THE STRUCTURE OF THALMINE

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The oxidation of the alkaloid thalmidine, isolated from the epigeal part of Thalictrum minus L., has given 2-methoxy-1, 1'-diphenyloxide-4', 5-dicarboxylic acid [1]. This shows that thalmidine belongs to the ether-like bis-benzylisoquinoline bases. The degradation of thalmidine with sodium in liquid ammonia gave a phenolic base similar in properties to N-methylisococlaurine (IIIa). Methylation of the latter with methyl iodide in alkaline solution gave the methiodide of O-methylarmepavine. Consequently, the phenolic product of the degradation of thalmidine is N-methylisococlaurine. The nonphenolic product of the degradation of thalmidine is an oil whose methiodide is identical with the methiodide of O-methylarmepavine (IIIb). Products analogous to (IIIa) and (IIIb) were obtained by the degradation of O-methylthalicberine [2]. Thus, thalmidine must be identical with O-methylthalicberine. The results of a direct comparison of thalmidine with O-methylthalicberine kindly given to us by T. Tomimatsu have shown that these substances are identical.

The alkaloid thalmine, isolated from the epigeal part of Th. minus is also one of the ether-like bis-benzylisoquinolinium bases [1]. On oxidation it gives 2-methoxy-1, 1'-diphenyloxide-4', 5-dicarboxylic acid (I). Its molecular weight, determined by Rast's method, confirms that thalmine is a bimolecular base. A functional analysis shows that the substance contains three methoxyl and two methylimido groups. Thalmine is insoluble in alkali and in Klaisen's cryptophenol reagent and is not methylated by diazomethane. However, the IR spectrum of acetylthalmine has bands at 1770 and 1195 cm^{-1} showing the presence in it of a phenolic ester group. Consequently, thalmine must have at least one phenolic hydroxyl group.

The weak phenolic properties of thalmine and the fact that its oxidation gives the acid (I) excludes the presence of its phenolic group in the benzyl part of the molecule; this group must be located in the isoquinoline nucleus.

The methylation and ethylation of thalmine with the corresponding iodides in alkalie give O-methyl- and O-ethylthalmines.

Degradation of thalmine with sodium in liquid ammonia gives (+)-1-(4'-methoxybenzyl)-2-methyl-6-methoxytetrahydroisoquinoline (II), identified by a comparison of the constants of the base and the products of its Hofman degradation with published data [3]. This product is evidently obtained from the half of the thalmine molecule that contains a methoxyl group in the benzyl part. We were unable to isolate the second degradation product in the crystalline state, and we therefore degraded O-methylthalmine with sodium and liquid ammonia. The phenolic fraction yielded an oxalate which was identified by a comparison of the IR spectra with armepavine oxalate [4]. Armepavine (IIIc) has a hydroxyl group in position 4' and corresponds to that half of the O-methylthalmine molecule which does not contain the methoxyl group in the benzyl part.

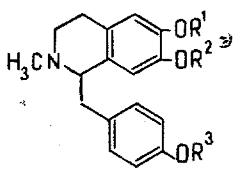
The hydroxyl group in the base (IIIc) was formed by the reductive cleavage of the ether bridge in the benzyl part of the thalmine molecule.

The production of the degradation products 1-(4'-methoxybenzyl)-2-methyl-6-methoxytetrahydroisoquinoline and armepavine (IIIc) enables us to assume that thalmine has only one other bridge, in the benzyl part of the molecule. In this case, the oxidation of O-methylthalmine should give 1-oxo-6, 7-dimethoxy-N-methyltetrahydroisoquinoline (IVa) . However, the oxidation of O-methylthalmine with potassium permanganate in acetone solution gave a bimolecular tetrahydroisoquinolone, which shows the presence in thalmine of a second ether oxygen bridge joining the tetrahydroisoquinoline moieties.

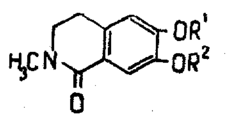
To elucidate the number and position of the phenolic hydroxyl groups in thalmine, we degraded its ethyl ether with sodium in liquid ammonia. A phenolic (V) and a weakly phenolic fraction were obtained. The latter consisted of an oil which, with methyl iodide in alkali, gave O-methylarmepavine methiodide. Consequently the substituting groups in the weakly phenolic product of the degradation of O-ethylthalmine occupy positions, 6, 7, and 4'. A hydroxyl group cannot be present in position 4', since the base possesses weak phenolic properties. To elucidate the nature of the substituting groups, we ethylated the weakly phenolic product and then oxidized it. A weakly basic substance was isolated whose melting point corresponded to that of 1-oxo-6-methoxy-7-ethoxy-N-methyltetrahydroisoquinoline (IVb) [5].

Thus, the weakly phenolic product of the degradation of O-ethylthalmine is 1-(4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyltetrahydroisoquinoline (IIId). The hydroxyl group in the base (IIId) can arise only by the reductive cleavage of an ether oxygen bridge.

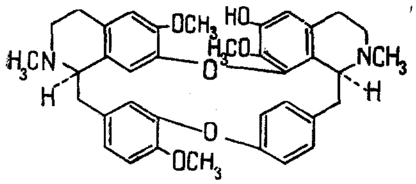
The phenolic fraction (V) formed a crystalline oxalate. When this was made alkaline with ammonia, a base was isolated from it with properties similar to those of (+)-1-(4'-hydroxybenzyl)-6-ethoxy-7-methoxy-N-methyltetrahydroisoquinoline (IIIe). To confirm this, the phenolic base was oxidized with potassium permanganate in acetone solution. The melting point of the oxidation product corresponded to 1-oxo-6-ethoxy-7-methoxy-N-methyltetrahydroisoquinoline (IVc). For a direct comparison, we used compound (IVc) from salsoline. The two oxidation products were identical.



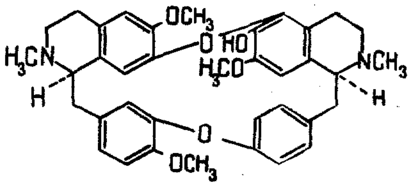
III a) $R^1=R^3=H$; $R^2=CH_3$
b) $R^1=R^2=R^3=CH_3$
c) $R^1=R^2=CH_3$, $R^3=H$
d) $R^1=R^3=CH_3$, $R^2=H$
e) $R^1=C_2H_5$, $R^2=CH_3$; $R^3=H$



IV a) $R^1=R^2=CH_3$
b) $R^1=CH_3$; $R^2=C_2H_5$
c) $R^1=C_2H_5$; $R^2=CH_3$



VI



VII

Consequently, the phenolic base obtained by the degradation of O-ethylthalmine has the structure (IIIe), and thalmine contains one phenolic hydroxyl group in position 6 in the tetrahydroisoquinoline part of the molecule.

On the basis of the above results, structure (VI) has been put forward as the most probable structure of thalmine [6]. It can be seen from formula (VI) that O-methylthalmine must be a diastereoisomer of O-methyloxyacanthine. Consequently, we have also compared the products of reactions of O-methylthalmine and O-methyloxyacanthine, which contain no asymmetric centers. The two bases were subjected to twofold Hofmann degradation. The nitrogen-free substances obtained proved not to be identical. Moreover, it was found that the diaminodialdehydes obtained by the ozonolysis of the des-bases of O-methylthalmine and of O-methyloxyacanthine were also nonidentical. Thus, the assumption that thalmine is an alkaloid of the oxyacanthine series was not confirmed.

When bis-benzylisoquinoline bases having a methoxyl group at C_8 are subjected to degradation with sodium in liquid ammonia, the methoxyl group undergoes hydrogenolysis [7]. Since the products of the degradation of thalmine corresponded to the products of the degradation of bases of the type of oxyacanthine and the products of the Hofmann degradation of these bases were not identical, we have assumed that thalmine contains a methoxyl group at C_8. In this case, the degradation of thalmine with sodium and liquid ammonia, being accompanied by hydrogenolysis of the methoxyl group at C_8, would again give products (IIId) and (IIIe).

However, the diaminodialdehydes obtained by the ozonolysis of the des-base of O-methylthalmine and hernandezine also proved not to be identical. Consequently, there is no methoxyl group in position 8 of thalmine.

Considering the results presented above, we propose structure (VII) for thalmine.

Since the degradation of O-methylthalmine gave (+)-1-(4'-methoxybenzyl)-6-methoxy-7-hydroxy- and (+)-1-(4'-hydroxybenzyl)-6-ethoxy-7-methoxy-N-methyltetrahydroisoquinolines, thalmine has the LL configuration.

Experimental

Degradation of thalmidine with sodium in liquid ammonia. With stirring, a solution of 2 g of thalmidine in 50 ml of benzene was added to a solution of 3 g of sodium in 300 ml of liquid ammonia over 15 min. Stirring was continued for a further 1 hr at −48° to −38° C. The ammonia was evaporated off at room temperature. The residue was treated with 100 ml of water and extracted with ether. This alkaline solution was saturated with ammonium chloride and the base was extracted with ether. The yield of phenolic fraction was 1.4 g.

N-Methylisococlaurine hydrochloride. 1.4 g of the phenolic fraction obtained from the degradation of thalmidine was dissolved in alcohol, and an alcoholic solution of hydrogen chloride was added. This gave 0.6 g of a hydrochloride with mp 161°–165° C (decomp.), $[\alpha]_D$ +69.7° (H_2O), +79.3° C (c 1.50; methyl alcohol).

N-Methylisococlaurine (IIIa). A solution of 0.3 g of the hydrochloride in water was made alkaline with concentrated ammonia solution and extracted with ether. Evaporation of the ethereal solution led to the precipitation of N-methylisococlaurine in the form of needles associated into rosettes. Yield 0.25 g, mp 206°–207° C.

N-Methylisococlaurine hydrobromide. The addition of concentrated hydrobromic acid to an alcoholic solution of the base precipitated the hydrobromide with mp 145° -148° C (decomp.).

O-Methylarmepavine methiodide. A mixture of 0.28 g of isococlaurine, 5.6 ml of 0.5N caustic potash in methanol, and 0.5 ml of methyl iodide was heated for 3 hr. The solvent was evaporated off. The residue was crystallized from methanol. This gave 0.1 g of the methiodide (IIIb) with mp 133°–134° C (decomp.). A mixture with authentic O-methylarmepavine methiodide gave no depression of the melting point. Their IR spectra were identical.

A solution in 2 ml of methanol of 0.17 g of the nonphenolic fraction obtained from the degradation of thalmine was heated for 2 hr with 0.3 ml of methyl iodide. The solvent was evaporated off, and the residue was crystallized from methanol. This gave 0.08 g of the methiodide (IIIb) with mp 129°–130° C (decomp.). A mixture with authentic O-methylarmepavine methiodide gave no depression of the melting point. Their IR spectra were identical.

Thalmine. The base was recrystallized from a mixture of alcohol and chloroform and was dried under vacuum.

Found, %: C 71.7, 71.8; H 7.08, 7.12; N 4.4, 4.41; OCH_3 14.9, 15.1; N CH_3 3.7; mol. wt. 615, 619 Rast. Calculated for $C_{37}H_{40}N_2O_6 \cdot C_2H_5OH$, %: C 71.55; H 7.03; N 4.28; 3 OCH_3 14.22; 2N–CH_3 4.59; mol. wt. 654.

Acetylthalmine. A mixture of 0.5 g of thalmine and 4 ml of acetic anhydride was boiled for 2 hr. After the excess of reagent had been eliminated, a dark yellow powder remained giving a single spot on a chromatogram in the butanol–acetic acid–water (4 : 1 : 5) system and distinguished by its R_f value from the initial thalmine $[\alpha]_D$ –219° C (c 0.83; chloroform). IR spectrum: (KBr, UR-10); 1770 and 1195 cm^{-1}.

O-Methythalmine dimethiodide. A solution of 2 g of thalmine in 200 ml of methanol was treated with 0.13 g of sodium in 2 ml of methanol and 3 ml of methyl iodide. The mixture was heated for 30 hr, sodium methoxide being added every 6 hr. The solvent was eliminated. The residue was washed with water. The resulting amorphous powder had mp 244°–250° C (decomp.), $[\alpha]_D$ +48° C (c 1.74; methanol), +34.9° C (c 1.1; 50% alcohol).

O-Methylthalmine. A mixture of 5 g of O-methylthalmine dimethiodide and 5 ml of monoethanolamine was heated for 40 min at 170°–175° C. After cooling, chloroform was added to the reaction mixture and it was washed with water. The chloroform solution was extracted with 10% sulfuric acid. The acid extract was washed with ether and made alkaline with 25% ammonia solution, and the base was extracted with ether. This yielded 2.8 g of O-methylthalmine in the form of a bright yellow powder, $[\alpha]_D$ –68.5° C (c 1.75; chloroform).

O-Ethylthalmine dimethiodide. 2 g of thalmine was heated for 3 hr with 3 ml of methyl iodide in 20 ml of methanol. The solvent was distilled off to dryness. The residue was treated with 70 ml of alcohol, 3 ml of ethyl iodide, and 0.1 g of sodium in 5 ml of alcohol and heated for 30 hr, sodium ethoxide being added every 6 hr. After the solvent had been eliminated, the residue was washed with water. The resulting amorphous powder had mp 234°–238° C (decomp.), $[\alpha]_D$ +56° C (c 2.86; chloroform).

O-Ethylthalmine. In a similar manner to O-methylthalmine dimethiodide, 5 g of O-ethylthalmine dimethiodide was treated with 5 ml of monoethanolamine. Yield 2.7 g, mp 190°–193° C (decomp.).

Degradation of thalmine with sodium in liquid ammonia. A solution of 4.8 g of thalmine in 600 ml of a mixture of benzene and toluene was added dropwise to a solution of 6 g of sodium in 600 ml of liquid ammonia over 2 hr, and the mixture was stirred for 5 hr. The ammonia was evaporated off at room temperature and the phenolic (0.25 g) and nonphenolic (1.93 g) bases were separated.

1-(4'-Methoxybenzyl)-6-methoxy-N-methyltetrahydroisoquinoline (II). 5.9 g of the nonphenolic fraction of the products of the degradation of thalmine was crystallized from petroleum ether. This gave 4.4 g of substance with mp 62°–63° C; after additional purification of alumina the mp was 64°–65° C, $[\alpha]_D$ +54.4° C (c 1.6; chloroform), +94.3° C (c 1.9; alcohol).

Found, %: C 76.9, 76.9; H 8.44, 8.44; N 4.70, 4.98; OCH_3 20.2; mol. wt. 297.6, 295.1 (titration in a nonaqueous solvent). Calculated for $C_{19}H_{23}NO_2$, %: C 76.8; H 7.75; N 4.71; 2 OCH_3 20.9; mol. wt. 297.

1-(4'-Methoxybenzyl)-6-methoxy-N-methyltetrahydroisoquinoline methiodide. A mixture of 0.5 g of the base (II), 20 ml of methanol, and 0.5 ml of methyl iodide was heated for 3 hr. The solvent was eliminated. The methiodide (II) was crystallized from water, mp 95° C.

The des-base of 1-(4'-methoxybenzyl)-6-methoxy-N-methyltetrahydroisoquinoline. A mixture of 0.5 g of the methiodide (II) and 10 ml of 30% methanolic caustic potash was heated for 3 hr. The solvent was eliminated, water was added, and the mixture was extracted with ether. The ethereal extract was dried, and the oily residue was purified by chromatography on alumina. It was eluted with benzene, the solvent was distilled off from the eluate and the residue was treated with petroleum ether. Crystals of the des-base (II) were deposited with mp 63° C, $[\alpha]_D$ ±0° C (methanol); a picrate with mp 174°-175° C and a dihydro-des-base (II) with mp 191°-192° C were obtained.

Nitrogen-free product from 1-(4'-methoxybenzyl)-6-methoxy-2-methyltetrahydroisoquinoline. A methanolic solution of the des-base (II) was heated with methyl iodide for 2 hr. The solvent was eliminated. The resulting methiodide of the des-base (II) was treated with 20 ml of a 30% methanolic solution of caustic potash. It was again heated for an hour. The methanol was evaporated off and water was added. The nitrogen-free product was extracted with ether and crystallized from methanol, mp 69°-175° C.

Degradation of O-methylthalmine with sodium in liquid ammonia. A solution of 2.26 g of the base in 350 ml of benzene was added in drops with stirring over 1.5 hr at −33° to −32° C to a solution of 3 g of sodium in 400 ml of liquid ammonia. Stirring was continued for 2 hr. The ammonia was evaporated off and the residue was separated into a phenolic and a nonphenolic fraction. This gave 1.13 g of an oily nonphenolic fraction and 0.95 g of a phenolic fraction from which 0.5 g of an oxalate with mp 202°-203° C was isolated. A mixture with armepavine oxalate melted at 210° C (armepavine oxalate has mp 210° C). The IR spectra of the oxalates were identical.

Oxidation of O-methylthalmine. With stirring, 1.75 g of potassium permanganate in acetone was added in drops to a solution of 1 g of the base in 250 ml of acetone. The manganese dioxide that precipitated was filtered off and washed with hot acetone. The filtrate was evaporated to dryness and the residue was triturated with 10% hydrochloric acid. The acid solution was made alkaline to pH 5 and was extracted with ether. The concentrated ethereal extract was left in the cold; wart-like crystals with mp 172°-173° C were slowly deposited. UV spectrum (SF-4M, alcohol): λ_{max} 222, 246, 258, 295 mμ (log ε 4.78, 4.32, 4.3, 4.06, respectively); IR spectrum: 1650 cm^{-1}.

Found, %: OCH_3 19.2; mol. wt. 424.2, 421.6 (Rast). Calculated for $C_{23}H_{26}N_2O_6$, %: $3OCH_3$ 21.8; mol. wt. 426.

Degradation of O-ethylthalmine with sodium in liquid ammonia. A solution of 4.4 g of O-ethylthalmine in 600 ml of benzene was added in drops with stirring to 6.6 g of sodium in 600 ml of liquid ammonia over 1.5 hr at −45° to −41° C. Stirring was continued for a further 2.5 hr. The ammonia was evaporated off, and the residue was separated into a phenolic and a nonphenolic fraction. This yielded 1 g of a weakly phenolic fraction in the form of an oil and 2.6 g of a phenolic fraction which gave 0.8 g of an oxalate with mp 210°-211° C, $[\alpha]_D$ +80.4° C (c 0.83; methanol).

1-(4'-Hydroxybenzyl)-6-ethoxy-7-methoxy-N-methyltetrahydroisoquinoline (IIIe). A solution of 0.8 g of the oxalate in water was made alkaline with concentrated ammonia solution and extracted with ether. The yield of phenolic base was 0.5 g, mp 140°-142° C, $[\alpha]_D$ +81° C (c 1.18; chloroform).

1-Oxo-6-ethoxy-7-methoxy-N-methyltetrahydroisoquinoline (IVc). With stirring, 0.35 g of potassium permanganate in 50 ml of acetone was added in drops over an hour at 20°-24° C to a solution of 0.2 g of (IIIe) in 10 ml of acetone. The precipitate of manganese dioxide which was deposited was filtered off with suction and washed with hot acetone. The acetone was evaporated off. The residual oil was treated with a 10% solution of hydrochloric acid. The acid solution was filtered, neutralized with ammonia to pH 5, and extracted with ether. Crystals with mp 96°-97° C were deposited from the concentrated ethereal extract. UV spectrum: λ_{max} 223, 250, 258, 297 mμ (log ε 4.23, 4.09, 4.03, 3.86, respectively). IR spectrum: 1650 cm^{-1}. A mixture with the analogous substance obtained from salsoline gave no depression of the melting point, and their IR spectra were identical.

O-Methylarmepavine methiodide from the weakly phenolic fraction from the degradation of O-ethylthalmine. 2 g of the base (IIIe) was chromatographed on a column of alumina. Elution with chloroform containing 2% of methanol gave 1.3 g of a base in the form of an oil. Part of the oil (0.2 g), 2 ml of methanol, 0.2 ml of methyl iodide, and 0.1 g of caustic potash was heated for 3 hr. The methiodide of (IIIb) with mp 134°-136° C (decomp.) was isolated. A mixture with O-methylarmepavine methiodide gave no depression of the melting point, and the IR spectra were iidentical.

1-Oxo-6-methoxy-7-ethoxy-N-methyltetrahydroisoquinoline (IVb). Another part of the oil (0.5 g), 3 ml of methanol, and 0.2 ml of methyl iodide were heated for 1 hr. The solvent was evaporated. The residue was treated with 10 ml of a 0.5 N alcoholic solution of caustic potash and 0.5 ml of ethyl iodide and the mixture was heated for 3 hr. The solvent was eliminated. The residue was heated with 0.5 ml of monoethanolamine at 160°-170° C for 0.5 hr. The reaction mixture was cooled, treated with 10 ml of chloroform, and washed with water. The chloroform solution was concentrated to give a residue in the form of an oil (0.4 g).

The oil (0.2 g) was dissolved in 10 ml of acetone and, with stirring, 0.35 g of potassium permanganate in acetone was added over 1 hour. After working up similar to that for the isolation of substance (IVc), crystals with mp

115°–118° C were obtained. UV spectrum: λ_{max} 223, 260, 268, 296 mμ (log ε 4.44, 3.96, 3.92, 3.84, respectively); IR spectrum: 1650 cm^{-1}.

Nitrogen-free substance from O-methylthalmine. A mixture of 2 g of O-methylthalmine methiodide, 40 ml of methanol, and 12 g of caustic potash was heated for 2 hr. The solvent was evaporated off and the residue was treated with water and extracted with chloroform. This gave 1.6 g of a mixture of the des-base of O-methylthalmine in the form of an amorphous powder, $[\alpha]_D$ −162° C (c 1.16; methanol).

A mixture of the des-base (1.6 g), 2 ml of methyl iodide, and 15 ml of methanol was heated for 3 hr. Evaporation of the solvent yielded 2 g of the dimethiodide of the des-base of O-methylthalmine with mp 232° C (alcohol), $[\alpha]_D$ −303.9° C (c 1.81; methanol). A mixture of 2 g of the dimethiodide and 20 ml of 30% methanolic caustic potash was heated for 1 hr. Trimethylamine was isolated. The solution was concentrated and the residue was treated with water and extracted with chloroform. The concentrated extract deposited 0.2 g of crystals with mp 137°–140° C. Recrystallization from methanol–chloroform raised the mp to 208°–210° C. A mixture with the analogous substance obtained from O-methyloxyacathine (215° C) gave no depression of the melting point.

Ozonolysis of the des-base of O-methylthalmine. 1 g of the mixture of des-bases of O-methylthalmine was dissolved in 20 ml of 10% sulfuric acid. It was ozonized for 3.5 hr at 0° C. The acid solution was washed with ether, shaken with fine platinum powder, and reduced with hydrogen. Then the acid solution was filtered, made alkaline with 25% ammonia solution, and treated with ether, after which it was mixed with an equal volume of 50% caustic potash. The diaminodialdehyde obtained was extracted with ether (0.35 g). When 0.5 ml of methyl iodide was added to an acetone solution of the diaminodialdehyde, it immediately became turbid and a resin was deposited which on trituration formed a powder with mp 190°–195° C (decomp.); on paper chromatography it gave a spot with R_f 0.25. UV spectrum: λ_{max} 225, 280 mμ (log ε 4.47, 4.2, respectively).

The diaminodialdehyde dimethiodide was heated for 15 min with 18 ml of 5% aqueous caustic soda. The reaction mixture was extracted with chloroform, the chloroform solution was concentrated, and a few drops of alcohol were added. On cooling, crystals of the divinyldialdehyde with mp 140°–141° C (alcohol) were formed. UV spectrum: λ_{max} 245, 250 mμ (log ε 4.6, 4.20). The analogous substance from O-methyloxyacanthine has mp 137° C. UV spectrum: λ_{max} 250, 294 mμ (log ε 4.66, 4.30). A mixture of the two substances gave a depression of the melting point (128° C).

Ozonolysis of the des-base of hernandezine. A solution of 4 g of hernandezine in chloroform was treated with 3 ml of methyl iodide. The hernandezine dimethiodide was dissolved in 8 ml of methanol, 60 ml of a 30% methanolic solution of caustic potash was added and the mixture was heated for 2 hr. The solvent was evaporated off, and the residue was treated with water and extracted with ether. The ether was evaporated off. This gave 1 g of the inactive des-base of hernandezine, mp 189°–190° C (from acetone), giving a hydrochloride with mp 235°–237° C (decomp.). The mother liquor, on treatment with methanol, gave 1 g of an optically active des-base with mp 151°–152° C, $[\alpha]_D$ +442° (c 1.7; chloroform).

Ozone was passed through a cooled solution of 1.3 g of the inactive des-base of hernandezine in dilute acetic acid for 2 hr. The acid solution was washed with ether, shaken with platinum black, and reduced with hydrogen. Then it was filtered, made alkaline with an equal volume of 50% caustic potash, and treated with ether. This yielded 0.65 g of the diaminodialdehyde in the form of an oil. The latter was dissolved in acetone and treated with 0.5 ml of methyl iodide. The resulting diaminodialdehyde dimethiodide was crystallized from alcohol, mp 211°–212° C (decomp.); R_f 0.31; UV spectrum: λ_{max} 222, 280 mμ (log ε 4.72, 4.24).

Summary

1. On the basis of the isolation of 2-methoxy-1-1'-diphenyloxide-4',5-dicarboxylic acid (I) it has been established that thalmidine and thalmine are bis-benzylisoquinoline bases.

2. By the preparation of (+)-N-methylisococlaurine and (+)-O-methylarmepavine it has been shown that thalmidine is identical with O-methylthalicberine.

3. The nature of the degradation products isolated shows that thalmine has the LL configuration.

4. Since the diaminodialdehydes obtained by the ozonolysis of the des-bases of O-methylthalmine, O-methyloxyacanthine, and hernandezine are not identical, structure (VII) (taking the degradation products into account) is proposed for thalmine.

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