STRUCTURE OF THALSIMINE

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The alkaloid thalsimine is isolated from the seeds and leaves of Thalictrum simplex L. From the results of elementary analysis and a determination of the molecular weight, the formula $C_{38}H_{40}O_7H_2$ has been established for it [1]. The oxidation of thalsimine with potassium permanganate in acetonic solution gives 3, 4'-dicarboxy-6-methoxy-(diphenyl oxide), which shows that thalsimine belongs to the series of ether-like bimolecular bis-benzylisoquinoline bases.

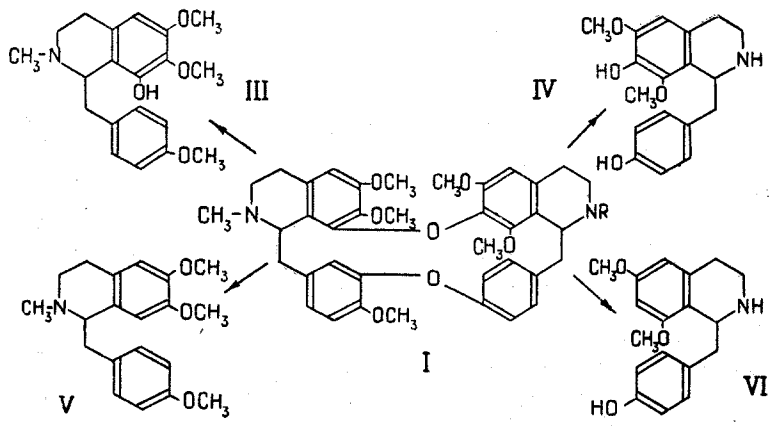
The UV spectrum of thalsimine has maxima characteristic for 3, 4-dihydroisoquinolines (λ_{max}: 278, 310 mμ; log ε 4.02, 4.76).

On catalytic reduction by Adams' method, thalsimine absorbs two atoms of hydrogen. Dihydrothalsimine gives a positive reaction for a secondary amino group. The UV spectrum of dihydrothalsimine is characteristic for the benzyltetrahydroisoquinoline bases. The IR spectrum of thalsimine has a triplet in the 1550-1630 cm^{-1} region which is characteristic for 3, 4-dihydroisoquinolines and is absent from the spectrum of the reduced substance. A doublet at 1560-1625 cm^{-1} in the spectrum of dihydrothalsimine indicates that it contains a 1, 2, 3, 4-tetrahydroisoquinoline nucleus [2].

The IR spectrum of dihydrothalsimine shows only slight absorption for a secondary amino group, but the presence of this group is confirmed by the acetyl derivative (I; R = OC—CH_3), which gave the expected strong absorption band at 1647 cm^{-1}. Cases in which secondary bases exhibit low absorption for a secondary amino group have been described in the literature [3]. A determination of the number of acetyl groups in the IR spectrum of a solid sample of N-acetyldihydrothalsimine by the method of band integration showed the presence of one N-acetyl group [4].

The methylation of dihydrothalsimine by Hess's method leads to the N-methyl derivative. The latter, after two stages of Hofmann degradation, gives trimethylamine and a nitrogen-free substance absorbing eight atoms of hydrogen on catalytic hydrogenation by Adams' method. The octahydro nitrogen-free substance crystallizes from alcohol with mp 204-205°. It was identified by a mixed-melting-point test and UV and IR spectra with the corresponding derivative of hernandezine [5]. Consequently, thalsimine differs from hernandezine by the presence of a double bond at C_1—N. The position of this bond was established by the reductive splitting of thalsimine with sodium in liquid ammonia. Under these conditions, a secondary phenolic base (II) was obtained. Ethylation of the latter with subsequent oxidation led to p-ethoxybenzoic acid. The presence of an o-methoxy group in a diphenyl oxide weakens the C—O bond, and rupture of the bond always takes place unambiguously with the formation of a hydroxyl group on the unsubstituted benzene ring[6]. Consequently, the dihydroisoquinoline part of the molecule of thalsimine must be connected to an unsubstituted benzene nucleus.

The formation of a secondary base in the degradation of thalsimine with sodium in liquid ammonia indicates that, in addition to the rupture of ether linkages, reduction of a C=N bond takes place with the formation of a secondary base, which is also confirmed by the isolation of the base (II) from the products of the degradation of dihydrothalsimine. On the basis of the aforesaid, it was decided that dihydrothalsimine has the following structure (I; R = H):

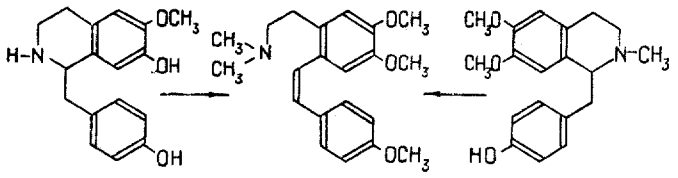


The reaction of thalsimine (dihydrothalsimine) with sodium in liquid ammonia can give rise to four products: O-methylarmepavine (V) [7], 6, 8-dimethoxy-7-hydroxy-1-(p-hydroxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline (IV), corpaverine (III) [8], and 6, 8-dimethoxy-1-(p-hydroxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline (VI). The bases (IV) and

(VI) have not been described in the literature. The base which we isolated contains only one methoxy group, while bases (IV) and (VI) must contain two methoxy groups. Moreover, acetylation with acetic anhydride in the presence of pyridine led to a O, O, N-triacetyl derivative. Consequently, the product of the degradation of thalsimine (dihydrothalsimine) with sodium in liquid ammonia is neither of the bases (IV) or (VI). The physical and chemical properties of the base (II) and its derivatives are similar to those for coclaurine:

Coclaurine and its derivatives	Mp, °C	Base obtained and its derivatives	Mp, °C
Coclaurine	220-221 $[\alpha]_D \pm 0$	Base	220-221 $[\alpha]_D \pm 0$ (CH_3OH)
O, O, N-Triacetate	174-175	O, O, N-Triacetate	174-176
Hydrochloride (dried over P_2O_5)	263-264	Hydrochloride	252-254

The base was methylated with methyl iodide in the presence of sodium methoxide and was subjected to Hofmann degradation. The oily substance so obtained could not be crystallized; however, it formed a crystalline hydrochloride which was identified by a mixed-melting-point test and UV and IR spectra with the hydrochloride of the des-base of O-methylarmepavine [7].



II VIII VII

Consequently, the product of the degradation of thalsimine is coclaurine. The formation of the latter can be explained if it is assumed that hydrogenolysis of the methoxy group takes place at C_8 with the production of a base of the tetrandrine type, the degradation of which leads to coclaurine.

The second product of the degradation of thalsimine must be O-methylarmepavine. However, O-methylarmepavine was not found in the reaction product. Exhaustive methylation of the mother liquors obtained after the separation of the coclaurine with methyl iodide in the presence of sodium methoxide led to O-methylarmepavine methiodide. Thus, the reductive degradation of the ethereal bond is accompanied by the demethylation of the methoxy group [9].

It has been reported that an attempt to degrade the alkaloid hernandezine was unsuccessful. Only a bimolecular phenolic base was obtained [10], the formation of which is possible by the rupture of one of the two oxygen bridges or the demethylation of the methoxy groups. Unfortunately, the authors of this paper do not give the results of a molecular weight determination, and the melting point given for the phenol also corresponds to the hemihydrate of N-methylcoclaurine [11]. Consequently, we were interested in the degradation of hernandezine. Hernandezine was degraded by sodium in liquid ammonia under conditions similar to those for the degradation of thalsimine. Part of the initial hernandezine was recovered and a mixture of phenolic bases giving two spots on a paper chromatogram was obtained. However, we were unable to isolate crystalline phenolic bases. Exhaustive methylation of the mixture of phenols with methyl iodide in the presence of sodium methoxide gave O-methylarmepavine methiodide. As can be seen from the structural formula of hernandezine (I; R = CH_3), hydrogenolysis of the methoxy group at C_8 and demethylation of the methoxy group in the other half of the molecule with rupture of the two oxygen bridges should give phenolic products the methylation of which will in any case lead to O-methylarmepavine.

Since thalsimine has one asymmetric carbon atom, the reduction of the dihydroisoquinoline nucleus may be expected to give rise to the formation of two diastereoisomeric products. The reduction of thalsimine with zinc in sulfuric acid gave two sulfates differing in their solubility in water. Decomposition of the sparingly soluble sulfate gave dihydrothalsimine-A. This gives a series of crystalline derivatives: dichloro- and dibromodihydrothalsimine, dihydrothalsimine dihydriodide, and N-acetyldihydrothalsimine. Methylation by Hess's method gave N-methyldihydrothalsimine-A, which a comparison of the IR spectra showed to be identical with hernandezine.

From the soluble sulfate, dihydrothalsimine-B, which does not give crystalline salts, was isolated. N-Methyldihydrothalsimine-B was obtained by Hess methylation, mp 257-258° (softening at 237°) $[\alpha]_D^{28}$ – 127° (c 1.29; $CHCl_3$). The base is sparingly soluble in alcohol, acetone, and methanol, readily soluble in benzene, and insoluble in water and petroleum ether. The des-base N-methyldihydrothalsimine-B gives a crystalline methiodide identical, from the IR spectra, with the corresponding derivative of hernandezine. Consequently, the reduction of thalsimine with zinc in sulfuric acid leads to the formation of two diastereoisomeric products.

Experimental

Degradation of thalsimine with sodium in liquid ammonia. A solution of 2.7 g of thalsimine in a mixture of 50 ml of benzene and 100 ml of toluene was treated with 450 ml of liquid ammonia and, with constant stirring, 6.5 g of sodium was added to the solution over 3 hr, and then the ammonia was evaporated off at room temperature. After all the ammonia had evaporated, the residue was poured into a dish, water was added, and the mixture was extracted with ether. The ethereal extract was dried and distilled, giving a residue weighing 0.85 g. The alkaline mother liquors were acidified with concentrated hydrochloric acid, made alkaline with 25% ammonia, and extracted with chloroform. The chloroform was dried and distilled giving a residue weighing 1.58 g.

Coclaurine hydrobromide. The residue obtained after the distillation of the chloroform was dissolved in methanol. Concentrated hydrobromic acid was added to the solution. The bromide precipitated in the form of prisms with mp 260-261° (CH_3OH); $[\alpha]_D \pm 0$ (CH_3OH). UV spectrum, λ_{max}: 285 mμ (log ε 3.80).

Found: Br 21.7, 21.4; N 3.92, 4.04; OCH_3 8.3, 8.0%. Calculated for $C_{17}H_{19}O_3N$; HBr: Br 21.84; OCH_3 8.47; N 3.82%.

Coclaurine. 0.35 g of the hydrobromide was dissolved in boiling water and the hot solution was made alkaline with 25% ammonia. The base precipitated in the form of a dark powder. This was filtered off with suction, washed with water, and dried. Yield 0.24 g. On the addition of ether to the methanolic solution, the base crystallized in the form of colorless needles with mp 220-221° (alcohol); $[\alpha]_D \pm 0$ (CH_3OH). UV spectrum, λ_{max}: 286 mμ (log ε 3.64).

Found: OCH_3 11.6, 11.8%. Calculated for $C_{17}H_{19}O_3N$: OCH_3 10.89%.

Coclaurine hydrochloride was obtained by mixing alcoholic solutions of hydrochloric acid and the base. Needles, mp 252-254° (H_2O).

Coclaurine N, O, O-triacetate. A mixture of 0.27 g of coclaurine hydrobromide, 2 ml of acetic anhydride, and a few drops of pyridine was heated until dissolution was complete and was left for three days at room temperature. Then the reaction mixture was poured onto ice and was made alkaline with caustic potash. The resin which precipitated was washed with water. The acetate was crystallized from a mixture of methanol and ethanol. Yield 0.17 g, mp 174-176° (CH_3OH). IR spectrum 1647 cm^{-1} (N-acetyl group), 1740, 1755 cm^{-1} (O-acetyl group).

Hydrochloride of the des-base of O, O-dimethylcoclaurine. A mixture of 0.5 g of coclaurine, 10 ml of 0.5 N methanolic caustic potash, and 0.45 ml of methyl iodide was heated for 4 hr. After drying in vacuum, a residue was obtained in the form of a bright yellow powder and this was dissolved in 7.6 ml of methanol. The solution was treated with 1.9 g of caustic potash and boiled for 1 hr. The residue was treated with 8 ml of water and extracted with ether. The ether was distilled off. The residue, 0.8 g, was dissolved in 2% hydrochloric acid. The acid solution was washed with ether, made alkaline with 25% ammonia, and extracted with ether. The oily des-base obtained after the distillation of the ether was dissolved in ether and alcoholic hydrochloric acid was added. On cooling the solution, the hydrochloride precipitated. Needles, mp 216-218° (according to literature data 229-230°).

Hydrochloride of the des-base of O-methylarmepavine (VIII · HCl). A mixture of 0.9 g of armepavine (VII), 4.5 ml of methyl iodide, and 12 ml of 0.5 N methanolic caustic potash was heated as described above for coclaurine. The hydrochloride of the des-base melted at 224-226°. A mixture with the hydrochloride of the des-base of O, O-dimethylcoclaurine gave no depression of the melting point.

Degradation of hernandezine with sodium in liquid ammonia. With stirring, 3.3 g of hernandezine, dissolved in 100 ml of dry benzene, was added dropwise to a solution of 5 g of sodium in 400 ml of liquid ammonia. The solution of the base was added over 2 hr. The mixture was stirred for a further 5 hr. The tube containing the reaction mixture was left overnight in a Dewar vessel. The ammonia evaporated off freely. The excess of sodium was decomposed with methanol. The contents of the tube were transferred to a porcelain dish. The solvent was evaporated off. The residue was treated with 300 ml of water and the mixture was extracted with ether (ethereal extract A).

The alkaline mother liquor was saturated with ammonium chloride and extracted with ether (ethereal extract B). Ethereal extract A was dried. The ether was distilled off. The residue, 1.25 g, was dissolved in benzene and was chromatographed on alumina. Evaporation of the eluate gave an oil, which was treated with boiling petroleum ether. The ether was decanted off and the residue was crystallized from alcohol. The resulting needles had mp 157-158°, 123-124° (acetone); $[\alpha]_D$ + 220° (c 0.78; $CHCl_3$). The substance was identified as hernandezine by a comparison of the IR spectra.

Treatment of the ethereal extract B. Evaporation of the solvent gave 1.5 g of a viscous brown resin exhibiting two spots on paper chromatography. 0.3 g of the mixture of phenols, 4 ml of methyl iodide, and 0.11 g of caustic potash were heated for 3 hr. The excess of methyl iodide was distilled off and the residue was dried in vacuum. The methiodide was crystallized from methanol to form lustrous needles with mp 135-136° (decomposition). UV spectrum, λ_{max}: 284 mμ (log ε 3.66).

The substance was identified as the methiodide of O-methylarmepavine by a comparison of the IR spectra.

Reduction of thalsimine. A mixture of 3 g of thalsimine, 50 ml of 20% sulfuric acid, and 6 g of zinc dust was heated for 6 hr. At the end of each hour, a further 10 ml of acid and 1.9 g of zinc were added. Then the solution was cooled and filtered (filtrate C). The residue from the filtrate was carefully triturated with ammonia and was extracted with ether. The ethereal extract was dried and distilled. The residue was crystallized from acetone. The base had no sharp melting point: it shrank at 115° and softened at 130-132°, $[\alpha]_D^{15}$ + 241° (c 2.6; $CHCl_3$).

The dihydrochloride of dihydrothalsimine-A was obtained by mixing alcoholic solutions of the base and hydrochloric acid. Needles, mp 237-241° (H_2O); $[\alpha]_D^{25}$ + 211° (c 1.2; H_2O).

Found: N 4.08%. Calculated for $C_{38}H_{42}O_7N_2 \cdot 2\,HCl$: N 4.1%.

Dihydriodide. Concentrated hydriodic acid was added to an alcoholic solution of the base, the hydriodide precipitating immediately. Bright yellow needles with mp 236-237° (decomposition).

The dihydrobromide was obtained by mixing an alcoholic solution of the base and hydrobromic acid. Mp 250-251° (decomposition; CH_3OH); $[\alpha]_D^{29}$ + 188° (c 2.2; H_2O).

N-Acetyldihydrothalsimine-A. A mixture of 0.3 g of dihydrothalsimine, 2 ml of acetic anhydride, and 0.5 ml of pyridine was kept at room temperature for 3 days. Then the reaction mixture was poured onto ice, made alkaline with 40% caustic potash solution, and extracted with ether. The ethereal extracts were dried and distilled. The residue was crystallized from methanol to form needles with mp 171° (sinters at 168°), $[\alpha]_D^{28}$ + 90° (c 1.1; ethanol); +143° (c 1.1; $CHCl_3$); UV spectrum λ_{max}: 282 mμ (log ε 3.88). The hydrochloride of N-acetyldihydrothalsimine-A was obtained by mixing alcoholic solutions of the base and hydrochloric acid, mp 239-242° (decomposition, H_2O).

N-Methyldihydrothalsimine-A (hernandezine). A mixture of 2.7 g of dihydrothalsimine-A, 27 ml of formic acid, and 27 ml of 37% formaldehyde solution was heated for 2 hr. Then the cooled mixture was made alkaline with ammonia and extracted with ether. The ether was dried and distilled off. Yield 2.73 g, mp 156-158° (alcohol); 122-123° (acetone); $[\alpha]_D^{20}$ + 220° (c 2.5; $CHCl_3$); UV spectrum, λ_{max} 286 mμ (log ε 3.76).

Treatment of the filtrate C. The acid solution was made alkaline with ammonia and was extracted with ether. The ether was dried and distilled. This gave an amorphous base with $[\alpha]_D$ −42° (c 5.2; $CHCl_3$), giving an amorphous dihydrochloride and dihydrobromide.

N-Methyldihydrothalsimine-B was obtained by a similar method to that described above. Mp 157-158° (ethanol; methanol; acetone; $[\alpha]_D^{27}$ − 127° (c 1.29; $CHCl_3$); UV spectrum, λ_{max} 282 mμ (log ε 3.84).

Found: N 4.28, 4.23; OCH_3 23.3, 23.7%. Calculated for $C_{39}H_{44}O_7N_2$: N 4.29, 5.00; (OCH_3) 23.75%.

Methiodide of the des-base of hernandezine. The methiodide of N-methyldihydrothalsimine-B was obtained by heating 2 g of the base, 160 ml of acetone, 40 ml of chloroform, and 6 ml of methyl iodide. Then the methiodide was dissolved in 10 ml of methanol, 60 ml of 30% methanolic caustic potash was added, and the mixture was heated for 2 hr. The methanol was evaporated off, and the residue was treated with 75 ml of water and extracted with chloroform. The des-base was dissolved in 30 ml of ethanol and treated with 2 ml of methyl iodide. The mixture was heated until crystals began to form and was then cooled and filtered. Yield 0.8 g. The methiodide obtained charred above 260°C. UV spectrum, λ_{max}: 198; 286 mμ (log ε 4.84; 4.40).

Found: OCH_3 16.4, 16.1%. Calculated for $C_{43}H_{54}O_7N_2I_2$: 5 (OCH_3) 16.08

It was identified as the methiodide of the des-base of hernandezine by a comparison of the IR spectra.

Summary

1. The degradation of thalsimine, dihydrothalsimine, and hernandezine with sodium in liquid ammonia gives rise to derivatives of coclaurine.

2. In thalsimine, besides the splitting of the ether bridges, reduction of the dihydroisoquinoline nucleus takes place.

3. The reduction of thalsimine with zinc in sulfuric acid gives rise to two diastereoisomeric products. Methylation of the latter by Hess's method gives hernandezine and N-methyldihydrothalsimine-B with mp 257-258°, $[\alpha]_D$ − 127° ($CHCl_3$).

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