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TOTAL SYNTHESIS OF THE CALYCANTHACEOUS ALKALOIDS[1]

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Abstract—The total synthesis of DL-calycanthine and DL-chimonanthine is described; following biogenetic precedent, the synthesis route involves oxidative dimerization of N-carbethoxy-oxytryptamine followed by reductive cyclization. The alkaloids are interconverted by acid-catalyzed isomerization. The structures of some synthetic byproducts are also discussed.

INTRODUCTION

ALTHOUGH the structure of calycanthine, the principal alkaloid of the order Calycanthaceae, may be considered one of the classical problems of alkaloid chemistry, owing to its isolation as early as 1888,[3] it did not attract a considerable degradative effort in the first half of this century.[4] In this period the complexity of the alkaloid, $C_{22}H_{26}N_4$, manifested itself in degradations producing a surprisingly wide variety of nitrogenous heterocycles. In particular the formation of both indole and quinoline derivatives created difficulties in interpretation and led to some bizarre structural proposals.[4]

The deduction of the correct structure stands as a tribute to the power of modern biogenetic and mechanistic theory in structural elucidation.[5] Thus, the presence of calycanthine in another species (*Meratia praecox*) taxonomically distant from *Calycanthus* suggested a simple biogenesis while the facile production of N-methyltryptamine on pyrolysis of calycanthine pointed to this common metabolite as the rational biogenetic precursor. In fact, since the empirical formula of the alkaloid is just two hydrogens less than the sum of two methyltryptamine molecules, an oxidative dimerization of N-methyltryptamine affords an obvious biogenetic hypothesis. Since on mechanistic grounds electrons are primarily available for this oxidative coupling of two indoles at the β-position, the primary product of such coupling would be I, an isomer of calycanthine. This may be regarded as equivalent, via hydrolysis, to the tetraamino-dialdehyde (II) which may now form internal N-acetals with loss of two

[1] A preliminary communication appeared in *Proc. Chem. Soc.* 383 (1962).

[2] Alfred P. Sloan Foundation Fellow.

[3] G. R. Eccles, *Proc. Amer. Pharm. Assoc.* **84**, 382 (1888).

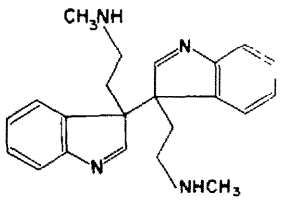
[4] Reviews of this degradative work are to be found in *The Alkaloids* (Edited by R. H. F. Manske) Vol. II, p. 434 ff. Academic Press, New York; Edited by L. Marion (1952) and by J. E. Saxton, Vol. VII; p. 147 ff. (1960).

[5] The deduction of the structure of calycanthine was first promulgated by Woodward in an advanced course on natural products at Harvard in 1952, at which time the synthesis of the degradation product, calycanine (*vide infra*), was accomplished in corroboration.[6] The same suggestion was later presented by Robinson and Teuber.[7]

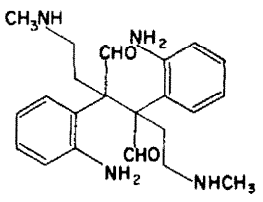
[6] R. B. Woodward, N. C. Yang, T. J. Katz, V. M. Clark, J. Harley-Mason, R. F. J. Ingleby and N. Sheppard, *Proc. Chem. Soc.* 76 (1960).

[7] R. Robinson and H. J. Teuber, *Chem. & Ind.* 783 (1954).

molecules of water. In this way one may construct five structural isomers (III), labeled α–ϵ for convenience below, of which the α-isomer is now known from chemical[6] and X-ray[8] evidence to be natural calycanthine.



I



II

Several features of these isomers are worth noting. Since the oxidative coupling produces two asymmetric centers (the β-indolic positions) there are two possible diastereomers of formula II, one of which is *meso*-, and the other racemic or optically active. (The natural alkaloids are all optically active.) Each gives rise in turn to a series of five isomers (III); in the *meso*-series, however, only four isomers (α–δ) possess a center of symmetry and are themselves *meso*- while the ϵ-isomer is structurally dissymmetric and hence potentially optically active. In each series, moreover, the five isomers should be easily interconvertible by acid hydrolysis of the N-acetal groups (e.g., via II or equivalent species) and reclosure. Such interconversions can readily account for the varied production of quinolines (from α or β) and indoles (from γ or δ) in the classical degradation studies.

Synthesis of the natural alkaloids

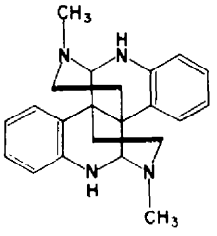
We considered the most economical route to the synthesis of calycanthine and its isomers to be one modeled after the elegant synthesis employed by the plant. In order to prevent oxidation of the secondary amine, however, we proposed utilizing instead a urethan grouping which could later be converted to the requisite N-methyl by lithium aluminum hydride reduction.

Of greater concern was the availability of two potentially reactive sites for oxidation on the indole nucleus. Accordingly, the oxindole analog was chosen as it can only react at the β-position; furthermore, the anion obtained from oxindole with base is known to react exclusively and rapidly at the β-position (rather than at nitrogen) in alkylation reactions and in hydroxylation with molecular oxygen.[9] The ease with which the β-anion is formed derives from its stability both as an enolate and as an indole.

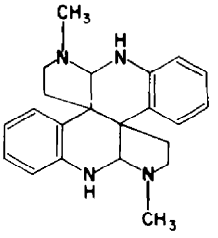
The synthesis (IVa–f) of oxytryptamine hydrochloride (IVf) was developed from a previously reported preparation[10] into a convenient procedure capable of an overall yield of 30% in five steps on a large scale. Shaking an aqueous alkaline solution of oxytryptamine with ethyl chloroformate in chloroform smoothly afforded the urethan (V) in high yield.

Inasmuch as the desired oxidative coupling is a one-electron process, initial efforts were made with metal salts capable of one-electron reductions, but such efforts using

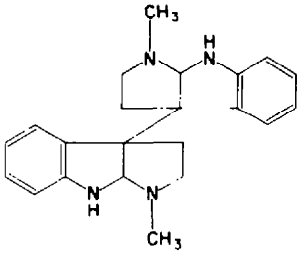
[8] T. A. Hamor, J. M. Robinson, H. N. Shrivastava and J. V. Silverton, *Proc. Chem. Soc.* 78 (1960).
[9] P. L. Julian, E. W. Meyer and H. C. Printy, *Heterocyclic Compounds* (Edited by R. W. Elderfield) vol. III. Wiley, New York (1952), p. 126 ff.
[10] J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.* 3639 (1958).



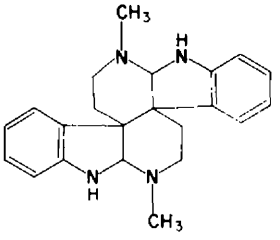
III α



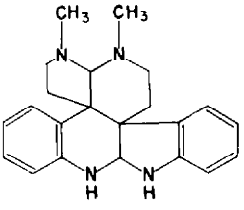
III β



III γ

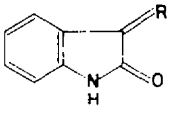


III δ

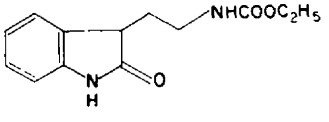


III ε

cupric, ferric or silver ions[11] yielded only starting material as did electrolytic and t-butyl hydroperoxide[12] oxidations. Following the precedent of the coupling of sodiomalonate with iodine,[13] however, proved a more hopeful approach. The oxindole



IV a, R=O
b, R=C(CN)COOCH$_3$
c, R=H, CH(CN)COOCH$_3$
d, R=H, CH(CN)COOH
e, R=H, CH$_2$CN
f, R=H, CH$_2$CH$_2$NH$_3^{\oplus}$ Cl$^{\ominus}$



V

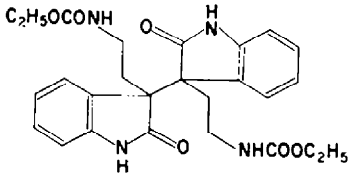
[11] For some analogous dimerizations see R. Royer, *Ann. chim.* 12, **1**, 429 (1946), (Fe^{+++}); H. E. Fierz-David, L. Blangey and H. Dubendorfer, *Helv. Chim. Acta* **29**, 1661 (1946), (Fe^{+++}); P. Peteticoas, R. Sureau, J. Frenkiel and R. Goupil, *Bull. Soc. Chim.* 5, **16**, 103 (1949), (Cu^{++}); A. Baeyer and C. A. Knop, *Liebigs Ann.* **140**, 1 (1866), (Ag^+ on oxindoles).

[12] Cf. dimerizations of pyrazolones: S. Veibel and S. C. Linholt, *Acta Chem. Scand.* **8**, 1383 (1954).

[13] C. A. Bischoff, *Ber. Dtsch. Chem. Ges.* **16**, 1046 (1883); S. B. Baker, T. H. Evans and H. Hibbert. *J. Amer. Chem. Soc.* **70**, 60 (1948).

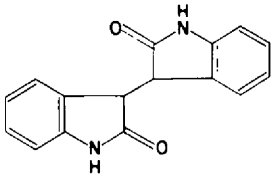
enolate was preformed by the addition of sodium hydride to the urethan (V) in dry tetrahydrofuran. When a solution of iodine in benzene was slowly added, the color was discharged to the extent of about 75–80% of one equivalent and isolation of the products yielded sodium iodide and a mixture of organic products, separation of which on alumina afforded two very similar high-melting isomers of the correct constitution. That these were the two desired diastereomeric dimers (VIa and VIb) was shown by analysis and the close spectral similarity (IR and UV) of the dimers to each other as well as to the much lower-melting monomer V.

The oxidative coupling of the oxindoles affords the skeleton of I in a higher oxidation state (the formal hydrolysis of VI, analogous to I–II, would yield a diacid instead of a dialdehyde), so that reduction of the skeleton as well as the urethan groups is required to secure a calycanthine isomer. There was some precedent[14] for

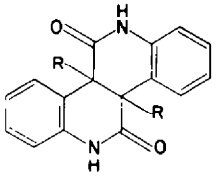


VI

expecting that the hydride reduction envisioned above for conversion of urethan to N-methyl would also effect a reductive cyclization to the desired N-acetal groupings. In order to obtain calycanthine itself (III α), however, requires a regrouping of the skeleton (the dimers VI can only cyclize directly to the γ- and δ-isomers). Just such an interconversion had already been effected in the synthesis of calycanine[6] by acid-catalyzed hydrolytic opening and reclosure of the lactams of *leuco*-isoindigo (VII) yielding VIIIa. Accordingly, a wide range of solvolytic conditions were examined for



VII



VIII a, R = H
b, R = $CH_2CH_2NHCOOC_2H_5$

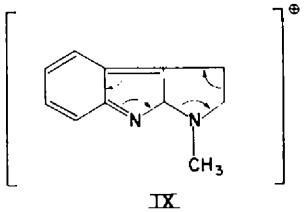
the analogous transformation of the dimers VI into VIIIb. In no case, in acidic or basic media, however, were we able to observe any significant development of the characteristic δ-lactam absorption in the infrared and the starting materials were generally recovered. Since in the course of these experiments we observed that strong alkali removed the urethan groups, we made several attempts at determining which series (VIa or b) was racemic by partial asymmetric saponification in hot aqueous brucine but succeeded in developing no optical activity thereby in either dimer (Experimental).

[14] cf. The chemical reduction of an oxindole bearing a pendant amine to eserethole by reduction with sodium in alcohol: P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.* **57**, 539, 563 (1935).

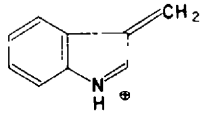
The above argument that the calycanthine isomers III should be hydrolytically interconvertible and our demonstration that calycanthine itself is substantially recovered from long heating in aqueous acid led us to consider direct reduction of the dimers and subsequent acid isomerization to calycanthine, which appears to possess a substantial thermodynamic preference over the other isomers in this equilibrium. A spectral pecularity of the ϕ-NH—CH—N(CH_3)— chromophore in the isomers III allows an easy distinction to be made between these products, from reductive cyclization of VI, and any products which might arise from total reduction of the oxindoles to indolines without cyclization. Thus, while both products would show a similar aniline chromophore in the ultraviolet, in simple indolines this absorption is destroyed in acid by protonation of the free electrons of the aniline nitrogen whereas in the N-acetals of III initial protonation of the more basic aliphatic amine leaves the aniline nitrogen and hence its characteristic chromophore unaffected.[15]

Reduction of the two dimers with lithium aluminum hydride yielded mixtures of basic products the chromophores of which were not destroyed in acid. From VIa was obtained a crystalline base, A-1, initially believed to be an isomer of calycanthine from its analysis, which could be transformed to an isomer, A-2, by boiling in aqueous acid; in each compound, however, the mass spectrum[16] showed the molecular weight to be 344, two hydrogens less than calycanthine, and the UV spectrum was significantly different from that of calycanthine (Table 1 and further discussion below). The crystalline product, B-1, from reduction of VIb, however, while different from calycanthine in the infrared, showed very similar ultraviolet properties (Table 1). The analysis and mass spectrum[16] showed it to be an isomer (mol. wt. 346) which had, furthermore, two preponderant fragments in the mass spectrum, one at m/c 172 (45 times as intense as the parent peak) and a second at m/c 130 about half as intense. The first which represents half of the molecular weight, can only be derived in such intensity from the γ-isomer, in which the halves are joined by only a single bond.

The symmetrical fragmentation of III can yield a highly stabilized benzyl cation which may lose hydrogen to form a fragment IX of m/c 172 and this in turn may fragment as shown to a β-methylene indolenine fragment (X) of m/e 130. These fragments also appear in the mass spectrum of calycanthine but only at a nominal intensity, less than that of the parent peak. The other peaks (all less intense than the parent) in the calycanthine spectrum also correspond to those in the spectrum of B-1,



IX



X

[15] The ϵ-isomer, distinguished by its asymmetry above, may also be expected to differ in its UV absorption behavior since protonation of one nitrogen in each N-acetal, as above, will lead in the ϵ-isomer to destruction of only one of the two aniline chromophores, so that one would expect the intensity of the long-wavelength peak to drop by half but not vanish.

[16] Mass spectra were kindly performed in Prof. Klaus Biemann's laboratory at M.I.T. We should like to acknowledge our deep gratitude for this assistance and discussion of the results which provided information of great importance in our structural assignments.

being primarily peaks corresponding to losses of the two aliphatic moieties CH_2NCH_3 (mass 43) and $CH_2CH_2NCH_3$ (mass 57), i.e., m/e 302 (= 346 − 43 − 1), 288 (= 346 − 57 − 1), 259 (= 346 − 2 × 43 − 1), 245 (= 346 − 43 − 57 − 1), and 231 (=346 − 2 × 57 − 1). The peak at m/e 231 corresponds to protonated calycanine and is the second peak in intensity after the parent in the mass spectrum of calycanthine. These correspondences are important in confirming the familial resemblance of B-1 and calycanthine.

Not long after the isolation and characterization of B-1, Smith announced the isolation of a new alkaloid, chimonanthine, from *Meratia praecox*[17] and showed[18] that it was in fact the γ-isomer of calycanthine; this was subsequently confirmed by x-ray analysis.[19] Comparison of spectra (IR, UV, MS, NMR) of a sample of chimonanthine, very generously provided by Dr. Smith, with those of B-1 showed a very close correspondence but thin-layer chromatographic comparisons in several solvent systems revealed that while they were very similar, they were not identical. The only reasonable conclusion was that B-1 was the γ-isomer in the *meso*-series, since natural chimonanthine is levorotatory. Accordingly, the non-crystalline basic residues from the reduction of VIa were chromatographed and the fractions examined by thin-layer chromatography. In this way it was possible to locate and purify fractions with the chromatographic behavior of the natural alkaloids.

The first crystalline compound, obtained in 3% yield and labeled A-3, was shown to be DL-chimonanthine as its IR and UV (neutral and acid) spectra were absolutely superimposable with those of the natural alkaloid. The NMR and mass spectra were also identical as were the mobilities of the two in many thin-layer chromatograph systems (including those which separate B-1). The NMR spectrum was in accord with the γ-isomer, exhibiting a complex multiplet of eight aromatic protons at 2·7–3·5τ, singlets of two protons (N—CH—N) at 5·62τ and six protons (N—CH_3) at 7·70τ, and complex absorption due to the eight non-equivalent aliphatic ring protons between 7·5 and 8·1τ. This spectrum is quite similar to that of calycanthine.[6] In view of the complete correspondence of the racemic synthetic A-3 with natural L-chimonanthine in five different physical comparisons capable of high discrimination it was deemed superfluous to resolve the material for a melting point comparison[20] in further proof of their identity.

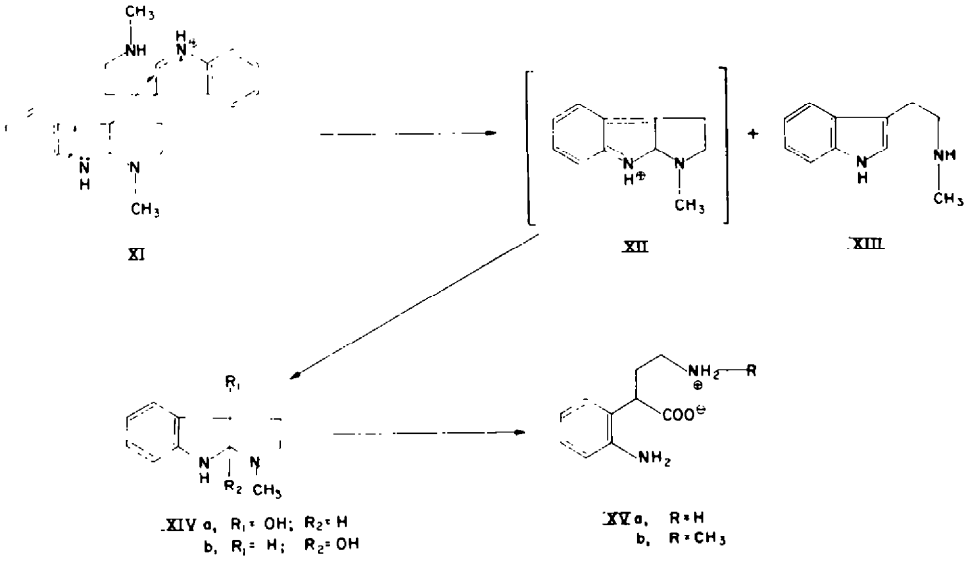
Compound A-5, isolated in 0·2% yield from chromatography of the hydride reduction bases, was shown to be identical with natural α-calycanthine[21] by IR and UV spectra as well as a series of thin-layer chromatographic systems. It could be obtained more easily by the acid isomerization of synthetic DL-chimonanthine, described below.

The other alkaloids from Calycanthaceae are calycanthidine and folicanthine, which have been shown[17,18] to be respectively, N-methyl and N,N′-dimethyl

[17] H. F. Hodson, B. Robinson and G. F. Smith, *Proc. Chem. Soc.* 465 (1961).
[18] J. E. Saxton, W. G. Bardsley and G. F. Smith, *Proc. Chem. Soc.* 148 (1962).
[19] I. J. Grant, T. A. Hamor, J. M. Robertson and G. A. Sim, *Proc. Chem. Soc.* 148 (1962).
[20] The m.ps are: L-chimonanthine,[17,21] 188°–189°; A-3 (DL-chimonanthine), 184°; D-calycanthine,[21] 250°–251°; A-5 (DL-calycanthine), 253–258°.
[21] Authentic natural samples of L-chimonanthine and hodgkinsine were generously supplied by Dr. G. F. Smith of Manchester, a sample of D-calycanthine by Professor R. B. Woodward of Harvard. We should like to record our grateful appreciation of this cooperation.

derivatives of chimonanthine. Since chimonanthine and calycanthidine have both been methylated to yield folicanthine,[22] the present synthesis of calycanthine and chimonanthine also serves formally as a synthesis of folicanthine.

Implicit in the chemistry of the calycanthine isomers is the potential for equilibration of the five isomers in acidic media, via species such as I and II. In accordance with this view it was found that the γ-isomer, A-3, on heating to 150° for an hour or on the steam bath a longer time with dilute hydrochloric acid, and separating the bases on thin-layer plates, produced a pattern of five or six spots, the major ones corresponding to A-3, A-5 and N-methyltryptamine, in yields of about 25%, 40% and 5% respectively. The lesser spots, which may represent other calycanthine isomers, were present in amounts too insignificant to isolate. Isolation from a preparative thin-layer chromatograph afforded a crystalline sample of A-5[20], identical with natural calycanthine by the same physical criteria applied to chimonanthine. The yield of synthetic calycanthine from VIa is therefore 1·2%. That this hydrolytic interconversion was indeed an equilibrium was shown by production of a virtually identical thin-layer pattern when calycanthine was subjected to the same treatment. The formation of N-methyltryptamine (XIII) in this reaction is not surprising in view of its appearance in the reduction products as well and may be rationalized by the acid-catalyzed sequence XI → XII + XIII. The cation XII may further hydrate to XIVa, dehydrate to the corresponding indole and rehydrate to XIVb. In the case of oxytryptamine (IVf) in aqueous basic solution, formation of an intermediate analogous to XIVb is believed to be the source of the zwitterion XVa, which is not extractable from aqueous solution; similar formation of the N-methyl analog XVb in the present case would be expected to retain this fragment in water so that it would not appear with the bases in the chromatogram.



[22] G. F. Smith, private communication.

[23] K. Freter, M. Weissbach, B. Redfield, S. Udenfriend and B. Witkop, *J. Amer. Chem. Soc.* **80**, 983 (1958); J. B. Hendrickson, Ph.D. thesis, Harvard, 1955.

The equilibration of the isomers raises a further stereochemical question. Calycanthine and chimonanthine are biosynthesized by two quite different plants utilizing a route which develops the only non-epimerizable asymmetric centers (the two central carbons of the diphenylethane backbone) in a single reaction. In each case it is the optically active rather than the *meso*-diastereomer which is formed, but, since calycanthine is dextrorotatory ($[\alpha]_D$ +684°)[17] and chimonanthine is levorotatory ($[\alpha]_D$ −329°)[17], there is the possibility that the two plants have generated opposite optical antipodes, i.e., that the chimonanthine produced by equilibrating D-calycanthine might be D-chimonanthine, the enantiomer of the natural compound. When natural D-calycanthine was isomerized, however, and the generated chimonanthine separated by thin-layer chromatography, it was found to be levorotatory, i.e., the natural alkaloid. Thus we may conclude that the two plants both produce alkaloids of the same absolute stereochemistry at the two non-epimerizable centers.

The synthetic byproducts

The other basic product from the reduction was the incompletely reduced material A-1 with a molecular weight indicating a structure of two hydrogens less than calycanthine. Like the calycanthine isomers A-1 equilibrates in acid to a mixture (containing no calycanthine isomers, as indicated by thin-layer chromatography) which is predominantly A-2, isomeric with A-1. The isomers of molecular weight 344 (dehydrocalycanthines: A-1 and A-2) have spectra very similar to each other but significantly different from the corresponding spectra of the molecular weight 346 isomers (calycanthines: A-3, A-5, B-1). Thus, the IR spectra of A-1 and A-2 are characterized by medium intensity absorption at 6·2 and 6·9 μ and a strong peak at 6·4 μ while those of the calycanthine isomers show only medium bands at 6·2 and 6·7 μ. Both groups show sharp NH peaks (2·8–2·9 μ) and no carbonyl absorption. The UV absorption of the dehydrocalycanthines reveals a maximum around 285 mμ which undergoes a minor shift to lower wavelength and intensity, but is not destroyed, on addition of acid; the corresponding peaks in the calycanthine are above 300 mμ (Table 1). Finally, the proton spectra of A-1 and A-2, while generally similar to the others, differed most notably in having two N-methyl peaks instead of only one and a lower intensity at 5·6τ (N—CH—N).

These features led us to formulate A-1 and A-2 as mono-amidines corresponding to two of the five calycanthine isomers; since an amidine is sterically impossible in the α-calycanthine structure,[6] we are left with four choices: β–ϵ. The mass spectra of A-1 and A-2 confirmed the general familial resemblance to the calycanthine isomers, with major peaks at m/e 344, 300 (344 − 43 − 1), 287 (344 − 57), 171 − 172, 159, 143 and 130, all of which correspond to major peaks in calycanthine-chimonanthine. The absence of peaks (cf., m/e 259, 245 and 231 in the calycanthine isomers) arising from loss of *both* ethanamine bridges is consistent with the unsymmetrical monoamidine formulation, while the peaks at 171–172 were of the same order of intensity as the parent, thus ruling out the γ-isomer. The proton spectra of the N-methyl groups allowed a choice among the remaining isomers: in calycanthine and chimonanthine, the N-methyl singlet appears at 7·70τ whereas A-1 shows a pair of singlets at 6·73 and 7·35τ, those of A-2 at 6·73 and 7·76τ. The difference between the two N-methyl chemical shifts in the dehydrocalycanthines strongly implies that one (the

lower) is an amidine methyl, thus ruling out the ϵ-isomer, in which the environments of the two N-methyl groups are saturated and very similar, and leaving for A-1 and A-2 only the choice between β- and δ-dehydrocalycanthine (XVI and XVII, respectively). In the NMR spectrum of A-1 the peak arising from the N-methyl of the N-acetal is shifted downfield markedly ($7{\cdot}35\tau$) whereas in A-2 it is essentially normal ($7{\cdot}7\tau$); this shift may well be occasioned by the proximity of the N-methyl to the benzene ring and the magnetic field arising from the ring current therein. Models imply that only in the β-isomer is this close juxtaposition physically possible, thus suggesting XVI for A-1, XVII for A-2.[24]

The formation of A-1 in the reduction is easily understood if the reduction of one oxindole moiety in VIa leads to a salt XVIII assumed to resist the further action of hydride.[25] On protonation the anion XVIII may be expected to open to the lactone XIX which in turn will be attacked by one of the basic aliphatic amino groups, yielding either a γ- or a δ-lactam. As A-1 is a kinetically controlled product and not the thermodynamically most stable isomer,[24] it is reasonable to suggest that closure of the five-membered ring, being especially favored sterically in XIX, will proceed by preference here, affording the pyrrolidone XX (or an N-acetal). From XX dehydration can only proceed to a dehydrocalycanthine bearing the ethanamine chain in a five-membered ring, i.e., only the β-, γ-, or ϵ-isomers. Therefore, this argument also supports the formulation of the β-isomer as A-1.[27] The intermediate XVIII on the strong acidification of an acidic work-up may in part also take an alternative course via a reasonable mechanism (analogous to XI) involving cleavage of the central C—C bond and affording N_b-methyl-oxytryptamine, the zwitterion form of which (XVb) would presumably remain in the aqueous phase on extraction and result in the lowered and variable yields of basic fraction experienced in this acidic work-up of the reduction (Experimental).

Several attempts to reduce the dehydrocalycanthine isomer, A-1, uniformly resulted in failure, sodium and alcohol or lithium aluminum hydride reductions yielding only starting material in good yield while hydrogenation in acetic acid did not proceed at all until mineral acid was added. In the latter case, hydrogenation was incomplete, yielded a crude mixture with a virtually unchanged ultraviolet spectrum and a chromatographic profile of several spots. Digestion of this mixture under the acid equilibration conditions produced no components corresponding to calycanthine or chimonanthine on thin-layer plates.

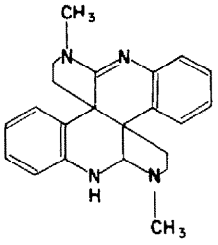
The hydride reduction of VIa also yielded several other very minor spots on the thin-layer chromatograms, none in quantities sufficient for adequate characterization.

[24] Unfortunately, although the acid equilibration experiments show A-2 to be the more stable isomer of the two, consideration of the models does not allow a clear distinction to be made between the thermodynamic stabilities of XVI and XVII on grounds of steric strain since the molecules are not only complex but very similar.

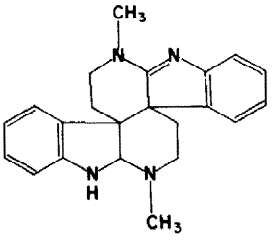
[25] A similar linear pentacyclic ether, in the fully reduced state (i.e., –H substituted for $-O^-$ in XVIII), was in fact isolated by Hino[26] in some model hydride reductions although we have not encountered such a compound in our series.

[26] T. Hino, *Chem. Pharm. Bull. Japan* **9**, 993 (1961).

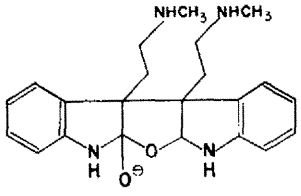
[27] Should initial ring-opening of XVIII on protonation yield the less likely alternative oxindole intermediate, kinetic considerations are likewise reasonably convincing that a pyrrolidone XX will result. An aqueous solution of the monomeric zwitterion XVa also yields the pyrrolidone isomer of oxytryptamine on extensive continuous extraction.[23]



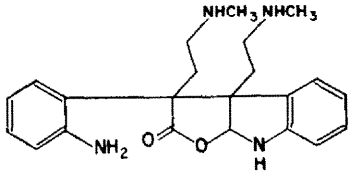
XVI



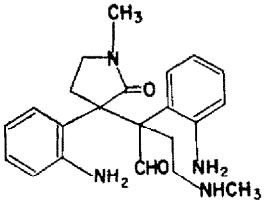
XVII



XVIII



XIX



XX

The component A-4, which was obtained crystalline, did not belong to the spectral families (IR and UV) of either the calycanthines or the dehydrocalycanthines despite a general similarity (—NH but no carbonyl and bands at 6·1, 6·2 and 6·9 μ in the infrared; UV absorption in Table 1). The mass spectrum revealed a mass of 344 and no other major peaks above m/e 186, the largest peak, at m/e 143, being 13 times the intensity of the parent.

The alkaloid hodgkinsine, presently under study by Smith,[21] was thought to be an isomer of calycanthine[1,28] and indeed has very similar IR and UV spectra, but mass spectra reveal it to have a molecular weight two hydrogens less. On acid equilibration it yields several components, none of which correspond in chromatographic behavior to any of the compounds discussed here.

EXPERIMENTAL

M.ps are corrected; analyses were performed by Miss Heather King of UCLA and Schwarzkopf Laboratories, Woodside 77, N.Y. IR spectra were commonly determined on a Perkin-Elmer Infracord, the identity comparisons on the Perkin–Elmer model 21. UV spectra were obtained on the Cary 14 Spectrophotometer. NMR spectra were run on the Varian A-60 and HR-60 instruments and mass spectra were obtained via the kind offices of Professor Klaus Biemann.[16] Mol. wts. were obtained from the mass spectra.

[28] E. F. L. J. Anet, G. K. Hughes and E. Ritchie, *Austr. J. Chem.* **14**, 173 (1961).

TABLE 1. ULTRAVIOLET SPECTRA

UV spectra in 95% ethanol (neutral) and with conc. HCl added to 0·2M, recorded as λ_{max} (log ϵ), inflections or shoulders as (S).

	Neutral	Acid
Urethan monomer (V)	249(3·85), 281(S)(3·22)	—
Dimers A and B (VI)	250(4·19), 285(3·59)	—
A-1	220(4·25), 275(4·06), 283(4·07), 297(S)(3·82)	219(4·19), 265(3·88), 271(3.88), 290(3·75)
A-2	218(4·47), 280(4·30), 285(4·31), 305(S)(3·84)	218(4·29), 265(4·16), 275(4·11), 294(4·01)
A-3 and L-Chimonanthine	245(4·15), 302(3·78)	240(4·14), 294(3·72)
B-1	246(4·16), 305(3·78)	239(4·18), 295(3·73)
A-4	235(4·06), 300(3·98), 320(S)(3.84)	225(4·15), 278(3·92), 290(S)(3·84)
A-5 and D-Calycanthine	250(4·28), 309(3·80)	240(4·30), 293(3·72), 302(3·73)
A-6 (N_b-Methyltryptamine)	222(4·29), 275(3·67), 289(3·61)	(unchanged)
Hodgkinsine	246(4·03), 308(3·69)	238(4·00), 295(3·61)

The following procedure for the preparation of oxytryptamine is adapted from Harley-Mason;[10] the final compounds were identical to those obtained by his route.

Methyl isatylidene-cyanoacetate (IVb). Isatin (1 kg) and 680 g methyl cyanoacetate were mixed in 3 l. methanol and 2 ml piperidine and refluxed overnight. The red-purple crystals of IVb were filtered, washed with ether and used directly in the next step, yield, 1·47 kg (95%), m.p. 245°–247°.

Methyl-3-oxindolyl-cyanoacetate (IVc). Compound IVb (1 kg) was refluxed with stirring in 2·7 l. glacial acetic acid in a 5 l. 3-neck flask; 1 kg Zn dust was added in batches over a 2 hr period and the mixture stirred under reflux (addn. 1 hr). The slurry was filtered hot and the filtrate poured into 8 kg ice with stirring. When the resultant colorless oil congealed overnight it was filtered and dried (1 day over KOH *in vacuo*) yielding 770 g colorless solid IVc; a further 20 g was obtained by extraction of the residual Zn with methylene chloride, yield, 790 g (80%).

3-Oxindolyl-cyanoacetic acid (IVd). Nitrogen was bubbled through 3 l. 2N KOH for a few min and the solution boiled; 1 kg IVc was then added (15–20 min) with good stirring. The mixture was immersed, still stirring, into an ice bath for 10 min, by which time all the ester had dissolved. The alkaline solution was poured into 600 ml HCl containing enough ice to keep cold. After a few hr or overnight the mixed oil and crystals turned to fine yellow crystals which were filtered and recrystallized from about 850 ml hot water, but not dried, for the next reaction, yield 880 g.

3-Oxindolylacetonitrile (IVe). Ethylene glycol (1 l.) was heated to 175° in a 5 l. flask and 1 kg IVd added as fast as convenient (5–10 min) with stirring. The temp went down to 130° and was then heated to 175° again (about 20 min) by which time bubbling had largely ceased. The solution was poured onto 6–8 kg ice and the crystals filtered, recrystallized from 500 ml ethanol, and dried *in vacuo* yielding 450 g pale yellow crystals in two crops, m.p. 160–163° (lit.[10], 164°), overall yield from isatin, 42%. On a smaller scale using *dry* recrystallized cyano-acid, this procedure afforded 78% nitrile.

Oxytryptamine hydrochloride (IVf). Nitrile IVe (50 g) was suspended in 180 ml ethanol and 80 ml conc. HCl with 0·5 g PtO_2 and shaken 2 days on a Parr shaker, until the uptake levelled off at 50 lbs/sq.in., 300 ml water was added, the platinum filtered off and the clear solution evaporated *in vacuo* on a rotary evaporator from a bath not over 50° to a volume of about 40 ml. The precipitated crystals were then filtered off and a second crop obtained by further evaporation, total yield, 50 g (81%) after drying *in vacuo*, m.p. 242–245° (dec).

3-(β-Ethoxycarbamidoethyl)-oxindole (V). Oxytryptamine hydrochloride (15 g) (IVf) was dissolved (sat. Na_2CO_3 aq.), poured into a solution of 7·5 g ethyl chloroformate in chloroform, and shaken vigorously for about 3 min. The chloroform phase was washed with water, dried and evaporated to yield a solid which was recrystallized from acetone–ether, yielding 16 g (91%) urethan (V), m.p. 130–133°, recrystallized sample for analysis m.p. 136–138°. (Found: C, 63·00; H, 6·68; N, 11·14. Calc. for $C_{13}H_{16}N_2O_3$: C, 62·89; H, 6·50; N, 11·28).

Oxidative dimerization of the urethan (V). Well-dried urethan (V; 12 g) was dissolved in 300 ml dry tetrahydrofuran (refluxed with and distilled from $LiAlH_4$) in a scrupulously dry flask fitted for nitrogen and stirring. Sodium hydride (3 g) suspension in oil (50%) was added and the mixture stirred under a nitrogen stream for 15 min. A solution of iodine (3 g) in 300 ml dry benzene was added slowly, with stirring, until the color was no longer discharged (about 1 hr consuming only 75–80% iodine solution). Some sodium iodide precipitated, more during evaporation. The solvents were evaporated on the rotary evaporator and the oily residue taken up in chloroform, washed with aqueous thiosulfate and with water, dried, and evaporated to a pale yellow oil which was chromatographed directly on 150 g activity I alumina (Woelm).

Initial fractions in benzene contained the oil from the sodium hydride while subsequent fractions produced the following:

(a) Dimer A by elution with 1% methanol in chloroform: 1·5 g (13%) white crystals after recrystallization from chloroform–methanol; m.p. 243°–246°, uncontaminated with dimer B as shown by thin-layer chromatography. (Found: C, 62·99; H, 6·33; N, 11·17. Calc. for $C_{26}H_{30}N_4O_6$: C, 63·14; H, 6·11; N, 11·33).

(b) Dimer B by elution with 3% methanol in chloroform: 1·0 g (8%) white crystals after recrystallization from methanol–ether; m.p. 214–216°, uncontaminated with dimer A. (Found: C, 63·04; H, 6·38; N, 11·21. Calc. for $C_{26}H_{30}N_4O_6$; C, 63·14; H, 6·11; N, 11·33).

The IR spectra (nujol) of the dimers were very similar to each other and to that of the monomer V; principal bands below 6·5 μ: 2·95, 3·3–3·4, 5·80, 5·90 μ. The three UV spectra were also very similar to each other as well as to that of oxindole (Table 1).

Attempted isomerizations of the dimer. The procedure in acidic solvolyses was in general to pour the cooled reaction mixture onto ice, extract with chloroform, dry and evaporate for a total crude IR spectrum in search of the band at 6·0–6·1 μ characteristic of the dihydroquinolone system of VIII. In no case did such a band appear and subsequent crystallization of the crude product commonly yielded the starting oxindole dimer shown by m.p. and mixed m.p. The following cases are representative: 100 mg VIa refluxed 18 hr in 5% H_2SO_4 in n-propanol yielded 93 mg crude product (IR spectrum of VIa), 30 mg crystalline VIa; after 20 hr in 80% H_2SO_4 at room temp or 6N HCl at reflux, 30–40 mg VIa or VIb could be recovered crystalline from 40 mg starting samples, but a sample of VIa heated in conc. H_2SO_4 yielded only dark gums. The total crude sample recovered from 15 hr heating of VIa in glacial acetic acid and sodium acetate at 200° showed the spectrum of VIa, with no evidence of 6 μ absorption.

In alkali, the urethan was generally cleaved so that the common procedure involved shaking the aqueous alkaline solution with ethyl chloroformate in chloroform before isolation of the neutral product. If this is not done the free amine cannot be extracted and probably exists in aqueous solution as the zwitterion analogous to that formed by oxytryptamine.[23] Thus, 50 mg samples refluxed in 5% KOH overnight or 40% KOH for 2 hr were recovered (43 and 38 mg respectively) crystalline and unchanged. Finally sodium acetate fusion (20 min at 270°) on 20 mg VIa yielded a dark organic product with an IR spectrum substantially identical to that of starting material. Since alkali saponified the urethan grouping, partial asymmetric hydrolysis was tried in an attempt to identify the racemic dimer. 50 mg of each dimer were refluxed with 100 mg brucine in 10 ml ethylene glycol and 2 drops water for 1 hr. The mixtures were evaporated *in vacuo* and dissolved in $CHCl_3$–20% H_2SO_4 aq., the chloroform layer yielding neutral material (31 mg from VIa, 35 mg from VIb) which showed no optical rotation (sodium D-line in $CHCl_3$).

Reduction of the dimers. 1·5 g dry dimer A (VIa, dried *in vacuo* over P_2O_5), and 5 g $LiAlH_4$ were refluxed in 100 ml dry (as above) tetrahydrofuran for 24 hr. The mixture was cooled and the following added successively, dropwise: 3·6 ml water in 36 ml tetrahydrofuran; 6 ml 10% NaOH aq.; and 6 ml water. The solution was filtered and evaporated to yield 1·0 g foam. Warming the filter cake with conc. NaOH aq. and chloroform afforded only 15 mg more from the organic layer. The foam was chromatographed as described below.

The total product always contained material absorbing at 5·8–5·9 μ in the infrared despite the presence of active hydride at the end of the reduction. The reduction was tried as well with an acidic work-up, pouring the hydride slurry very slowly into ice and H_2SO_4, washing the solution with ether, making it then strongly alkaline and extracting with methylene chloride. In such cases the yields of basic fraction were variable, 60–80% of theoretical, also containing some carbonyl absorption. No improvement in these results was affected by longer refluxing, hotter temp (in dioxane), or addition of aluminum chloride.

Dimer B (VIb) was reduced in the same way with completely analogous results.

Chromatographic separations of the products. Although compounds A-1 and B-1 could be separated in low yield by direct crystallization of the foams from the respective hydride reductions, chromatography of the entire mixture was the more efficient procedure. The total crude product from the reduction was placed on 30x the weight of Woelm alumina (activity I) and eluted with benzene–chloroform (1:1 and 4:6), followed by pure chloroform, then mixtures of 1%, 2% and 10% methanol in chloroform. The fractions were examined by thin-layer chromatography on silica with the several solvent systems: chloroform–methanol, 9:1; methanol–ethyl acetate–diethylamine, 1:2:1; and benzene–ethyl acetate–diethylamine, 1:2:1 and 7:2:1; the last was the most generally useful system (R_f values below). Spots were developed with iodine vapor. Fractions containing components which migrated in these systems were rechromatographed as were mother liquors from fractions that crystallized. In many cases rechromatography on an alumina column did not serve to separate components so that these fractions were separated preparatively on thin-layer plates (up to 100 mg per 8 × 8 mm plate), the regions of the plates containing desired components being scraped off and extracted with chloroform. The R_f values below are thin-layer values on silica with the system benzene-ethyl acetate–diethylamine, 7:2:1.

A. From chromatography of products from reductions of dimer A totalling 2·0 g.

A-1. From the benzene–chloroform fractions, 0·43 g (31%) white crystals, recrystallized from ether, m.p. 238–242°, R_f 0·38 (Found: C, 76·37; 76·45; H, 7·44, 7·28; N, 15·99, 16·40; mol. wt. 344. Calc. for $C_{22}H_{24}N_4$: C, 76·71, H, 7·02; N, 16·27%; mol. wt. 344).

A-2. Traces only from later fractions, R_f 0·06; see isomerizations below.

A-3. From A-1 mother liquors and chloroform fractions, 44 mg (3%) white crystals, recrystallized from methanol–ether, m.p. 184°; R_f 0·21 (Found: C, 76·12; H, 7·45; N, 16·29; mol. wt. 346. Calc. for $C_{22}H_{26}N_4$: C, 76·26; H, 7·56; N, 16·17%; mol. wt. 346).

A-4. 4 mg (0·3%) crystals, m.p. 210°, R_f 0·03, mol. wt. 344.

A-5. Fractions showing the characteristic grey-red spot of calycanthine in thin-layer chromatograms using the amine system (7:2:1) were separated preparatively in that system and then further in the chloroform–methanol (9:1) system, producing finally 2 mg (0·2%) colorless foam, R_f 0·64, with IR and UV spectra like those of natural calycanthine and R_f values in all four of the above thin-layer systems identical with those of natural calycanthine. Crystalline synthetic samples were prepared from A-3 by isomerization (below).

A-6. 15 mg of oil R_f 0·06, isolated from one preparative thin-layer plate was shown to have IR and UV spectra identical to those of N_b-methyltryptamine as well as identical mobilities in the several thin-layer chromatography systems used.[29] A total yield for A-6 was not ascertained.

B. From chromatography of products from reduction of 0·30 g dimer B

B-1. From the benzene–chloroform fractions, 13 mg (6%) white crystals, recrystallized from acetone–ether, m.p. 203–204°, R_f 0·28 (Found: C, 75·96; H, 7·62; N, 16·39; mol. wt. 346. Calc. for $C_{22}H_{26}N_4$: C, 76·26; H, 7·56; N, 16·17%; mol. wt. 346).

Preparation of DL-*calycanthine* (A-5) *by isomerization of* A-3. Trial equilibration experiments were first made in 0·01M HCl at 150° for 70 min in sealed capillaries; thin-layer chromatography of the bases produced substantially the same patterns as in the preparative experiment below. Longer times led to diminution of the component spots but no new ones except for a spot at the chromatograph origin.

38 mg crystalline A-3 (DL-chimonanthine) were heated in 23 ml 0·01M HCl on the steam bath for 6 1/2 hr. The cooled solution was made basic, extracted with chloroform and the organic phase dried and evaporated to 36 mg yellow froth which was chromatographed on silica on a thin layer plate; three major spots appeared on development with the 7:2:1: solvent system. The spots corresponded to A-6 (N_b-methyltryptamine), A-3 (starting DL-chimonanthine), and A-5 (DL-calycanthine). Removal of the components as above afforded 5 mg (ca. 13%) of A-6 as an oil identified by spectra as above and 14 mg (39%) crystalline A-5, which was recrystallized from acetone–ether, m.p. 253–258°, R_f 0·64. About 9 mg (25%) A-3 was recovered.

A similar acid isomerization on 108 mg natural D-calycanthine in 64 ml acid for 5 days yielded 96 mg total product, separated into the same three major components with isolation of 45 mg (42%) calycanthine and 14 mg (13%) N-methyltryptamine; the chimonanthine was not separated. In another experiment[30] 108 mg D-calycanthine was similarly isomerized 4 days yielding, by thin-layer chromatography, 77 mg calycanthine and 12 mg crude chimonanthine, $[\alpha]_D = -210°$.

An earlier isomerization of 43 mg B-1, however, in 6M HCl 40 min on the steam bath, led to recovery of only 30 mg oil with a large carbonyl absorption in the infrared; virtually nothing of this passed through an alumina column in chloroform, in striking contrast to B-1 itself or calycanthine.

Preparation of A-2 *by isomerization of* A-1. A solution of 30 mg A-1 in 3 ml 6M HCl was heated 40 min on the steam bath and worked up as in the preceding experiment; the chromatogram show only traces of several other spots besides the major spot corresponding to A-2, which could be separated as 14 mg (47%) white crystals, recrystallized from acetone–ether, m.p. 204–205°, R_f 0·06 (Found: C, 75·89; H, 7·04; mol. wt. 344. Calc. for $C_{22}H_{24}H_2$: C, 76·71; H, 7·02%; mol. wt. 344).

Attempted reductions of A-1. 24 hr refluxing of 25 mg each of A-1 and $LiAlH_4$ in tetrahydrofuran yielded only 21 mg crystalline A-1. When 90 mg A-1 in ethanol were treated with 1·0 g sodium by addition of small pieces and the basic fraction isolated and chromatographed on a silica thin-layer

[29] The authentic N_b-methyltryptamine was prepared for other studies by Dr. John Littlehailes of this laboratory via a hydride reduction of β-indolyl-N-methylglyoxamide.

[30] Kindly performed by Dr. Camille Ganter.

plate (7:2:1 solvent system, above) it revealed several spots, the major one corresponding to A-1. The UV spectra (neutral and acid) were essentially the same as those of A-1. Isomerization of the total bases in 0·01M HCl at 100° or 160° for 1 hr and subsequent chromatography revealed no trace of a component corresponding to calycanthine.

After prehydrogenation of 14 mg PtO_2 in 10 ml glacial acetic acid, 34 mg A-1 were added, but no hydrogen uptake was observed in 4 hr. After addition of 2 drops of conc. H_2SO_4 an uptake of 1·9 ml hydrogen (one equiv. = 2·1 ml) was observed in 20 min; 2 hr further stirring resulted in no further consumption. The catalyst was filtered, the filtrate poured into excess solid K_2CO_3 and extracted with chloroform. The UV spectra showed substantially the dehydrocalycanthine absorption pattern, quite distinct from that of the calycanthine isomers (Table 1). The same procedure as above of chromatography before and after isomerizations revealed no calycanthine isomers.

Comparison of synthetic and natural alkaloids. The crystalline samples of DL-calycanthine and DL-chimonanthne were compared with crystalline samples of D-calycanthine and L-chimonanthine.[21] In each case the UV spectra were superimposable (Table 1) as were the very detailed IR spectra of each pair in chloroform solution, run at the same concentration on the same graph. (Solid-state IR spectra run on the racemic and optically active calycanthine in KBr discs were remarkable dissimilar.) Solution spectra of *meso*-chimonanthine (B-1) showed small but significant differences from those of the chimonanthine samples, both in the UV (Table 1) and IR. NMR spectra of the synthetic and natural bases in deuterochloroform, although run on different instruments at different times, were identical within the range of definition common to such experimental variation. The spectrum of calycanthine has been published;[6] that of the two chimonanthine samples was very similar, exhibiting a complex multiplet of 8 protons at 2·7–3·5τ (aromatic protons), a singlet of 2 protons (N—CH—N) at 5·63τ and 6 protons (N—CH_3) at 7·70τ, and complex absorption from the 8 non-equivalent protons of the ring methylenes centering at 7·5τ (N—CH_2—) and 7·9τ(C—CH_2—). The mass spectra[16] were also identical in showing all the same peaks and at comparable intensities.

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