heated to 60–80° (bath temperature) for 1 hr under N_2. During the heating period an additional 0.8 g of zinc dust was added in small portions. The mixture was cooled to 0–10° and a solution of 40 ml of concentrated HCl in 10 ml of water was added in small portions. After the mixture was stirred vigorously for 18 hr at 20°, a flocculent, gray precipitate had formed. An additional 4.0 g of zinc dust was added and the mixture was heated to gentle reflux under N_2 for 1 hr. The mixture was cooled, filtered through glass wool, and extracted with ether. The acidic aqueous layer was saturated with NaCl and extracted with ether. The combined ether extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a semisolid residue. Trituration with pentane gave solid **23** (0.56 g, 18%), mp 110–116°, which was purified by sublimation: mp 122–123°; $\nu_{max}^{CHCl_3}$ 3010, 2945, 2905, 2830, 1712, 1601, 1578, 1469, 1429, 1304, 1225, 1150, 1080, 1033, and 1012 cm^{-1}; λ_{max}^{EtOH} 216 mμ (ε 11,100) 234.5 (11,100), 270.5 (5750), and 298 (934); nmr ($CDCl_3$) δ 7.19–6.81 (multiplet, 3 H), 3.89 (singlet, 2 H), and 3.79 (singlet, 3 H).

Anal. Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found: C, 59.94; H, 4.48; S, 17.88.

Methyl 2-(Methyl carboxymethyl)-4-methoxyphenylmercaptoacetate (24).—To a slurry of thiolactone **23** (226 mg, 1.26 mmol) in 5 ml of 80% methanol–water under N_2 was added solid KOH (160 mg, 2.85 mmol). The solution was stirred for 15 min at room temperature and methyl bromoacetate (301 mg, 1.97 mmol) was added. The mixture was stirred for 15 min at room temperature and then heated under reflux for 1 hr. Water (10 ml) and 6 *N* HCl (0.5 ml) were added and 5 ml of distillate was collected. The mixture was cooled and extracted with three 30-ml portions of ether. The combined ether extracts were washed with water and saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a yellow oil. The oil was dissolved in 10 ml of ether; the solution was cooled to 0° and treated with a solution of diazomethane in ether (prepared from 715 mg N′-nitro-N-methyl-N-nitrosoguanidine and a mixture of 3 ml of 50% aqueous KOH and 18 ml of ether)[33] until a yellow color persisted. After the mixture was stirred for 10 min while it warmed to room temperature, the yellow color was carefully discharged with a few drops of glacial HOAc. The ether solution was diluted to 100 ml (ether), dried ($MgSO_4$), and evaporated to give 332 mg (93%) of **24**. A sample of this material was purified by short-path distillation [Klagen tube, bath temperature 210° (0.1 mm)] to give a nearly colorless oil: $\nu_{max}^{CCl_4}$ 3003, 2954, 2838, 1742, 1596, 1569, 1480, 1467, 1433, 1335, 1300–1230, 1156, 1068, 1028, and 1008 cm^{-1}; nmr (CCl_4) δ 7.44 (doublet of doublets, J = 7 and 2 cps, 1 H), 6.74 (doublet, J = 2 cps, 1 H), 6.70 (doublet of doublets, J = 7 and 2 cps, 1 H), 3.81 (singlet, 2 H), 3.69 (singlet, 3 H), 3.60 (singlet, 3 H), 3.55 (singlet, 3 H), and 3.35 (singlet, 2 H).

(33) A. F. McKay, *J. Amer. Chem. Soc.*, **70**, 1974 (1948).

Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.91; H, 5.67; S, 11.28. Found: C, 55.04; H, 5.77; S, 11.14.

6-Methoxythiochroman-3-one (6).—Sodium hydride (*ca.* 50% Nujol dispersion, 115 mg, *ca.* 2.4 mmol) was washed free of Nujol with three 5-ml portions of *n*-hexane under N_2 and 5 ml of ether was added. The vigorously stirred slurry was treated dropwise during 45 min with a solution of **24** (339 mg, 1.2 mmol) in ether (10 ml) containing 3 microdrops of methanol. A mildly exothermic evolution of H_2 took place after a short while with development of a light yellow color and formation of a copius gray to tan precipitate. Stirring at room temperature was continued for 0.5 hr longer and the mixture was heated under reflux for 1 hr (bath temperature 45°). The mixture was cooled and poured into a slurry of ice–water (20 g) and glacial HOAc (0.3 g). The layers were separated and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether extracts were washed with water (20 ml), a mixture of saturated $NaHCO_3$ solution (2 ml) and water (8 ml), and saturated NaCl solution, dried (Na_2SO_4), and evaporated to give 285 mg (94%) of crude β-keto ester as an amber, partially crystallized oil (keto/enol forms, *ca.* 3:1).

The crude β-keto ester was heated under reflux with 1 ml of 6 *N* HCl (oil bath, 130–140°) under N_2 for 45 min. The mixture was cooled and poured into a solution of Na_2CO_3 (0.50 g) in water (9 ml). The mixture was shaken, the layers were separated, and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether extracts were washed with 2 *N* NaOH (10 ml), water, and saturated NaCl solution, dried ($MgSO_4$), and evaporated to give a dark residue which was distilled (Klagen tube, *ca.* 0.6 mm) to give 17.1 mg of a light yellow oil. The major component was collected by vpc and was identical in all respects with the sample of **6** from irradiation of **3**.

Registry No.—**1**, 18926-31-3; **2**, 4426-76-0; **3**, 16994-31-3; **4**, 16994-30-2; **5**, 16895-58-2; **6**, 18926-35-7; **9**, 16994-33-5; **10**, 18926-36-8; **11**, 18926-37-9; **14**, 16994-29-9; **15**, 18926-39-1; **16**, 5254-94-4; **18**, 18926-41-5; **18** (acid chloride), 18926-42-6; **19**, 18926-43-7; **20**, 18926-44-8; **21**, 18926-45-9; **22**, 18944-99-5; **23**, 18926-46-0; **24**, 18945-00-1; *m*-methoxybenzylmercaptoacetic acid, 18926-47-1; *o*-methylbenzylisothiuronium bromide, 18926-48-2; *o*-methylbenzylmercaptoacetic acid, 18926-49-3; 1-napthylisothiuronium chloride, 18945-01-2; 1-napthylmercaptoacetic acid, 10404-24-7; 6-methoxythiochroman-3-one, 18926-35-7; 5-methylthiochroman-3-one, 18927-04-3; methyl *m*-methoxyphenylacetate, 18927-05-4.

Synthesis of New Indole Alkaloid Types

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A new series of compounds related to tubulosine has been synthesized. The designation "methylenebis type" is proposed for this general structural class. The compounds were prepared by condensing various esters represented by **5a** with homoveratrylamine or tryptamine; the resulting amides (*e.g.*, **6a**) were cyclized with phosphoryl chloride. Reduction of **7a** with sodium borohydride gave mixtures of the corresponding epimeric pair **8a**. This mixture was separated, and the major epimer was N-methylated *via* lithium aluminum hydride reduction of its N-formamide. The mass spectra of the compounds described showed fragmentation patterns analogous to those arising from emetine and tubulosine, thereby confirming the structures expected on the basis of the synthetic sequence.

For many years, the ipecacuanha alkaloids,[1] as represented by the pharmacologically important compound emetine[2] (**1a**), were the only compounds of the "methylenebis"[3] alkaloid type known to occur naturally. Members of this series possess benzoisoquinolizidine and isoquinoline moieties, connected by a methylene bridge.

(1) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p 370.

(2) The Merck Index, 7th ed, Merck and Co. Inc., Rahway, N. J., 1960, p 401.

(3) We propose the general designation "methylenebis type" for this class of alkaloids and related substances containing two discrete basic moieties connected by a methylene bridge.

TABLE I
ANALYTICAL DATA

Compd	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6a	273–275	82	$C_{29}H_{37}N_3O_3$	73.26	7.84	8.84	72.98	8.08	8.66
6b	155–157	63	$C_{30}H_{39}N_3O_4$	71.26	7.77	8.31	71.13	7.79	8.28
7a	260–262 dec	64	$C_{29}H_{37}Cl_2N_3O_2 \cdot 2H_2O$[a]	61.47	7.29	7.42	61.55	7.14	7.50
7b	234–237 dec	68	$C_{30}H_{39}Cl_2N_3O_3 \cdot 1.5H_2O$[a]	61.32	7.20	7.15	61.22	7.28	6.94
8a	305–307 dec	7	$C_{29}H_{39}Cl_2N_3O_3 \cdot 0.5H_2O$[a]	64.32	7.44	7.75	64.54	7.59	7.80
	266–268 dec	63	$C_{29}H_{39}Cl_2N_3O_2 \cdot 2H_2O$[a]	61.26	7.61	7.39	61.56	7.64	7.26
8b	265–267 dec	66	$C_{30}H_{41}Cl_2N_3O_3 \cdot H_2O$[a]	62.06	7.47	7.24	62.20	7.52	7.05
9a	295	71	$C_{30}H_{41}Cl_2N_3O_2 \cdot 0.5H_2O$[a]	64.85	7.62	7.56	65.01	7.82	7.47
9b	231–233	47	$C_{31}H_{43}Cl_2N_3O_3 \cdot H_2O$[a]	62.62	7.63	7.08	62.82	7.76	6.88
10a	188–189	57	$C_{29}H_{34}N_4O$	76.62	7.54	12.33	76.31	7.67	12.10
10b	187–189	47	$C_{30}H_{36}N_4O_2$	74.35	7.49	11.56	74.05	7.48	11.52
11a	301–303 dec	70	$C_{29}H_{34}Cl_2N_4 \cdot 0.5H_2O$[a]	61.47	7.29	7.42	61.55	7.14	7.50
11b	263–265 dec	53	$C_{30}H_{36}Cl_2N_4O \cdot 1.5H_2O$[a]	63.59	6.93	9.89	63.30	7.14	9.69

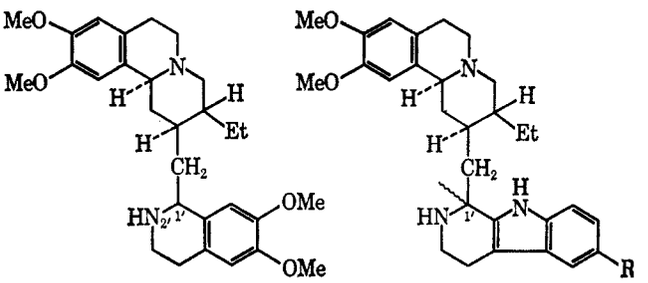
[a] Analyzed as the dihydrochloride.

Recently, a new series of "methylenebis" type alkaloids containing β-carboline residues similarily linked to benzoquinolizidine residues has been isolated. Examples of this group are the first known member, tubulosine[4] (**2a**), desoxytubulosine,[5,6] isotubulosine,[7] and alangimarckine.[8] Structural assignments for these alkaloids were based primarily on the interpretation of their mass spectra, using as a standard the fragmentation pattern obtained from a synthetic specimen of *dl*-deoxytubulosine prepared[9] several years before for another study. More recently, the skeletal structure of tubulosine and deoxytubulosine was confirmed, and their absolute configurations established by total synthesis.[5,10]

Two additional types of "methylenebis" compounds are biogenetically plausible, based on the theory of Robinson[11] as elaborated by Battersby and Harper[12] and Brauchli, *et al.*[4] They are exemplified by **7a** and **11a.** Although they have not yet been found in nature, it is interesting that, during a structural study, Potier, *et al.*,[13] synthesized a crude specimen of **3** in order to examine it as a possible structure (negative result) for the alkaloid cinchophyllamine.

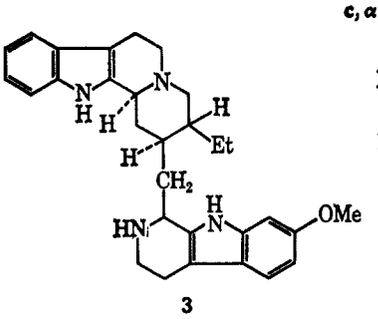
As it is anticipated that these compounds exist as natural products, and because of a pharmacological interest in compounds of these classes, synthesis of several compounds, including **7a** and **11a,** was initiated.

Several approaches to the preparation of this type of substance are on record. Potier, *et al.*,[13] prepared crude **3** by condensing dihydrocorynantheal with 6-methoxytryptamine. Battersby, *et al.*,[9] prepared the base **2b** by condensing the mixed anhydride of ethyl hydrogen carbonate and the amino acid **4** with tryptamine, and cyclizing the resultant amide with phosphoryl chloride.

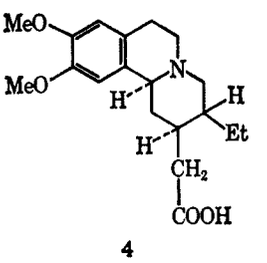


1a
b, $\Delta^{1'(2')}$

2a, R = OH
b, R = H; $\Delta^{1'(2')}$
c, α or β (epimeric at C-1')



3



4

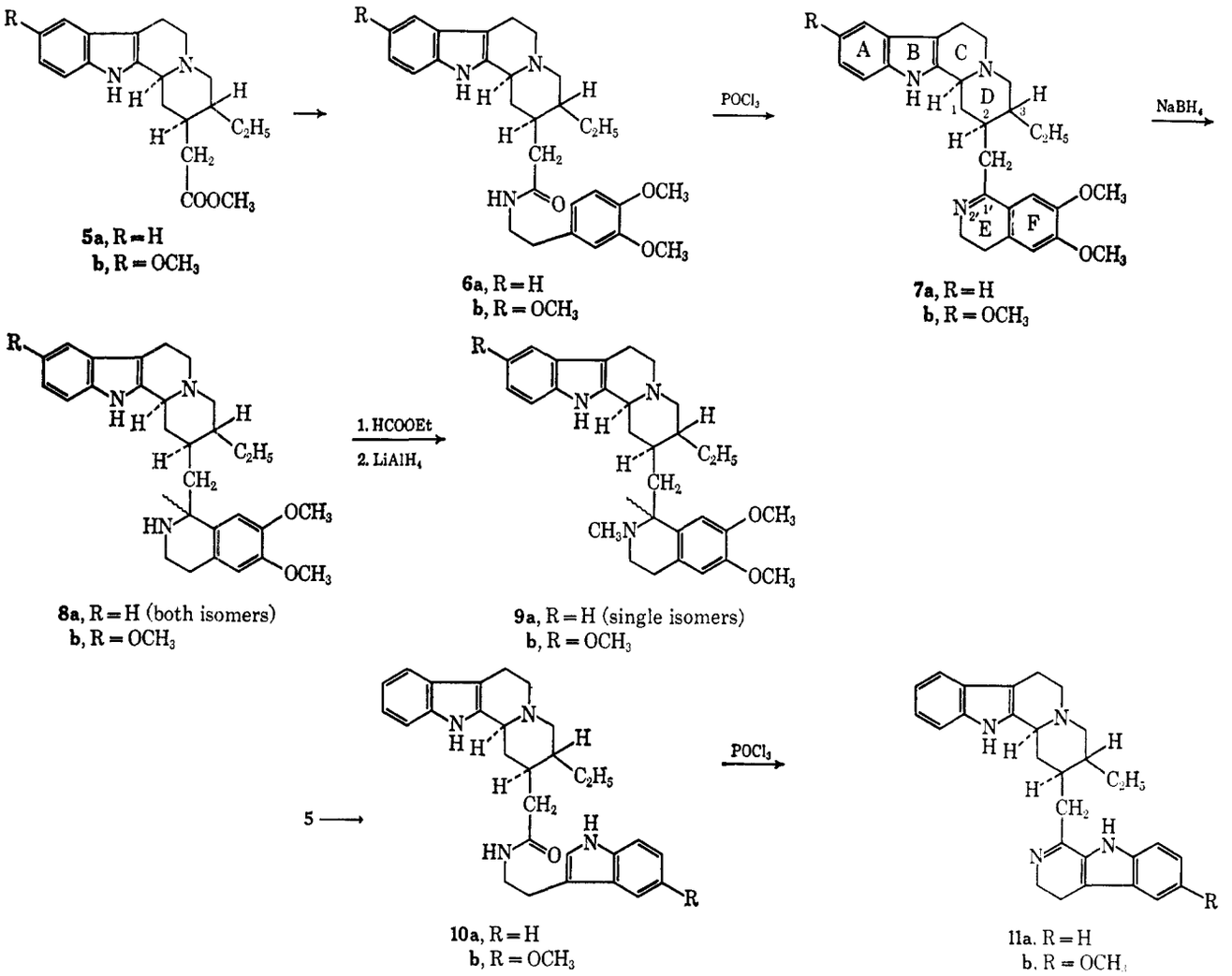
Catalytic hydrogenation or sodium borohydride reduction of the base **2b** gave the mixture **2c.** A modification of these procedures established a pattern for preparation of the bases listed in Table I. Esters of formula **5**[14] were heated with homoveratrylamine or tryptamine to give amides **6** and **10** (Scheme I). Cyclization of the amides with phosphorus oxychloride gave bases **7** and **11.** Sodium borohydride reduction of **7a** gave a separable mixture of disastereoisomers **8a** (stereochemistry undetermined), **7** and 63%, respectively.

Methylation was achieved by converting the more abundant isomer into its formyl derivative, and reducing this to the corresponding N-methyl compound (**9a**) with lithium aluminum hydride.

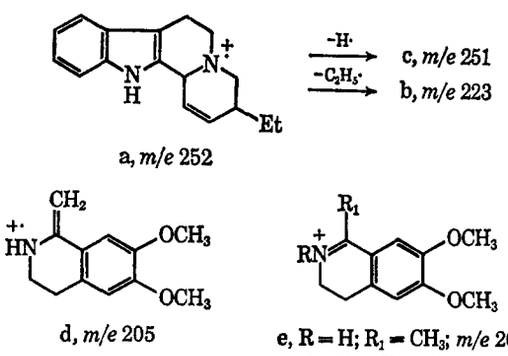
The mass spectra of the ipecacuanha alkaloids, as well as of tubulosine, have been interpreted.[4,15,16]

(4) P. Brauchli, V. Deulofeu, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86,** 1895 (1964).
(5) A. R. Battersby, J. R. Merchant, E. A. Ruveda, and S. S. Salgar, *Chem. Commun.*, 315 (1965).
(6) H. Monteiro, H. Budzikiewicz, C. Djerassi, R. R. Arndt, and W. H. Baarschers, *ibid.*, 317 (1965).
(7) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, 5077 (1966).
(8) A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *ibid.*, 4965 (1966).
(9) A. R. Battersby, G. C. Davidson, and J. C. Turner, *J. Chem. Soc.*, 3899 (1961).
(10) H. T. Openshaw and N. Whittaker, *Chem. Commun.*, 131 (1966).
(11) R. Robinson, *Nature*, **162,** 524 (1948).
(12) A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, 1748 (1959).
(13) P. Potier, C. Kan, J. LeMen, M. M. Janot, H. Budzikiewicz, and C. Djerassi, *Bull. Soc. Chim. Fr.*, 2309 (1966).
(14) J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Lett.*, 3457 (1965).
(15) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry, Vol. I: Alkaloids," Holden-Day, Inc., London, 1964, p 184.
(16) H. Budzikiewicz, S. C. Pakrashi, and H. Vorbrüggen, *Tetrahedron*, **20,** 399 (1964).

SCHEME I



Similar patterns were exhibited by compounds **7a, 8a,** and **9a,** and the structures of the latter compounds were thereby confirmed. Thus, the molecular ion peak of **7a,** which is characterized by a 1′, 2′ double bond in ring E, is at *m/e* 457. Its base peak, which occurs at *m/e* 252, may be assigned to the ion radical a. The peaks at *m/e* 251 (b) and 223 (c) correspond to fragments arising from the ion radical a through the loss of hydrogen and of the allylic ethyl groups. The fragments corresponding to 156, 169, 170, and 184 characteristically occur in tetrahydro-β-carbolines.[17] The peaks at *m/e* 205 and 206 correspond to d and e, while 190 and 192 are characteristic of isoquinoline ions; they are also found in the spectrum of psychotrine methyl ester (**1b**).



The molecular peak of **8a** is at *m/e* 459. In **8a,** which possesses a tetrahydroisoquinoline system, the intensity of the fragments found on the spectrum of **7a** is reduced. Benzylic activation of the 1′-methylene bridge gives a high-intensity peak at *m/e* 192 (fragment f) as in emetine (**1a**). The mass spectrum of **9a** is similar to that of **8a.** The ion peak appears at *m/e* 473, with a base peak at *m/e* 206 (fragment g); the mass shift is due to the methyl group present in **9a.**

Experimental Section

Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Microanalyses were performed in the Analytical Department of Smith Kline and French Laboratories. Infrared spectra were determined on a Perkin-Elmer Model 137B spectrophotometer. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E instrument.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-N-(3′,4′-dimethoxyphenethyl)indolo[2,3-*a*]quinolizine-2-acetamide (**6a**).—A mixture of ester (2.3 g, 0.0074 mol) and homoveratrylamine (3 g, 0.0165 mol) was heated under nitrogen at 190–210° for *ca.* 2 hr, or until ester carbonyl absorption at 5.75 μ disappeared. The mixture was cooled, and the resulting viscous oil was dissolved in methylene chloride. When it was diluted with ether, 1.9 g of the amide **6a** crystallized, mp 165–168°. An additional 0.5 g of the same melting point material (total yield 71%) was obtained when the mother liquor was chromatographed on Florisil (eluted with

(17) Reference 15, p 81.

chloroform–methanol, 99:1). An analytical sample of **6a** melted at 171–173°; uv, λ_{max}^{EtOH} 227 mμ (ε 45,100), 279 (10,400). *Anal.* Calcd for $C_{29}H_{37}N_3O_3$: C, 73.26; H, 7.84; N, 8.84. Found: C, 72.98; H, 8.08; N, 8.66.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-(3′,4′-dihydro-6′,7′-dimethoxyl-1-isoquinolinyl)methylindolo[2,3-*a*]quinolizine Dihydrochloride (7a).—The amide **6a** (5 g, 0.001 mol) in 100 ml of 1,2-dichloroethane was refluxed for 3.5 hr with 10 ml of phosphorus oxychloride, then cooled to 4°. The excess phosphorus oxychloride was decomposed with water, and 10% dilute ammonium hydroxide solution was added until the solution was basic. The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated. The residue in chloroform was chromatographed on Florisil. Fractions eluted with chloroform–methanol (99:1) crystallized from methylene chloride–ether. The product **7a** (3.1 g, 64% yield) melted at 180–183°. A perfect analysis for the base could not be obtained. It was converted into the hydrochloride on treatment with methanolic HCl and the product was recrystallized from methanol–ethyl acetate. The analytical sample melted at 260–262°; uv, λ_{max}^{EtOH} 220 mμ (ε 44,600), 248 (15,200), 273 (9600), 282 (10,300), 290 (10,200), 306 (8500), 360 (7400). *Anal.* Calcd for $C_{29}H_{35}N_3O_2 \cdot 2HCl \cdot 2H_2O$: C, 61.47; H, 7.29; N, 7.42; mol wt (free base), 457.6. Found: C, 61.55; H, 7.14; N, 7.56; mol wt (mass spectrum), 457.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-(1′,2′,3′,4′-tetrahydro-6′,7′-dimethoxy-1-isoquinolinyl)methylindolo[2,3-*a*]quinolizine Dihydrochloride (8a).—The base **7a** (3 g, 0.0066 mol) in 120 ml of methanol and 5.0 ml of water was reduced with 0.6 g of sodium borohydride for 0.5 hr at reflux and 1 hr at 25°. Excess hydride was destroyed with acetic acid, the methanol was evaporated, and the residue was made basic with 10% ammonium hydroxide solution. The chloroform extracts were washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated. The amorphous residue was converted into the hydrochloride by treatment with methanolic HCl, and recrystallized from methanol to yield 0.25 g of one isomer of **8a** (7%). Further recrystallization from methanol–ethyl acetate gave an analytical sample with mp 305–307°. *Anal.* Calcd for $C_{29}H_{37}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 64.32; H, 7.44; N, 7.75; mol wt (free base), 459.6. Found: C, 64.54; H, 7.59; N, 7.80; mol wt (mass spectrum), 459.

Another isomer (2.35 g, 62.5% yield) was obtained when the mother liquors were crystallized from methanol–ethyl acetate. The analytical sample melted at 266–268°; uv, λ_{max}^{EtOH} 223 mμ (ε 44,600), 281 (11,400), 288 (sh) (9300). *Anal.* Calcd for $C_{29}H_{37}N_3O_2 \cdot 2HCl \cdot 2H_2O$: C, 61.26; H, 7.61; N, 7.39. Found: C, 61.56; H, 7.61; N, 7.26.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-(1′,2′,3′,4′-tetrahydro 6′,7′-dimethoxy-2′-methyl-1-isoquinolinyl)methylindolo[2,3-*a*]-quinolizine Dihydrochloride (9a).—The major isomer **8a** (1.97 g) was liberated from its hydrochloride with dilute ammonium hydroxide and extracted into chloroform. The solution was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated. The residue in 30 ml of ethyl formate was heated for 16 hr on a steam bath under 40 psi pressure. The mixture was cooled, the solution was evaporated, and the residue was partitioned between chloroform and 10% ammonium hydroxide solution. The chloroform layer was washed with saturated sodium chloride solution and dried over sodium sulfate. On concentration to dryness, 1.86 g of amorphous formyl compound was obtained.

A solution of the formyl compound (1.7 g) in 30 ml of tetrahydrofuran was added to a solution of 1 g (0.03 mol) of lithium aluminum hydride in 100 ml of tetrahydrofuran, and heated at reflux for 6 hr. The mixture was cooled, excess hydride was destroyed with water, and the mixture was filtered. The filtrate was acidified with 10% sulfuric acid, washed with ether, made basic with 10% ammonium hydroxide solution, and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was converted into the dihydrochloride of **9a**, which was crystallized from methanol–ethyl acetate. It melted above 295°; uv, λ_{max}^{EtOH} 220 mμ (ε 54,200), 273 (sh) (12,600), 279 (12,900), 288 (11,900). *Anal.* Calcd for $C_{30}H_{39}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 64.85; H, 7.62; N, 7.56; mol wt (free base), 473.6. Found: C, 65.01; H, 7.82; N, 7.47; mol wt (mass spectrum), 473.

Registry No.—**6a**, 19202-96-1; **6b**, 19203-01-1; **7a**, 19202-97-2; **7b**, 19203-02-2; **8a** (α), 19202-98-3; **8a** (β), 19203-03-3; **8b**, 19203-04-4; **9a**, 19202-99-4; **9b**, 19233-86-4; **10a**, 19203-05-5; **10b**, 19203-06-6; **11a**, 19203-07-7; **11b**, 19203-08-8.

Structure Elucidation and Chemistry of *Catharanthus* Alkaloids. IV.[1,2] Structures of Horhammericine and Horhammerinine

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Several α-methyleneindoline bases have been reported isolated and characterized from *Catharanthus*, as well as from other species of plants. None of the monomeric α-methyleneindoline alkaloids from *Catharanthus* species have been shown to elicit antitumor activity; however, we have shown that lochnerinine exhibits significant cytotoxicity in cell culture against Eagle's 9 KB carcinoma of the nasopharynx.[3]

The purpose of this report is to present our evidence for the structures of two new α-methyleneindoline bases which we have recently isolated and characterized from the apocynaceous plant *Catharanthus lanceus*, namely, horhammericine (**1**) and horhammerinine (**2**).[4,5]

Both **1** and **2** could be analyzed in comparison with three other alkaloids of known structure, *i.e.*, lochnericine (**3**),[6–9] lochnerinine (**4**),[6–9] and minovincinine (**5**).[10,11]

The mass spectral fragmentations of **3** and **4** are presented in Scheme I.[6,9] It can readily be seen that

(1) This study was supported, in part, by Research Grants CA-08509, CA-08228, and FR-05445, from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md. The mass spectrometry was performed under Grant FR-00273 from the National Institutes of Health.

(2) For the previous paper in this series, see D. J. Abraham and N. R. Farnsworth, *J. Pharm. Sci.*, in press. Inquiries should be directed to D. J. Abraham.

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(4) R. N. Blomster, N. R. Farsnworth, and D. J. Abraham, *Naturwissenschaften*, **55**, 298 (1968).

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