 118 – 118.5° and 119.5 – 120°, resp.) of the resulting base was subjected to ion exchange on Dowex 1-X4 (Cl^-, 2.5 × 15 cm), using spectroscopically pure ethanol as solvent. After evaporation of the solvent, the hydrochloride was dissolved in 3.0 ml of ethanol. The UV spectrum of this freshly prepared solution showed no maximum or shoulder between 250 and 340 nm, nor any change when aqueous alkali was added.

Reduction and acetylation of VII. VII was reduced with an excess of lithium tetrahydridoaluminate in refluxing ether (1 h). After the addition of a tetrahydrofuran-water mixture and filtration, the one-phase system was concentrated, and the residue dried (Na_2SO_4) in carbon tetrachloride. The acetylation was effected by passing ketene through an acetone solution of the alcohol. The product showed in GLC two peaks (relative retentions 1:1.14) in the ratio 12:88, respectively, corresponding to compounds each of which gave a mass spectrum indistinguishable from that of (+)-*exo*-1-acetoxymethylpyrrolizidine (laburnine acetate [21]).

Epimerisation of chysine. Chysine (0.23 g) was added to the reaction mixture of sodium (0.035 g) and methanol (5 ml). After 12 h at 58°, the mixture was cooled and poured into cold dilute hydrochloric acid, the pH adjusted to 3 – 4, and the aqueous layer washed with carbon tetrachloride. The epimerisation product was then extracted from the alkaline aqueous layer with carbon tetrachloride. Preparative GLC gave pure XII, $[\alpha]_D^{24} + 42°$ (*c* 1.0, chloroform). The reduction and acetylation of XII was carried out as described above.

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REFERENCES

1. Bull, L. B., Culvenor, C. C. J. and Dick, A. T. *The Pyrrolizidine Alkaloids*, North-Holland, Amsterdam 1968.
2. Hart, N. K., Johns, S. R. and Lamberton, J. A. *Austr. J. Chem.* **21** (1968) 1393.
3. Leonard, N. J. and Felley, D. L. *J. Am. Chem. Soc.* **72** (1950) 2537.
4. Babor, K., Ježo, I., Kaláč, V. and Karvaš, M. *Chem. Zvesti* **13** (1959) 163; Leonard, N. J. and Blum, S. W. *J. Am. Chem. Soc.* **82** (1960) 503.
5. Červinka, O., Pelz, K. and Jirkovský, I. *Collection Czech. Chem. Commun.* **26** (1961) 3116.
6. Likhosherstov, A. M., Likhosherstov, L. M. and Kochetkov, N. K. *Zh. Obshch. Khim.* **33** (1963) 1801.
7. Nair, M. D. and Adams, R. *J. Org. Chem.* **26** (1961) 3059.
8. Kochetkov, N. K., Likhosherstov, A. M. and Lebedeva, A. S. *Zh. Obshch. Khim.* **31** (1961) 3461.
9. Leonard, N. J. and Sato, T. *J. Org. Chem.* **34** (1969) 1066.
10. Oddo, B. *Gazz. Chim. Ital.* **50** (1920) 265.
11. Schweitzer, E. E. and Bach, R. D. *Org. Syn.* **48** (1968) 129.
12. Schweitzer, E. E. and Bach, R. D. *J. Org. Chem.* **29** (1964) 1746.
13. Schweitzer, E. E. and Light, K. K. *J. Am. Chem. Soc.* **86** (1964) 2963.
14. Schweitzer, E. E. and Light, K. K. *J. Org. Chem.* **31** (1966) 870.
15. Flitsch, W. and Heidhues, R. *Chem. Ber.* **101** (1968) 3843.
16. Lundin, C. and Lüning, B. *Unpublished result.*
17. Flitsch, W., Heidhues, R. and Paulsen, H. *Tetrahedron Letters* **1968** 1181.
18. Lüning, B. and Tränkner, H. *Acta Chem. Scand.* **22** (1968) 2324.
19. Strube, R. E. *Org. Syn. Coll. Vol.* **4** (1963) 417.
20. Southwick, P. L. and Seivard, L. L. *J. Am. Chem. Soc.* **71** (1949) 2535.
21. Lindström, B. and Lüning, B. *Acta Chem. Scand.* **23** (1969) 3352.
22. Lüning, B. and Tränkner, H. *Unpublished result.*

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