STRUCTURE OF CORAMINE

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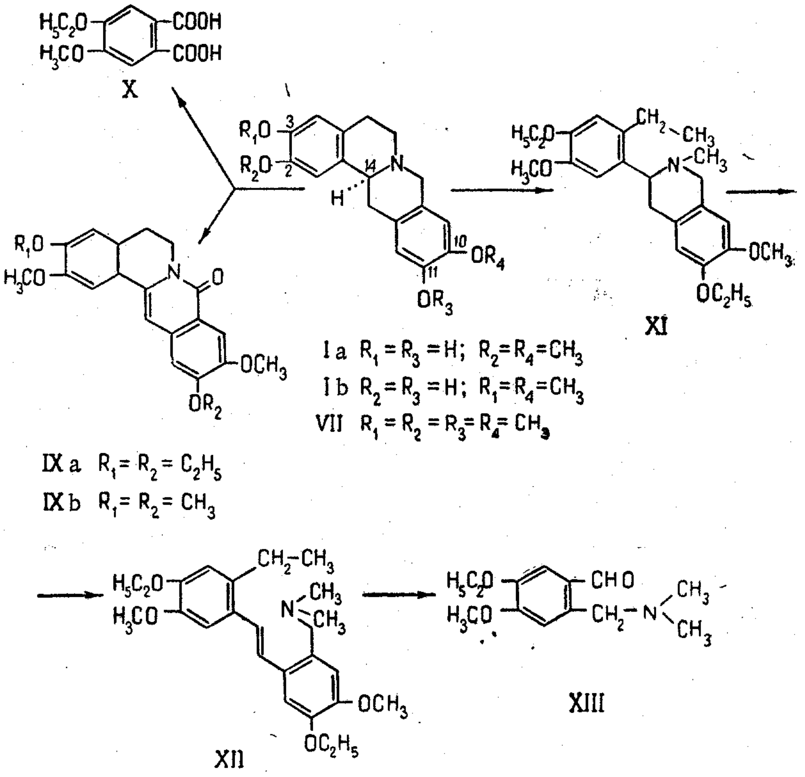
From Corydalis pseudoadunca we have isolated the phenolic base coramine (Ia) which is an alkaloid of the diisoquinoline type [1]. The base is insoluble in the usual organic solvents but is readily soluble in pyridine and alkalies; it contains two methoxy and two phenolic hydroxy groups, which is confirmed by the production of a O, O-diacetyl derivative (II). The IR spectrum has an absorption band at 3470 cm^{-1} (hydroxyl). Methylation with methyl iodide in an alkaline medium gives O, O-dimethylcoramine methiodide (III), which, on heating with ethanolamine, is converted into O, O-dimethylcoramine (IV). The Hofmann degradation of substance (IV) (two stages) forms a nitrogen-containing product.

According to the UV spectra, the first des-base (V) is a styrene derivative, and in the second stage of the Hofman degradation the hydrogenated first des-base forms a stilbene derivative (VI). The first des-base is optically inactive, which is evidently due to its racemization under the reaction conditions. Taking into account the facts mentioned, and also the high rotation of the alkaloid and its UV spectrum [λ_{max} 288 mμ (log ε 3.74)], we have assigned it to the alkaloids of the diisoquinoline type. The identity of O, O-dimethylcoramine (IV) with xylopinine (VII), a sample of which was kindly given to us by Dr. Schmutz (Switzerland), has confirmed our assumption.

In order to elucidate the mutual arrangement of the substituting groups, O, O-diethylcoramine (VIII) was oxidized with potassium permanganate in an aqueous medium. However, the desired reaction product (a methoxyethoxytetrahydroisoquinolone) was not isolated. A product was obtained in good yield which, according to analysis and the results of the UV and IR spectra, has the structure (IXa). The UV spectrum of this substance has absorption maxima in the same positions as the product of the oxidation of (+)-norcoralydine (IXb) [2]



X

XI

I a $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$
I b $R_2 = R_3 = H$; $R_1 = R_4 = CH_3$
VII $R_1 = R_2 = R_3 = R_4 = CH_3$

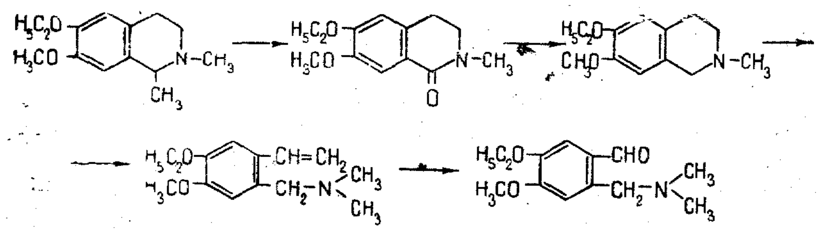
IX a $R_1 = R_2 = C_2H_5$
IX b $R_1 = R_2 = CH_3$

XII

XIII

The more vigorous oxidation of O, O-diethylcoramine led to the formation of 5-ethoxy-4-methoxyphthalic acid (X).

It was possible to establish the positions of the substituting groups by the ozonolysis of I-des-O, O-diethylcoramine (XII) obtained by the Hofmann degradation of the hydrogenated I-des-O, O-diethylcoramine (XI). The ozonolysis product, which contained nitrogen, proved to be identical with the 2-dimethylaminomethyl-5-ethoxy-4-methoxybenzaldehyde (XI) obtained from O-ethyl-N-methylsalsoline. Thus, one of the hydroxy groups is in position 11. And since coreximine (Ib) has hydroxy groups in positions 2 and 11 [4], only structure (Ia) remains for coramine.



In view of the identity of O, O-dimethylcoramine (IV) and xylopinine (VII), for which the configuration of the asymmetric center has been established [3], coramine must be assigned the same configuration. The IR spectra of coramine and its derivatives have absorption bands at 2750 and 2800 cm^{-1} which are characteristic for quinolizidine systems with the trans-axial arrangement of the hydrogen atom at C_{14} with respect to the electron pair of the nitrogen. This band is absent in the product of the oxidation of O, O-diethylcoramine (IXa).

Experimental

O, O-Diacetylcoramine (II). A mixture of 0. 5 g of the base, 5 ml of acetic anhydride, and 0. 2 ml of pyridine was left at room temperature for 3 days. The solution was poured onto ice and made alkaline with concentrated caustic potash. The resin and amorphous precipitate which deposited were triturated with water and the resulting powder was treated with benzene. The insoluble part was filtered off and the benzene was evaporated. The residual mass was treated with a mixture of benzene and ether (1 : 1). Crystals of O, O-diacetylcoramine deposited with mp 191°–193° C (methanol + ether); IR spectrum 1765 cm^{-1}.

O, O-Dimethylcoramine methiodide (III). A solution of 0. 15 g of the base and 0. 1 g of caustic potash in 5 ml of methyl alcohol was treated with 1 ml of methyl iodide and the mixture was boiled for 2 hr. The solution was evaporated and the residue was washed with water, mp 243°–246° C (water).

O, O-Dimethylcoramine (IV). A mixture of 0. 25 g of O, O-dimethylcoramine methiodide and 0. 8 ml of ethanolamine was kept for 40 min at 160°–170° C. The reaction mixture was dissolved in a mixture of chloroform and alcohol (10 : 1), the solution was washed with water, and the solvent was evaporated off. The residual mass was treated with alcohol to give a crystalline product with mp 178°–180° C (alcohol). The substance gave no depression of the melting point in admixture with xylopinine. The UV spectra of the bases obtained proved to be identical. The melting point of the hydrochloride was 217°–220° C (alcohol-ether) and that of the hydrobromide 224°–226° C (methanol).

Hofman degradation of O, O-dimethylcoramine. A mixture of 0. 5 g of (III) and 10 ml of 30% alcoholic caustic potash was boiled for 4 hr. The solvent was evaporated off, 10 ml of water was added, and the mixture was shaken with ether. The ethereal extract was dried over sodium sulfate and distilled. The residual oily mass was dissolved in alcohol and hydrogenated in the presence of a platinum catalyst. The catalyst was removed, 1 ml of methyl iodide was added, and the solution was boiled for 1. 5 hr. The crystals of the methiodide of hydrogenated I-des-coramine were separated off and washed with alcohol; mp 232°–233° C. The methiodide was boiled for 3 hr with 30% alcoholic caustic potash. On cooling, acicular crystals of II-des-coramine with mp 121°–122° C (alcohol) separated out. UV spectrum: λ_{max} 330 mμ (log ε 4. 34). The substance obtained was dissolved in alcohol and hydrogenated by Adams' method. The hydrogenation product melted at 81°–83° C (alcohol). UV spectrum: λ_{max} 282 mμ (log ε 3. 82).

O, O-Diethylcoramine (VIII). A mixture of 0. 3 g of (Ia), 5 ml of ethanol, and 1 ml of methyl iodide was boiled for 1 hr. The solvent was evaporated off, and then 5 ml of alcohol, 1 ml of ethyl iodide, and 0. 1 g of caustic potash were added and the mixture was boiled for 2 hr. Then the solvent was eliminated, the residue was washed with water, and the O, O-dimethylcoramine methiodide was recrystallized from methanol, mp 225°–227° C.

Under conditions analogous to those for substance (IV), this was converted into O, O-diethylcoramine with mp 164°–166° C (alcohol, incipient shrinking at 155° C). The melting point of the hydrochloride was 199°–201° C (water + methanol).

Oxidation of O, O-diethylcoramine. A 5% solution of sodium acetate was added to a solution of 0. 36 g of (VIII) in 10% sulfuric acid until a turbidity appeared. The solution was cooled with ice water and, with stirring, 0.66 g of potassium permanganate in 20 ml of water was added over 40 min. Thirty minutes after the addition of the whole amount of potassium permanganate, the reaction mixture was heated to 50° C and then the manganese dioxide was separated off. The reaction product was extracted with ether. This gave light yellow crystals of substance (IXa) with mp 182°–184° C (from methanol.) UV spectrum: λ_{max} 230, 266, 334 mμ (log ε 4.46, 4.42, 4.33). IR spectrum: 1650 cm^{-1}. Found, %: N 3.5. Calculated for $C_{23}H_{25}O_5N$, %: N 3.6.

The mother liquor, after the removal of substance (IXa), was heated in a water bath and stirred while a solution of potassium permanganate was added until a permanent purple coloration was produced. The manganese dioxide was separated off, the solution was evaporated to small bulk and acidified with concentrated hydrochloric acid, and the reaction product was extracted with ether. The oily mass remaining after the distillation of the ether was converted, by treatment with benzene, into a yellow powder, which was dissolved in alcohol and mixed with an alcoholic solution of ethylamine. The precipitate which deposited was recrystallized from aqueous alcohol. After prolonged drying at 70° C, the substance had mp 200°–204° C (incipient shrinking at 192° C). It gave no depression of the melting point in admixture with the product obtained by mixing alcoholic solutions of 4-methoxy-5-ethoxyphthalic acid, obtained from O-ethylsalsoline, and ethylamine.

Hofmann degradation of O,O-diethylcoramine. A solution of 0.7 g of the methiodide of (VIII) in 20 ml of 30% alcoholic caustic potash was boiled for 4 hr. The solvent was evaporated off, the residue was treated with 15 ml of water, and the reaction product was extracted with ether. The yield of I-des-O,O-diethylcoramine was 0.4 g, mp 121°–122° C (ether + methanol). The melting point of the hydrochloride was 148°–150° C (water, incipient softening at 140° C). IR spectrum: λ_{max} 214, 262, 288 mμ (log ε 4.5, 4.12, 3.86). The I-des-base was hydrogenated by Adams' method for 40 min. The yield of substance (XI) was 0.35 g, mp 100°–103° C (alcohol).

A mixture of 0.3 g of (XI), 5 ml of methanol, and 1 ml of methyl iodide was heated in a water bath for 2 hr. After the elimination of the solvent, 0.4 g of the methiodide of (XI) with mp 207°–209° C (acetone + methanol) remained. UV spectrum: λ_{max} 284 mμ (log ε 4).

A mixture of 0.4 g of the methiodide (XI) and 15 ml of 30% caustic potash was boiled for 2 hr. The solvent was evaporated off, the residue was treated with 15 ml of water, and the product was extracted with ether. This gave 0.2 g of substance (XII), with mp 154°–155° C (acetone). UV spectrum: λ_{max} 300 (inflection), 330 mμ (log ε 4.2, 4.28).

2-N-Dimethylamino-5-ethoxy-4-methoxybenzaldehyde. 0.17 g of (XII) was suspended in 20 ml of 10% sulfuric acid and ozonized with ice cooling for 5 hr. The reaction mixture was washed with ether, made weakly alkaline with ammonia, and extracted with ether. After the ether had been distilled off, substance (XIII) remained in the form of an oil. This was dissolved in 5 ml of methanol and the solution was treated with 1 ml of methyl iodide and 0.1 g of caustic potash and boiled for 40 min. The solvent was eliminated and the crystalline residue washed with water. This yielded the methiodide of (XIII) with mp 207°–209° C (methanol) giving no depression of the melting point in admixture with an authentic sample obtained from O-ethyl-N-methylsalsoline. The methiodide (XIII) formed a 2,4-dinitrophenylhydrazone with mp 237°–239° C. The IR spectra of the two products were identical. IR spectrum: 1685 cm^{-1}.

Summary

1. It has been established that the base coramine isolated from *Corydalis pseudoadunca* is a diisoquinoline alkaloid.

2. It has been shown that the dimethyl ether of coramine is identical with xylopinine.

3. The structure of coramine has been established by a study of the ozonolysis of the products of the Hofman degradation of its diethyl ether.

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