THE STRUCTURE OF FETIDINE

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Khimiya Prirodnykh Soedinenii, Vol. 2, No. 1, pp. 43-48, 1966

The isolation from the epigeal part of Thalictrum foetidum L. of a new binary alkaloid fetidine (I) has been reported previously [1]. In this paper we give data on its structure.

The UV spectrum of fetidine shows maxima characteristic for the aporphine alkaloids. However, the molecular weight, determined by the Beckmann method, is approximately 630. The empirical formula of this base is $C_{40}H_{46}O_8N_2 \cdot H_2O$. Fetidine (I) contains two methylimino and six methoxyl groups. The IR spectrum of (I) has, in addition to other maxima, a maximum at 3400 cm^{-1} showing the presence of a hydroxyl group. Consequently, the formula of base (I) can be developed in the following form: $C_{32}H_{21}(N-CH_3)_2(OCH_3)_6(OH)(-O-)$.

Fetidine was degraded by the action of metallic sodium in liquid ammonia. According to the reaction conditions, three bases were obtained: a non-phenolic base (IIa), and phenolic bases (IIb) and (III).

Base (IIa) has the composition $C_{21}H_{27}O_4N$, $[\alpha]_D$ + 48.1°, and contains one methylimino and four methoxyl groups. Its UV spectrum shows the maximum at 282 mμ (log ε 3.82) characteristic of alkaloids of the benzyltetrahydroisoquinoline series. The properties both of the base itself and of the products of its Hofmann degradation agree well with the properties of laudanosine and its products. The oxidation of substance (IIa) with potassium permanganate in acetone solution gave veratric acid and compound (V). The latter was shown to be identical with an authentic sample of 1-oxo-2-methyl-6, 7-dimethoxytetrahydroisoquinoline obtained by the oxidation of armepavine [2]. These results show that the base (IIa) is (+)-laudanosine [3]. A mixed melting point and the IR spectra of (+)-laudanosine and (±)-laudanosine showed their identity.

The phenolic base (IIb), of composition $C_{20}H_{25}O_4N$, contained one methylimino group, three methoxyl groups, and one hydroxyl group. The IR spectrum had a maximum at 285 mμ (log ε 3.82), which is characteristic for benzyltetrahydroisoquinoline alkaloids. The methylation of (IIb) with diazomethane gave laudanosine (IIa). To ascertain the position of the hydroxy group, substance (IIb) was ethylated with diazoethane and the resulting amorphous substance was subjected to oxidation. Compound (V) was isolated from the reaction products, the formation of this showing that the hydroxyl group is present in the benzyl part of the molecule. The properties of (IIb) and laudanidine [4] coincided. For identification, (±)-laudanosine with metallic sodium in liquid ammonia [5]. The IR spectra of (IIb) and (±)-laudanidine were identical.

Compound	Base (III)	Isoboldine
	mp, °C and $[\alpha]_D$, degrees	
Base (from methanol)	122—124 (Decomp.)	123 (Decomp.)
(from benzene)	96—97 (Decomp.)	97—98 (Decomp.)
(after drying)	180 (Decomp.)	180 (Decomp.)
(in alcohol)	+43.5	+41 [9,10]
(in chloroform)	+45.7	+83.2
O, O, N-Triacetate	165—166	168—169
3, 6-Dimethoxy-2, 5-diethoxy-8-vinylphenanthrene	123—124	120—121
3, 6-Dimethoxy-2, 5-diethoxyphenanthrene-8-carboxylic acid	204—205	205—206
3, 6-Dimethoxy-2, 5-diethoxyphenanthrene	138—139	139—140 [8,11]

The second phenolic base (III), of composition $C_{19}H_{21}O_4N$, had the three maxima in the UV spectrum at 220, 280, and 306 mμ (log ε 4.54, 4.12, 4.18) assigned to 2, 3, 5, 6-tetrahydroxyaporphines [6]. A broad band at 3480 cm^{-1} in the IR spectrum of (III) shows the presence of a hydroxyl group. Acetylation of substance (III) with acetic anhydride gave no acetate in the IR spectrum of which the maximum for the hydroxyl group had disappeared and maxima at 1765 and 1228 cm^{-1} (O-acetyl group) and 1640 cm^{-1} (N-acetyl group) had appeared. A quantitative determination of the acetyl groups in the acetate by means of a measurement of the intensity of the bands in the IR spectrum [7] showed the presence of three acetyl groups. Consequently, compound (III) contains two hydroxyl groups. Analysis also established the presence of two methoxy groups and one methylimino group. On the basis of these results it may be assumed that substance (III) is a dihydroxy-dimethoxyaporphine. This assumption is confirmed by the fact that the methylation of (III) with methyl iodide in the presence of sodium methoxide gave glaucine methiodide.

To determine the positions of the hydroxyl groups, base (III) was ethylated with ethyl iodide in sodium ethoxide solution, and the resulting product was subjected to two fold Hofmann degradation. This gave a substance (IVa) which, on oxidation, gave an acid (IVb). Decarboxylation of the acid (IVb) with a copper-chromium catalyst led to a neutral substance (IVc).

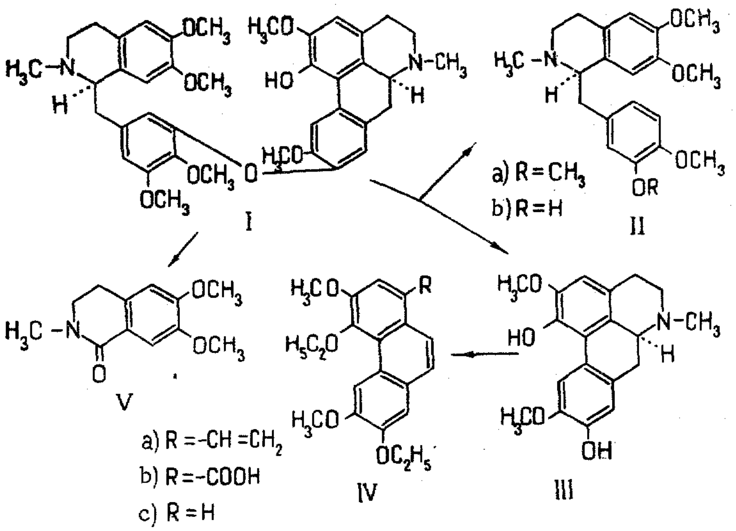
Data on the comparison of the physical properties of the base (III) and its derivatives and Hofmann degradation products with the corresponding compounds of isoboldine [8] are given in the table. As can be seen from the table, the aporphine base (III) is identical with isoboldine.

To determine the position of the ether link between the benzyltetrahydroisoquinoline and the aporphine parts of the molecule, fetidine was oxidized with potassium permanganate in acetone solution, and compound (V) was isolated. This shows that the ether link must be present in the benzyl part of laudanosine.

Aporphine bases having a hydroxyl group in position 5 possess weakened phenolic properties [12]. Since fetidine has three properties, the hydroxyl group that it contains must occupy the C_5 position of the aporphine part of the molecule. The second hydroxyl group in isoboldine (III) in the C_2 position was formed by cleavage of the ester bridge in fetidine.

In view of the fact that the absolute configurations of (+)-laudanosine and (+)-glaucine have been ascertained previously [13], the absolute configuration of fetidine (I) is expressed by LL.

On the basis of the results described, the decomposition of fetidine (I) can be illustrated by the following scheme:



Experimental

Chromatography was carried out by the ascending method in the systems 1) butanol-acetic acid-water (100:5:100), 2) the same solvents (4:1:5), with development by Dragendorff's reagent.

Isolation of the alkaloids. After being steeped in 10% ammonia, 90 kg of the air-dry ground epigeal part of Th. foetidum was extracted with ether. The ethereal extract was treated with 10% sulfuric acid. The acid solution was made alkaline with 25% ammonia and the alkaloids were extracted with ether. After the ether had been distilled off, 575 g (0.63%) of a mixture of alkaloids was obtained. This was dissolved in 10% hydrochloric acid, and the crystals which deposited were filtered off using a filter pump (307.5 g or 0.34%) and recrystallized from water (1:1); mp 228-230°C (decomp.), $[\alpha]_D^{20}$ −30.93° (c 2.58; water).

Found, %: Cl 8.62, 8.59. Calculated for $C_{40}H_{46}O_8N_2 \cdot H_2O \cdot 2HCl$, %: Cl 9.1.

Fetidine (I). A solution of 40 g of fetidine dihydrochloride in 80 ml of water was made alkaline with 25% ammonia, and the base was extracted with ether. Evaporation of the ether left 35 g of white amorphous powder, which crystallized from ethyl acetate (1:1). Yield 31.5 g, mp 132-135°C, $[\alpha]_D^{15}$ + 121.4° (c 2.09; methanol), R_f 0.44 in system 1, type "M" paper of Leningrad Mill No. 2. UV spectra (taken in alcoholic solution on a SF-4 instrument): λ_{max} 220, 280, 305 mμ (log ε 4.80, 4.36, 4.24), IR spectra [taken on a UR-10 double-beam spectrophotometer (Zeiss) in tablets moulded with KBr]: 3400 (OH), 2830 (OCH_3), 2800 ($N-CH_3$), 1605, 1580, 1515 (aromatic ring) cm^{-1}.

Found, %: C 68.70, 68.80; H 6.83, 6.88; N 3.78, 3.61; $N-CH_3$ 3.57, 3.83; OCH_3 26.25, 26.16; equiv. 348.8, 346.7 by titration; mol. wt. 630 (Beckmann). Calculated for $C_{40}H_{46}O_8N_2 \cdot H_2O$, %: C 68.55; H 6.61; N 3.99;

$2N-CH_3$ 4.28; 6 OCH_3 26.52; equiv. 350.3; mol. wt. 700.7.

Degradation of fetidine with sodium in liquid ammonia at −45°C. Over 2.5 hr, 3 g of fetidine in a mixture of 20 ml of benzene and 20 ml of toluene was added to a solution of 4.5 g of metallic sodium in 600 ml of liquid ammonia. Stirring was continued for a further 4.5 hr. The reaction mixture was left for 12 hr, and then the ammonia was evaporated off. The residue was treated with 200 ml of water acidified with 20% hydrochloric acid, and was then made alkaline with 25% ammonia and extracted with ether (A). The ethereal extract was washed with 2% caustic potash solution (alkaline solution B).

(+)-Laudanosine (IIa). The ethereal extract (A) was concentrated to 10 ml. This gave a precipitate of 0.6 g of crystals with mp 86-87°C (from acetone), $[\alpha]_D^{15}$ + 48.1° (c 2.12; chloroform), R_f 0.78 in system 2. UV spectrum: λ_{max} 282 mμ (log ε 3.82); IR spectrum: 2830, 1270, 1240 (OCH_3), 2780 ($N-CH_3$), 1610, 1580, 1520 (aromatic ring) cm^{-1}. The IR spectrum of substance (IIa) was identical with the spectrum of (±)-laudanosine.

Found, %: C 69.90, 69.70; H 7.71, 7.88; N 3.96, 4.10; OCH_3 33.0, 33.0. Calculated for $C_{21}H_{27}O_4N$, %: C 70.50; H 7.61; N 3.91; 4 OCH_3 34.4.

Laudanosine methiodide, small prisms with mp 218-220°C (from alcohol).

De-N-methyl laudanosine, white silky crystals with mp 80-82°C.

De-N-methyl laudanosine methiodide, needles with mp 227-229°C.

The nitrogen-free substance derived from laudanosine, needles with mp 79-81°C.

Substance (V). A solution of 0.44 g of potassium permanganate in 70 ml of acetone was added to a solution of 0.3 g of laudanosine in 20 ml of acetone. The subsequent treatment was the same as for armepavine [2]. Needle-like crystals with mp 124-125°C (from acetone), R_f 0.85 in system 2, were formed. Yield 80 mg. The IR spectrum of the crystals showed their identity with substance (V) isolated from armepavine. A mixture of the two substances gave no depression of the melting point.

Veratric acid. The precipitate of manganese dioxide was washed with 5 ml of 2% caustic potash and 15 ml of water. The alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether (1 l). The residue had mp 177-178°C (from benzene). The methyl ester of the acid formed needles with mp 55-56°C (from alcohol). A mixed melting point and the IR spectra of the acid itself and of its ester showed their identity with veratric acid and its ester.

(+)-Laudanidine (IIb). The alkaline solution (B) (100 ml) was acidified with concentrated hydrochloric acid, and was then made alkaline with 25% ammonia and extracted with ether. Evaporation of the ether gave 1.75 g of a brownish residue which gave a precipitate of prismatic crystals when treated with methanol. Yield 0.76 g, mp 178-179°C, $[\alpha]_D^{17}$ + 74.6°C (c 1.01; chloroform), R_f 0.67 in system 2. UV spectrum: λ_{max} 285 mμ (log ε 3.82).

Found, %: C 70.20, 70.30; H 7.81, 7.69; N 3.93, 4.05; $N-CH_3$ 4.00, 3.70; OCH_3 26.10, 26.40. Calculated for $C_{20}H_{25}O_4N$, %: C 69.92; H 7.93; N 4.07; $N-CH_3$ 43.3 OCH_3 27.0.

(+)-Laudanosine (IIa) from (IIb). A mixture of 0.5 g of laudanidine in 10 ml of methanol and an ethereal solution of diazomethane was left for 36 hr. The residue had mp 85-86°C (from petroleum ether). A mixed melting point and the IR spectrum of substance (IIa) confirmed its identity with the laudanosine obtained from fetidine.

Production of (V) from O-ethyllaudanidine. 0.5 g of laudanidine was ethylated with diazoethane. The amorphous O-ethyllaudanidine (0.35 g) was oxidized in acetone solution in a similar manner to the oxidation of armepavine. Needle-shaped crystals with mp 119-121°C were isolated. A mixed melting point of the crystals and their IR spectrum showed their identity with substance (V) obtained from armepavine.

Degradation of fetidine with sodium in liquid ammonia at −32°C. A solution of 2.5 g of fetidine in 40 ml of tetrahydrofuran was added over 30 min to a solution of 4 g of sodium in 600 ml of liquid ammonia. Stirring was continued until the ammonia had volatilized off completely (7 hr). The residue was treated with 60 ml of methanol, which was evaporated off, with 30 ml of water, and was then extracted with ether; 2.1 g of a mixture of bases remained.

(+)-Laudanidine (IIB). The residue (2.1 g) was dissolved in 5 ml of acetone. On standing, 0.6 g of crystals with mp 177-178°C deposited. A mixture with laudanidine gave no depression of the melting point (176-178°C). The IR spectra of the two substances were identical.

Isoboldine hydrobromide, mp 255-257°C (decomp., from water). UV spectrum: λ_{max} 220, 280, 306 mμ (log ε 4.48, 4.17, 4.21).

Found, %: Br 18.1, 18.6. Calculated for $C_{19}H_{21}O_4N \cdot HBr$, %: Br 19.6.

Isoboldine (III). From 0.8 g of the hydrobromide was isolated 0.6 g of the base, which was recrystallized from ethyl acetate-methanol (1:1), mp 122-124°C (decomp.); the crystals from benzene had mp 96-97°C (decomp.), after drying at 110°C under vacuum for 10 hr mp 180°C (decomp.), $[\alpha]_D^{20}$ + 43.5° (c 1.72; chloroform), $[\alpha]_D^{30}$ + 45.7° (c 1.18; ethanol), R_f 0.26 in system 1. UV spectrum: λ_{max} 220, 280, 306 mμ (log ε 4.54, 4.12, 4.18). IR spectrum: 3480 (OH), 2800 ($N-CH_3$), 2855, 1248, 1122 (OCH_3), 1615, 1525 (aromatic ring) cm^{-1}.

Found, %: C 69.95, 69.98; H 6.73, 6.65; N 4.45, 4.30; $N-CH_3$ 3.8, 4.4; OCH_3 19.5, 19.5. Calculated for $C_{19}H_{21}O_4N$, %: C 69.72; H 6.42; N 4.28; $N-CH_3$ 4.58; 2 OCH_3 18.56.

Isoboldine O, O, N-triacetate. A mixture of 0.1 g of isoboldine (III), 1 ml of acetic anhydride, and one drop of pyridine was heated for 2 hr at 100°C, and was then evaporated to dryness. The residue had mp 165-166°C (from methanol). IR spectrum: 1765, 1228 ($-O-COCH_3$), 1640 ($N-COCH_3$) cm^{-1}.

Glaucine methiodide from (III). mp 213-215°C (from alcohol). A mixed melting point of this substance (mp 214°C) and the IR spectra showed its identity with (+)-glaucine methiodide.

3, 6-Dimethoxy-2, 5-diethoxy-8-vinylphenanthrene (IVa). A mixture of 1.2 g of isoboldine, sodium ethoxide (0.2 g of sodium in 10 ml of ethanol), and 2 ml of ethyl iodide was boiled for 10 hr and evaporated, and the residue was subjected to twofold Hofmann degradation. This yielded 1.0 g of needle-like crystals of (IVa) with mp 123-124°C (from alcohol). UV spectrum: λ_{max} 228, 272, 322 mμ (log ε 4.66, 4.82, 4.30). IR spectrum: 2880, 1244, 1125 (OCH_3 and OC_2H_5), 995, 920 ($-CH{=}CH_2$) cm^{-1}.

3, 6-Dimethoxy-2, 5-diethoxyphenanthrene-8-carboxylic acid (IVb). An acetone solution of potassium permanganate (1.05 g in 300 ml) was added to a solution of 0.7 g of substance (IVa) in 100 ml of acetone. This yielded crystals with mp 204-205°C (from methanol). UV spectrum: λ_{max} 222, 268, 310 mμ (log ε 4.38, 4.68, 4.02). IR spectrum: 3300 and 2500 (OH), 1700 (C=O), 1250, 1120 (OCH_3 and OC_2H_5) cm^{-1}.

3, 6-Dimethoxy-2, 5-diethoxyphenanthrene (IVc). A mixture of 0.2 g of the acid (IVb), 0.6 g of copper-chromium catalyst, and 2 ml of quinoline was boiled for 50 min. The yield of the product was 0.1 g (mp 138-139°C, from methanol). UV spectrum: λ_{max} 214, 265, 314, 344, 360 mμ (log ε 4.36, 4.89, 4.08, 3.34, 3.22; IR spectrum: 2840, 1240, 1100 (OCH_3 and OC_2H_5), 1600, 1515 (aromatic ring) cm^{-1}.

Production of (V) from fetidine. A solution of 4.5 g of potassium permanganate in 360 ml of acetone was added to a solution of 3 g of fetidine in 35 ml of acetone. The further treatment was as described for the oxidation of armepavine. This gave 0.55 g of white needle-like crystals with mp 124-125°C, R_f 0.84, (system 2). A mixed melting point (mp 124°C) and the IR spectrum of the crystals showed their identity with an authentic sample of (V).

Summary

Fetidine is a binary aporphine-benzyltetrahydroisoquinoline alkaloid. A structural formula for fetidine has been proposed on the basis of the isolation of (+)-laudanosine (IIIa) and (+)-isoboldine (IV) from the degradation of fetidine (I) with sodium in liquid ammonia.

The obtaining of (+)-laudanosine and (+)-glaucine has established the absolute configuration of the two asymmetric centers of fetidine.

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6 August 1965

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