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THE STRUCTURE OF BREVICOLLINE

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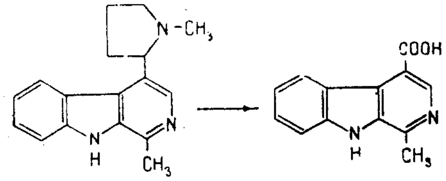
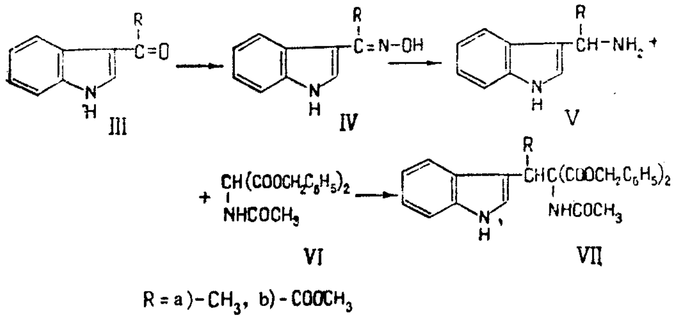
In a preceding communication [1] it was shown that in the oxidation of brevicolline (I)—an alkaloid isolated from Carex brevicollis DC—one of the products is harmane-4-carboxylic acid (II) which has not previously been described.



Scheme 1

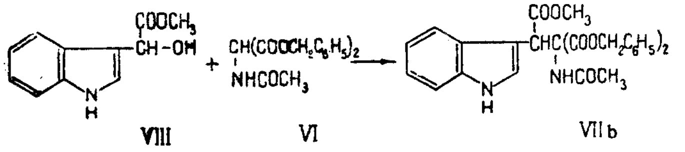
In order to identify this acid, we have effected the synthesis of its methyl ester. It was resolved to use the Bischler-Napieralski cyclization of the corresponding substituted N-acetyltryptophan (VII) [2]. Since the condensation of α-substituted harmines with derivatives of acetamidomalinic ester does not always take place smoothly [3], for the preparation of the starting material we used the possibility of this reaction with primary amines (V), i.e., with 3-(1-aminoethyl)indole (V; R=CH_3) and the methyl ester of indolylglycine (V; R=$COOCH_3$) [4].



Scheme 2

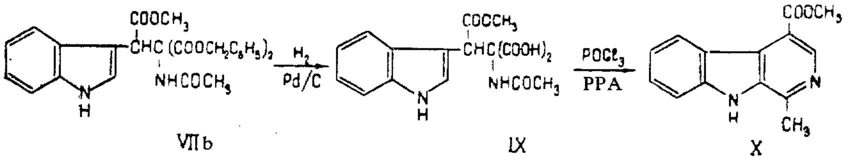
A study of the reaction (see Scheme 2) showed that the products (V) are formed with good yields (60–90%), but the condensation with dibenzyl acetamidomalonate (VI) gives results depending greatly on the nature of the substituent in the indole derivative. Where R= CH_3, the yield of substance (VIIIa) is 80%. If R= $COOCH_3$ (VIIb), the yield of desired condensation products is only 20%.

In view of this, we attempted to carry out the condensation of the methyl ester of indolylglycollic acid (VIII), obtained by the reduction of indolylglyoxylic ester. Such reactions of carbinols have been reported in the literature [5]. Although the yield in this stage proved to be low, the over-all result was incomparably better because of the simplification of procedure.



Scheme 3

Further reactions were carried out in a similar manner to that described by Werber and Snyder [6]. After the hydrogenolysis of the dibenzyl methoxycarbonylskatylacetamidomalonate (VIIb) we carried out decarboxylation, cyclization, and dehydrogenation in one stage by means of phosphorus oxychloride in polyphosphoric acid and obtained methyl harmane-4-carboxylate (X).



Scheme 4

From its melting point and IR spectrum, the product proved to be identical with the methyl ester of the acid obtained by the oxidation of brevicolline.

Experimental

Synthesis of the initial compounds. 3-Acetylindole oxime was obtained from 3-acetylindole [7] by boiling it in ethanolic solution with hydroxylamine hydrochloride in the presence of pyridine. The methyl esters of indolylglycollic and indolylaminoacetic acids were also synthesized by a published procedure [4].

3-(1-Aminoethyl)indole. A flask fitted with a reflux condenser was charged with 5 g of 3-acetylindole oxime and 500 ml of moist ether, and 10 g of amalgamated aluminum foil was added to the solution in portions. The mixture was left overnight at room temperature. The aluminum hydroxide that had formed was filtered off and the precipitate was washed several times with ether. The combined ethereal filtrate was dried with anhydrous sodium sulfate and the ether was distilled off (finally in vacuum). The reaction product was crystallized from benzene.

3-(1-Aminoethyl)indole forms white lamellar crystals with mp 97° C. It is very readily soluble in methanol and ethanol and sparingly soluble in water. When it is heated to the melting point, ammonia is evolved. Yield 2.5 g.

Found, %: C 75.21; H 7.32; N 17.43. Calculated for $C_{10}H_{12}N_2$, %: C 75.00; H 7.50; N 17.50.

Dibenzyl 3-indolylethylideneacetamidomalonate. A few milligrams of sodium methoxide was added to a solution of 6.5 g of dibenzyl acetamidomalonate and 3 g of 3-(1-aminoethyl)indole in 25 ml of dry toluene, and the mixture was boiled for 8 hr. Then the toluene was distilled off in vacuum. The residual oil solidified on trituration with acetone. The solid product was crystallized from acetone. After two crystallizations from isopropanol, the melting point of the substance was 166° C [2].

Found, %: C 71.93; H 5.96; N 5.78. Calculated for $C_{29}H_{28}N_2O_5$, %: C 71.90; H 5.83; N 5.79.

Dibenzyl methoxycarbonylskatylacetamidomalonate. A. A mixture of 3 g of the methyl ester of indolylglycine, 5 g of dibenzyl acetamidomalonate, and a few milligrams of sodium methoxide in 19 ml of toluene was heated at a gentle boil for 9 hr, after which the toluene was distilled off in vacuum. The residue was dissolved in acetone and boiled with carbon, the carbon was filtered off, and the acetone was distilled off to small bulk. The crystals that separated were recrystallized from acetone, mp 187–188° C. Yield 1.5 g.

B. A mixture of 4.8 g of methyl indolylglycollate, 8 g of dibenzyl acetamidomalonate, 40 ml of toluene, and a small amount of sodium methoxide were boiled for 5 hr in a flask connected with a reflux condenser through a water separator. After the reaction mixture had cooled, the precipitate that had deposited was filtered off and extracted with acetone. The solvent was distilled off from the acetone extract and the residue was recrystallized from ethanol, mp 187° C. A mixture of the substance obtained with the sample described above gave a depression of the melting point. Yield 4.7 g.

IR spectrum (paraffin oil): 710, 730, 770, 1500, 1515, 1630, 1675, 1740, 1750, 3300, 3410 cm^{-1}.

Found, %: C 68.03; H 5.25; N 5.41. Calculated for $C_{30}H_{28}N_2O_7$, %: C 68.18; H 5.34; N 5.66.

Methyl harmane-4-carboxylate. Four grams of dibenzyl methoxycarbonylskatylacetamidomalonate was subjected to hydrogenolysis over 10% palladium on carbon in 350 ml of ethanol. The reaction took 10 hr. Then the catalyst was filtered off and the ethanol was distilled off in vacuum. The solid residue was poured in portions with stirring into a mixture of 40 g of polyphosphoric acid and 8 ml of phosphorus oxychloride. The mixture was heated at 120° C in an oil bath for 1.5 hr, after which it was poured onto ice. The aqueous solution formed was filtered and made alkaline with ammonia. The alkaline solution was extracted with chloroform. From the combined chloroform extract the solvent was distilled off in vacuum, and the residue was treated three times with 50-ml portions of boiling benzene. The benzene extract was evaporated to small bulk and left for crystallization; the product had mp 194° C (from benzene). Yield 0.2 g.

A mixture with the methyl harmane-4-carboxylate obtained by the oxidation of brevicolline melted without depression.

Summary

Methyl harmane-4-carboxylate has been synthesized and has been shown to be identical with the methyl ester of the harmanecarboxylic acid obtained by the oxidation of brevicolline.

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