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Studies on Orchidaceae Alkaloids

XXXI.* Synthesis of 1-Ethoxycarbonyl-$\Delta^{1,8}$-dehydropyrrolizidine and Some Other Pyrrolizidine Derivatives

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The UV absorption band at 290 nm previously ascribed to the alkaloid chysin (I) has been shown to be due to the presence of small amounts of 1-methoxycarbonyl-$\Delta^{1,8}$-dehydropyrrolizidine (II), formed by dehydrogenation of I during preparative GLC. The homologous ethyl ester (VI) has been synthesised from the corresponding saturated ester (III). VI has been shown not to be a major product from the dehydration of 1-hydroxy-1-ethoxycarbonylpyrrolizidine (V) with phosphoryl chloride and pyridine. *Exo*- and *endo*-2- and 3-methoxycarbonylpyrrolizidine have been prepared, the 3-isomers by using a trichloroacetylation of the pyrrole XIV as the key step.

The alkaloid chysin (I), characterised in 1968 by Lüning and Tränkner,[2] showed an unaccounted for UV absorption band at 290 nm (ε 40, hexane) which in ethanol [3] shifted to 302 nm. The band disappeared on acidification and was absent in the spectrum of the corresponding sodium carboxylate. It was not possible to demonstrate any Cotton effect associated with the absorption band. The material used in these investigations had been purified by preparative GLC.

In a recent paper [4] we described the synthesis of the racemic ethyl homologue of I (III). After a thorough hydrogenation and purification *via* its picrate, III showed no absorption band in the 300 nm region, which implies that the natural material had been contaminated.

From the spectral results given above, it seemed probable that the contaminating compound was the $\Delta^{1,8}$-dehydroester (II). The UV spectrum obtained is similar to those reported [5] for β-amino acrylic esters. Furthermore, it was possible to remove the absorption band by reduction with sodium tetrahydridoborate in methanol. 1-Ethoxycarbonyl-$\Delta^{1,10}$-dehydroquinolizidine (IV) has previously been transformed into its corresponding saturated ester by the same reagent.[6,7]

* Part XXX, see Ref. 1.

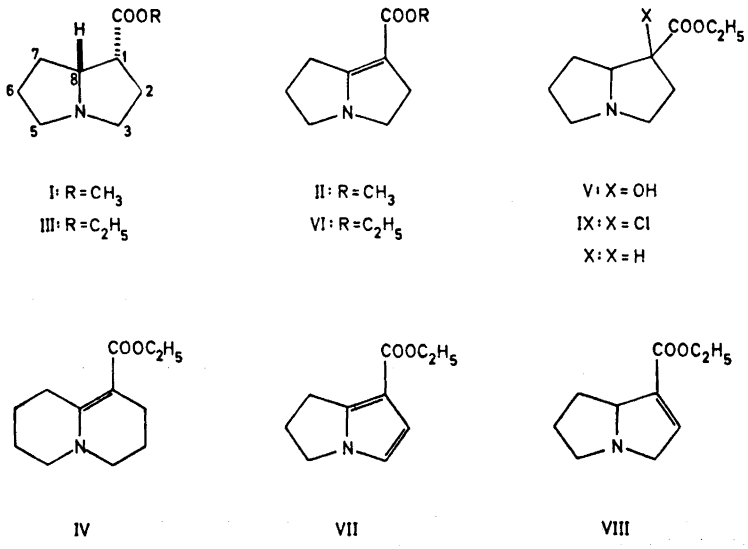


Fig. 1. Only one enantiomer from the racemate III is depicted.

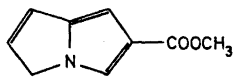
To obtain more convincing evidence for the presence of II in the chysin sample we needed the UV absorption spectrum of II or VI. The latter compound was considered by Kochetkov *et al.* to be an intermediate in their synthesis of (±)-isoretronecanol.[8] In the synthesis, 1-hydroxy-1-ethoxycarbonylpyrrolizidine (V) was treated with phosphoryl chloride and pyridine and the resulting distilled product was considered (no spectral data were given) to be the $\Delta^{1,8}$-dehydroester because its lithium tetrahydridoaluminate reduction product behaved like an enamine.[8,9] In our hands, however, V on treatment with phosphoryl chloride and pyridine yielded after distillation a six-component mixture, the two main components of which were isolated by preparative GLC and characterised by IR, NMR, and mass spectrometry. These two products were identified as the 1-chloroester (IX) and the $\Delta^{1,2}$-dehydroester (VIII). Minor components were the starting material, the $\Delta^{1,8}$-dehydroester (VI), the pyrrolic ester (VII) and another compound, probably the saturated ester (X). The two latter compounds were shown to be disproportionation products from heating the $\Delta^{1,2}$-dehydroester. The main spectral characteristics of our $\Delta^{1,2}$-dehydroester agree with those reported [10] (see also Ref. 11) for 1-methoxycarbonyl-$\Delta^{1,2}$-dehydropyrrolizidine, synthesised by a different route.

Other routes to VI were then investigated. III [4] was transformed into its *N*-oxide (XIX) by reaction with *m*-chloroperbenzoic acid according to the general method of Cymerman Craig and Purushothaman.[12] XIX was then reacted with trifluoroacetic anhydride,[13] a reagent known to favour elimination of a tertiary hydrogen adjacent to nitrogen.[14] In the present case this reaction directly led to the unsaturated ester VI. The *N*-oxide was less suc-

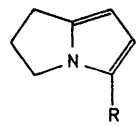
cessfully treated with potassium chromate in water solution, a method for converting *N*-oxides into carbinolamines,[15] favouring elimination of a primary hydrogen adjacent to nitrogen.[16] Other ways to VI were attempted without success. Thus manganese dioxide oxidation of III yielded in excellent yield the pyrrolic compound VII (*cf.* Ref. 17), and treatment of III with triphenylmethyl perchlorate [18] gave no reaction (*cf.* Ref. 19). Compound VI showed a UV absorption maximum at the same wavelength as the sample of chysin, which had been purified by GLC. Based on extinction calculations, the amount of II present in the chysin sample was less than 1 %.

As the chysin sample on which the UV measurement was performed was obtained by preparative gas chromatography and as the separation between III and VI, and hence between I and II, was good, the effect of preparative gas chromatography on III was investigated. When III, which after treatment with sodium tetrahydridoborate showed no absorption band at 303 nm, was subjected to preparative GLC (one injection, col. 160°, det. 180°) an absorption peak (ε 6) was obtained in the spectrum of the collected material. This absorption peak (ε 25) was also obtained when III was stored in chloroform (ethanol-stabilised) solution in the dark at room temperature for eleven days. The mechanism of this reaction might be similar to that proposed for the reaction between tertiary amines and carbon tetrachloride,[20] or might alternatively be an autoxidative attack at H-8 followed by elimination.

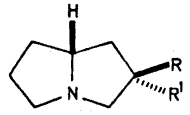
In this connexion we also wish to report the syntheses and properties of the 2- and 3-isomers of methoxycarbonylpyrrolizidine. 6-Methoxycarbonyl-3H-pyrrolizine (XI), prepared [21] from methyl 3-(2′-formyl-*N*-pyrryl)propionate, was hydrogenated to *endo*-2-methoxycarbonylpyrrolizidine (XII). Treatment



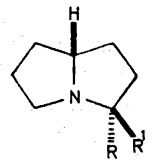
XI



XIV: R=H
XV: R=COCCl$_3$
XVI: R=COOCH$_3$



XII: R=H, R^1=COOCH$_3$
XIII: R=COOCH$_3$, R^1=H



XVII: R=COOCH$_3$, R^1=H
XVIII: R=H, R^1=COOCH$_3$

Fig. 2. Only one enantiomer from each of the racemates XII, XIII, XVII and XVIII is depicted.

of XII with sodium methoxide in methanol gave only a partial epimerisation to the *exo* compound (XIII). Both XII and the mixture of XII and XIII showed after preparative GLC a shoulder around 300 nm (ε 3) which disappeared on acidification. By dehydrogenation of these compounds, it is possible to obtain a $\Delta^{2,3}$-dehydroester. The 3-esters were prepared from 1,2-dihydro-3H-pyrrolizine[22] (XIV), which was acylated in 92 % yield with trichloroacetyl chloride and pyridine at $-80°$ to 1,2-dihydro-5-trichloroacetyl-3H-pyrrolizine (XV). Treatment of XV with sodium methoxide yielded, in analogy with the findings of Houben and Fischer,[23] the methyl ester XVI, which upon hydrogenation was converted to *endo*-3-methoxycarbonylpyrrolizidine (XVII). Epimerisation of XVII with sodium methoxide gave XVII and the corresponding *exo* compound (XVIII) in the ratio 2:98. 3-Methoxycarbonylpyrrolizidine of unknown stereochemistry has previously been synthesised by Seiwerth and Djokic.[24]

EXPERIMENTAL

Melting points are corrected. NMR spectra were recorded on a Varian A-60A, UV spectra on a Beckman DK2 and IR spectra on a Perkin-Elmer 257 spectrometer. Mass spectra were measured on an LKB 9000 instrument equipped with a GLC inlet system (2.8 m 1 % SE-30). Preparative GLC operations were carried out with helium as carrier gas using 20 % SE-52 on Chromosorb AW DMCS in a metal column (0.8 × 240 cm) mounted in an Aerograph A-90-P chromatograph with a hot wire detector, through which the whole sample had to pass. For analytical GLC a Perkin-Elmer 900 instrument was used with a 20 % SE-52 on Chromosorb AW DMCS column (0.2 × 190 cm) and nitrogen as carrier gas.

Dehydration of 1-ethoxycarbonyl-1-hydroxypyrrolizidine (V). The title compound V (6.4 g), on treatment with phosphoryl chloride as described by Kochetkov *et al.*,[8] yielded a mixture (2.85 g), b.p. 59 – 64°/0.5 mm, consisting (GLC, 174°) of six compounds, V – X: *1-Ethoxycarbonyl-$\Delta^{1,2}$-dehydropyrrolizidine (VIII)*, ret. time 3.3 min, nearly 50 % of the total yield. NMR ($CDCl_3$): τ 3.27 (q, 1H). UV (EtOH): 212 nm (ε 7700). IR (CCl_4): 1726 (s) and 1643 (m) cm^{-1}. MS: $M^+ = 181$ (52), 136 (100), 108 (36), 80 (53). Lit.[10] values for the corresponding methyl ester. NMR: τ 3.40 (q, 1H). UV (EtOH): 214 nm (ε 7375). IR (film): 1727 (s), 1645 (m) cm^{-1}. *1-Ethoxycarbonyl-1-chloropyrrolizidine (IX)*, ret. time 4.8 min, nearly 50 % of the total yield. (Found: C 54.9; H 7.34; Cl 16.1; N 6.43; O 14.9. Calc. for $C_{10}H_{16}ClNO_2$: C 55.2; H 7.71; Cl 16.3; N 6.44; O 14.7.) IR (CCl_4): 1743 (s) cm^{-1}. MS: $M^+ = 219$ (2) and 217 (5), 83 (100). *1-Ethoxycarbonyl-$\Delta^{1,8}$-dehydropyrrolizidine (VI)*, ret. time 6.4 min. Its mass spectrum and ret. time were identical with those of the synthetic sample described below. *7-Ethoxycarbonyl-1,2-dihydro-3H-pyrrolizine (VII)*, ret. time 7.1 min. MS: $M^+ = 179$ (37), 150 (70), 134 (100), 106 (47). *1-Ethoxycarbonylpyrrolizidine (X)*, ret. time 3.0 min. (identical with that of III). As this peak appeared only as a shoulder of the much larger peak from the $\Delta^{1,2}$-dehydroester, no mass spectrum was obtained. The shoulder was absent before the distillation. The starting material V had the ret. time 3.9 min.

Disproportionation of 1-ethoxycarbonyl-$\Delta^{1,2}$-dehydropyrrolizidine (VIII). The title compound was heated (200°, 1 h) in a sealed tube. The reaction mixture contained (GLC-MS) large amounts of the pyrrole VII and the saturated ester (X) and smaller amounts of VI and the starting material.

endo-*1-Ethoxycarbonylpyrrolizidine N-oxide (XIX).* A solution of *m*-chloroperbenzoic acid (0.39 g) in chloroform (2.5 ml) was added in portions to a stirred solution of III[4] (0.40 g) in chloroform (2.5 ml). Stirring was continued overnight at room temperature. The concentrated reaction mixture was passed through basic alumina. Chloroform and then methanol-chloroform (1:3) eluted the *N*-oxide, which after evaporation of the solvent, addition of chloroform (100 %), and evaporation and drying in a vacuum de-

siccator weighed 0.36 g (dark oil). Picrate (from EtOH), m.p. 98 – 100°. (Found: C 45.1; H 4.63; N 13.1; O 37.2. Calc. for $C_{16}H_{20}N_4O_{10}$: C 44.9; H 4.71; N 13.1; O 37.4.)

Reaction of XIX with trifluoroacetic anhydride. XIX (40 mg, 0.20 mmol) was dissolved in chloroform (0.5 ml, 100 %) and trifluoroacetic anhydride (72 mg, 0.34 mmol) was added. Water was added after the solution had stood for 30 min, the pH was adjusted to 9 and the chloroform layer was washed twice with water. Most of the Dragendorff-positive material was left in the chloroform layer, which contained (GLC) a mixture of 7 % of VII, 50 % of VI, and approximately 40 % of unidentified products, giving several irreproducible peaks. Pure VI was obtained by preparative GLC (160°). IR (CCl_4): 1679 (s) and 1627 (s) cm^{-1}. UV (hexane): 289 nm (ε 13 000). UV (EtOH): 303 nm (ε 18 000). Retention time on the analytical column, 174°: 6.4 min. MS: $M^+ = 181$ (55), 153 (8) 152 (17), 136 (100), 109 (51), 108 (57).

Reaction of XIX with potassium chromate. XIX (40 mg, 0.20 mmol), dissolved in water (0.5 ml), was mixed with a solution of potassium chromate (58 mg, 0.30 mmol) in water (1.0 ml). The solution was kept at 65° for 15 min and was then cooled and the pH adjusted to 9. Two extractions with chloroform left most of the Dragendorff-positive material in the aqueous layer. The chloroform layer contained (GLC) VI and VII in the ratio 2:1.

Manganese dioxide oxidation of III. A mixture of III [4] (25 mg), active manganese dioxide (Merck, 1.3 g), and methylene chloride (20 ml) was stirred at room temperature for 22 h. The product, which formed a single peak on GLC, was identified (GLC-MS) as VII. The use of 180 mg of MnO_2 and 35 mg of III resulted in approximately 50 % conversion to VII, but no VI was formed.

endo-*2-Methoxycarbonylpyrrolizidine (XII).* The pyrrolizine XI [21] (1.5 g) was hydrogenated over 5 % rhodium on alumina (1.0 g) in acetic acid (25 ml). After 1.5 h the solvent was evaporated, water was added and the solution washed four times with ether. Potassium carbonate was added until pH 9 was reached, XII (contaminated by less than 5 % of the corresponding *exo*-isomer XIII, see below) was extracted with chloroform and was then purified by preparative GLC. (Found: C 63.8; H 8.98; N 8.23; O 19.1. Calc. for $C_9H_{15}NO_2$: C 63.9; H 8.93; N 8.28; O 18.9.)

Epimerisation of XII. XII (50 mg) was added to a solution of sodium methoxide (from 0.1 g of sodium) in methanol (5 ml). The mixture was refluxed for 19 h, after which it was cooled and acetic acid (1 ml) was added. After evaporation of the solvent and addition of water (5 ml), the pH was adjusted to 9 and the aqueous layer extracted with chloroform. Two peaks having approximately the same area were obtained on GLC (116°), ret. times 38.5 min (XII) and 42.5 min (XIII).

1,2-Dihydro-5-trichloroacetyl-3H-pyrrolizine (XV). Pyridine (13.0 g, 0.165 mol), followed by a solution of 1,2-dihydro-3H-pyrrolizine, XIV [22] (5.5 g, 0.051 mol) in methylene chloride (15 ml), were added dropwise to a stirred and cooled solution (– 80°) of trichloroacetyl chloride (9.5 g, 0.052 mol) in methylene chloride (15 ml). The reaction mixture, after being kept cooled (– 80° for 1 h, – 20° for 20 h), was poured onto dilute hydrochloric acid and ice. Extraction with chloroform, washing with water, drying ($MgSO_4$) and evaporation of the solvent left a crystalline residue (11.9 g, 92 %) which could be recrystallised from ether-hexane leaving analytically pure XV, m.p. 84 – 85°. (Found: C 42.9; H 3.23; Cl 42.2; N 5.66; O 6.34. Calc. for $C_9H_8Cl_3NO$: C 42.8; H 3.19; Cl 42.1; N 5.55; O 6.34.) IR (CCl_4): 1672 (s) cm^{-1}.

1,2-Dihydro-5-methoxycarbonyl-3H-pyrrolizine (XVI). XV (11.9 g, 0.047 mol) was dissolved in a solution of sodium methoxide (from 2.0 g of sodium, 0.087 mol) in methanol (200 ml). After 3 h part of the methanol was evaporated and the residue partitioned between hydrochloric acid and chloroform. After drying (Na_2SO_4), the chloroform was evaporated. Distillation at 82 – 84°/0.6 mmHg yielded XVI (5.7 g, 73 %). (Found: C 65.3; H 6.66; N 8.64; O 19.5. Calc. for $C_9H_{11}NO_2$: C 65.4; H 6.71; N 8.48; O 19.4.) IR ($CHCl_3$): 1708 (s) cm^{-1}.

endo-*3-Methoxycarbonylpyrrolizidine (XVII).* The ester XVI (1.0 g) was hydrogenated (23 atm., 25°, 20 h) over 5 % rhodium on alumina in acetic acid (75 ml) and the product was worked up as above, yielding a mixture (0.93 g) consisting (GLC) of XVII (96 %) and the corresponding *exo*-compound (XVIII, 4 %, see below). (Found: C 63.9; H 8.83; N 8.29; O 19.1. Calc. for $C_9H_{15}NO_2$: C 63.9; H 8.93; N 8.28; O 18.9.) IR (CCl_4): 1740 (s) cm^{-1}.

exo-*3-Methoxycarbonylpyrrolizidine (XVIII)*. Treatment of XVII with sodium methoxide in boiling methanol for 4 h afforded (GLC 130°) a mixture of XVIII (98 %) and XVII (2 %). IR (CCl_4): 1748 (s) cm^{-1}.

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