the solution refiltered. The clear filtrate was acidified and lyophilized. The residue from lyophilization was shaken with absolute alcohol–ether (3:1) and filtered. The filtrate was evaporated to yield 4.4 g of oil. This oil was chromatographed over 125 g of silica gel using a mixture of solvents for elution made up of benzene–methanol–acetic acid (10:2:1). The fractions thus obtained were checked by thin layer chromatography (same system) using *dl*-propylsuccinic acid[20] as the control. Those fractions showing only material moving with the control were combined (1.83 g) and crystallized from benzene–Skellysolve B several times. The crystalline product, 280 mg, melted at 101.5–103.5° and rotated at +23° (water).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.48; H, 7.67.

cis- and *trans*-**1-Carbobenzoxy-4-*n*-propyl-L-proline (30).** The amine salt (6, 10 g) was shaken with ether and 2% potassium hydroxide. The aqueous layer was separated and acidified. Extraction with methylene chloride led to the isolation of 6 g of oily acid. A mixture of 2 g of this oil and 800 mg of platinum on Dowex-1 catalyst[10] in 50 ml of methanol was shaken under 40 psi hydrogen pressure for 17 hr. The catalyst was removed by filtration and the solvent distilled *in vacuo*, leaving a residue of 2 g of oily **30**. Thin layer chromatography, using a methanol–5% ammonium hydroxide system and permanganate–periodate indicator spray, indicated that the double bond was hydrogenated. Ninhydrin gave a negative test. This product resisted crystallization and was used without purification in the next step.

cis- and *trans*-**Methyl N-(1′-Carbobenzoxy-4′-*n*-propyl-L-prolyl)-thiolincosaminide (31).** To a solution of 7.5 g of **30** and 4.25 ml of triethylamine in 700 ml of distilled acetonitrile cooled to 0° there was added 4.16 ml of isobutyl chloroformate in 5 ml of acetonitrile. The mixture was stirred at 0° (±5°) for 15 min. A solution of 7 g of methyl thiolincosaminide (**2**) in 100 ml of water was added rapidly. The resulting solution was stirred at 0° for 1 hr, the cooling bath removed, and stirring continued for another hour. The acetonitrile was removed by distillation under vacuum leaving a partially crystalline residue. The mixture was cooled to 10° and filtered. After drying at 55° under vacuum the crystalline product weighed 10.5 g and melted at 191–194°. *In vitro* assay *vs. S. lutea* showed <1% the antibacterial activity of lincomycin. This material was recrystallized twice from ethyl acetate containing a few drops of water to afford the analytical sample, mp 197–203°, $[\alpha]D$ +111° (MeOH).

Anal. Calcd for $C_{23}H_{38}N_2O_8S$: C, 57.01; H, 7.27; N, 5.32; S, 6.09. Found: C, 56.93; H, 7.45; N, 5.35; S, 6.03.

cis- and *trans*-**Methyl N-(4-Propyl-L-prolyl)thiolincosaminide Hydrochloride (32·HCl).** A solution of 8.95 g of **31** in 200 ml of methanol was shaken over 2 g of 10% Pd–C under 40 psi hydrogen pressure for 6 hr. The catalyst was removed by filtration and the solution concentrated under vacuum. The residue was dissolved in 75 ml of 0.5 *N* hydrochloric acid and 250 ml of water with warming to about 35°. Dilution with 1500 ml of acetone precipitated **32**·HCl which was collected by filtration. The crystals, dried at 55° under vacuum, weighed 6.0 g (82.3% yield) and melted at 202–205°. The rotation was +151° (H_2O).

Anal. Calcd for $C_{17}H_{32}N_2O_6S \cdot HCl$: C, 47.57; H, 7.75; N, 6.57; S, 7.47. Found (corrected for 3.31% water): C, 47.67; H, 7.72; N, 6.53; S, 7.14.

In one experiment the free base crystallized from acetone. It melted at 178–180°.

Anal. Calcd for $C_{17}H_{32}N_2O_6S$: C, 52.02; H, 8.22; N, 7.14. Found: C, 51.97; H, 8.01; N, 7.00.

Lincomycin Hydrochloride (1) and *cis*-Lincomycin Hydrochloride (33). Two grams of **32**·HCl, 2.4 ml of formalin, and 800 mg of 10% palladium on carbon in 200 ml of methanol was shaken under 40 psi hydrogen pressure for 5 hr. The catalyst was removed by filtration. Triethylamine (1 ml) was added and the solution evaporated. The residue was chromatographed twice over silica gel using for elution a solvent mixture of ethyl acetate–acetone–water (8:5:1). The various fractions were monitored by thin layer chromatography on silica gel using the same solvent system and fractions showing only **1** and **33** combined. The crude **1** (free base) fraction weighed 320 mg. It was dissolved in dilute hydrochloric acid and **1**·HCl precipitated by the addition of acetone. The yield of **1**·HCl was 290 mg. After two recrystallizations from the same solvent it melted at 155–157° dec. This material had identical spectra with lincomycin hydrochloride by infrared and nmr. It possessed full antibacterial activity when compared with lincomycin hydrochloride.

The slower moving fraction, 570 mg, from above was similarly converted to its hydrochloride. After recrystallization from acetone–water it melted at 138–145° dec and was identical in the infrared and nmr with *cis*-lincomycin hydrochloride (**33**) prepared as described above.

(20) P. A. S. Smith and J. P. Horwitz, *J. Am. Chem. Soc.*, 71, 3418 (1949).

The Morphine–Thebaine Group of Alkaloids. IX.[1] The Reaction of Thebaine with Magnesium Iodide

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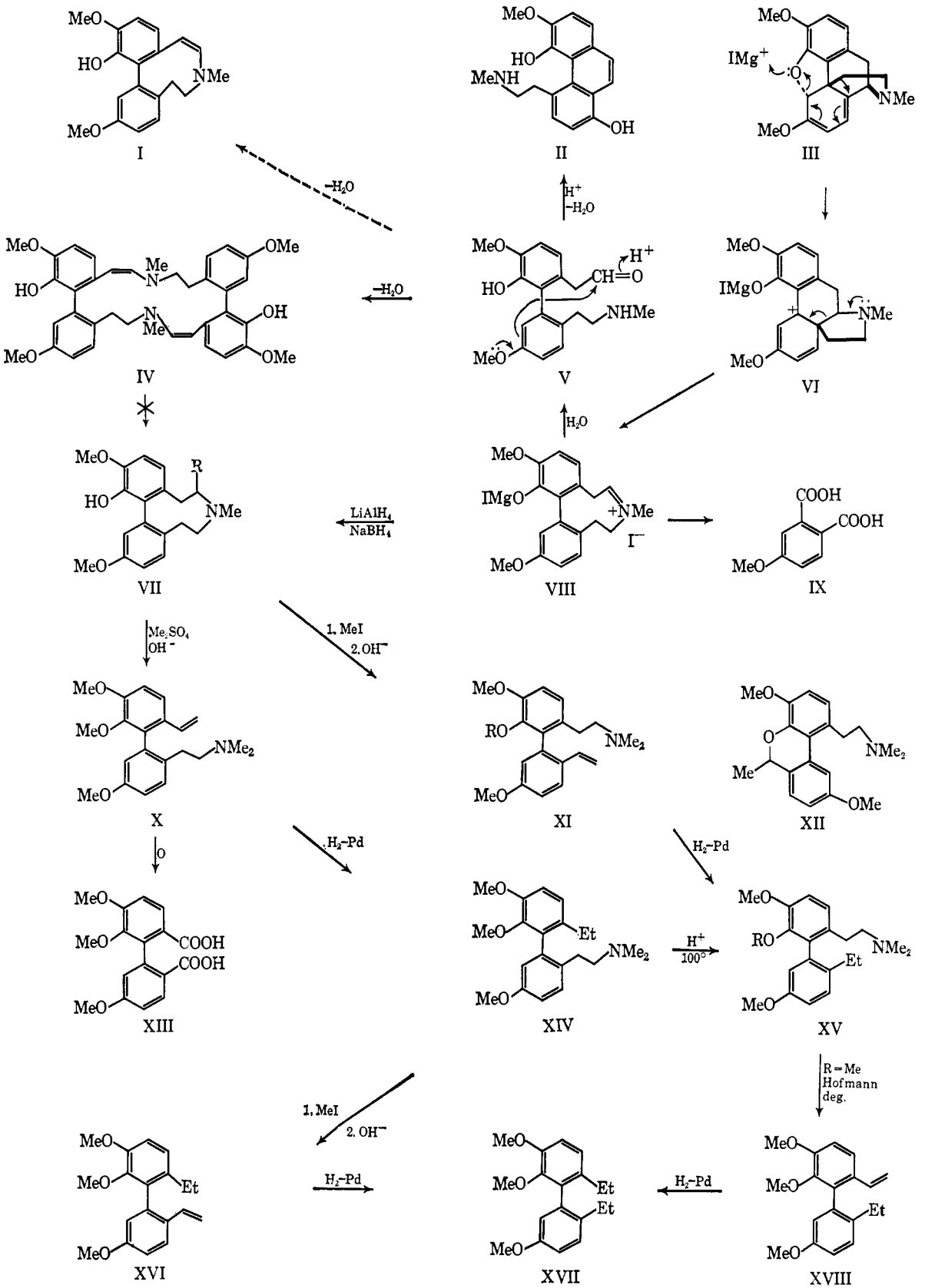
Contribution from The Research Laboratories, Reckett and Sons Ltd., Kingston-upon-Hull, England. *Received September 26, 1966*

Abstract: The reaction of thebaine with anhydrous magnesium iodide has been shown to give the iminium salt VIII, the structure of which has been deduced from its oxidation to 4-methoxyphthalic acid, its hydrolysis and cyclodehydration to thebenine (II), and its reduction to neodihydrothebaine (VII, R = H). The structure of neodihydrothebaine has been confirmed by degradation and spectral studies. Hydrolysis and recyclization of the iminium salt VIII has been found to give an enamine, kryptothebaine, which is clearly not the enamine I and is assigned structure IV.

The reaction of thebaine (III) with anhydrous magnesium iodide in ether and benzene has previously been shown[2] to give a product containing magnesium and iodine, to which the iminium salt structure VIII was assigned on the basis of its conversion into phenyldihydrothebaine (VII, R = Ph) on treatment with phenylmagnesium bromide. This assignment of structure is now supported by the reduction of the salt to neodihydrothebaine (VII, R = H), by its oxidation to 4-

(1) Part VII: K. W. Bentley, J. C. Ball, and J. P. Ringe, *J. Chem. Soc.*, 1963 (1956); the paper by K. W. Bentley and S. F. Dyke, *ibid.*, 2574 (1959), is now regarded as part VIII of this series.

(2) K. W. Bentley and R. Robinson, *ibid.*, 947 (1952).



methoxyphthalic acid (IX),[3] and by its conversion into thebenine (II).

Reduction of the iminium salt VIII with lithium aluminum hydride in ether or with sodium borohydride in ethanol takes place very rapidly and affords a very good yield of (+)-neodihydrothebaine (VII, R = H);[4] the

(3) In an earlier report of this reaction,[2] it was stated that 4-methoxyphthalic acid could not be isolated from the products of the oxidation under the conditions used for the oxidation of phenyldihydrothebaine. This acid has now been isolated after oxidation of the iminium salt with very much larger quantities of permanganate than previously used, and it seems probable that in the earlier work oxidation was incomplete probably not progressing even to the production of a homophthalic acid.

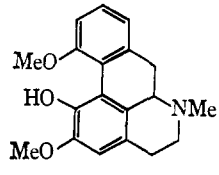
(4) This reaction was previously reported[2] to give a noncrystalline uncharacterizable product. It is now known that the lithium aluminum hydride used in the earlier work was seriously contaminated with aluminum chloride, which is known to affect the course of reductions with

mild conditions involved in the formation and reduction of the salt were insufficient to cause racemization of the diphenyl system, which is generated in one configuration only. The structure assigned to neodihydrothebaine (VII, R = H) has been confirmed by degradation of the base and its methyl ether. Hofmann degradation of neodihydrothebaine methiodide occurs readily in aqueous potassium hydroxide to give the isomethine XI (R = H) only, the structure of the product being demonstrated by its easy cyclization to the nonphenolic base XII on heating with concentrated hydrochloric acid. The phenolic nucleus apparently inhibits Hofmann degradation on one side of the nitrogen since only the isomethine XI (R = H) is produced during this reaction, and the methiodide of the isomethine is resistant to further degradation in refluxing 40% aqueous potassium hydroxide. By contrast, however, the isomethine methyl ether (XI, R = Me) methiodide can be degraded in aqueous solution to a neutral product, which is presumably the olefin XVIII (Et = $CH{=}CH_2$), but which could not be adequately characterized owing to the speed with which it polymerized. Catalytic reduction of the isomethine XI (R = H) proceeded very rapidly and gave the dihydro base XV (R = H). The methiodide of this base, like that of the parent phenol XI (R = H) resists further Hofmann degradation in aqueous solution, though the methiodide of the methyl ether XV (R = Me) can be easily degraded to the olefin XVIII.

Hofmann degradation of neodihydrothebaine methyl ether methiodide, unlike the degradation of the parent phenol, affords a mixture of two products, readily separated as the methiodides. The minor component is identical with the isomethine methyl ether (XI, R = Me) and hence the major product, which is isomeric with this base, may be assigned the structure X of the methine base. Evidently in the absence of the stabilizing effect of the phenolic hydroxyl degradation can occur with ring fission on either side of the nitrogen atom.[5] Oxidation of the mixture of methine and isomethine bases obtained in this way with alkaline potassium permanganate afforded an uncrystallizable yellow acid, which is presumably a mixture of α-keto acids since on further oxidation with alkaline hydrogen peroxide it gave a good yield of 5,6,5′-trimethoxydiphenic acid (XIII), identical with material prepared from phenyldihydrothebaine (VII, R = Ph) and from acetylthebaol. The structure of this acid was further confirmed by its cyclization to 1,5,6-trimethoxyfluorenone-4-carboxylic acid.

this reagent. It may be noted that the characteristics of the reduction product described in the earlier communication bear a striking resemblance to those of the product of reduction of kryptothebaine (IV) reported in this paper.

(5) A similar difference in behavior on Hofmann degradation has been observed between methyldihydrothebaine (VII, R = Me) and its O-acetyl derivative [L. F. Small and E. M. Fry, *J. Org. Chem.*, **3**, 509 (1939)], and between isothebaine (i) methiodide and methyl ether methiodide [V. V. Kiselev and R. A. Konovalova, *J. Gen. Chem. USSR*, **19**, 148 (1949)].



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Further Hofmann degradation of the methine base X methiodide proceeds readily with the formation of the same readily polymerized olefin XVIII (Et = $CH{=}CH_2$) as is obtained by the degradation of the isomethine methyl ether (XI, R = Me) methiodide. Hydrogenation of the methine base X proceeds rapidly and gives the dihydromethine XIV, the methiodide of which can be degraded to a nitrogen-free product XVI isomeric with that XVIII obtained by the degradation of the dihydroisomethine methyl ether (XV, R = Me) methiodide. These two nitrogen-free products afford the same 2,2′-diethyl-5,6,5′-trimethoxydiphenyl (XVII) on catalytic reduction.

The spectra of the various compounds in this series are in accord with the assigned structures. The ultraviolet spectra of the bases X and XI, R = H, and the nitrogen-free products XVI and XVIII are styrenoid, and the infrared spectra of all four compounds show bands at 10.77–10.83 μ attributed to the vinyl group, whereas the spectra of the bases VII (R = H), XV (R = H), XV (R = Me), XIV, XII, and the nitrogen-free product XVII, from which the vinyl compounds are derived or into which they have been converted, show no absorption bands in this region.

The nmr spectrum of neodihydrothebaine (VII, R = H) shows a complex signal at δ 7.4–6.6 (5 aromatic H) and signals at δ 5.25 (OH), 3.86 (OCH_3), 3.75 (OCH_3), approximately 2.5, complex (8 H as CH_2), and 2.25 (NCH_3). The spectrum of the isomethine XI (R = H) shows a complex signal at δ 7.8–6.6 (5 aromatic H) and signals at δ 5.69 and 5.25 (double doublet, C-16 H, $J_{15,16\ trans}$ = 18 cps; $J_{16,16}$ = *ca.* 3 cps), δ 5.09 and 4.82 (double doublet, C-16 H, $J_{15,16\ cis}$ = 10 cps; $J_{16,16}$ = *ca.* 3 cps), δ 5.90 (OH), 3.85 (OCH_3), 3.76 (OCH_3), *ca.* 2.35 (4 H as CH_2), and 2.0 (6 H as NMe_2). In dimethyl sulfoxide the hydroxyl proton of the isomethine gave a signal at δ 7.95, and the signal due to the C-15 proton, which was obscured in the spectrum of the base in deuteriochloroform by the aromatic and hydroxyl proton signals, appeared as a double doublet with centers at δ 6.17 and 5.77 ($J_{15,16\ trans}$ = 18 cps; $J_{15,16\ cis}$ = 10 cps). The spectrum of 2,2′-diethyl-5,6,5′-trimethoxydiphenyl (XVII) showed signals at δ 7.6–6.6 (5 aromatic H), 3.9, 3.8, and 3.59 ($3OCH_3$), 2.3 (quartet, 4 H), and 1.02 (triplet 6H), the latter two signals being attributable to two ethyl groups in virtually identical environments.

The iminium salt VIII is very rapidly decomposed by dilute acids and even by water, and the product may be assumed to be the amino aldehyde V, since on warming with mineral acid the iminium salt is converted into thebenine (II), which is the product of cyclodehydration of the aldehyde V.[6] From the mechanism of this cyclodehydration thebenine, not its O-methyl ether, would be expected to be the product of this reaction.

Attempts to isolate the amino aldehyde V were all unsuccessful and led to the recovery of a new base isomeric with thebaine in empirical formula and showing an infrared absorption band at 1645 cm^{-1} indicating that the base is an enamine. This base, like the iminium salt VIII is very rapidly converted by hot 2 *N*

(6) In the earlier communication[2] thebenine was not clearly identified as the product of this reaction. The iminium salt used in that work was not freshly isolated, and the use of partially autoxidized material has a profound effect on the fluorescence of the resulting thebenine in alkaline solution, though not in acids.

hydrochloric acid into thebenine (II), presumably by way of its hydrolysis product, the amino aldehyde V. The simplest structure for this enamine would be that shown in formula I, which could be formed from the amino aldehyde V or directly by deprotonation of the iminium salt VIII, and the nmr spectrum of the base is compatible with such a structure. The spectrum shows signals at δ 6.9–6.6 (5 aromatic H), 6.2 (doublet, C-10 H, $J_{10,9\ cis}$ = *ca.* 13 cps), 4.55 (doublet, C-9 H, $J_{9,10\ cis}$ = *ca.* 13 cps), 4.65 (OH), 3.9 (OCH_3), 3.81 (OCH_3), *ca.* 2.6 (4 H as CH_2), and 2.35 (NCH_3). This structure for the product is untenable, however, since on reduction catalytically or with sodium borohydride the enamine is reduced to an uncharacterizable base, which is clearly different in solubility, R_f value, and sign of optical rotation from neodihydrothebaine (VII, R = H), although the two bases have virtually identical infrared absorption spectra. The only rational explanation of these results is that the enamine has the dimeric structure IV, the 18-membered ring of which might be expected to be formed from the amino aldehyde V more readily than the nine-membered ring of the simpler base I, since rings of the latter size are notoriously difficult to close. The nmr spectrum of the enamine is equally compatible with the structures IV and I in which the environments of the protons are virtually identical. Similarly, the environments of all of the atoms in neodihydrothebaine (VII, R = H) and the base that would result from the reduction of the enamine IV are virtually identical, and it is reasonable to assume that the infrared absorption spectra of the two bases would be almost indistinguishable. The sign of optical rotation of the reduced enamine is the same as that of the isomethine XI (R = H), in which the relatively rigid nine-membered ring of neodihydrothebaine (VII, R = H) has been cleaved. Hydrolysis of the enamine IV would, of course, afford the amino aldehyde V, convertible by acids to thebenine (II). Formation of the enamine IV from the amino aldehyde V would be expected to be accompanied by the formation of a small amount of the enamine I and a considerable quantity of a linear polymeric enamine, and indeed a very good yield of crude enamine can be obtained but only about 25–30% of this is recoverable as a crystalline solid from 2-ethoxyethanol, and material recovered from the mother liquors defies all attempts at crystallization. Catalytic reduction of the crude enamine, however, affords about 5–8% of neodihydrothebaine, readily separable from other products by virtue of its solubility in ether. A good yield of thebenine is, however, obtained from the crude enamine on boiling with 2 *N* hydrochloric acid, as would be expected, since all three possible enamines would give the amino aldehyde V on hydrolysis. These results suggest that the crude enamine consists of about 5% of the simple base I, 30% of the dimeric base IV, and 65% of a mixture of polymeric enamines.

Experimental Section

Reaction of Thebaine with Anhydrous Magnesium Iodide. A solution of anhydrous magnesium iodide (28 g, 0.1 mole) prepared from iodine (25.6 g) and excess (8 g) of magnesium in dry ether (200 ml) and dry benzene (300 ml) was added over 45 min to a vigorously stirred boiling solution of thebaine (31.1 g, 0.1 mole) in dry benzene (250 ml) under nitrogen. A light green-brown precipitate rapidly formed. The mixture was stirred under reflux for another 45 min. For most purposes this mixture was used directly without isolation of the product. Isolation of the product by filtration of the mixture afforded a solid which, on washing well with ether and rapid drying in air, was obtained as an off-white powder that rapidly became green and degenerated to a sticky dark product in moist air.

Oxidation of the Thebaine–Magnesium Iodide Reaction Product VIII. The product of the above reaction, isolated as above (30 g) was vigorously stirred on the boiling water bath with water (350 ml), potassium hydroxide (50 g), and potassium permanganate (300 g) over a period of 4 hr, the oxidizing agent being added in portions of 50 g. The mixture was filtered, and the residue was washed with three 100-ml portions of boiling water. The filtrate was heavily contaminated with colloidal manganese dioxide which was coagulated by passing sulfur dioxide through the solution, which was filtered, concentrated to 300 ml, and acidified by the cautious addition of concentrated hydrochloric acid. Continuous ether extraction of the resulting mixture over 2 days afforded, on evaporation of the dried extract, a solid product that gave a derivative of fluorescein on fusion with resorcinol and concentrated sulfuric acid. A portion of this material was dissolved in aqueous methylamine, and the solution was evaporated. The residue was heated strongly and the volatile matter evolved was condensed and recrystallized from ethanol, when 4-methoxy-N-methylphthalimide was obtained as very pale yellow needles, mp 156° alone or mixed with an authentic specimen. A further portion of the oxidation product was heated alone and the volatile matter was condensed and recrystallized from a 1:1 mixture of benzene and light petroleum (bp 60–80°); 4-methoxyphthalic anhydride was obtained as pale yellow needles, mp 94° alone or mixed with an authentic specimen.

Action of Hydrochloric Acid on the Thebaine–Magnesium Iodide Reaction Product VIII. The freshly isolated reaction product (4 g) was boiled with 2 *N* hydrochloric acid (20 ml) for 5 min. The mixture was cooled and basified with ammonia, and the amorphous product was collected and washed well with water. Comparative chromatographic studies on thin layer plates indicated that this product was thebenine (II). It was dissolved in hot 2 *N* hydrochloric acid (15 ml), and the solution was cooled in ice when a viscous hydrochloride separated. This crystallized on trituration with ice–water and was obtained as pale yellow needles, mp 234–236°, identical in melting point, mixture melting point, infrared absorption, and R_f value with thebenine hydrochloride.

Neodihydrothebaine (VII, R = H). a. A solution of lithium aluminum hydride (4.5 g) in anhydrous ether (200 ml) was added to a vigorously stirred suspension of the product of reaction of thebaine (31.1 g) with anhydrous magnesium iodide (28 g) in ether–benzene. A vigorous reaction ensued and the light green-brown suspended material became white. The mixture was stirred for 1 hr; the excess of hydride was cautiously decomposed by the addition of water, and the product was dissolved by the addition of 2 *N* hydrochloric acid. The organic layer was discarded, and the aqueous layer, after extraction once with ether to remove all of the benzene, was diluted with saturated sodium potassium tartrate and ammonium chloride, covered with a layer of ether, and basified with ammonia. The precipitated base dissolved rapidly in the ether, which was separated, dried, and passed through a column of Florisil (60–100 mesh) (30 g) to remove a small amount of purple material. Evaporation of the ether then afforded neodihydrothebaine (VII, R = H) as a very pale brown oil that slowly crystallized on standing. The base was recrystallized with difficulty from 90% methanol below 0°, when it was obtained as almost colorless prisms, mp 98–100°, $[\alpha]^{20}D$ +63.7° (*c* 2.0, $CHCl_3$).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 73.3; H, 7.4. Found: C, 73.6; H, 7.5.

The base was readily soluble in aqueous alkalis, and the solution coupled instantaneously with diazotized sulfanilic acid to give a blood red dye.

The **methiodide** formed rapidly in ethanol and was obtained as pale cream prisms, mp 249–250° from ethanol.

Anal. Calcd for $C_{19}H_{23}NO_3 \cdot CH_3I$: C, 53.1; H, 5.6. Found: C, 52.8; H, 5.8.

The **methyl ether methiodide** was prepared by the addition of methyl sulfate to a solution of the phenol in aqueous potassium hydroxide, when the initial precipitate of the methyl ether rapidly dissolved, followed by the addition of potassium iodide. The precipitated salt crystallized rapidly and was collected and recrystallized from water as white plates, mp 260–261°.

Anal. Calcd for $C_{20}H_{25}NO_3 \cdot CH_3I \cdot 0.5H_2O$: C, 52.7; H, 6.1. Found: C, 52.8; H, 6.0.

b. The same base was obtained by reduction of the suspension of the iminium salt VIII in ether–benzene by the addition of

sodium borohydride (8.0 g) in hot ethanol (200 ml). The finely divided suspension rapidly coagulated to a sticky green mass that dissolved quickly as the reduction proceeded. The mixture was finally diluted with aqueous ammonium chloride, and the ether–benzene layer was removed, washed twice with water, dried, passed through Florisil as in part a above, and evaporated *in vacuo*. The residual base was identified with that produced in part by a thin layer chromatography and by conversion into the methiodide and methyl ether methiodide.

Identical results were obtained when the iminium salt VIII was isolated, washed with dry ether, and added to a vigorously stirred solution of sodium borohydride in ethanol, with isolation of the product by the addition of aqueous ammonium chloride and ether extraction.

Neodihydrothebaine Isomethine (XI, R = H). Potassium hydroxide was added to a boiling solution of neodihydrothebaine methiodide (4 g) in water (50 ml) until the solution became turbid due to the separation of a potassium salt. The solution was clarified by the addition of a small volume of water and then boiled for 30 min, during which time a viscous oil separated. The mixture was cooled in ice–salt and the liquid decanted from the hard brown glass, which was then dissolved in 2 *N* hydrochloric acid (50 ml) and methanol (30 ml). The base was precipitated as a crystalline solid by the slow addition of aqueous ammonia to the vigorously stirred acid solution, and was collected, washed with water, and recrystallized from aqueous methanol, and obtained as off-white prisms, mp 128–129°, $[\alpha]^{20}D$ −24.5° (*c* 2.0, $CHCl_3$).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.5; H, 7.7. Found: C, 73.7; H, 7.1.

The **methiodide** was obtained from ethanol as off-white prisms, mp 268–269°.

Anal. Calcd for $C_{20}H_{25}NO_3 \cdot CH_3I$: C, 53.8; H, 6.0. Found: C, 53.8; H, 5.9.

The **methyl ether methiodide** was obtained by the addition of aqueous potassium iodide to the aqueous solution finally resulting from the methylation of the base in aqueous potassium hydroxide with methyl sulfate. It was readily recrystallized from water and obtained as white needles, mp 205°.

Anal. Calcd for $C_{21}H_{27}NO_3 \cdot CH_3I$: C, 54.6; H, 6.2. Found: C, 54.4; H, 6.0.

The **methyl ether methoperchlorate** was prepared by the addition of perchloric acid to a solution of the methyl ether methiodide in aqueous ethanol. On recrystallization from aqueous ethanol it was obtained as white elongated plates, mp 161–162°.

Anal. Calcd for $C_{21}H_{27}NO_3 \cdot CH_3ClO_4$: C, 58.1; H, 6.65. Found: C, 57.9; H, 6.6.

Cyclization of Neodihydrothebaine Isomethine (XI, R = H). Neodihydrothebaine isomethine (0.5 g) was boiled with concentrated hydrochloric acid (5 ml) for 3 min. The solution was diluted with water and poured into an excess of aqueous potassium hydroxide. The precipitated nonphenolic base XII was isolated by ether extraction, but could not be induced to crystallize, and was characterized as the **picrate**, yellow prisms, mp 208–210°.

Anal. Calcd for $C_{20}H_{25}NO_3 \cdot C_6H_3N_3O_7$: C, 56.2; H, 5.1. Found: C, 56.4; H, 5.4.

Neodihydrothebaine Dihydroisomethine (XV, R = H). Neodihydrothebaine isomethine (XI, R = H) (1 g) was shaken under hydrogen at 20° (750 mm) in the presence of 10% palladium-on-charcoal catalyst (0.25 g). Hydrogen (70 ml) was absorbed over 15 min. Filtration and evaporation of the solution afforded the dihydroisomethine (XV, R = H) as a colorless oil, $[\alpha]^{20}D$ −10.0° (*c* 2.1, $CHCl_3$), that could not be crystallized.

The **methiodide** was obtained readily as white prisms, mp 286–288° from ethanol.

Anal. Calcd for $C_{20}H_{27}NO_3 \cdot CH_3I$: C, 53.55; H, 6.4. Found: C, 53.6; H, 6.7.

The **methyl ether methiodide** was obtained as white prisms, mp 228–230° from water.

Anal. Calcd for $C_{21}H_{27}NO_3 \cdot CH_3I$: C, 54.5; H, 6.6. Found: C, 54.6; H, 6.6.

Hofmann Degradation of Neodihydrothebaine Isomethine Methyl Ether (XI, R = Me) Methiodide. Potassium hydroxide was added to a boiling solution of neodihydrothebaine isomethine methyl ether methiodide (1 g) in water (25 ml) until separation of an oil began. The mixture was then boiled for 1 hr, during which time a base (trimethylamine) was evolved, and an insoluble oil separated. The mixture was cooled and extracted with ether, and the ether extract was shaken twice with 2 *N* hydrochloric acid and evaporated, to leave an uncrystallizable fluorescent (blue) neutral oil that was rapidly converted into a rubbery solid on attempted distillation or (more slowly) on standing. Thin layer chromatographic studies indicated that this product, presumably the divinyldiphenyl XVIII (Et = CH=CH_2), was identical with the product of degradation of neodihydrothebaine methine methyl ether (X) methiodide.

Hofmann Degradation of Neodihydrothebaine Dihydroisomethine Methyl Ether (XV, R = Me) Methiodide. Neodihydrothebaine dihydroisomethine methyl ether methiodide (2 g) was degraded by the process given above to yield **2′-ethyl-5,6,5-trimethoxy-2-vinyldiphenyl** (XVIII) as a pale brown oil which was distilled under high vacuum, and was obtained as a colorless oil, bp 190–200° (bath temp) (0.05 mm).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.6. Found: C, 76.4; H, 7.7.

2,2′-Diethyl-5,6,5′-trimethoxydiphenyl (XVII). 2′-Ethyl-5,6,5′-trimethoxy-2-vinyldiphenyl (XVIII) (0.8 g) in ethanol (25 ml) was shaken under hydrogen at 20° (760 mm) in the presence of 10% palladium-on-charcoal catalyst (0.25 g). Hydrogen (66 ml) was absorbed over 10 min. The solution was filtered and evaporated, and the residual oil was distilled when the diphenyl XVII was obtained as a colorless oil, bp 190–200° (bath temperature) (0.05 mm).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 76.1; H, 8.1. Found: C, 76.2; H, 8.1.

The same product, identical in behavior with the above on thin layer chromatography, was obtained by the hydrogenation of 2-ethyl-5,6,5′-trimethoxy-2′-vinyldiphenyl (XVI), obtained by the degradation of the methiodide of neodihydrothebaine dihydromethine methyl ether (XVI).

Neodihydrothebaine Methine Methyl Ether (X). Neodihydrothebaine methyl ether methiodide (5 g) was dissolved in boiling water (50 ml), and potassium hydroxide was added to the solution until separation of an oil began. The mixture was then boiled for 30 min, cooled, and diluted, and the product was isolated by ether extraction. Thin layer chromatographic studies showed that the uncrystallizable oil contained two bases. It was converted into the methiodide by heating with methyl iodide and ethanol, and on cooling the solution slowly deposited neodihydrothebaine isomethine methyl ether methiodide (0.5 g), mp 205°, identical with the salt prepared from the isomethine (see above). Evaporation of the mother liquors after removal of this salt afforded material that could not be obtained crystalline from ethanol or from water. It was converted into **neodihydrothebaine methine methyl ether methoperchlorate** by the addition of perchloric acid to a solution of the methiodide in water. The methoperchlorate was obtained as white needles, mp 150–151°, on recrystallization from water.

Anal. Calcd for $C_{21}H_{27}NO_3 \cdot CH_3 \cdot CH_3ClO_4$: C, 58.1; H, 6.65. Found: C, 58.1; H, 6.55.

Oxidation of Neodihydrothebaine Methine Methyl Ether. Neodihydrothebaine methine methyl ether, containing some of the isomethine methyl ether (1.8 g), was stirred on the boiling water with potassium hydroxide (2.0 g), potassium permanganate (4.0 g), and water (50 ml) for 4 hr. The mixture was filtered, and the yellow filtrate was acidified with hydrochloric acid; the precipitated product was isolated by ether extraction and obtained as a viscous yellow oil. Thin layer chromatographic studies showed this material to consist of two yellow products and about 10% 5,6,5′-trimethoxydiphenic acid. The material was dissolved in 2 *N* potassium hydroxide solution (50 ml), and the solution was warmed on the water bath for 10 min with 30% hydrogen peroxide (1 ml). Acidification of the solution then afforded 5,6,5′-trimethoxydiphenic acid (1.2 g) as white prisms, mp 215°, from aqueous methanol; the melting point was undepressed on mixing with authentic specimens prepared from acetylthebaol and phenyldihydrothebaine.

The trimethoxydiphenic acid was warmed with concentrated sulfuric acid at 50° for 15 min. Dilution of the solution with water precipitated 1,5,6-trimethoxyfluorenone-4-carboxylic acid as yellow needles from 50% acetic acid, mp 256° alone or mixed with an authentic specimen.

Hofmann Degradation of Neodihydrothebaine Methine Methyl Ether (X) Methiodide. Degradation of the methiodide of the base X by the process described above for the degradation of neodihydrothebaine isomethine methyl ether methiodide afforded a neutral product identical with that obtained in that degradation.

Neodihydrothebaine Dihydromethine Methyl Ether (XIV). Neodihydrothebaine methine methyl ether (containing about 10% of the isomethine methyl ether) (5.4 g) was shaken in ethanol (50 ml) with 10% palladium on charcoal (0.25 g) under hydrogen at 20° (760 mm). Hydrogen (348 ml) was absorbed over 40 min. Filtration and evaporation afforded a noncrystalline gum, which was converted into the methiodide. Two recrystallizations of the methiodide afforded the dihydromethine methyl ether methiodide

free of the isomethine derivative (tlc) as white prisms, mp 200–201°.

Anal. Calcd for $C_{21}H_{29}NO_3 \cdot CH_3I$: C, 54.5; H, 6.6. Found: C, 54.5; H, 6.6.

Hofmann Degradation of Neodihydrothebaine Dihydromethine Methyl Ether (XIV) Methiodide. The methiodide (2.0 g) was degraded in boiling aqueous potassium hydroxide, when trimethylamine was evolved and **2-ethyl-5,6,5′-trimethoxy-2′-vinyldiphenyl (XVI)** was isolated by ether extraction and distillation and obtained as a colorless oil, bp 190–200° (bath temperature) (0.05 mm).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.6. Found: C, 76.5; H, 7.4.

Catalytic reduction of this compound proceeded readily in ethanol over 10% palladium on charcoal, and gave 2,2′-diethyl-5,6,5′-trimethoxydiphenyl (XVII), identical in thin layer chromatographic behavior with material prepared by the reduction of 2′-ethyl-5,6,5′-trimethoxy-2-vinyldiphenyl (XVIII) described above.

Kryptothebaine (IV). The product of reaction of thebaine (31.1 g) with anhydrous magnesium iodide in ether–benzene suspension was treated with 2 *N* hydrochloric acid. A sticky insoluble mass (presumably a hydriodide) was obtained, and the aqueous and organic solutions were poured off. After the material was dissolved in methanol, the solution was diluted with ice water and cautiously basified with ammonia. A further quantity of base was obtained by adding ammonia to the aqueous acid layer separated as above. The precipitated solid was collected and recrystallized from ethanol and from aqueous 2-ethoxyethanol; the same product, kryptothebaine (IV), was obtained in each case as green-gray prisms, mp 274° (8.5 g). Recrystallization from aqueous 2-ethoxyethanol with the addition of a drop of aqueous sodium dithionite gave the enamine as pale cream prisms, mp 274°, but these rapidly became green on standing, the color darkening to almost black after several days.

Anal. Calcd for $C_{38}H_{32}N_2O_6$: C, 73.3; H, 6.75; mol wt, 622. Found: C, 73.3; H, 6.8; mol wt (Rast in camphor), 586.

Reduction of this base catalytically over 10% palladium on charcoal was sluggish and was only complete after 10 hr, and reduction with sodium borohydride was slow even in boiling 2-ethoxyethanol. The same base was obtained in each case, and unlike neodihydrothebaine (which it closely resembled in infrared absorption), it was completely insoluble in ether. No crystalline salts of this uncrystallizable base could be prepared.

Catalytic reduction of the crude product (2 g) obtained on basification of the aqueous methanolic solution of the hydriodide, however, gave, slowly, a product part of which dissolved in ether. Evaporation of the ether gave neodihydrothebaine (0.16 g) identified as its methiodide, mp 249–250° from ethanol.

Reaction of Kryptothebaine (IV) with Hydrochloric Acid. Kryptothebaine (IV), prepared as above (2 g), was boiled with 2 *N* hydrochloric acid (10 ml) for 5 min. The solution, on cooling, deposited a viscous gum (2.0 g), which crystallized from water at 0° as yellow needles, mp 234–236°, identical in melting point, mixture melting point, infrared absorption, and R_f value with thebenine (II) hydrochloride prepared in the same way from thebaine.

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The Structures of Deserpideine and Raujemidine[1]

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Abstract: The indole alkaloids deserpideine and raujemidine correspond to expressions I and Ia, respectively. The most interesting transformation of deserpideine is its hydrogenation and hydrogenolysis with Adams catalyst to yield products II, III, X, and XII.

The initial investigation of the alkaloids of *Rauwolfia nitida* Jacq. by Salkin and his group[4] led to the isolation of ajmalicine, isoreserpiline, isoreserpinine, raunitidine, raunitidine, reserpiline, and reserpinine.

We have now found that the weakly basic alkaloid fraction from certain samples of *R. nitida* yields, in addition to the known alkaloid deserpidine (II), a new crystalline alkaloid, deserpideine (I), $C_{32}H_{36}N_2O_8$, mp 149–152°, $[\alpha]^{25}D$ −133° (pyridine), whose ultraviolet spectrum is identical with its companion deserpidine. The infrared spectrum of deserpideine is also very similar to that of deserpidine, but varies slightly from the latter in the fingerprint region. In analogy with deserpidine (II), the Bohlmann bands between 3.4 and 3.6 μ were missing in deserpideine (I), indicating a *cis* C–D ring fusion.

The chemistry of deserpideine (I) initially indicated a behavior that somewhat paralleled the chemistry of deserpidine (II). The reaction of deserpideine (I) with sodium methoxide at room temperature gave the expected methyl 3,4,5-trimethoxybenzoate (IIIa) and methyl deserpideate (IV), $C_{22}H_{26}N_2O_4 \cdot H_2O$, mp 159–162°, $[\alpha]^{25}D$ +8° (pyridine). Hydrolysis of either deserpideine or methyl deserpideate with potassium hydroxide in aqueous methanol gave deserpideic acid (V), $C_{21}H_{24}N_2O_4$, mp 224–226°, $[\alpha]^{25}D$ −29° (50% methanol–water), which could be converted to deserpideic acid lactone (VI), $C_{21}H_{22}N_2O_3$, mp 159–161°, $[\alpha]^{25}D$ −58° (50% methanol–water), on treatment with acetic anhydride in pyridine. When deserpideic acid lactone was allowed to stand at 0° in sodium methoxide in methanol, methyl deserpideate (IV) was obtained. Deserpideine (I) itself could be reconstituted by treatment of methyl deserpideate with 3,4,5-trimethoxy-

(1) Preliminary communications of some of these results appeared in (a) E. Smith, R. S. Jaret, M. Shamma, and R. J. Shine, *J. Am. Chem. Soc.*, **86**, 2083 (1964); (b) M. Shamma and R. J. Shine, *Tetrahedron Letters*, 2277 (1964); and (c) E. Smith, R. S. Jaret, M. Shamma, and R. J. Shine, *Lloydia*, **27**, 440 (1964).

(2) Deceased October 23, 1965.

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(4) R. Salkin, N. Hosansky, and R. Jaret, *J. Pharm. Sci.*, **50**, 1038 (1961).