[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Stereochemistry of the Ipecac Alkaloids[1]

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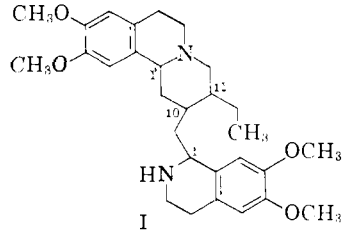
The results of stereospecific synthesis, supplemented by other definitive findings, are used to derive the first complete stereochemical formula (XXIX) for emetine and related Ipecac alkaloids.

Interest in the Ipecac alkaloid group, accentuated by the importance of emetine (I) in the treatment of amoebic dysentery, has resulted in degradative investigations sufficient to establish complete gross structures for all the known members of the family. In addition, the total synthesis of emetine has

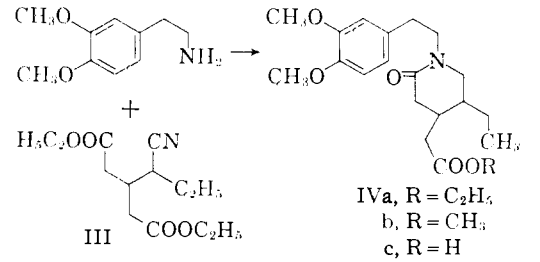


I

been accomplished, the first success belonging to Preobrazhensky and co-workers.[2-5] It is remarkable that, in contrast to the usual case of programs dealing with natural product structures, none of the information acquired in these investigations lends itself to stereochemical interpretation, and thus the interrelation of the four asymmetric centers in emetine remained unknown. The solution of this stereochemical problem is the subject of this publication.

Because of a particular foundation of experience already established in this Laboratory,[6-8] a seemingly expedient approach to positions 10 and 11 of emetine involved proving, through independent rational synthesis, the stereochemistry of a key intermediate in the Russian approach to emetine.[2] The route described by Preobrazhensky, *et al.*, involves addition of cyanoacetic ester to glutaconic ester; the resulting cyanotriester II was ethylated and decarboethoxylated to give the cyanodiester III. Reductive coupling with 3,4-dimethoxy-β-phenethylamine, carried out under hydrogenation conditions in the presence of nickel catalyst, led to the lactam ester IVa. In the generation of this intermediate, an opportunity for diastereoisomerism develops, and it was reported that substantial amounts of both isomers were formed.

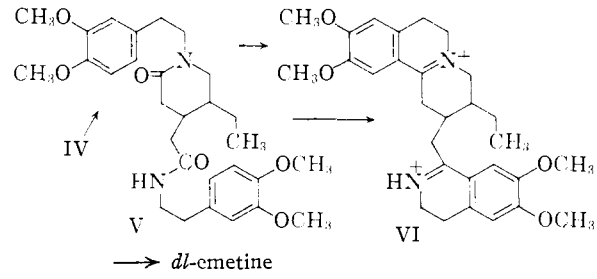
$H_5C_2OOCCH_2CH{=}CHCOOC_2H_5 + CNCH_2COOC_2H_5 \longrightarrow (H_5C_2OOCCH_2)_2CHCH(CN)COOC_2H_5$ (II) $\longrightarrow (H_5C_2OOCCH_2)_2CHC(CN)C_2H_5COOC_2H_5 \longrightarrow$



III

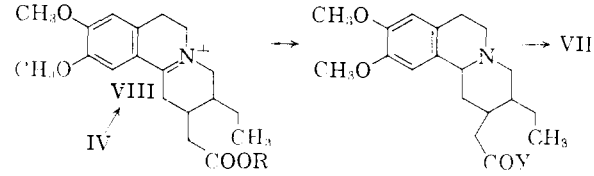
IVa, R = C_2H_5
b, R = CH_3
c, R = H

One of these piperidones, without elucidation of its stereochemistry, was carried through the steps IV–VII by the Russian workers in order to com-



dl-emetine

plete the synthesis.[2a] Alternatively, the piperidone IVa could be first cyclized (VIII) and reduced to the tricyclic ester IX; the latter was reported also



IX, Y = OR
X, Y = $3,4(OCH_3)_2C_6H_2CH_2CH_2NH$—

to yield emetine, after conversion to the corresponding 3,4-dimethoxyphenethylamide (X), followed by a second cyclization–reduction sequence.[2b] Clearly the operations proceeding from IV cannot affect the stereochemical relationship already established in this intermediate, and therefore assignment of its stereochemistry would define also the corresponding spatial configurations in emetine itself.

The necessity of securing intermediate IV provided the occasion for repeating the procedures of Preobrazhensky and co-workers. The steps leading to the cyanodiester III were reproduced, although on occasion some difficulty was encountered in effecting the last step, *viz.*, the selective hydrolysis and decarboxylation of the cyano-

(1) First reported in Communications to the Editor, THIS JOURNAL, (a) **79**, 4817 (1957); (b) **81**, 507 (1959).

(2) (a) R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova and N. A. Preobrazhensky, *Doklady Akad. Nauk., U.S.S.R.*, **75**, 539 (1950); (b) N. A. Preobrazhensky, R. P. Evstigneeva, T. S. Levchenko and K. M. Fedyshkina, *ibid.*, **81**, 421 (1951); (c) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958).

(3) M. Barash and J. M. Osbond, *Chemistry & Industry*, 490 (1958).

(4) A. R. Battersby and J. C. Turner, *ibid.*, 1324 (1958).

(5) A. W. Burgstahler and Z. J. Bithos, THIS JOURNAL, **81**, 503 (1959).

(6) E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 950 (1954); *cf.* G. Stork and R. K. Hill, *ibid.*, **76**, 949 (1954).

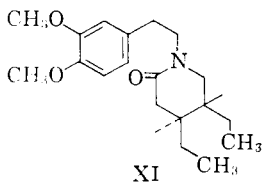
(7) E. E. van Tamelen, M. Shamma and P. E. Aldrich, *ibid.*, **78**, 4628 (1956).

(8) E. E. van Tamelen, P. E. Aldrich and T. J. Katz, *Chemistry & Industry*, 793 (1956); THIS JOURNAL, **79**, 6426 (1957).

acetic ester moiety.[9] The non-crystalline isomers (IVa) produced by reductive alkylation of 3,4-dimethoxy-β-phenethylamine with the cyanodiester were characterized by the Russian group only as "toluene-soluble" ("isomer-A") and "toluene-insoluble" ("isomer-B"); the "toluene-insoluble" material was used in the conversion to emetine. Although we could not confirm the reported solubility behavior, we were able to separate, by means of chromatography on silicic acid, the mixture of piperidonecarboxylic acids (IVc) obtained by mild saponification of the crude ester mixture. There were isolated two pure isomers, m.p.'s 151.2–152.5° and 155.2–156.3°,[10] the infrared and ultraviolet spectra of which were completely consistent with the structure IV.

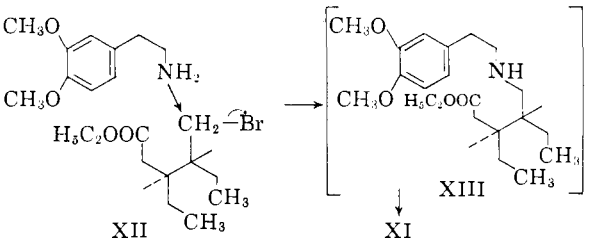
Because there was no way for us to associate either of these piperidonecarboxylic acids with the material used by the Russians in carrying through the total synthesis, we also were required to demonstrate which acid is convertible to the alkaloid. Thus, the methyl ester IVb of each of the acids was transformed by heating with 3,4-dimethoxy-β-phenethylamine to the lactam amide V, which was cyclized by treatment with phosphorus oxychloride. The bis-quaternary salt VI obtained from the higher-melting acid, on catalytic hydrogenation over platinum, gave product which, after purification by crystallization in the form of the hydrochloride salt, was identified as *dl*-emetine, contaminated with some *dl*-isoemetine (the C-1 epimer of emetine). On the other hand, the lower melting piperidone acid gave material at the emetine stage which did not easily form crystalline salts; infrared analysis showed the absence of *dl*-emetine.

The plan evolved for proving the stereochemistry of the piperidone acids included (i) transformation of one of these isomers, through routes which cannot alter the stereochemistry, to the lactam XI of *dl*-N-(3′,4′-dimethoxy-β-phenethyl)-*threo*-



XI

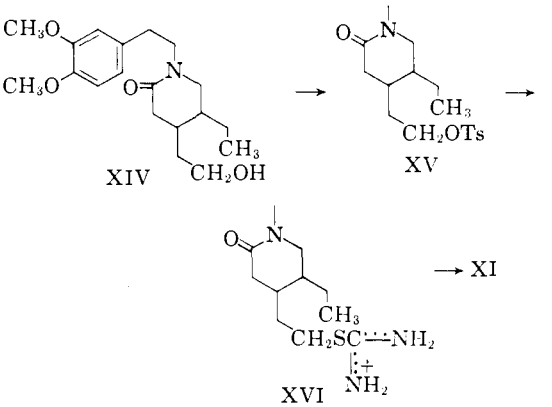
3,4-diethyl-5-aminovaleric acid, and (ii) stereorational synthesis of this reference compound through N-alkylation of 3,4-dimethoxy-β-phenethylamine with ethyl *dl-threo*-3,4-diethyl-5-bromovalerate (XII). The synthesis and stereochemistry of this bromoester were known from earlier work carried out in this Laboratory.[8] The conversion of XII to XI proceeded smoothly; as expected, the intermediary alkylation product, the aminoester



XII XI

XIII, cyclized under the conditions of the reaction to the desired *trans*-lactam XI, a high-boiling liquid.

In order to accomplish the correlation between the emetine synthesis intermediate IV and the diethyl lactam stereoisomer XI, the methyl ester of the higher melting piperidone acid was reduced selectively through the use of lithium borohydride under carefully defined conditions to the lactam alcohol XIV, m.p. 115.8–118.0°.[11] Preparation of the corresponding tosylate XV was followed by conversion to the isothiouronium salt XVI; reductive desulfurization with Raney nickel then gave rise to a good yield of product identical



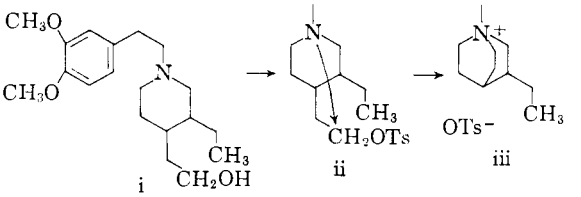
XIV XV XVI

with the lactam XI of known stereochemistry.[12] The identification of the lactam IV as a member of the *trans* series was substantiated by phosphorus oxychloride cyclization and catalytic hydrogenation of the lactam XI from both sources; the two specimens of crystalline hydrochlorides, as well as the

(9) In order to circumvent this last pair of steps, benzyl—rather than ethyl—cyanoacetate was utilized in the Michael addition to diethyl glutaconate. Following the alkylation of the resulting monobenzyl, diethyl ester, removal of the benzyl group by palladium-catalyzed hydrogenolysis was accompanied by decarboxylation, thereby affording cyanodiester identical with material provided by the original route. This modification was not, however, entirely free of practical difficulties, and offers no advantage over the original procedure.

(10) Preparation of these acids also has been reported by Barash and Osbond[3] and by Battersby and Turner.[4]

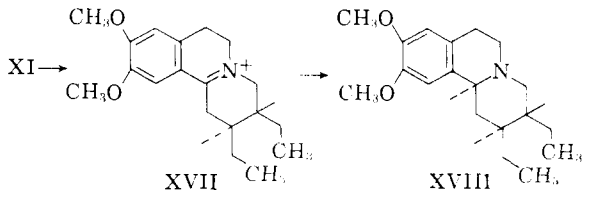
(11) Reduction of the ester group with maintenance of the lactam function appeared to be necessary for the successful prosecution of the scheme outlined above. Thus, although total reduction with lithium aluminum hydride is attractive because of its simplicity, tosylation of the resulting alcohol i would very likely be followed by cyclization



i ii iii

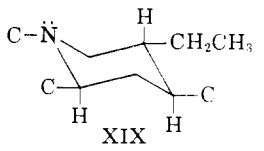
(ii) to the quinuclidine quaternary salt (iii); because of the symmetry properties of the latter, the stereochemical relationship characteristic of the preceding intermediates would be absent in this substance.

(12) Because our supply of the *trans*-lactam acid IV was limited, the conditions for its conversion to the *trans*-diethyl compound XI were developed in a model series. β-Phenethyl tosylate was converted to the isothiouronium tosylate, which, on nickel desulfurization (E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946)) provided a 95% yield of ethylbenzene.

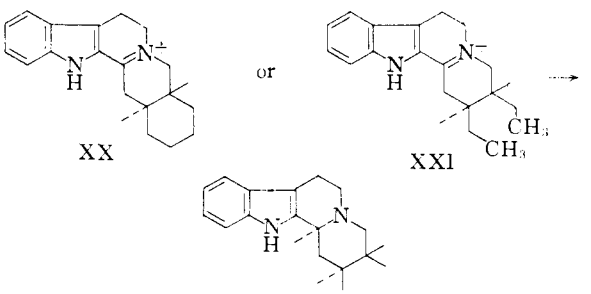


tetrahydroisoquinoline free bases XVIII, were indistinguishable. In this way, the *trans* stereochemical relationship of C-10 and C-11 in emetine was established.[13,14]

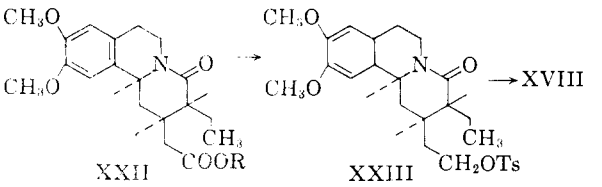
All of the available evidence indicates that the hydrogen at C-1′ in emetine is *cis* oriented with respect to the hydrogen at C-10. The fact that emetine, rather than a diastereoisomer, is produced from the $\Delta^{1',2'}$-unsaturated intermediate VI by catalytic reduction suggests that this more stable configuration, *i.e.*, C-1′ axial hydrogen (XIX), is generated. Since similarly constituted substances,



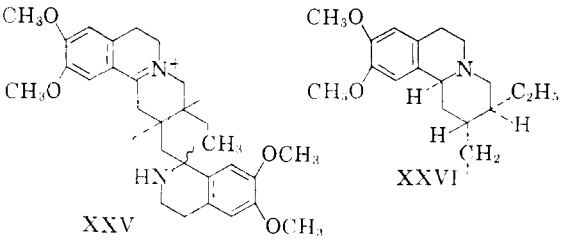
e.g., Δ^3-dehydroyohimbane (XX) and -corynantheane (XXI) (both D/E *trans*) are reduced to members of the C-3, C-15-*cis* category,[6-8] similar



behavior might be anticipated in the case under scrutiny. Support for this tentative conclusion was acquired in several ways. First, lithium aluminum hydride reduction of the cyclized intermediate VI yielded the same products formed by catalytic reduction. This imine salt does not present any exceptional steric barrier to reduction and, in the absence of such a factor, hydride reduction to the more stable product would be expected. Second, sodium and alcohol reduction of one of the reference compounds, the imine salt XVII, gave rise to the same tetrahydroisoquinoline isomer produced by catalytic hydrogenation, with no detectable amount of its epimer.[15] The reduction product must have, therefore, the more stable configuration, and the stereochemistry already portrayed in structure XVIII follows. Catalytic reduction of the emetine synthesis intermediate VI is closely akin to that of XVII, and one would expect the same stereochemical outcome at C-1′. Finally, a correlation independent of certain assumptions implicit in the above arguments, has been achieved: the conversion, by means of an unambiguous method, of the emetine synthesis intermediate XXII[5] to the tricyclic reference compound XVIII. Lithium borohydride reduction followed by tosylation provided the lactam XXIII; lithium aluminum hydride reduction of the latter then afforded the base XVIII, of established *trans* stereochemistry.[16]



During the course of the work described above, and after our preliminary results were announced,[1a] the assignment of relative stereochemistry at C-1′ was questioned by Brossi, Cohen, Osbond, Plattner, Schnider and Wickens.[14] These authors alleged that (i) contrary to the report of Preobrazhensky *et al.*, the tricyclic intermediate IX gave rise to—not emetine—but two diastereoisomers of the natural base (Aa_1 and Ab_2); (ii) again in conflict with the Russian investigators, catalytic reduction of the tetradehydroemetine VI afforded 80% of the emetine isomer Ab_2; and (iii) the intermediate XXV on hydrogenation led to only a 20% yield

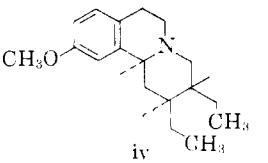


of emetine, in addition to Ab_2. Brossi, *et al.*, accepted the previous findings[1a] which required that the reduction processes described generate the more stable configuration at C-1′, and therefore were obliged to entertain a new stereochemical expression (XXVI) for emetine and related alkaloids, in which the assignment at C-1′ was the reverse of that initially proposed. More recently,

(13) A synthesis of XI, identical with the one described above, constitutes the unambiguous portion of the evidence cited in support of the 10,11-*trans* relationship by Battersby, *et al.* (*Chemistry & Industry*, 982, 983 (1957)), who, without reference to our previous work,[8] described the same bromo ester intermediate XII, and synthesis thereof, first used in another connection in this Laboratory.

(14) The 10,11-*trans* assignment to emetine was supported by A. Brossi, A. Cohen, J. M. Osbond, Pl. A. Plattner, O. Schnider and J. C. Wickens (*Chemistry & Industry*, 491 (1958)), who related the *cis*-piperidoneacetic acid (IV) to ethyl cincholoiponate, the stereochemistry of which had been established previously (V. Prelog and E. Zalan, *Helv. Chim. Acta*, **27**, 535 (1944)).

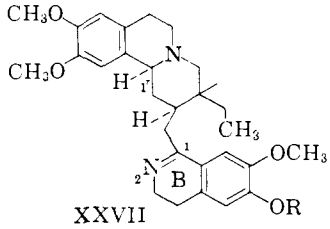
(15) In addition to the normal reduction product, there was isolated a second substance, which elemental, methoxyl and spectral analysis showed to be demethoxylated material. This course of sodium and alcohol reduction is precedented by the case of O-methylpsychotrine (XXVII, R = CH_3) (F. L. Pyman, *J. Chem. Soc.*, 111, 419 (1917)) and structure iv is assigned to this reductive cleavage product.



(16) The preparation and reduction to tosylate XXIII were carried out by A. W. Burgstahler and Z. J. Bithos,[5] to whom we are indebted for coöperation.

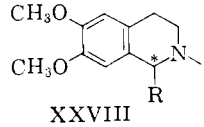
the question of the reduction products was reinvestigated in several laboratories,[1b,17,18] with the result that the contentions of Brossi, *et al.*, were disproved, and the findings of Preobrazhensky, *et al.*, verified. Thus the original stereochemical expression XIX has been vindicated.

Past investigations in the Ipecac field have shown that all of the known side alkaloids of emetine possess the same stereochemistry in the benzoquinolizidine ring system as emetine itself.[19] Consequently, the relative stereochemistry depicted in formula XXVII describes: psychotrine (R = H), O-methylpsychotrine (R = CH_3), cephaeline (R = H, 1,2-double bond saturated), emetamine (R = CH_3, ring B aromatic), emetine and isoemetine (R = CH_3, 1,2-double bond saturated).



XXVII

Connected to the now thoroughly explored tricyclic region by only a methylene bridge, the second, insular tetrahydroisoquinoline ring of emetine bears a fourth asymmetric center more or less free from the influence of the other three, and consequently difficult to relate stereochemically to them by any direct, conventional means. For example, catalytic or chemical reduction of O-methylpsychotrine leads, respectively, to isoemetine, or a mixture of emetine and isoemetine; however, in our present state of knowledge, these observations do not allow a configurational conclusion to be drawn. Now, the presence of two similarly composed 6,7-dimethoxytetrahydroisoquinoline rings, bearing asymmetric centers in comparable environments, brings to mind the possibility of correlating their configurations in an absolute sense and in this way establishing the configuration of C-1 relative to the other center. Conversion of each of the bicyclic moieties to a structurally common degradation product in which the asymmetric center is retained



XXVIII

(XXVIII), would constitute a rigorous stereochemical proof, but also an onerous experimental chore. A simpler means is possible by virtue of the fact that, of the four asymmetric carbons, only C-1 and C-1′ adjoin ultraviolet chromophores, and therefore the optical rotatory dispersion pattern[20] of emetine should be comprised largely of the individual contributions of these two centers. More exactly, if the assumption is made that the optical behavior of centers C-1 and C-1′ will be similar when their absolute configurations are the same, then in the stereoisomer where the two centers are "antipodal," the individual contributions might be expected to cancel each other in the range 300–700 mμ, with the result that, in an ideal case, no rotational change would characterize this region of the spectrum. Conversely, in the case where the absolute configurations are the same, the individual optical contributions should be additive, and the normal change of rotation with wave length should be observed. In Fig. 1 are reproduced the optical rotatory dispersion curves of emetine hydrobromide and its C-1 epimer, isoemetine hydrobromide.[21]

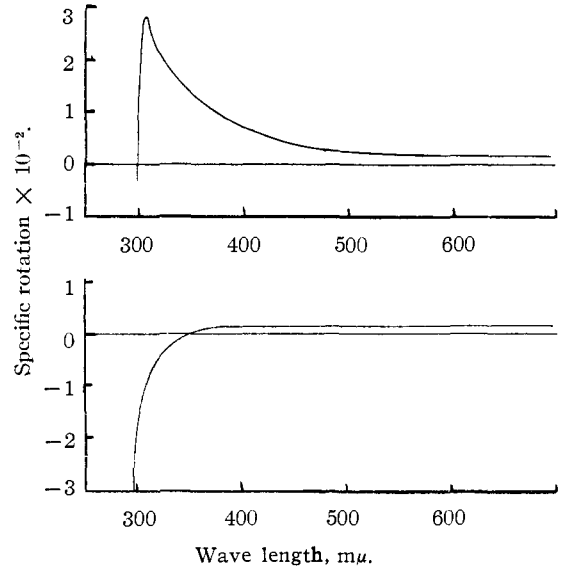
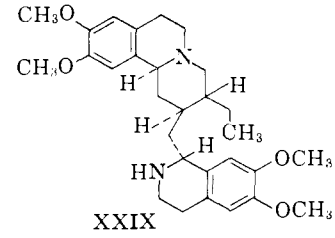


Fig. 1.—Upper: isoemetine hydrobromide, *c* 0.277 (700-400 mμ), *c* 0.0554 (375-300 mμ) in water; lower: emetine hydrobromide, *c* 0.189 (700-305 mμ), *c* 0.0378 (300-295 mμ) in water.

In the former case, the optical rotation remains constant at a small positive value between approximately 350 and 700 mμ, thereby suggesting that C-1 and C-1′ possess the opposite absolute configurations. In the case of isoemetine, however, a gradual increase in positive rotation with a



XXIX

maximal rotation at 300 mμ, is found—welcome confirmation of the conclusion that the corresponding set of asymmetric carbons are alike in this

(17) A. Battersby, *Chemistry & Industry*, 1324 (1958).
(18) J. M. Osbond, *ibid.*, 257 (1959).
(19) M.-M. Janot, R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. III, Academic Press, Inc., New York, N. Y., 1953, pp. 363–394.
(20) C. Djerassi, *Bull. soc. chim. France*, 741 (1957).
(21) The authors are grateful to Professor Djerassi for supplying the optical rotatory dispersion data, and to Dr. Openshaw for a sample of isoemetine.

case.[22] These findings,[1b] along with those previously described, define the relative configuration of all the asymmetric centers in emetine; the relationships are expressed in XXIX, which represents the first correct proposal of a complete stereoformula for this alkaloid.[23,24]

Acknowledgment.—The authors are grateful to the Wisconsin Alumni Research Foundation and to the National Institutes of Health (RG-3892) for financial support.

Experimental[25]

Ethyl 5-Ethyl-1-homoveratryl-2-piperidone-4-acetate (IVa).—The mixture of *cis* and *trans* isomers[2] was prepared by reducing 53.4 g. (0.295 mole) of homoveratrylamine and 11.3 g. (0.0443 mole) of III in an autoclave with 12 g. of W-2 Raney nickel and 23 ml. of commercial absolute ethanol for several hours at 110°.

After the product had been cooled and removed from the bomb, it was filtered, and the excess alcohol was evaporated from the filtrate. A little ice was added, and ice-cold concentrated hydrochloric acid was added with stirring until the solution was acid to congo red. The solution was extracted with chloroform several times, and the chloroform extracts were washed with saturated sodium chloride solution until the washings were no longer acid to congo red. The chloroform extracts were dried with anhydrous magnesium sulfate, filtered and evaporated. The residue was taken up in a small amount of warm benzene and allowed to come slowly to room temperature. Some homoveratrylamine hydrochloride (somewhat soluble in chloroform) crystallized and was filtered off.

The benzene filtrate was chromatographed on Merck acid-washed alumina. The chromatogram was run many times, but the successful eluent for the lactam was inconstant and varied from benzene to 50% chloroform in ether (vol.: vol.), even though the same batch of alumina was used. The various fractions were examined by infrared spectroscopy, and those fractions having the lactam absorption band at 6.19 μ were retained, whereas the other fractions were rejected. The yield of carefully chromatographed ester having the 6.19 μ band was 4.86 g. (29% of theory). This was a mixture of stereoisomers which appeared not to be satisfactorily separated by further chromatography.

***trans* and *cis*-5-Ethyl-1-homoveratryl-2-piperidone-4-acetic Acid (IVc).**—To 10 ml. of ethanol was added 1.62 g. (4.28 mmoles) of the mixture of esters IVa (as obtained in the preceding preparation), and 4.43 ml. of 0.966 *N* potassium hydroxide (4.28 meq.). The mixture was refluxed 5 hours. After standing overnight at room temperature, the mixture was evaporated, water was added and the mixture was extracted with chloroform. The chloroform extracts yielded 176 mg. of a neutral oil, which was not further investigated.

The aqueous layer was acidified to congo red with hydrochloric acid and extracted with chloroform, which was washed with saturated sodium chloride. The chloroform extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give 1.37 g. of crude oily crystals.

The crude acid was carefully chromatographed on Mallinckrodt Analytical Reagent 100 mesh silicic acid (washed with acetone and dried overnight at about 75°). Elution with commercial reagent grade chloroform gave 499 mg. (33%) of *trans*-acid, m.p. 152–154° (Kofler). The acid was soluble in chloroform, slightly soluble in ethyl acetate and benzene, and insoluble in petroleum ether. For analysis, the acid was crystallized to constant melting point from ethyl acetate, m.p. 155.2–156.3°.

Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79. Found: C, 65.50; H, 7.71.

The *cis*-acid was eluted by chloroform *after* the *trans*-acid. The yield of *cis*-acid was 93 mg. (6% yield). Recrystallization of the *cis*-acid from ethyl acetate to constant melting point gave material having m.p. 151.2–152.5°. The infrared spectra of the acids were similar, but differed in detail. Mixed melting point comparison showed a marked depression.

Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79. Found: C, 65.4; H, 7.51.

***trans*-4-β-Hydroxyethyl-5-ethyl-1-homoveratryl-2-piperidone (XIV).**—The *trans*-acid IVc (508 mg., 1.35 mmoles) was converted to its methyl ester IVb by diazomethane esterification in a mixture of ether and methanol. The infrared spectrum of the ester was consistent with structure IVb. The ester was transformed with the aid of ethanol to a 20-ml. flask equipped with reflux condenser and drying tube, all solvent was evaporated off, and 10 ml. of 0.844 *M* lithium borohydride in tetrahydrofuran was added. (The standardization of the lithium borohydride solution is described below.) The mixture was refluxed; the refluxing was stopped periodically, and the infrared spectrum of a microsample was taken to check on the course of the reaction. After a total of 20 minutes of reflux time, the ester absorption band at 5.81 μ had disappeared, whereas after 45 minutes of refluxing the amide band at 6.18 μ was not noticeably changed.

The cooled product was washed several times with saturated sodium chloride solution. (This conveniently removed the excess lithium borohydride without the inconvenience of formation of insoluble boric acid and violent hydrogen evolution due to acidification.) Washing was continued with slightly acidified saturated sodium chloride solution, alkaline sodium chloride solution, and finally twice again with neutral sodium chloride solution. The organic layer was concentrated at reduced pressure, azeotroped with toluene, ethanol and chloroform and filtered to remove sodium chloride. Evaporation of the chloroform solution gave an oil which could be induced to crystallize with a drop of ethyl acetate. Recrystallization from ethyl acetate gave 397 mg. (81%) of the alcohol, m.p. 109–113°. It was recrystallized to constant m.p. 115.8–118°.

Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71. Found: C, 68.20; H, 8.65.

Standardization of Lithium Borohydride Solution.—A known excess of standard hydrochloric acid was added to a volume of the tetrahydrofuran solution of lithium borohydride. After the vigor of the reaction had subsided, the excess acid was titrated with standard 0.1 *N* potassium hydroxide. A *p*H meter was used to determine the end-point. The method is a modification of the analytical method of Davis, Mason and Stegeman for borohydrides.[26]

***trans*-4,5-Diethyl-1-homoveratryl-2-piperidone (XI).**—(A) The alcohol XIV (94.1 mg., 0.0281 mmole) was dissolved in 300 mg. of dry pyridine with a little warming. The solution was cooled in an ice-bath, and 68.1 mg. (0.0356 mmole) of *p*-toluenesulfonyl chloride was dissolved in the mixture. The mixture was protected from moisture and stored at 5° overnight. A drop of water was added and the mixture was allowed to stand for 15 minutes at 5° to allow the excess toluenesulfonyl chloride to decompose. Excess water was added, the mixture was extracted successively with these various ice-cold washes: dilute sulfuric acid, water, dilute sodium bicarbonate and water (twice). The chloroform layer was dried with sodium sulfate, filtered and evaporated to dryness. There resulted 138 mg. of an almost colorless oil, which was chromatographed on silicic acid with chloroform to give 110 mg. (75%) of colorless oil. The infrared spectrum showed the expected tosylate ester absorption bands and was free of hydroxyl absorption bands.

The tosylate ester XV (110 mg., 0.208 mmole) was refluxed with thiourea (16 mg., 0.21 mmole) in 20 drops of absolute ethanol for five minutes. The ethanol was evaporated to give a colorless oil which could not be induced to crystallize. The infrared spectrum of the product was consistent with the structure XVI.

(22) The regions below 350 mμ approach the point at which the ultraviolet absorption maxima of the alkaloids appear, and therefore minor structural variations at C-1 and C-1′ may produce dramatic (and for the present purpose, irrelevant) rotational behavior.

(23) The absolute configuration implied by XXIX follows from Battersby's assignment, based on molecular rotation data, of the absolute configuration to C-1 (reference, footnote 13).

(24) Subsequent to our preliminary proposal[1b] of stereoformula XXIX, A. R. Battersby and S. Garratt (*Chemistry & Industry*, 86, 1959)) as well as Y. Ban, M. Terashima and O. Yonemitsu, *ibid.*, 568, 569 (1959), disclosed different sets of results in support of the assigned configurational relationship of C-1 to the other centers.

(25) All melting points are corrected, except those taken on a Kofler hot-stage.

(26) W. D. Davis, L. S. Mason and G. Stegeman, THIS JOURNAL, **71**, 2775 (1949).

The isothiouronium tosylate salt XVI was refluxed with 0.5 g. of W-2 Raney nickel in a 10-ml. flask with 5 ml. of ethanol for 30 minutes. The mixture was filtered to give a pale green solution. This was evaporated to dryness and triturated with chloroform and filtered. The chloroform solution was chromatographed on silicic acid with chloroform to give 39 mg. (59%) of the oily piperidone XI.

(B) Homoveratrylamine (1.50 g., 8.79 mmoles), ethyl *threo*-5-bromo-3,4-diethylvalerate[8,9] (1.96 g., 7.40 mmoles) and anhydrous potassium carbonate (1.0 g., 15 meq.) were refluxed with a crystal of potassium iodide as a catalyst in 20 ml. of dry dioxane for 110 hours. The product was filtered, and the filtrate was evaporated to dryness. The residue was taken up in ether and washed with dilute acid and saturated sodium chloride solution. The ether layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The resulting oil was chromatographed on alumina. Those fractions which possessed the characteristic lactam infrared absorption band at 6.20 μ were combined and distilled at 0.1 mm. in a creased sublimation tube at a jacket temperature of 128–130°. The distillate weighed 996 mg. (43%), $n^{25}D$ 1.5305.

Anal. Calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.15; H, 8.92.

The infrared spectra of the piperidones prepared by methods A and B were indistinguishable. The products from procedures A and B were independently carried through to the tricyclic compound XVIII (*vide infra*).

7,8-Diethyl-4′,5′-dimethoxy-3,4,6,7β,8α,9-hexahydro-10α-benzo[1′,2′,1,2]quinolizine Hydrochloride (XVIII).—The lactam XI (348 mg., 1.10 mmoles) was refluxed with 1 ml. of freshly distilled phosphorus oxychloride in 10 ml. of toluene for 2 hours. The product was evaporated at reduced pressure, taken up in chloroform, and washed with saturated sodium chloride. The chloroform extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to give a dark viscous oil, presumably crude material of structure XVII.

The oil was hydrogenated at atmospheric pressure in 12 ml. of ethanol over platinum (37 mg. of platinum dioxide). The material took up 80% of one molar equivalent of hydrogen within 30 minutes. The product was filtered, and the ethanol was gradually replaced with ethyl acetate at the steam-bath until crystallization began to take place. On cooling, 261 mg. (74%) of the hydrochloride salt of XVIII crystallized, m.p. 247.5–248.5°.

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 67.13; H, 8.90. Found: C, 66.70; H, 8.57.

This procedure was carried out for material from both procedures A and B (*vide supra*). The mixed melting point of the hydrochloride salt from the two sources showed no depression. The free base was prepared from the hydrochloride as a colorless oil by treatment with dilute ammonium hydroxide and extraction with chloroform. The infrared absorption spectra of the base from the two different sources were identical. The free base was rather unstable and darkened slowly on long standing.

Sodium in Alcohol Reduction of *trans*-7,8-Diethyl-4′,5′-dimethoxy-$\Delta^{5(10)}$-dehydro-3,4,6,7,8,9-hexahydrobenzo-1′,2′,-1,2-quinolizinium Chloride (XVII).—The lactam XI (987 mg., 3.09 mmoles) was refluxed with 3 ml. of freshly distilled phosphorus oxychloride in 20 ml. of toluene and worked up as in the preceding preparation to give 1.16 g. of the crude tricyclic dehydro-compound XVII.

The crude product was placed in a 200-ml. flask equipped with paddle-stirrer, reflux condenser, nitrogen inlet and dropping funnel. While a nitrogen atmosphere was maintained, 5 ml. of absolute ethanol and 1 g. of sodium were added. More absolute alcohol was added from time to time to keep the mixture fluid. After 30 minutes the sodium had dissolved. The product was acidified with dilute, ice-cold hydrochloric acid. The solution was made basic with 30% sodium hydroxide and extracted with ether to give 703 mg. (76%) of crude base.

Chromatography of the products on silicic acid gave poor separation of the bases. However, by a combination of chromatography and fractional crystallization of the hydrochlorides of the bases, it was possible to separate out the dimethoxy-compound XVIII, identical with material obtained by catalytic hydrogenation. The hydrochloride of the other base, *viz.*, 7,8-diethyl-5′-methoxy-3,4,6,7β,8α,9-hexahydro-10α-benzo[1′,2′,1,2]quinolizine (iv), was not crystalline, but the hydriodide could be crystallized in the following way. The oily base was taken up in ether, and dry hydrogen chloride was bubbled into the solution to give the insoluble, oily hydrochloride salt. The material was centrifuged, and the ether layer was decanted off. The residue was dissolved in chloroform and shaken with a concentrated aqueous solution of sodium iodide. The chloroform layer was washed with two small portions of water and evaporated to dryness. The product crystallized when a few drops of ethyl acetate were added. Recrystallization from ethyl acetate to constant melting point gave material having the m.p. 205–207° (Kofler).

Anal. Calcd. for $C_{18}H_{28}INO$: C, 53.88; H, 7.03; CH_3O, 7.44. Found: C, 53.64; H, 7.03; CH_3O, 7.77.

The Model Series. β-Phenethylisothiouronium *p*-toluenesulfonate was prepared by heating 3.81 g. (13.1 mmoles) of β-phenethyl *p*-toluenesulfonate (m.p. 38.8–40.0°) and 1.00 g. (13.1 mmoles) of thiourea in about 2 ml. of ethanol on the steam-bath for 5–10 minutes. On cooling, the material began to crystallize. The first crop weighed 3.69 g. (76%) and had m.p. about 181°. Recrystallization from ethanol gave the m.p. 180–183° (Kofler).

The isothiouronium salt (1.00 g., 2.71 mmoles) was refluxed with 3 g. of W-2 Raney nickel in 95% ethanol for 30 minutes. The nickel was filtered off, and the product was distilled. The ultraviolet spectrum of the material showed a yield of ethylbenzene of 95%, based upon the reported extinction coefficient of 216 at 267 mμ for ethylbenzene.[27]

***dl-trans*-5-Ethyl-1-(3,4-dimethoxyphenethyl)-2-piperidone-4-(N-3,4-dimethoxyphenethyl)-acetamide (V).**—A solution of 529.2 mg. (1.52 mmoles) of the *trans*-lactam acid IV (R = H), m.p. 154–156°, in a small amount of ice-cold ethanol was titrated with an ethereal solution of diazomethane. After the solvent had been removed on the steam-bath the crude methyl ester was dissolved in 626.3 mg. (3.45 mmoles) of 3,4-dimethoxyphenethylamine, b.p. 116° (0.7 mm.), and heated under nitrogen at 180–200° for 3 hr. Excess amine then was washed from a chloroform solution of the reaction mixture with dilute hydrochloric acid; the chloroform extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate and concentrated at reduced pressure to yield 936.9 mg. of the crude diamide V. This was purified by chromatography on Merck acid-washed alumina. A homogeneous oil (812.9 mg., 104%) which was pure enough for subsequent reactions was eluted from the column with chloroform.

The Hydrochloride of *dl*-Δ¹-Dehydro-O-methylpsychotrine Chloride (VI).—A mixture of 470.7 mg. (0.92 mmole) of the diamide V, 8 ml. of anhydrous toluene and 800 mg. of freshly distilled phosphorus oxychloride was allowed to reflux under nitrogen for 1.5 hours. Concentration of the reaction mixture *in vacuo* yielded a thick residue which was washed repeatedly with absolute ether to remove traces of phosphoric acid and phosphorus oxychloride. The red oil thus obtained was used directly for subsequent reductions.

***dl*-Emetine (VIIa) and *dl*-Isoemetine (VIIb) from VI.**—A solution of VI, prepared from 269.2 mg. (0.526 mmole) of the diamide V, in absolute ethanol was hydrogenated at atmospheric pressure over a prereduced platinum oxide catalyst. The hydrogenation proceeded with difficulty; it was, therefore, necessary to replace the catalyst two times over a period of 3 hours in order to obtain 62% of the theoretical hydrogen uptake. To ensure complete reduction the material finally was subjected to hydrogenation over platinum oxide at a hydrogen pressure of 1900 p.s.i. for 30 minutes. The catalyst was then removed by filtration through Filtercel, and the filtrate was concentrated to dryness. The residual hydrochloride was dissolved in water and treated with dilute ammonium hydroxide to precipitate the free base. This was extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over anhydrous potassium carbonate and concentrated to yield a tan oil which was taken up in a small amount of ether and treated with an ethereal solution of anhydrous hydrogen chloride. The resulting hydrochloride was crystallized several times from ethanol–ethyl acetate to obtain a compound which began to turn dark at 207° and became fluid at 230° on the hot-stage. It was dissolved in water and the free base was precipitated with dilute ammonium hydroxide, collected by vacuum filtration and dried over soda lime at 0.1 mm. for

(27) A.P.I. Research Project No. 44, Ultraviolet Absorption Spectrogram, N.B.S., Washington, D. C., Serial No. 20.

12 hours, m.p. 59–65° (uncor.). This amorphous solid had an infrared spectrum which was identical to that of a mixture of authentic *l*-emetine[28] and *l*-isoemetine.[29]

B. An aqueous solution of VI was treated with a dilute sodium iodide solution; the iodide salt thus formed was extracted with chloroform; the chloroform extracts were washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated to yield a red oil. A solution of 344.5 mg. (0.471 mmole) of this material in chloroform was placed into a 200-ml., 3-necked flask fitted with a mechanical stirrer and vacuum take-off. To this solution was added a small amount of dry sea sand, and the solvent was removed *in vacuo* with stirring thus depositing the hydroiodide on the sand and increasing its surface area. Last traces of chloroform were removed by distilling two portions of dry benzene from the mixture and finally allowing it to dry under reduced pressure for several minutes. Fifty milliliters of dry tetrahydrofuran then was added to the flask and the system was evacuated and filled three times with nitrogen. Lithium aluminum hydride (182.1 mg., 4.8 mmoles) then was added and the mixture was allowed to reflux for 3.5 hours with stirring. After the excess hydride had been decomposed with water the solvent was concentrated *in vacuo* to 5-10 ml., and the resulting mixture was poured into 200 ml. of a 5% sodium hydroxide solution. This was extracted with ether; the ether extracts then were extracted with dilute hydrochloric acid which was made ammoniacal to reprecipitate the free base. The latter was extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over potassium carbonate and concentrated to yield 184.2 mg. (71%) of crude free base. This material was not purified further; however, its infrared spectrum indicated that it was composed largely of *dl*-emetine.

Methyl 4′,5′-Dimethoxy-6-ethyl-3,4,5,6,7,8-hexahydrobenzo[1′,2′,1,2]quinolizine-7-acetate (IX, X = OMe).—An ice-cold ethanolic solution of the *trans*-lactam acid IV (R = H, 146.6 mg., 0.542 mmole, m.p. 154.5–158°) was treated with an excess of an ethereal solution of diazomethane. The solution was concentrated to dryness *in vacuo* and the residue was purified by chromatography on silicic acid. With a 1% solution of ethanol in chloroform 147.8 mg. of a light yellow oil (IV, R = CH_3) was eluted. This was dried in a vacuum desiccator over potassium hydroxide for 12 hours. It was then dissolved in 5 ml. of anhydrous toluene, treated with 0.5 ml. of freshly distilled phosphorus oxychloride, and refluxed gently under nitrogen. As the reaction proceeded the solution rapidly became cloudy, and a red oil was deposited on the bottom of the flask. After 1.5 hours the reaction mixture was cooled and concentrated to dryness *in vacuo*. The residue was taken up in chloroform, washed with a saturated sodium chloride solution, dried over sodium sulfate and concentrated to yield a red oil (VIII, R = Me). This was not further purified but was dissolved in ethanol and hydrogenated at atmospheric pressure over a prereduced platinum oxide catalyst. After 30 minutes the reaction had stopped and 102% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by vacuum filtration through Filter-cel and the filtrate was concentrated to dryness. This hydrochloride was taken up in water, cooled in an ice-bath, made ammoniacal with dilute ammonium hydroxide and extracted with ether. The ether extracts were washed with saturated sodium chloride, dried over anhydrous potassium carbonate, and concentrated to yield 148.4 mg. of crude free base which was purified by silicic acid chromatography. The produce (IX, X = OMe) was eluted with a 1% ethanol–chloroform solution and crystallized from petroleum ether (b.p. 65–67°) to yield 117.2 mg. (80.5%) of colorless needles, m.p. 78–82° (uncor.). This compound was soluble in practically all organic solvents. It was crystallized from petroleum ether for analyses, m.p. 78.9–79.2° (cor.); λ_{max} 282 mμ (ε 3900), λ_{max} 296 mμ (ε 3920), shoulder 223 mμ (ε 8780).[30]

By way of confirmation, a solution of 24.8 mg. of IX (X = OMe), m.p. 79–100° (uncor.), in ether was treated with an ethereal solution of anhydrous hydrogen chloride and concentrated to dryness. The residue was dried in a vacuum desiccator over potassium hydroxide and crystallized several times from methyl acetate to yield 20.5 mg. of the hydrochloride, m.p. 202.8–204.0° (cor., sealed tube). Regeneration of the free base from this hydrochloride in the usual manner followed by crystallization from petroleum ether yielded needles, m.p. 79–101° (uncor.).

It is also noteworthy that 3,4-dimethoxyphenethylamide (IX) of good quality was formed by heating IX (X = OMe) with homoveratrylamine.

The hydrochloride of IX (X = OMe) was crystallized from methanol–methyl acetate for analysis, m.p. 205.6–206.1° (cor., sealed tube).

Anal. Calcd. for $C_{20}H_{29}O_4N\cdot HCl$: C, 62.57; H, 7.88. Found: C, 62.60; H, 7.95.

4′,5′-Dimethoxy-6-ethyl-7-(ω-hydroxyethyl)-3,4,5,6,7,8-hexahydrobenzo[1′,2′,1,2]quinolizine (XXIII).—To a solution of 75.9 mg. (0.219 mmole) of the tricyclic ester IX (X = OMe), m.p. 79–82°, in about 10 ml. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, was added, under nitrogen, a suspension of 85.2 mg. (2.24 mmoles) of lithium aluminum hydride in 10 ml. of tetrahydrofuran. After being allowed to stand for 1 hour at room temperature the reaction mixture was allowed to reflux for 30 minutes. It then was cooled in an ice-bath, and the excess hydride was decomposed with water. The mixture was concentrated to about 5 ml. *in vacuo* and diluted with a 5% solution of sodium hydroxide. This was extracted with ether and the ether extracts were washed consecutively with a 5% sodium hydroxide solution, water and saturated sodium chloride. The combined ether extracts were dried over sodium sulfate and concentrated to yield 90.1 mg. of an oil which was purified by chromatography on silicic acid. With a 1–2% solution of ethanol in chloroform 53.7 mg. of an oil was eluted from the column. This was converted to its hydrochloride which was crystallized from ethanol–ethyl acetate to yield 36.2 mg. (46.6%) of colorless plates, m.p. 197–209° dec. (uncor.). It was crystallized from ethanol–ethyl acetate for analysis, m.p. 243.2–244.7° (cor., sealed tube).

Anal. Calcd. for $C_{19}H_{29}O_3N\cdot HCl$: C, 64.12; H, 8.50. Found: C, 63.99; H, 8.33.

Some of the pure hydrochloride was dissolved in water and made ammoniacal with dilute ammonium hydroxide. The free base was extracted with ether, and the ether extracts were washed with saturated sodium chloride, dried over anhydrous potassium carbonate, concentrated to dryness at reduced pressure and dried at 0.1 mm. over potassium hydroxide for 2 hours. An infrared spectrum of this material was identical to that of an authentic sample of the alcohol XXIII, obtained from Professor A. W. Burgstahler.[5]

4′,5′-Dimethoxy-6-ethyl-3,4,5,6,7,8-hexahydrobenzo[1′,2′,1,2]quinolizine-(N-3,4-dimethoxyphenethyl)-7-acetamide (IXa).—A mixture of 26.3 mg. (0.0758 mmole) of the tricyclic ester IX (X = OMe) and 92.8 mg. (0.513 mmole) of 3,4-dimethoxyphenethylamine was heated at 180–200° under nitrogen for 3 hours. The cooled reaction mixture was then dissolved in chloroform, treated with an excess of acetic anhydride and allowed to stand at room temperature. After 1 hour this solution was concentrated to dryness, and the residue was dissolved in dilute hydrochloric acid and washed with ether. Both the N-acetyl-3,4-dimethoxyphenethylamine and the hydrochloride of V remained in the aqueous phase and then were extracted with chloroform. The chloroform extracts were washed with a saturated salt solution, concentrated and chromatographed on silicic acid. N-Acetylhomoveratrylamine was eluted from the column with a 1% ethanol–chloroform solution while the hydrochloride of IXa was eluted readily with a 5% ethanol–chloroform solution. The free base was regenerated from the hydrochloride in the usual manner and crystallized from ethyl acetate, m.p. 150–153° (uncor.), yield 29.0 mg. (77.3%). It was crystallized from ethyl acetate for analysis, m.p. 154.2–155.7° (cor., sealed tube).

(28) Authentic *l*-emetine was obtained from The Inland Alkaloid Co. and purified as the hydrochloride by several recrystallizations from water, m.p. 233–249° (cor., sealed tube), $[\alpha]^{29}D$ +17.8° (*c* 5.0, water) (lit. m.p. 235–255°, $[\alpha]^{29}D$ +14.71 (*c* 5.0 water)).

(29) The sample of authentic *l*-isoemetine hydrochloride obtained from Dr. D. H. Openshaw was crystallized from water, m.p. 213–218° (uncor.) (lit. softened at 215°, transparent at 220° (cor.)).

(30) After standing for a few days the crystalline IX (X = OMe) began to melt over a wide range, m.p. 79–98° (uncor.) Subsequent preparations of IX (X = OMe) yielded exclusively this material, the melting point of which could not be improved by crystallization. It was assumed that this behavior was due to the formation of polymorphs which possessed about the same relative stability under the conditions used.

Anal. Calcd. for $C_{29}H_{40}O_5N_2$: C, 70.13; H, 8.12. Found: C, 70.08; H, 8.05.

Preparation of *dl*-Emetine (VIIa) and *dl*-Isoemetine (VIIb) from IXa—A mixture of 72.8 mg. (0.147 mmole) of the amide IXa, 0.5 ml. of freshly distilled phosphorus oxychloride and 5 ml. of anhydrous toluene was heated under nitrogen. At the beginning of the reaction, as the heterogeneous reaction mixture warmed up, the solid amide slowly went into solution and was replaced by a yellow amorphous solid. After 2 hours at 105–122° the reaction mixture was concentrated and the residue was dissolved in water, washed with ether and made ammoniacal. The free base was extracted with ether, and the ether extracts were washed with saturated sodium chloride, dried over anhydrous potassium carbonate and concentrated to yield 65.8 mg. (93.5%) of crude *dl*-O-methylpsychotrine (XXVII), R = Me). The hydrochloride of XXVII, R = Me, prepared in the usual manner, was dissolved in ethanol and hydrogenated over a prereduced platinum oxide catalyst at room temperature and atmospheric pressure. After 30 minutes the reduction had stopped with a total hydrogen uptake of 4.09 ml. (127.5% of theory). Concentration of the catalyst-free solution yielded two isomeric hydrochlorides (A and B), which were separated by fractional crystallization from ethanol–ethyl acetate. Isomer A, m.p. 266.8–267.8° (cor., sealed tube), yield 14.9 mg., was shown to be *dl*-isoemetine hydrochloride (VIIb, C_1-epimer of emetine) by comparison of the infrared spectrum of its free base with that of an authentic sample of *l*-isoemetine. In a similar manner the free base obtained from isomer B, hydrochloride m.p. 248.6–250.5° (cor., sealed tube), yield 19.5 mg., was shown to be *dl*-emetine (VIIa).

Resolution of *dl*-Isoemetine (VIIb).—An ethanolic solution of 19.8 mg. of *dl*-isoemetine and 15.5 mg. of (−)-dibenzoyltartaric acid was seeded with an authentic sample of *l*-isoemetine (−)-dibenzoyltartrate and allowed to stand at room temperature overnight. A crystalline material, m.p. 163–164° (uncor.), yield 13.2 mg., was obtained and recrystallized three times from ethanol, m.p. 162.6–163.4° (cor., sealed tube). The mixed melting point with an authentic sample was undepressed. The infrared spectra of the natural and synthetic *l*-isoemetine (−)-dibenzoyltartrates, taken in a potassium bromide pellet, were identical. The hydrobromide of synthetic *l*-isoemetine was prepared from the resolved free base with anhydrous hydrogen bromide. It was crystallized from ethanol, m.p. 276.4–278.6° (cor., sealed tube). A mixed melting point with the hydrobromide of natural *l*-isoemetine, m.p. 276.2–277.4° (cor., sealed tube) was 275.2–278.5° (cor., sealed tube). The optical rotation of synthetic *l*-isoemetine was: $[\alpha]_D$ −29.1 ± 2° (*c* 1.18, chloroform) (lit.[31] $[\alpha]_D$ −47.4° (*c* 3.15, chloroform)).

Diethyl β-(α′-Carbobenzoxy-α′-cyanomethylglutarate.—In a 500-ml. three-neck flask equipped with stirrer, reflux condenser and nitrogen inlet was placed 10 ml. of absolute ethanol. Sodium metal (0.25 g., 10.8 mmoles) was added and allowed to dissolve. Then the ethanol was evaporated *in vacuo;* when solid began to appear, an oil-bath at 190° was raised around the flask to produce dry sodium ethoxide; the flask was allowed to cool and nitrogen was admitted. Then 2.50 g. (14.3 mmoles) of benzyl cyanoacetate dissolved in benzene was added and the solution was distilled until nearly dry. The addition of 15 ml. of dimethylformamide (distilled from sodium hydride) completed the preparation of the catalyst, sodium benzyl cyanoacetate.

A dropping funnel was incorporated into the apparatus, and the catalyst was transferred with a pipet to the dropping funnel. Then 10 g. (53.8 mmoles) of benzyl cyanoacetate and 30 ml. of dimethylformamide were placed in the flask. The solution of sodium benzyl cyanoacetate was slowly dropped into the stirred mixture which was immersed in an oil-bath at 90°.

When the addition was complete, the solution was acidified with glacial acetic acid and distributed between ether and water. The ether layer was washed with dilute sodium bicarbonate and water, and then dried with magnesium sulfate and evaporated. The residue was distilled to give 9.78 g. (50%) of viscous liquid boiling at 191° (0.2–0.5 mm.), $n^{25}D$ 1.4916, d^{24}_4 1.1422, *MR* 91.76 (calcd. 91.07).

Anal. Calcd. for $C_{19}H_{26}O_6N$: C, 63.14; H, 6.42. Found: C, 63.28; H, 6.28.

Diethyl β-(α′-Carbobenzoxy-α′-cyanopropyl)-glutarate.—The apparatus used was described in the preceding experiment. Absolute ethanol (20 ml.) was placed in the flask and 0.64 g. (28 mmoles) of sodium was dissolved in it. As in the preceding experiment, dry sodium ethoxide was prepared by distilling off the excess ethanol, evacuating the flask with the water-pump, and finally raising a 190° oil-bath around the flask. The flask was allowed to cool and nitrogen was admitted to the system. A mixture of benzene and dimethylformamide was added to dissolve the sodium ethoxide. Then 10 g. (27.6 mmoles) of β-(α′-carbobenzoxy-α′-cyanomethyl)-glutarate was added. The benzene–alcohol was azeotroped off rapidly with stirring and heating.

The flask was cooled in an ice-bath, and 10 g. (64 mmoles) of ethyl iodide was added at once. The mixture was stirred for two hours in an oil-bath at 90–100°. At the end of this time, the mixture tested neutral with *p*H paper. The product was allowed to stand overnight; it then was taken up in ether and washed several times with water. After the ether had been distilled off, there remained a viscous liquid which could be distilled with some difficulty due to the high boiling point and high viscosity. The product was obtained as a pale yellow oil, b.p. 190° (0.03 mm.), $n^{23.5}D$ 1.4911, $d^{23.5}_4$ 1.1255, *MR* 100.2 (calcd. 10.03), yield 4 g. (37%).

Anal. Calcd. for $C_{21}H_{30}O_6N$: C, 64.76; H, 6.99. Found: C, 64.64; H, 6.80.

Diethyl β-(α′-Cyanopropyl)-glutarate.—The benzyl ester (2.71 g., 6.98 mmoles) was hydrogenated at atm. pressure in 25 ml. of acetonitrile with 200 mg. of 5% Pd–$BaSO_4$ as catalyst. Although it was necessary to replace the catalyst during the course of the hydrogenation, the theoretical amount of hydrogen was absorbed.

The product was filtered, and the filtrate was concentrated at reduced pressure. The residue was an oil which did not crystallize on standing. The oil was distilled at 7 mm. pressure in a Wood metal-bath at 220°. Redistillation gave 700 mg. (45%) of liquid, b.p. 176–179° (7 mm.), $n^{25}D$ 1.4450. Its infrared spectrum was identical with that of a sample prepared *via* the Russian route, and its refractive index compares favorably with that of the authentic sample, $n^{25}D$ 1.4441.

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(31) F. L. Pyman, *J. Chem. Soc.*, **113**, 222 (1918).