was dissolved in 1 *N* sodium hydroxide (10 ml.), and after standing at room temperature for 30 minutes, the solution was neutralized with dilute sulfuric acid. The solid that deposited was collected by filtration, washed with water (2 × 5 ml.), then acetone (25 ml.), and dried *in vacuo* over P_2O_5; yield 830 mg. (94%), m.p. > 264°; spectral data: λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 225 (9.6), 323 (22.6); *p*H 7, 228 (10.5), 320 (22.2); *p*H 13, 233 (14.3), 310 (22.0); $\bar{\nu}$ in cm.$^{-1}$: 3100 and 3030 (CH), 2900–2500 (acidic H), 1700 (C=O of COOH), 1610 and 1560 (C=C, C=N), 1205 (C—O of COOH).

Anal. Calcd. for $C_7H_6N_4O_2S$: C, 40.00; H, 2.88; N, 26.66. Found: C, 39.87; H, 3.04; N, 26.94.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES, PHILADELPHIA 1, PENNA.]

The Chemistry of Hortiamine and 6-Methoxyrhetsinine[1]

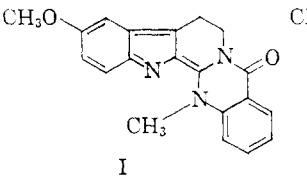
BY IRWIN J. PACHTER, RICHARD J. MOHRBACHER AND DAVID E. ZACHARIAS

RECEIVED AUGUST 22, 1960

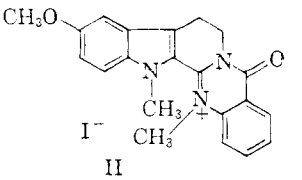
The structure recently assigned to 6-methoxyrhetsinine (III) on the basis of spectral considerations receives support from the nature of its chemical reaction products. The methylation, ethanolysis, lithium aluminum hydride reduction and acetylation of III were studied. The acetylation reaction gives rise to a compound XXVI which is isomeric with hortiamine (I) and which has structural features in common with a hitherto unreported type of rutaceous alkaloid isolated from *Hortia braziliana* Vel. The lithium aluminum hydride reduction of hortiamine (I) was investigated. A new synthesis of hortiamine is described.

In a previous paper,[2] the hypotensive red alkaloid hortiamine was shown to have structure I. Upon methylation it yielded a yellow methiodide (II) and upon hydrolysis it yielded a yellow compound which, on the basis of its spectral properties, was assigned structure III.[3] Compound III is the 6-methoxy derivative of the alkaloid rhetsinine, recently isolated from *Xanthoxylum rhetsa*[4–6] and from *Evodia rutecarpa*.[7]

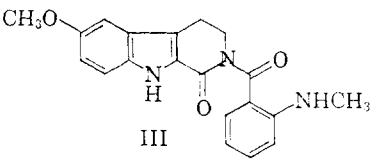
The present paper describes some new reactions of hortiamine (I) and 6-methoxyrhetsinine (III) and serves to confirm the structures previously advanced for rhetsinine[5] and its 6-methoxy derivative.[2]



I

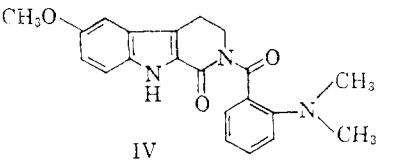


II

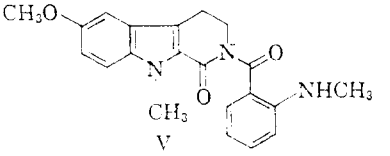


III

When 6-methoxyrhetsinine (III) is methylated with methyl iodide in dimethylformamide, the yellow dimethylamino compound IV is produced. This product is isomeric with 6-methoxy-9-methyl rhetsinine[2] (V), obtained upon mild basic hydrolysis of hortiamine methiodide (II).



IV



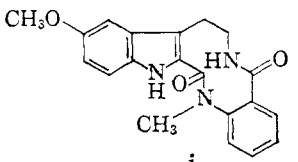
V

The structure of the methylation product IV was confirmed through synthesis. 5-Methoxytryptamine-2-carboxylic acid[8] (VI) reacts with N-methylisatoic anhydride (VII) to produce the *o*-methylaminobenzoyl derivative[9] VIII. Methylation of VIII with methyl iodide at 100° yields the

(1) Presented, in part, at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(2) I. J. Pachter, R. F. Raffauf, G. E. Ullyot and O. Ribeiro, THIS JOURNAL, **82**, 5187 (1960).

(3) At the outset of our studies we considered structure III and also the ten-membered ring diamide structure i for 6-methoxyrhetsinine. The latter was considered improbable when a Courtauld model of i showed that if the methoxyindole moiety and its attached carbonyl



i

group are coplanar, the remainder of the molecule must stand in an essentially right angle relationship to the plane. A compound of structure i should therefore have an absorption maximum located at a wave length similar to that of 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole (XIII, λ_{max}^{EtOH} 306 mμ). Instead, 6-methoxyrhetsinine actually displays an ultraviolet maximum at 318 mμ, which is almost identical in location to that of the 2-benzoyl derivative of XIII[2] (λ_{max}^{EtOH} 319 mμ), a model for structure III.

The data presented in the present paper lead us to reject structure i on chemical grounds.

(4) A. Chatterjee, S. Bose and C. Ghosh, *Tetrahedron*, **7**, 257 (1959).

(5) I. J. Pachter and G. Suld, *J. Org. Chem.*, **25**, 1680 (1960).

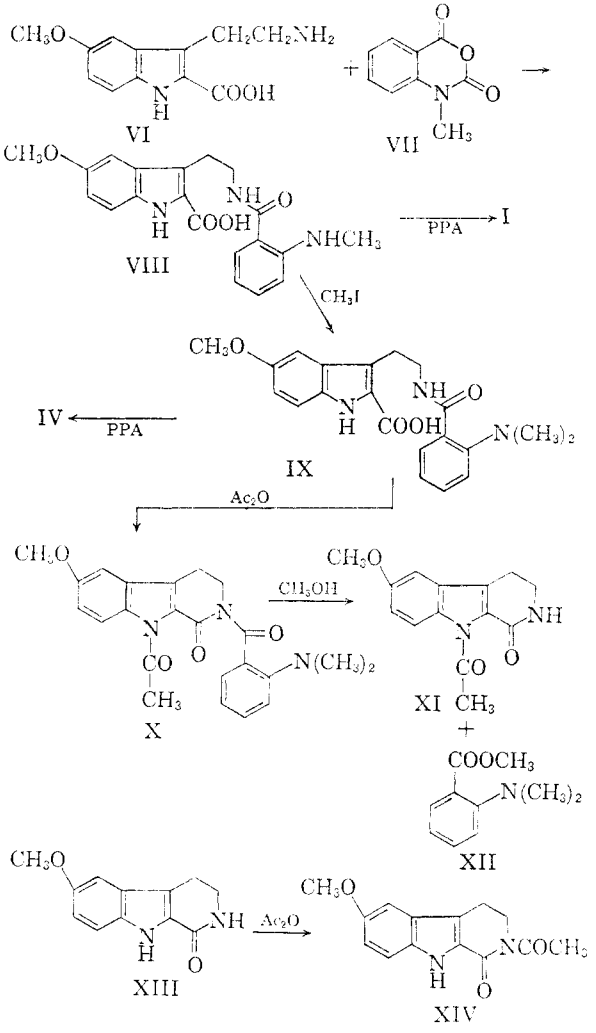
(6) K. W. Gopinath, T. R. Govindachari and U. R. Rao, *Tetrahedron*, **8**, 293 (1960).

(7) Prof. T. Ohta of the Tokyo College of Pharmacy, Tokyo, Japan, kindly called our attention to the results of the studies of Dr. Nakazato and co-workers of the Kobe Women's College of Pharmacy which were presented at the 13th General Meeting of the Pharmaceutical Society of Japan, Tokyo, Japan, April, 1960.

(8) R. A. Abramovitch and D. Shapiro, *J. Chem. Soc.*, 4589 (1956).

(9) A reaction similar to this was previously described by Y. Asahina and T. Ohta, *J. Pharm. Soc. Japan*, **49**, 1025 (1929); *C. A.*, **24**, 1386 (1930).

dimethylaminobenzoyl compound IX which, upon treatment with polyphosphoric acid, cyclizes to IV.



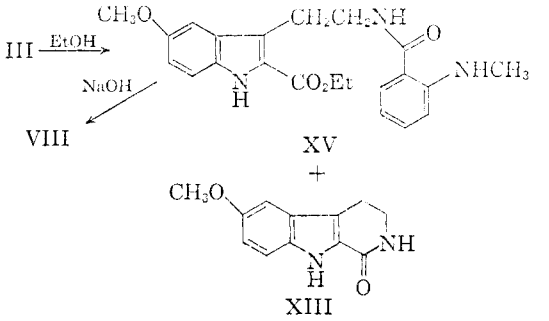
An attempt to prepare IV more directly through the action of *o*-dimethylaminobenzoyl chloride on 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid-[3,4b] indole[10] (XIII) was not successful.

When the intermediate VIII is treated with polyphosphoric acid, hortiamine (I) phosphate forms in quantitative yield, thus providing an alternate synthesis for the alkaloid and related substances.

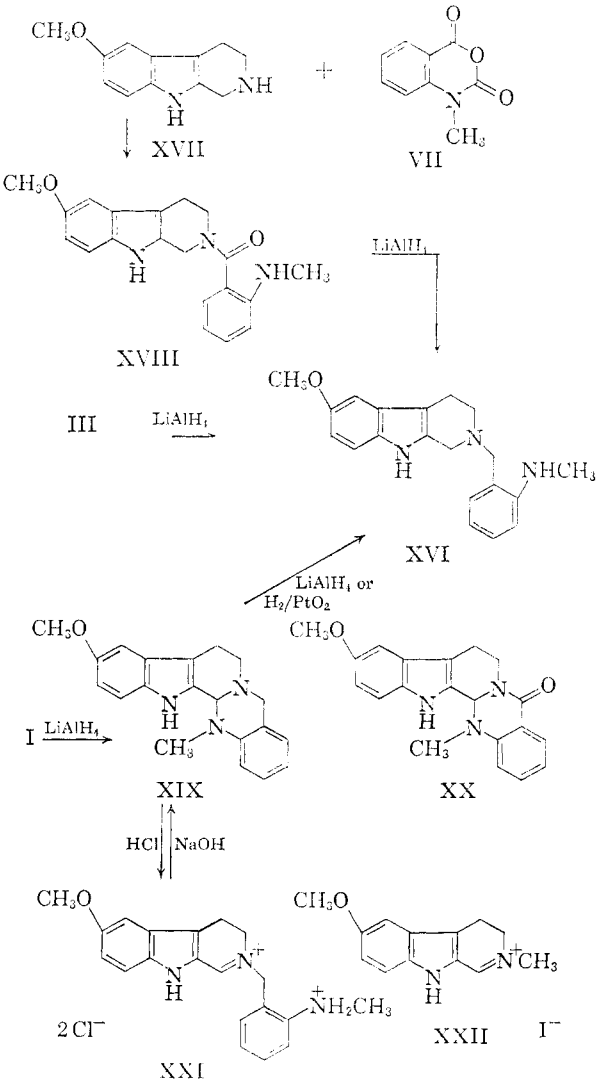
If acetic anhydride rather than polyphosphoric acid is used to cyclize compound IX, the yellow acetyl derivative X is produced. Compound X reacts readily with hydroxylic media. Hot methanol cleaves the imide grouping to form 9-acetyl-6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (XI) and methyl N,N-dimethylanthranilate (XII). 6-Methoxy-1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole (XIII) reacts with refluxing acetic anhydride to give only an isomeric acetyl derivative, which must therefore be 2-acetyl-6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (XIV).

(10) The heterocyclic nomenclature used in this paper follows that which we employed previously[3] and differs somewhat from the new recommendations of the second edition of "The Ring Index" by A. M. Patterson, L. T. Capell and D. F. Walker, American Chemical Society, Washington, D. C., 1960.

6-Methoxyrhetsinine (III) also undergoes alcoholysis, but at a much slower rate than does X. When heated with ethanol in the presence of potassium acetate, the imide opens in two directions and, in addition to XIII, the ester XV is produced. The nature of the ester is apparent from its hydrolysis by sodium hydroxide to the corresponding acid VIII.



Lithium aluminum hydride reduces 6-methoxyrhetsinine (III) to the corresponding desoxo compound XVI. The same product results when 6-methoxy-2-(*o*-methylaminobenzoyl)-1,2,3,4-tetra-

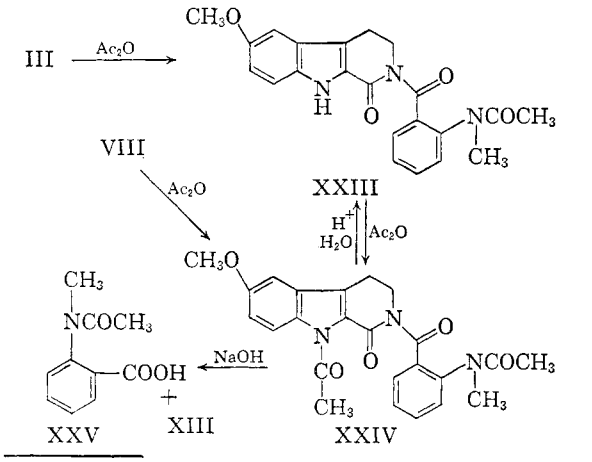


hydropyrid[3,4-b] indole (XVIII), prepared from 6-methoxy-1,2,3,4-tetrahydropyrid[3,4-b]indole[9] (XVII) and N-methylisatoic anhydride (VII), is reduced with lithium aluminum hydride.

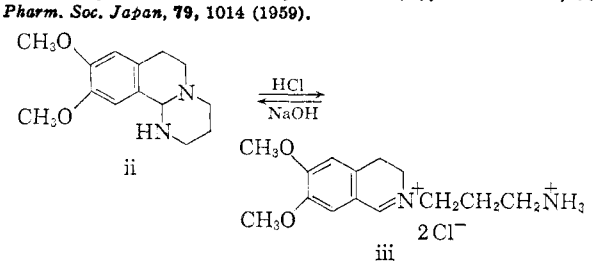
When hortiamine (I) is similarly reduced, the pentacyclic base dihydrodesoxohortiamine (XIX) rapidly forms. The base is colorless and its ultraviolet spectrum (Fig. 1) shows it to be related to dihydrohortiamine[2] (*dl*-10-methoxy-evodiamine, XX). Unlike the neutral compound XX, however, it dissolves in dilute hydrochloric acid to give rise to a yellow-colored solution from which the original colorless base XIX is recovered upon treatment with alkali. As demonstrated in Fig. 1, the yellow color can be attributed to the formation of the salt XXI, for the ultraviolet spectrum of an acid solution of XIX is virtually identical with the spectrum of 3,4-dihydro-6-methoxypyrid[3,4-b]indole methiodide (XXII), synthesized from 5-methoxytryptamine[8] through formylation, cyclization and methylation.[11]

Dihydrodesoxohortiamine (XIX) undergoes further reduction to XVI when subjected to the prolonged action of lithium aluminum hydride. Hydrogenation of XIX in the presence of Adams catalyst results in the uptake of one mole of hydrogen and also produces XVI.

Brief heating with acetic anhydride converts 6-methoxyrhetsinine (III) into two colorless neutral compounds and a pale yellow base. The major product, the colorless diacetyl compound XXIV, also results when the acid VIII is heated with acetic anhydride. Its structure was established by brief alkaline hydrolysis to N-acetyl-N-methylanthranilic acid (XXV) and 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (XIII).



(11) The conversion of XIX to XXI with acid and the reconversion of XXI to XIX with alkali is closely paralleled by the recently reported interconversion of 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-pyrimido[2,1-a]isoquinoline (ii) and 2-(3-aminopropyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium chloride hydrochloride (iii); T. Yamazaki, *J. Pharm. Soc. Japan*, **79**, 1014 (1959).



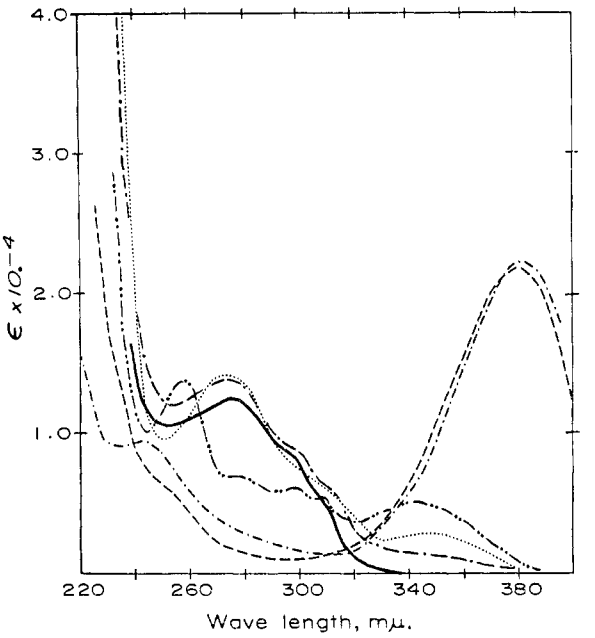


Fig. 1.—Spectra of: dihydrodesoxohortiamine (XIX), —; dihydrodesoxohortiamine + 1% hydrochloric acid (XXI), —·—·; dihydrohortiamine (*dl*-10-methoxyevodiamine, XX), ·— —·; 3,4-dihydro-6-methoxypyrid[3,4-b]indole methiodide (XXII), — — —; tetrahydroisohortiamine (XXX), ...; 5-methoxy-3-[β-(*o*-methylaminobenzoyl)-ethyl]-indole (XXXIII), —··—; materials dissolved in 95% ethanol.

Unlike the related compound X, XXIV shows little tendency to react at the imide grouping when boiled with alcohol. The more reactive position in XXIV appears to be the 9-amide group, for brief acid hydrolysis converts XXIV into the second neutral compound obtained in the acetylation reaction. It is the monoacetyl derivative XXIII. Acetic anhydride reconverts XXIII into XXIV.

The positions of λ_{max} in the ultraviolet spectra of acyl derivatives of XIII may be used to determine whether the compounds are 2-acylated or 9-acylated derivatives. As shown in Table I, an acyl group at the 2-position results in a bathochromic shift with respect to XIII, while a corresponding group at the 9-position has a hypsochromic effect.

The third product of the acetylation of 6-methoxyrhetsinine (III) proved to be a more remarkable product. By analysis it is an isomer of hortiamine (I) and still possesses a methoxyl group. Its infrared spectrum displays an NH band (3.13 μ) and an amide carbonyl band (6.15 μ). These bands are at virtually the same wave lengths (3.13 and 6.12 μ) as are the corresponding bands of dihydrohortiamine (XX). Its ultraviolet spectrum (Fig. 2) indicates the presence of a conjugated system more extensive than methoxyindole. In either acid or alkali the spectrum shows increased absorption at higher wave lengths. Upon alkaline hydrolysis, extensive decomposition occurs; N-methylanthranilic acid was isolated from the hydrolysate. The hortiamine isomer is called isohortiamine and is assigned structure XXVI.[12]

(12) A reaction which appears related to the formation of isohortiamine is the conversion of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole

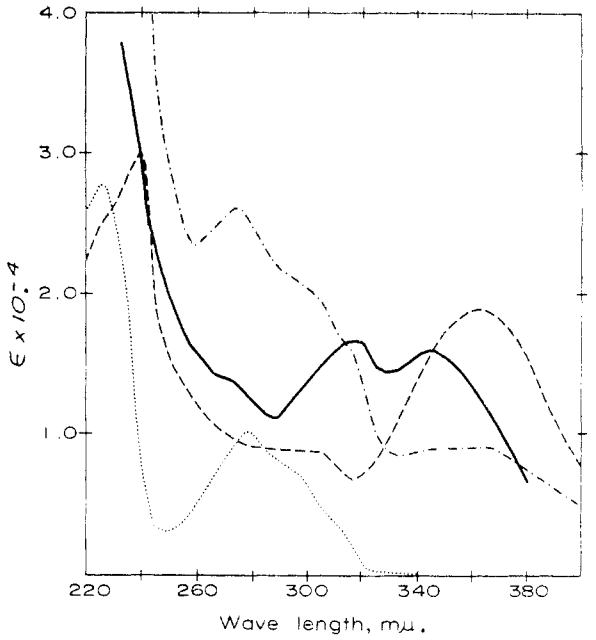
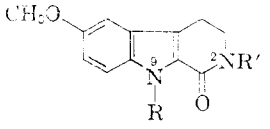


Fig. 2.—Spectra of: isohortiamine (XXVI), —; isohortiamine + 1% hydrochloric acid (XXVIII), — — —; isohortiamine + 25% 12 *N* sodium hydroxide (XXIX); —·—·—; dodecahydroisohortiamine (XXXII), ...; materials dissolved in 95% ethanol.

Isohortiamine is not soluble in dilute acetic acid, but dissolves readily in dilute hydrochloric acid with the formation of an intense yellow color. The color is attributed to the formation of resonance-stabilized ions to which structure XXVIII makes an important contribution. The original pale yellow base is regenerated upon treatment with aqueous ammonia.

TABLE I

WAVE LENGTHS OF ULTRAVIOLET ABSORPTION MAXIMA OF ACYLATED DERIVATIVES OF 6-METHOXY-1-OXO-1,2,3,4-TETRAHYDROPYRID[3,4-b]INDOLE

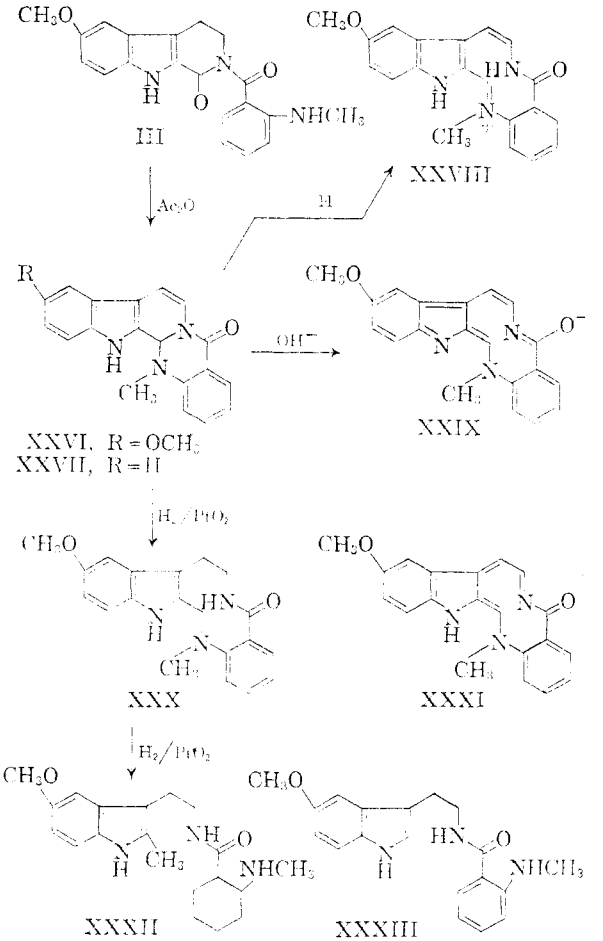


R	R′	λ_{max}, mμ[a]	λ_{max}, mμ[b]
H	H (XIII)	306	..
Acetyl	H (XI)	304	..
H	Acetyl (XIV)	319	..
H	*o*-Dimethylaminobenzoyl (IV)	323	318
Acetyl	*o*-Dimethylaminobenzoyl (X)	..[c]	312
H	*o*-Acetylmethylaminobenzoyl (XXIII)	325	320
Acetyl	*o*-Acetylmethylaminobenzoyl (XXIV)	315	..

[a] Spectra were taken in 95% ethanol. [b] Spectra were taken in acetonitrile. [c] Reacts with hydroxylic solvents.

(iv) into pyrid[3,4-b]indole (v) by phosphorus oxychloride in refluxing xylene (I. J. Pachter, unpublished data).

iv v



Although isohortiamine is insoluble in 1:1 aqueous ethanol, it dissolves in 1:1 ethanolic aqueous 5% sodium hydroxide with the formation of a deep yellow color. The color is attributed to the formation of resonance-stabilized ions for which one contributing structure is XXIX. The original base is regenerated upon treatment with acetic acid.

When subjected to the action of hydrogen in the presence of Adams catalyst, isohortiamine is converted into a colorless *neutral* compound XXX containing four additional hydrogen atoms. Dihydrohortiamine (XX) is not affected by these reagents. It is possible that reduction proceeds *via* the ten-membered ring structure XXXI, which is nearly equivalent to XXVI.

The ultraviolet spectrum of tetrahydroisohortiamine (XXX, Fig. 1) is very similar to that of dihydrohortiamine (XX), showing that reduction has resulted in the saturation of a double bond in conjugation with a methoxyindole nucleus. One significant difference between the spectra of XXX and XX occurs in the 340–345 mμ region. Absorption in this region is a measure of the interaction of the amino and carbonyl moieties of the anthranoyl portion of the molecule. Tetrahydroisohortiamine displays ε 3800 and dihydrohortiamine displays ε 1300. A model compound XXXIII, in which full interaction is possible, shows ε 5200. The dialkylamino and carbonyl groups thus appear to be considerably closer to coplanarity in tetrahydroisohortiamine than they are in dihydrohortiamine.

The infrared spectrum of tetrahydroisohortiamine XXX displays two NH bands (3.06 and 3.16 μ) and an amide carbonyl band (6.02 μ). The carbonyl band occurs at a considerably lower wave length than do the corresponding bands of compounds XV, XVIII, XX and XXXIII, each of which absorbs between 6.12 and 6.14 μ. The structural requirements of the ten-membered ring, which give rise to increased interaction in the anthranoyl portion of the molecule, at the same time appear to result in some twisting at the amide linkage and a decrease in amide character of the carbonyl.

Tetrahydroisohortiamine is a neutral molecule. This is not surprising, however, to one familiar with the neutral character of dihydrohortiamine (XX) and the alkaloid evodiamine, the structures of which are known beyond reasonable doubt.[2,13,14] Each of these compounds is soluble in concentrated hydrochloric acid, but precipitates from solution upon addition of water.

Tetrahydroisohortiamine undergoes hydrogenolysis upon prolonged hydrogenation. The colorless basic product isolated, however, is the dodecahydro derivative XXXII rather than the hexahydro compound. The ultraviolet spectrum of compound XXXII (Fig. 2) is that of a typical 2,3-disubstituted methoxyindole. Dodecahydroisohortiamine contains an amide carbonyl (band at 6.08 μ). It forms a benzenesulfonyl derivative under Hinsberg conditions.

Subsequent to the work described in this paper, a study of the alkaloids of *Hortia braziliana* Vel. was undertaken.[15] Eleven alkaloids were isolated among which are three containing three nitrogen atoms. One of the alkaloids is hortiamine (I). A second alkaloid, m.p. 268–269°, which is the major alkaloid of the plant, is isomeric with hortiamine. It is colorless, but dissolves in both dilute acid and alcoholic alkali to produce yellow-colored solutions. Upon catalytic hydrogenation it is converted into a colorless neutral tetrahydro derivative, m.p. 213–214°. Its ultraviolet spectra (Fig. 3) in neutral and acidic alcohol are related to those of isohortiamine, but the colorless nature of the substance indicates that it contains a less extensive chromophore than does pale yellow isohortiamine. Accordingly, the alkaloid rhetsinine[5] was subjected to the action of acetic anhydride; a base (XXVII) arose which is colorless, but otherwise displays the characteristic properties of isohortiamine. As shown in Fig. 3, desmethoxyisohortiamine (XXVII) in neutral solution possesses an ultraviolet spectrum virtually the same as the spectrum of the major alkaloid of *Hortia braziliana* Vel. In acid solution, the latter absorbs at somewhat longer wave lengths, perhaps as a result of a methoxyl in ring E. *The isohortiamine system is therefore of natural occurrence.* The third three-nitrogen base from *Hortia braziliana* Vel., a new orange alkaloid, remains to be characterized.

(13) Y. Asahina, *Acta Phytochim. (Japan)*, **1**, 67 (1923).

(14) Y. Asahina, *J. Pharm. Soc. Japan*, **503**, 1 (1924); *C.A.*, **18**, 1667 (1924).

(15) I. J. Pachter and A. F. Hopkinson, unpublished studies.

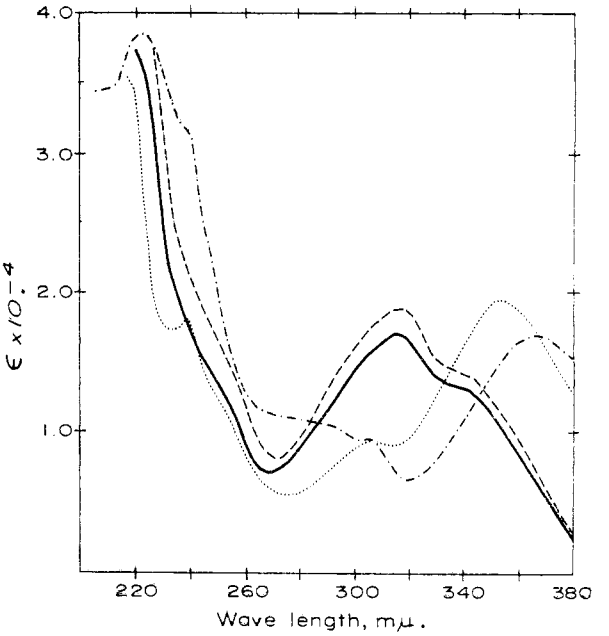


Fig. 3.—Spectra of: desmethoxyisohortiamine (XXVII), ——; desmethoxyisohortiamine + 1% hydrochloric acid, ...; *Hortia braziliana* Vel. alkaloid, — — —; *Hortia braziliana* Vel. alkaloid + 1% hydrochloric acid, —·—; materials dissolved in 95% ethanol.

Experimental[16]

Methylation of 6-Methoxyrhetsinine. 2-(*o*-Dimethylaminobnzoyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydroprid[3,-4-b]indole (IV).—A mixture of 0.50 g. of 6-methoxyrhetsinine and 10 ml. of dimethylformamide was warmed gently until the alkaloid dissolved. The pale orange solution was cooled, diluted with 5 ml. of methyl iodide and heated in a sealed bottle on a steam-bath for 90 minutes. It was then evaporated to dryness *in vacuo*. The residue was partitioned between 10% aqueous ammonia and chloroform. The red-colored chloroform solution (30 ml.) was extracted 3 times with 25 ml. of 10% acetic acid and 3 times with 15 ml. of water in order to remove unmethylated material. The chloroform was removed and the residue was further purified by dissolving as much as possible in a mixture of 15 ml. of 5% hydrochloric acid and 3 ml. of acetic acid, filtering, and basifying the filtrate with ammonia. The product thus obtained weighed 0.20 g. Recrystallization from ethyl acetate yielded 0.13 of yellow prisms, m.p. 240–241°; ultraviolet spectrum: λ_{max}^{EtOH} 318 (29200).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.02; H, 5.67; N, 11.74.

3-[β-(*o*-Methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic Acid (VIII).—A mixture of 12 g. of 5-methoxytryptamine-2-carboxylic acid[8] and 12 g. of N-methylisatoic anhydride was intimately mixed and finely powdered. It was thinly spread on the bottom of a 1-l. erlenmeyer flask which was immersed in an oil-bath heated to 190°. In 20 minutes, when the mixture had fused and evolution of carbon dioxide had ceased, the flask was cooled and the product was dissolved in a solution of 8.5 g. of potassium hydroxide in 125 ml. of water. The aqueous solution was filtered and acidified with acetic acid. The precipitated product was collected and recrystallized from ethanol with the aid of charcoal to yield 13.1 g. of VIII, m.p. 229–230° dec.

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.15; H, 5.66; N, 11.35.

3-[β-(*o*-Dimethylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic Acid (IX).—A mixture of 7.35 g. of 3-[β-(*o*-methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-

(16) We are grateful to Dr. Walter E. Thompson of these laboratories for spectral data and to Mrs. Doris Ralston for analytical data.

carboxylic acid (VIII), 50 ml. of methyl iodide and 25 ml. of methanol was heated on a steam-bath in a pressure bottle for 4 hours. The solvent was removed and the residue acidified with dilute hydrochloric acid and filtered. The filtrate was made basic with ammonia and the product precipitated and redissolved. It was reprecipitated with acetic acid, dried and recrystallized from methanol to give 6.3 g. of IX, m.p. 216–217° dec.

Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.12; H, 6.08; N, 11.02. Found: C, 66.12; H, 6.22; N, 10.99.

2-(*o*-Dimethylaminobenzoyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (IV).—An intimate mixture of 5.0 of finely powdered 3-[β-(*o*-dimethylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic acid (IX) and 100 g. of polyphosphoric acid was heated at 55° with occasional stirring for 40 minutes. The resulting orange paste was cooled, diluted with 700 ml. of water, cooled in ice and basified with aqueous ammonia. The precipitated product was filtered, dried and recrystallized from ethyl acetate to yield 3.2 g. of yellow prisms, m.p. 239–240°. The product did not depress the melting point of the compound obtained upon methylation of 6-methoxyrhetsinine and its infrared spectrum was identical with that of the latter.

The aqueous ammoniacal mother liquors, upon acidification with acetic acid, yielded 0.87 g. of recovered IX.

Hortiamine (I).—An intimate mixture of 1 g. of powdered 3-[β-(*o*-methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic acid (VIII) and 25 g. of polyphosphoric acid was heated at 60° for 2.5 hours with frequent stirring. The resulting brown-orange sirup was cooled to room temperature and diluted with 125 ml. of water. A bright yellow precipitate formed. It was collected and shaken with chloroform and aqueous ammonia until it dissolved. The red chloroform solution was dried over anhydrous potassium carbonate for 5 minutes and was then concentrated, diluted with benzene and reconcentrated almost to dryness. There was obtained 0.9 g. of red needles, m.p. 205–208° dec., identical with natural hortiamine.

9-Acetyl-2-(*o*-dimethylaminobenzoyl)-6-methoxy-1-oxo-1,2,3,4-tetra-hydropyrid[3,4-b]indole (X).—A solution of 2.0 g. of 3-[β-(*o*-dimethylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic acid in 20 ml. of acetic anhydride was heated under reflux for 1 hour during which time the solution turned from colorless to yellow. The solvent was removed *in vacuo* and the residue was recrystallized from ethyl acetate–acetic acid to give 1.53 g. of yellow prisms of X, m.p. 208–209°.

Anal. Calcd. for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.37. Found: C, 68.18; H, 5.87; N, 10.24.

Alcoholysis of 9-Acetyl-2-(*o*-dimethylaminobenzoyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (X). 9-Acetyl-6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole.—A 0.5-g. sample of X was boiled with methanol until it dissolved to give a colorless solution. Concentration and cooling gave colorless needles. The product crystallizes from alcohol as needles and from benzene as prisms, m.p. 183–185°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.04; H, 5.70; N, 11.11.

The methanolysis mother liquor possessed the characteristic odor of anthranilic esters. No attempt was made to isolate the ester.

2-Acetyl-6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]-indole (XIV).—A mixture of 2 g. of 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole and 20 ml. of acetic anhydride was heated under reflux for 1 hour. The acetic anhydride was removed *in vacuo* and the product crystallized. It was recrystallized twice from methanol containing a little chloroform to give 2.2 g. of colorless needles, m.p. 225–226°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.87; H, 5.42; N, 11.00.

Ethanolysis of 6-Methoxyrhetsinine. Ethyl 3-[β-*o*-Methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylate (XV).—To 10.5 g. of 6-methoxyrhetsinine was added 5 g. of potassium acetate and 1 l. of 99% ethanol. The mixture was heated under reflux for 48 hours and evaporated to a small volume, filtered, and the remaining alcohol removed. The residue which possessed the characteristic odor of anthranilic esters was dissolved in acetic acid. The solution was diluted with water and, after standing for 30 minutes, was filtered. This process removed most of the unchanged starting material. The crude filtered product was dissolved in acetic acid and the solution was diluted with 3 *N* hydrochloric acid and then with water. A neutral fraction separated and yielded 6-methoxy-1-oxo-1,2,3,4-tetradropyrid[3,4-b]indole (XIII). The dilute acetic–hydrochloric acid solution was made basic with ammonia and the precipitated bases were collected and recrystallized twice from ethanol to give 0.5 g. of colorless needles of XV, m.p. 162–163°. The compound is soluble in dilute hydrochloric acid, but insoluble in dilute acetic acid; ultraviolet spectrum: λ_{max}^{EtOH} 303(22000).

Anal. Calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.45; H, 6.39; N, 10.80.

Almost 8 g. of 6-methoxyrhetsinine was recovered from the acetic acid solution.

Hydrolysis of Ethyl 3-[β-(*o*-Methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylate.—A 50-mg. sample of the ester XV was heated with 2 ml. of 5% sodium hydroxide containing a few drops of ethanol until most of the material had gone into solution. The solution was filtered, acidified with glacial acetic acid and cooled. The resulting precipitate was collected and recrystallized from ethanol to give needles of 3-[β-(*o*-methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic acid (VIII), m.p. 227–229°. Admixture with an authentic sample of the acid gave no depression of melting point. The infrared spectra of both samples of acid were identical.

Lithium Aluminum Hydride Reduction of 6-Methoxyrhetsinine (III).—To a well stirred slurry of 0.65 g. (0.017 mole) of lithium aluminum hydride in absolute ether was added 2 g. (0.0057 mole) of 6-methoxyrhetsinine and 20 ml. of ether. A vigorous reaction with gas evolution ensued. The mixture was stirred at reflux for 2.5 hours, cooled, and decomposed by addition of 5 ml. of ethyl acetate followed by 4.2 ml. of water. The ethereal filtrate was washed once with water and then twice with saturated sodium chloride solution. After drying over sodium sulfate, the solution was evaporated to dryness to give 0.7 g. of solid, m.p. 145–155°. One recrystallization from absolute ethanol–hexane solution gave colorless needles, m.p. 160–161°. Further recrystallization of this material gave colorless needles, m.p. 164–166°, which on admixture with 6-methoxy-2-(*o*-methylaminobenzyl)-1,2,3,4-tetrahydropyrid[3,4-b]indole (XVI) showed no depression of melting point.

6-Methoxy-1,2,3,4-tetrahydropyrid[3,4-b]indole (XVII).[8]—A 60-g. sample of 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole was suspended in 2 l. of boiling dry butanol. The vigorously stirred suspension was treated with 150 g. of small pieces of sodium at such a rate as to maintain reflux. External heating was removed when the reaction was proceeding smoothly. Total time of addition was 25 minutes. The mixture was stirred at reflux for 30 minutes, cooled, and diluted successively with 1500 ml. of 95% ethanol and 200 ml. of water. A tan crystalline material separated and was collected by filtration and dried to give 22.6 g. of XVII, m.p. 220–223°. The alcoholic filtrate was steam distilled until alcohol no longer came over. A brown solid residue was collected, dissolved in warm 6 *N* hydrochloric acid, treated with charcoal and cooled to give 9.6 g. of the hydrochloride of XVII, m.p. 260–264°. Recrystallization from aqueous ethanol gave needles, m.p. 270–273°.

Anal. Calcd. for $C_{12}H_{15}ClN_2O$: C, 60.37; H, 6.33; N, 11.74. Found: C, 60.38; H, 6.22; N, 11.61.

The hydrochloride yielded an additional quantity of XVII upon basification. The total yield was 54.7%.

6-Methoxy-2-(*o*-methylaminobenzoyl)-1,2,3,4-tetrahydropyrid[3,4-b]indole (XVIII).—A pulverized mixture of 10 g. (0.043 mole) of 6-methoxy-1,2,3,4-tetrahydropyrid-[3,4-b]indole and 7.4 g. (0.046 mole) of N-methylisatoic anhydride in a round-bottomed flask was placed in an oil-bath at 60°. The temperature of the bath was slowly raised to 165°. At 105° the melt, which was stirred frequently with a thermometer, evolved carbon dioxide. When the rate of gas evolution diminished, the temperature was raised to 125° and then to 165°. The total time during which gas was evolved was 70 minutes. The melt was cooled, dissolved in benzene–hexane, and treated with charcoal. Upon cooling and filtration, 12.91 g. of crystalline material was collected, m.p. 159–164°. Evaporation of the filtrate yielded 1.43 g. of material, m.p. 154–160°. The combined solids were recrystallized once from benzene–hexane and twice from absolute ethanol to give hard, slightly yellow needles of 6-

methoxy - 2 - (*o* - methylaminobenzoyl) - 1,2,3,4 - tetrahydropyrid[3,4-b]indole (XVIII), m.p. 165–167°.

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.74, 71.86; H, 6.46, 6.21; N, 12.64, 12.67.

Reduction of XVIII to XVI.—To a suspension of 0.15 g. (0.0043 mole) of lithium aluminum hydride in 40 ml. of absolute ether was added 0.55 g. (0.0014 mole) of pulverized 6-methoxy-2-(*o*-methylaminobenzoyl)-1,2,3,4-tetrahydropyrid[3,4-b]indole (XVIII). The mixture was stirred at reflux for 3 hours, cooled, and decomposed with ethyl acetate, followed by water. The slurry was filtered and the filtrate washed with water and then with saturated sodium chloride solution. The ethereal solution was dried and evaporated to dryness to give a quantitative yield of solid, m.p. 150–156°. This material was recrystallized from benzene–hexane, then aqueous alcohol, to give colorless needles, m.p. 164–166°. A mixed melting point of this material with pure 6-methoxy-2-(*o*-methylaminobenzyl)-1,2,3,4-tetrahydropyrid[3,4-b]indole (XVI) showed no depression. The infrared spectra of the two compounds were identical.

Lithium Aluminum Hydride Reduction of Hortiamine.—A 30-g. sample of powdered hortiamine was added to a suspension of 10.4 g. of lithium aluminum hydride in 2.2 l. of ether. After stirring for 20 minutes, most of the red base had reacted and a white flocculent solid had formed. The mixture was stirred under reflux for 2 hours and an additional 1.7 g. of lithium aluminum hydride was added to remove the last traces of red base. After an additional hour, 12 ml. of ethyl acetate was cautiously added to the stirred mixture. Lithium salts were then decomposed by addition of wet ether followed by 45 ml. of water.

The solids were filtered, washed well with ether, dried and extracted twice with 500-ml. portions of boiling chloroform. Concentration and cooling of the chloroform extracts yielded 8.3 g. of colorless solid, m.p. 202–208°. Two recrystallizations from aqueous ethanol yielded colorless plates of 5,7,8,13,13b,14-hexahydro-10-methoxy-14-methylindolo[2,3-c]quinazo[3,2-a]pyridine (XIX), m.p. 206–208°; ultraviolet spectrum: λ_{max}^{EtOH} 277 (12500). The compound dissolves in dilute mineral acids to give deep yellow solutions from which the colorless base is precipitated unchanged by addition of aqueous ammonia.

Anal. Calcd. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.02, 75.28; H, 6.55, 6.80; N, 13.16, 13.35.

The ethereal filtrate and washings were dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue of yellow solid was boiled with 750 ml. of ether. A 0.9-g. quantity of insoluble material, m.p. 202–206°, proved to be additional XIX. The ethereal solution was concentrated to 200 ml. and, on standing, 7.2 g. of crystals, m.p. 164–166°, separated. Further recrystallization from benzene–hexane and then from aqueous ethanol gave colorless needles of 6-methoxy-2-(*o*-methylaminobenzyl)-1,2,3,4-tetrahydropyrid-[3,4-b]indole (XVI), m.p. 164–166°. The compound forms colorless solutions in dilute mineral acids.

Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.71, 74.84; H, 7.26, 7.22; N, 13.24, 13.12.

In one reduction experiment in which the reaction was quenched after 20 minutes, only XIX was isolated.

3-(β-Formylaminoethyl)-5-methoxyindole.—One gram of 5-methoxytryptamine and 10 ml. of ethyl formate were heated on a steam-bath in a pressure bottle for 2 hours. The excess ethyl formate was removed and the product was crystallized first from benzene containing a little methanol and then from ethyl acetate to give 0.7 g. of the formamide, m.p. 95–96°.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47. Found: C, 66.13; H, 6.66.

3,4-Dihydro-6-methoxypyrid[3,4-b]indole Methiodide (XXII).—A solution of 0.5 g. of 3-(β-formylaminoethyl)-5-methoxyindole in 20 ml. of alcohol-free chloroform was cooled in ice-water. A solution of 0.5 g. of phosphorus pentachloride in 20 ml. of dried chloroform was cooled and added slowly. A yellow oil separated from solution during the addition. It solidified on scratching. The chloroform was removed *in vacuo* and the total residue was treated with ice-water and then warmed to dissolve as much of the product as possible. A portion of oily material remained insoluble. The aqueous solution was made basic with ammonia and extracted with several portions of ethyl acetate. The combined ethyl acetate solutions were dried over magnesium sulfate, concentrated and warmed with 3 ml. of methyl iodide. A yellow methiodide oiled out of solution and solidified. It was collected and recrystallized from methanol to give orange yellow prisms, m.p. 230–232°; ultraviolet spectrum: λ_{max}^{EtOH} 380 (21800).

Anal. Calcd. for $C_{13}H_{15}N_2OI$: N, 8.19. Found: N, 7.97.

Lithium Aluminum Hydride Reduction of 5,7,8,13,13b,14-Hexahydro-10-methoxy-14-methylindolo [2,3-c]quinazo[3,-2-a] pyridine (XIX).—A 2.0-g. (0.0063 mole) sample of 5,7,8,13,13b,14-hexahydro-10-methoxy-14-methylindolo[2,3-c]-quinazo[3,2-a]pyridine (m.p. 206–208°) was added to a slurry of 0.71 g. (0.091 mole) of lithium aluminum hydride in 125 ml. of absolute ether. The mixture was stirred at reflux for 3 hours, cooled and decomposed by addition of 3.5 ml. of ethyl acetate followed by 3 ml. of water. The insoluble material was collected, dried and extracted with chloroform. Evaporation of the chloroform extracts gave 0.38 g. of material which after one recrystallization from aqueous alcohol melted at 205–208° (starting material). The ethereal filtrate of the original reaction mixture was washed successively with water and saturated sodium chloride solution and then cooled to give 1.09 g. of solid, m.p. 161–164°. A mixed melting point with 6-methoxy-2-(*o*-methylaminobenzyl)-1,2,3,4-tetrahydropyrid [3,4-b] indole (XVI) showed no depression. An additional 0.25 g. of solid (m.p. 155–164°) was isolated from the ethereal filtrate. The yield of reduced product was 80.2% of theory.

Catalytic Reduction of 5,7,8,13,13b,14-Hexahydro-10-methoxy - 14 - methylindolo[2,3 - c]quinazo[3,2 - a]pyridine (XIX).—A mixture of 0.5 g. of XIX and 15 mg. of platinum oxide in 20 ml. of acetic acid was hydrogenated at 60 p.s.i. for 3 hours. The catalyst was removed and the solution was evaporated, diluted with aqueous ammonia and filtered to give 0.48 g. of product which, upon recrystallization from aqueous ethanol, melted at 163–165° and did not depress the melting point of 6-methoxy-2-(*o*-methylaminobenzyl)-1,2,3,4-tetrahydropyrid[3,4-b]indole (XVI).

Acetylation of 6-Methoxyrhetsinine.—To 14 g. of powdered 6-methoxyrhetsinine was added 200 ml. of acetic anhydride. The mixture was heated. The base dissolved rapidly to form a dark brown solution which, after 2 minutes, precipitated a little solid and turned orange in color. All this occurred before the reaction temperature reached 80°. The boiling point was reached in 12 minutes and boiling was continued for an additional 2 minutes after which the solution was cooled to room temperature. Filtration yielded 0.2 g. of an orange precipitate which was not investigated further. The filtrate was concentrated *in vacuo* at 60°. Colorless prisms separated. When a volume of about 50 ml. remained, concentration was discontinued and the concentrate was cooled in ice and filtered. There was obtained 4.5 g. of colorless prisms. The filtrate was concentrated almost to dryness. The residue was diluted with methanol, cooled and filtered to yield an additional 1.1 g. of prisms.

The methanolic solution was made strongly acid with 3 *N* hydrochloric acid and diluted with water. A precipitate separated and was collected. The acid filtrate was saved. The precipitate was redissolved in methanol, treated with 3 *N* hydrochloric acid and again precipitated with water. The process was repeated 3 times and the filtrate was saved each time. Finally, the precipitate was triturated with a little methanol and an additional 0.2 g. of colorless prisms was obtained. The total yield of prisms, m.p. 238–239°, was 5.8 g. By analysis, the compound is diacetyl-6-methoxyrhetsinine (XXIV); ultraviolet spectrum: λ_{max}^{EtOH} 315 (26400).

Anal. Calcd. for $C_{24}H_{23}N_3O_3$: C, 66.50; H, 5.35; N, 9.70. Found: C, 66.49, 66.41; H, 5.35, 5.20; N, 9.66.

After removal of diacetyl-6-methoxyrhetsinine, the methanolic mother liquors deposited 0.7 g. of large pale yellow prisms of a second neutral compound. It melted at 150° with evolution of gas, resolidified and remelted at 246°. It thus appeared to be a methanol solvate. The compound was recrystallized from ethyl acetate and melted at 249°; ultraviolet spectrum: λ_{max}^{EtOH} 325 (30100). It is monoacetyl-6-methoxyrhetsinine (XXIII).

Anal. Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.50; H, 5.41; N, 10.74. Found: C, 67.42; H, 5.42; N, 10.96.

When heated under reflux with acetic anhydride, monoacetyl-6-methoxyrhetsinine was converted into diacetyl-6-methoxyrhetsinine.

The hydrochloric acid filtrates which were accumulated during the isolation of the neutral acetylation products were made basic with ammonia and 5.0 g. of crude bases was collected. After 3 recrystallizations from methanol–chloroform, 3.1 g. of pale yellow needles, which turned brown at 230–232° and melted at 340–343° dec., was obtained. The compound is insoluble in dilute acetic acid. It dissolves in dilute hydrochloric acid to form a deep yellow solution from which the original pale yellow base separates upon treatment with ammonia. The compound also dissolves in aqueous ethanolic sodium hydroxide to form a deep yellow solution from which the original material is obtained on neutralization. The compound is isomeric with hortiamine and is named isohortiamine (XXVI); ultraviolet spectrum: λ_{max}^{EtOH} 227 (42300), 318 (16900), 346 (16000).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 72.49; H, 5.17; N, 12.68; OCH_3, 9.37. Found: C, 72.17; H, 5.21; N, 12.99; OCH_3, 9.60, 9.53.

Alkaline Hydrolysis of Diacetyl-6-methoxyrhetsinine.—To 0.5 g. of diacetyl-6-methoxyrhetsinine (XXIV) was added 40 ml. of ethanol and the mixture was heated under reflux for several minutes. To it was added a hot solution of 1 g. of potassium hydroxide in 15 ml. of ethanol. The mixture was heated under reflux for 1 minute and cooled. The resulting solution was evaporated to dryness *in vacuo* and the residue was diluted with ether and a little water. The ethereal layer was separated, dried and concentrated to yield prisms of 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, m.p. 276°, which gave no depression of m.p. upon admixture with an authentic sample.[8]

The aqueous alkaline solution was cooled in ice and acidified with hydrochloric acid. An oil separated and was extracted with much ether. Removal of the ether left a partly crystalline residue which was extracted with a small volume of hot water. Upon cooling, the aqueous solution deposited needle-shaped prisms which, when recrystallized again from water, yielded plates, m.p. 193–194°. The product did not depress the melting point of N-acetyl-N-methylanthranilic acid prepared from the potassium salt of N-methylanthranilic acid and acetic anhydride.[17]

Acid Hydrolysis of Diacetyl-6-methoxyrhetsinine.—A 3-g. sample of diacetyl-6-methoxyrhetsinine (XXIV) was heated under reflux with 10 ml. of acetic acid and 5 ml. of 3 *N* hydrochloric acid for 10 minutes. The yellow solution was poured into ice-water and a gum separated and solidified. Repeated recrystallization from methanol yielded 0.4 g. of 6-methoxy-oxo - 1,2,3,4 - tetrahydropyrid[3,4-b]indole, identified through comparison with an authentic sample and 1.2 g. of large prisms of monoacetyl-6-methoxyrhetsinine methanolate, which melted at about 150° with evolution of gas, resolidified and melted at 248–249°. Recrystallization from ethyl acetate yielded a non-solvated product, m.p. 249°, which did not depress the m.p. of the monoacetylated product (XXIII) of the acetylation reaction. The two samples were spectrally identical.

Acetylation of 3-[β-(*o*-Methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic acid. Synthesis of Diacetyl-6-methoxyrhetsinine (XXIV).—A mixture of 0.5 g. of 3-3-[β-(*o*-methylaminobenzoyl)-aminoethyl]-5-methoxyindole-2-carboxylic acid (VIII) and 5 ml. of acetic anhydride was heated under reflux for 20 minutes. The anhydride was removed *in vacuo* and the residue was washed with dilute hydrochloric acid and stirred with ethanol. There was obtained 0.25 g. of prisms which, after recrystallization from ethanol, melted at 239–240°. The product was identical in m.p., m.m.p. and infrared spectrum with diacetyl-6-methoxyrhetsinine (XXIV).

Alkaline Degradation of Isohortiamine.—A solution of 1.0 g. of isohortiamine and 2 g. of potassium hydroxide in 30 ml. of ethanol was heated under reflux for 8 hours. The resulting dark solution was evaporated to dryness and the residue was dissolved in 10 ml. of water. It was made strongly acidic with concentrated hydrochloric acid. A reddish-black gum separated and was discarded. The yellow-orange solution was extracted once with ether and then adjusted to *p*H 6.5 with concentrated aqueous ammonia. The solution became cloudy. It was extracted 3 times with methylene chloride. The extracts were combined, dried over magnesium sulfate and evaporated to dryness. The residue crystallized. It was purified by vacuum sublimation to give 0.12 g. of colorless N-methylanthranilic acid which, upon recrystallization from aqueous ethanol, melted at 179°. It was identified through mixed m.p. and infrared spectral comparison with an authentic specimen.

Tetrahydroisohortiamine (XXX).—To 0.3 g. of isohortiamine was added 10 ml. of glacial acetic acid and 15 mg. of platinum oxide. The mixture was shaken under 40 lb. of hydrogen for 30 minutes. The catalyst was removed by filtration and the solution was diluted with 80 ml. of distilled water. The product separated and was recrystallized from ethanol to yield 0.2 g. of colorless prisms, m.p. 232–236°. The product was dissolved in ethyl acetate and passed rapidly through a short column of alumina in order to remove a persistent impurity. Evaporation of the eluate and recrystallization of the residue from ethanol gave plates, m.p. 239–240°; ultraviolet spectrum: λ_{max}^{EtOH} 227 (58000), 276 (14100), 346 (28000). The m.p. was depressed to 215° upon admixture with dihydrohortiamine.

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.59, 71.30; H, 6.48, 6.46; N, 12.52.

Extended Catalytic Reduction of Isohortiamine. Tetrahydroisohortiamine (XXX) and Dodecahydroisohortiamine (XXXII).—A mixture of 2.0 g. of isohortiamine, 40 ml. of acetic acid and 0.2 g. of platinum oxide was shaken under 50 p.s.i. of hydrogen for 6 hours. The catalyst was removed by filtration and the acid was removed *in vacuo*. The residue was diluted with 1 *N* hydrochloric acid and the aqueous layer was collected by filtration. The residue was taken up in chloroform and the chloroform solution was concentrated. Crystallization occurred and 0.6 g. of tetrahydroisohortiamine was obtained.

The hydrochloric acid solution was made basic with ammonia and the oil which separated was taken up in ether. The ethereal solution was dried over magnesium sulfate and evaporated to dryness. The residue partially crystallized. The crystals were not separated from the basic oil, but the entire residue was redissolved in a little ether and the ethereal solution was diluted with hexane and filtered. Amorphous resinous material was removed. The filtrate was again evaporated to dryness. The residue crystallized and the crystals were recrystallized first from ether and then from methanol to give 0.20 g of dodecahydroisohortiamine, m.p. 140–141°; ultraviolet spectrum: λ_{max}^{EtOH} 206 (26800), 226 (27800), 279 (10200).

Anal. Calcd. for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.24. Found: C, 69.63, 69.44; H, 8.34, 8.41; N, 12.03, 12.07.

A 0.3-g. sample of tetrahydroisohortiamine was similarly reduced and 20 mg. of dodecahydroisohortiamine, m.p. 138–140°, was obtained.

Dodecahydroisohortiamine reacted with benzenesulfonyl chloride and 10% sodium hydroxide to form a benzensulfonyl derivative (strong absorption at 7.5 and 8.6 μ) which crystallized from methanol to melt at 164–165°.

Anal. Calcd. for $C_{26}H_{33}N_3O_4S$: N, 8.69. Found: N, 8.82.

5-Methoxy-3-[β-(*o*-methylaminobenzoyl)-ethyl]-indole (XXXIII).—A pulverized mixture of 1.0 g. of 5-methoxytryptamine and 1.2 g. of N-methylisatoic anhydride was spread thinly on the bottom of a 125-ml. erlenmeyer flask and heated on a steam-bath for 1 hour. The mixture evolved gas and fused. It was taken up in methanol and the solution was concentrated and cooled. Crystallization occurred. The product was recrystallized from methanol to give 1.1 g. of XXXIII, m.p. 120°; ultraviolet spectrum: λ_{max}^{EtOH} 258 (13800), 275 (6940), 298 (6240), 308 (5500), 343 (5200).

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.55; N, 13.00. Found: C, 70.68, 70.47; H, 6.29, 6.72; N, 12.78, 13.07.

Desmethoxyisohortiamine (XXVII).—A 1.0-g. sample of rhetsinine was heated under reflux with 15 ml. of acetic anhydride. The solution was processed as described for the reaction of 6-methoxyrhetsinine. The acetyl derivatives were not isolated. The colorless basic product, desmethoxyisohortiamine, crystallized from methanol and melted at 235–236° with darkening; ultraviolet spectrum: λ_{max}^{EtOH} 315 (18000).

Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.75; H, 5.02; N, 13.95. Found: C, 75.57; H, 5.11; N, 13.99.

(17) J. Houben and T. Arendt, *Ber.*, **43**, 3533 (1910).