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Abstract

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Pyrrolizidine Alkaloids

The Absolute Configuration of 1-Methylenepyrrolizidine and Other Pyrrolizidine Bases

Recently we described the total synthesis of the alkaloid 1-methylenepyrrolizidine (^{1}), isolated by Culvenor and Smith (^{2}) from the perennial shrub *Crotalaria anagyroides* H. B. and K. In the present article we describe a stereospecific synthesis of this alkaloid, as a result of which it became possible to establish its absolute configuration, as well as the absolute configuration of related natural pyrrolizidine bases. The synthesis was carried out according to the scheme described previously in the synthesis of racemic 1-methylenepyrrolizidine:

$$\text{(I)} \longrightarrow \text{(II)} \xrightarrow{CH_2{=}CH{-}COOCH_3} \text{(III)} \longrightarrow$$
$$[\text{(IVa)} + \text{(IVb)}] \longrightarrow \text{(Va)} + \text{(Vb)} \longrightarrow \text{(VIa)} + \text{(VIb)}$$

As the starting material we used the ethyl ester of *L*-proline (II), obtained by esterification of natural proline (I). On condensation of II with methyl acrylate, the methyl ester of β-(N-2-carbethoxypyrrolidin)-propionic acid was obtained; this was subjected to Dieckmann cyclization. In the cyclization two keto esters (IVa and IVb) may be formed, from which ketonic cleavage should give one ketone. We did not isolate the keto esters in the individual state, but by heating with 10% hydrochloric acid converted them into pyrrolizidone-1. If the condensation proceeded with formation only of IVa, then optically pure Va should have been obtained; if, on the contrary, the condensation led only to IVb, racemic Vb would have been formed; and finally, if IVa and IVb are formed in the condensation, then partially racemized pyrrolizidone-1 (a mixture of Va and Vb) should be formed. In fact, pyrrolizidone-1 was obtained with $[\alpha]_D^{21} - 22.4^\circ$ (C 1.25; ethanol), but we had no possibility of comparing its rotation with that of an optically pure sample.

It should also be noted that, in contrast to ordinary α-keto amines, Va is fairly resistant to racemization. Thus, on storing it for twenty-four hours

at a temperature of about -30°, with subsequent redistillation, the angle of rotation changes only insignificantly, although pyrrolizidone-1 itself is a relatively labile compound. The comparative stability of pyrrolizidone-1 toward racemization is probably connected with the fact that formation of the enamine form necessary for racemization is, in this case, very unfavorable, since it is associated with flattening of the pyrrolizidine system, requiring a large expenditure of energy.

Pyrrolizidone-1, by the Wittig reaction (^{3}), was converted into 1-methylenepyrrolizidine, which had $|\alpha|_D^{28} - 33^\circ$ (C 1.02; ethanol) (natural 1-methylenepyrrolizidine has $|\alpha|_D^{20} - 43.1^\circ$). The substance is completely identical with the natural alkaloid in its IR spectrum.

These data unequivocally indicate that the absolute configuration of 1-methylenepyrrolizidine corresponds to the absolute configuration of *L*-proline. This result agrees with the modern concept of the biogenesis of pyrrolizidine bases, which is associated with transformations of amino acids. The difference in the angle of rotation of the synthetic product and the natural alkaloid indicates that in the Dieckmann reaction both possible keto esters IVa and IVb are formed in an approximate ratio of 3 : 1 (without taking into account possible racemizations in the course of this and subsequent transformations).

Since we carried out the synthesis of natural 1-methylenepyrrolizidine from natural proline, having the S configuration*, this shows that the alkaloid is ($7S$)-1-methylenepyrrolizidine, i.e., has structure VIa, which fully agrees with the data of Culvenor and Smith (^{2}).

Since it is known (^{2}) that hydrogenation of 1-methylenepyrrolizidine gives heliotridane and pseudoheliotridane, and since the relative configuration of pyrrolizidine bases is also well known (^{5}), it may be concluded that heliotridane is ($1S, 7S$)-1-methylpyrrolizidine, while its epimer, pseudoheliotridane, is ($1R, 7S$)-1-methylpyrrolizidine. Knowing the absolute configurations of these bases, one can readily establish the absolute configuration of all the other natural pyrrolizidine bases.

These conclusions, obtained on the basis of the direct stereospecific synthesis of 1-methylenepyrrolizidine, are in complete agreement with the data of Warren and Klemperer (^{6}), which were obtained in the study of the destruction products of natural pyrrolizidine bases, and also with Adams (^{7}), who came to the same conclusions.

Experimental Part

Ethyl ester of *L*-proline (II). To a mixture of 4.5 g of *L*-proline in 46 ml of absolute alcohol at a temperature of 0° and with good stirring, 3.4 ml of thionyl chloride was added dropwise. The reaction mass was left at room temperature for 48 h. The alcohol was distilled off, the residue was dissolved in 30 ml of dry chloroform, and, at a temperature not above 0°, 35 ml of dry chloroform saturated with ammonia was added. The mixture was kept for half an hour, the residue was filtered off, the chloroform was distilled off at a temperature not above 20°, and the residue was distilled in vacuo, collecting the fraction with b.p. 40°/2 mm. Yield 5 g (89%), n_D^{20} 1.4496. Literature data ([8]): b.p. 78°/12–14 mm.

Methyl ester of *L*-β-(N-2-carbethoxypyrrolidin)propionic acid (III). A mixture of 4.84 g of ethyl *L*-prolinate and 9 ml of methyl acrylate, containing traces of hydroquinone, was boiled under reflux for 24 h. The excess methyl acrylate was distilled off, and the residue was distilled in vacuo, collecting the fraction with b.p. 98–100°/1–1.5 mm. Yield 6.5 g (83%), d_4^{20} 1.0823, n_D^{20} 1.4564; $|\alpha|_D^{22} - 66.5^\circ$ (neat liquid); $|\alpha|_D^{22} - 72^\circ$ (C 3.49; ethanol).

Found, %: C 57.36; 57.39; H 8.35; 8.48; N 6.02; 6.14
$C_{11}H_{19}O_4N$. Calculated, %: C 57.58; H 8.39; N 6.11

Pyrrolizidone-1 (V). To sodium ethoxide, freed from alcohol (from 0.53 g of metallic sodium), were added 1.3 ml of absolute alcohol, 40 ml of absolute xylene, and 5 g of methyl ester of *L*-β-(N-2-carbethoxypyrrolidin)-propionic acid (III). The reaction mixture was heated on an oil bath (150-160°) for 1.5 h. After cooling, the reaction product was extracted with water (4 × 15). To the combined aqueous extracts were added 40 ml of concentrated hydrochloric acid, and the resulting solution was heated on a boiling water bath for 3 h. The reaction mixture was evaporated, the residue was dissolved in 10 ml of water, and, on cooling, the solution was saturated with potash and thoroughly extracted with ether. After removal of the ether, the product was evaporated with dry benzene and distilled in vacuo in a nitrogen atmosphere. Pyrrolizidone-1 was obtained as a colorless oily liquid, rapidly darkening in air. B.p. 56-58°/3 mm, yield 1.4 g (51%, calculated on III), n_D^{20} 1.4867, $|\alpha|_D^{21} - 45^\circ$ (neat liquid), $|\alpha|_D^{21} - 22.4^\circ$ (C 1.25; ethanol). After storage for 24 h at about −30° and redistillation, $|\alpha|_D^{21} - 21^\circ$ (C 1.25; ethanol).

Found, %: N 11.09; 11.42
$C_7H_{11}ON$. Calculated, %: N 11.19

1-Methylenepyrrolizidine (VI). To a solution of 1.22 g of sodium amide in 200 ml of liquid ammonia were added 11.2 g of triphenylmethylphosphonium bromide. The ammonia was replaced by absolute ether (200 ml), and the resulting mixture was boiled for 30 min. To the cooled ethereal solution of methylenetriphenylphosphorane was added a solution of 1.4 g of pyrrolizidone-1 in 30 ml of absolute ether. The reaction mixture was boiled for 2 h and left at room

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* We use the designation of the absolute arrangement of atoms at the asymmetric carbon atom as in ([4]).

temperature for 2 days. The reaction mixture was evaporated, and the resulting base was steam-distilled. The product was extracted with ether and dried with magnesium sulfate. The ether was distilled off; the residue was distilled in vacuo, collecting the fraction with b.p. 111-113°/172 mm. Yield 0.72 g, n_D^{20} 1.4884, $|\alpha|_D^{26} - 33^\circ$ (C 1.02; ethanol).

Found, %:	C 77.80; 77.51; H 10.66; 10.34; N 11.34; 11.63
$C_8H_{13}N$. Calculated, %:	C 77.99; H 10.64; N 11.37

Literature data (²): b.p. 120°/170 mm, $|\alpha|_D^{20} - 43.1^\circ$ (C 1.07; ethanol).

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