ALKALOIDS OF THALICTRUM FLAVUM

Structure of Thalflavine

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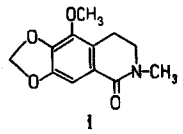
We have previously isolated berberine, cryptopine, and thalicsine from the roots of Th. flavum L. [1]. Continuing the separation of the mother liquors into phenolic and nonphenolic fractions, we have studied the alkaloids which have a nonphenolic nature. These were chromatographed, and two alkaloids were obtained.

The first alkaloid, which we have named "thalflavine," forms prismatic crystals with mp 132–133° C. Its IR spectrum has an absorption band at 1625 cm^{-1} corresponding to an amide carbonyl group. With gallic acid, thalflavine gives a positive reaction for a methylenedioxy group. The IMR spectrum has the signals of protons at τ 6.95 ppm (singlet, 3H) corresponding to an N-methyl group, at 6.16 ppm (singlet, 3H) for a methoxyl group, and at 4.05 ppm (singlet, 2H) for a methylenedioxy group. Triplets at 7.23 ppm (J = 7 Hz) and at 6.05 ppm (J = 7 Hz), each of two proton units, relate to two methylene groups. In the weak-field region at 2.68 ppm there is a one-proton singlet of an aromatic hydrogen.

The mass spectrum of thalflavine has the following peaks: the molecular ion with m/e 235 (100% intensity), ions with m/e 192 (95%), 164 (88%), and 150 (17%), and the doubly charged molecular ion with m/e 117.5 (5%).

On the basis of these results, we propose as the most probable structure for thalflavine that of 1-oxo-5-methoxy-2-methyl-6,7-methylenedioxytetrahydroisoquinoline (I).



I

The second alkaloid formed a yellowish amorphous powder with mp 105–106° C, $[\alpha]_D^{27}$ + 89° (c 1.0, chloroform). Its composition is $C_{41}H_{48}N_2O_8$ (II). The base II contains two N-methyl and seven methoxyl groups.

In the UV spectrum of II there are three absorption maxima, at 282, 303, and 316 mμ, which are characteristic for the aporphine bases [2]. The NMR spectrum of the base has signals of protons at τ 7.72 ppm (3H) and 7.63 ppm (3H) for two N-methyl groups and at 6.33 (3H), 6.26 (6H), 6.19 (6H), 6.11 (3H), and 6.06 (3H) for the seven methoxyl groups. In the weak-field region at 4.17–2.03 ppm the signals of seven aromatic protons are observed.

The above facts permit the formula of the base II to be developed in the following way:

$$C_{32}H_{21}(N-CH_3)_2(OCH_3)_7(-O-).$$

All the properties of the base that have been described are very similar to those of thalicarpine [3,4]. Not having a sample of thalicarpine for direct comparison, we subjected our base II to cleavage with sodium in liquid ammonia under various conditions. From the nonphenolic fraction of the cleavage products we isolated a base identified by means of its UV, NMR, and mass spectra, and also by a comparison of the properties of its salts and derivatives, as 3,6-dimethoxyaporphine [3]. By the oxidation of II we obtained 1-hydroxy-6,7-dimethoxy-2-methyltetrahydroisoquinoline, identical with an authentic sample from armepavine [5]. Thus, base II is thalicarpine.

The alkaloid foetidine which we have isolated from Th. foetidum L. [6] differs from thalicarpine by the presence of a hydroxyl group in place of methoxyl in position 5 of the aporphine part of the molecule. We have methylated foetidine with diazomethane and obtained thalicarpine. Consequently, the ether oxygen bridge of foetidine is attached to position 6' in the benzyltetrahydroisoquinoline part of the molecule, as in thalicarpine.

EXPERIMENTAL

The roots (30 kg) collected on May 20–25, 1962, in the valley of Chon-Kemin (KhirigizSSR) in the period of vigorous growth and budding of the plant were extracted with chloroform. This gave 302 g of combined alkaloids. Of them the ethereal fraction amounted to 209 g and the chloroform fraction to 93 g.

Thalflavine (I). The ethereal fraction (154 g) of the combined alkaloids was dissolved in benzene and passed through a column of alumina. Elution was carried out with benzene, 50-ml fractions being collected. The solvent was evaporated from the first fraction of the benzene eluate and the residue was treated with acetone. This gave 0.5 g of thalflavine.

Thalicarpine (II). The fractions 2–9 of the eluate were combined, the solvent was evaporated, and the residue (46 g) was dissolved in 100 ml of ether and again passed through the column. Elution with ether gave 25 g of an amorphous powder showing a single spot on TLC [ethyl acetate–chloroform (1 : 1) and benzene–methanol (20 : 1) systems]. The melting point of the base was 105–106° C, $[\alpha]_D^{27}$ + 89° (c 1.0, chloroform), λ_{max}: 284, 303, and 316 mμ (log ε 4.52, 4.38, and 4.30), ν_{max} 950, 1060, 1460, 1505, 1600, and 2935 cm^{-1}. Found, %: C 69.40; H 7.33; N 3.75; OCH_3 30.6. Calculated for $C_{41}H_{48}N_2O_8 \cdot H_2O$, %: C 68.90; H 7.00; N 3.92; OCH_3 30.1.

Thalicsine. The solvent was evaporated from fractions 10–28 and the residue (11 g) was treated with methanol. Thalicsine (1.5 g) was obtained, and it was shown by its UV and IR spectra to be identical with an authentic sample.

Cleavage of thalicarpine (II) with sodium in liquid ammonia. A) A solution of 2.5 g of thalicarpine in 30 ml of tetrahydrofuran was added dropwise over 30 min to a solution of 4 g of metallic sodium in 600 ml of liquid ammonia. Stirring was continued until the ammonia had evaporated off (12 hr). The residue was treated with 60 ml of methanol, the solvent was evaporated off, 50 ml of water was added, and the nonphenolic bases were extracted with ether. Yield 1.5 g. The alkaline solution was acidified with conc HCl, made alkaline with 25% ammonia, and extracted with ether. This gave 0.8 g of a phenolic fraction.

3,6-Dimethoxyaporphine. The nonphenolic fraction (1.5 g) of the cleavage product was dissolved in benzene and passed through a column of alumina, being eluted with benzene. A yellow oily substance was formed. Yield 0.9 g, λ_{max} 218, 270, 300, and 320 mμ. **3,6-Dimethoxyaporphine hydriodide.** Acicular crystals with mp 237–238° C (ethanol), λ_{max} 218, 267, 273, 300, 312, and 320 mμ (log ε 4.51, 3.87, 3.88, 3.55, 3.63, and 3.64). **3,6-Dimethoxyaporphine hydrobromide.** Acicular crystals with mp 241–242° C (ethanol), ν_{max} 860, 965, 1240, 1340, 1430, 1480, 1620, 2610, and 1940 cm^{-1}. **3,6-Dimethoxyaporphine methiodide.** Prismatic crystals with mp 164–165° C.

Cleavage at −45° C. B) The reaction was carried out in a glass tube with dry-ice cooling in a Dewar vessel. A solution of 3 g of thalicarpine in a mixture of 12 ml of benzene and 12 ml of toluene was added over 30 min to a solution of 5 g of metallic sodium in 600 ml of liquid ammonia. Then the stirring was continued for another 6 hr. The reaction mixture was left in the Dewar vessel for 12 hr, after which the tube was removed from the vessel and the ammonia was allowed to evaporate freely at room temperature. Further treatment was performed as in experiment A. This gave 2.0 g of nonphenolic and 0.7 g of phenolic fractions. The nonphenolic fraction yielded 1.05 g of 3,6-dimethoxyaporphine.

1-Oxo-6,7-dimethoxy-2-methyltetrahydroisoquinoline. One gram of thalicarpine in solution in purified acetone was oxidized with 1.5 g of potassium permanganate in 300 ml of acetone. The remainder of the process was as described previously [5]. White acicular crystals with mp 119–120° C deposited. Yield 0.15 g. A mixture of the product with an authentic sample of 1-oxo-6,7-dimethoxy-2-methyltetrahydroisoquinoline [5] gave no depression of the melting point. The UV and IR spectra were also identical.

CONCLUSIONS

The roots of Th. flavum L. have yielded thalicarpine and a new alkaloid, thalflavine, $C_{12}H_{13}NO_4$, for which the structure of 1-oxo-5-methoxy-2-methyl-6,7-methlenedioxytetrahydroisoquinoline is proposed.

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