Tetrahedron Vol 23, pp 4131 to 4141 Pergamon Press Ltd 1967 Printed in Great Britain

BIOGENETIC-TYPE SYNTHESIS OF THE CALYCANTHACEOUS ALKALOIDS*

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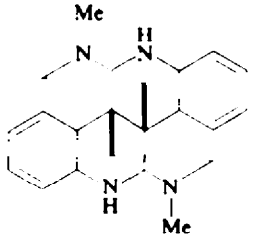
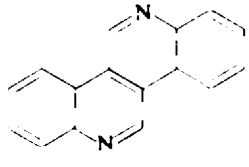
(*Received* 27 *January* 1967; *accepted for publication* 10 *February* 1967)

Abstract—Oxidative dimerization of N_b-methyltryptamine occurs exclusively *via* ββ-coupling in a one-step synthesis of *rac*- and *meso*-chimonanthine. Transformation of the former to *rac*-calycanthine completes a synthesis of all the dimeric alkaloids of *Calycanthus* species. The structure of some minor by-products of this oxidation are discussed.

CALYCANTHINE (Iα), the principal alkaloid of the order *Calycanthaceae* was isolated in 1888.[1] In the following seventy years comparatively little progress was made in structural elucidation until the correct molecular formulae, $C_{22}H_{26}N_4$, was derived



Iα



II

in 1939.[2] On the basis of its numerous degradation products, in particular N_b-methylcalycanine (II) and tryptamine (III), the postulate was made independently by Woodward[3] and by Robinson[4] that calycanthine represented one of five feasible dehydro dimers of III produced by coupling of the mesomeric tryptamine radical IV. The intermediate indolenine V could cyclize directly to one of the isomers Iγ

* Preliminary Communication: A. I. Scott, F. McCapra and E. S. Hall, *J. Am. Chem. Soc.* **86**, 302 (1964).

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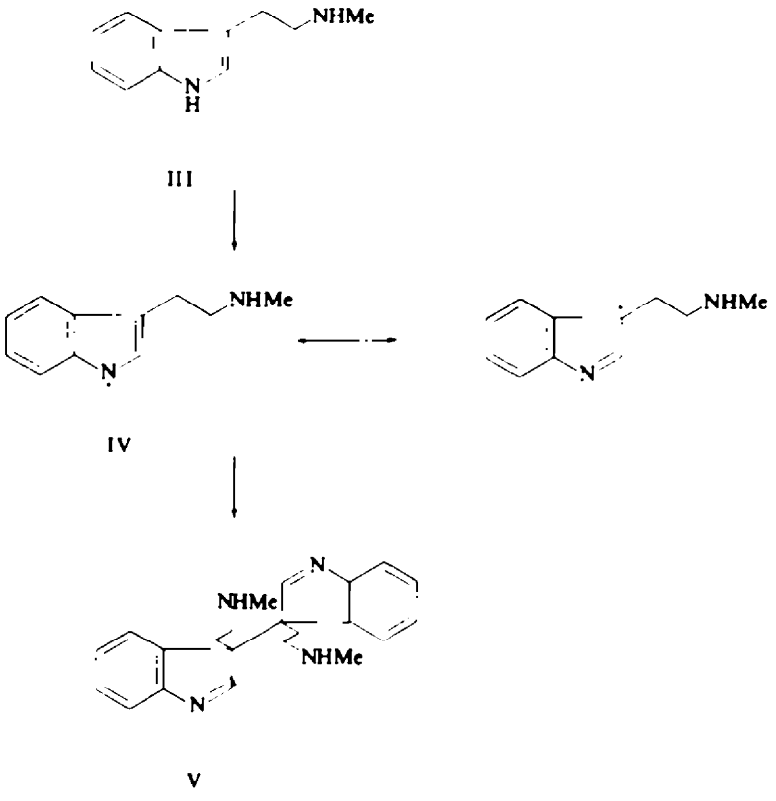
[1] G. R. Eccles, *Proc. Amer. Pharm. Assoc.* **84**, 382 (1888). For reviews of early chemistry see *The Alkaloids* (Edited by R. H. F. Manske) Vol. III; p. 434 seq. Academic Press, New York (1952); and Vol. VII; p. 147 seq. (1960).

[2] G. Barger, J. Madinaveitia and P. Streuli, *J. Chem. Soc.* 510 (1939).

[3] [a] R. B. Woodward, 1952, quoted in Ref. 13; [b] 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).

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

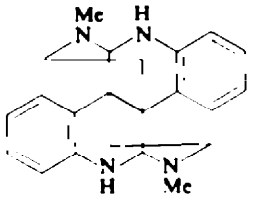
(now known to be chimonanthine) or suffer hydrolysis to the tetra-aminodialdehyde VI which in turn could serve as the progenitor of both Iα and Iγ and the remaining possible isomers (β, δ, ε).



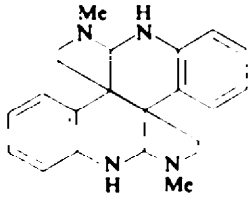
A choice in favour of Iα for calycanthine was made on the basis of X-ray diffraction[5] and spectroscopic data[3b] in 1960. A year later another of the possible isomers was discovered in nature and the structure Iγ assigned to this new member, chimonanthine. Once again spectroscopic and chemical data[6,7] were reinforced by the rigorous proof of X-ray analysis.[8] The remaining members of the set are folicanthine (VIIa) and calycanthidine (VIIb).[6,7] Since these N-methylated derivatives can be obtained by partial synthesis from chimonanthine[9] the synthesis of the latter would also constitute a formal synthesis of VIIa and VIIb.

Implicit in the formulations α–ε is a stereochemistry dependent on the two centres generated in the production of the dimer V. Thus each isomer may belong to a *rac*- or *meso*-series. Furthermore in the latter series *meso*-ε is dissymetric. At the outset

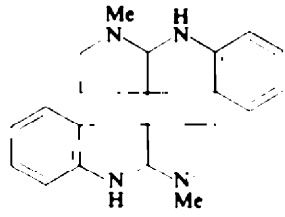
[5] T. A. Hamor, J. M. Robertson, H. N. Srivastava and J. V. Silverton, *Proc. Chem. Soc.* 78 (1960).
[6] H. F. Hodson, B. Robinson and G. F. Smith, *Proc. Chem. Soc.* 465 (1961).
[7] J. F. Saxton, W. G. Bardsley and G. F. Smith, *Proc. Chem. Soc.* 148 (1962).
[8] I. J. Grant, T. A. Hamor, J. M. Robinson and G. A. Sim, *Proc. Chem. Soc.* 148 (1962).
[9] G. F. Smith, private communication.



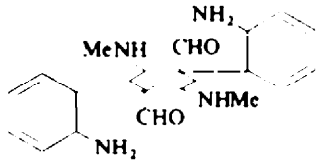
Iα



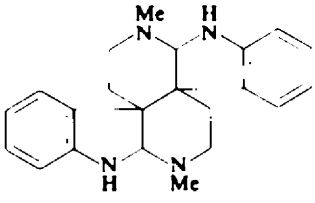
Iβ



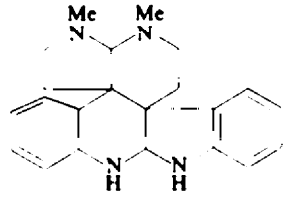
Iγ



VI



Iδ

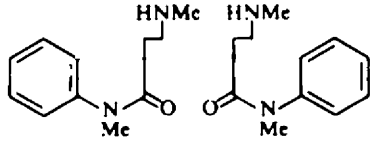


Iε

of our work all of the alkaloids of *Calycanthus* belonged to the optically active series but the possibility of obtaining *meso* compounds *in vitro* was borne in mind and, as will be revealed, had considerable relevance for the natural process.

Biogenetic-type synthesis of the alkaloids. The attractive postulate of oxidative coupling of suitably substantiated indoles in the hypothetical scheme for calycanthine biosynthesis seemed no less inviting as a basis of a simple synthesis of a series of dimeric hexacyclic alkaloids whose preparation by stepwise construction would indeed seem laborious.* However, preliminary experiments[12] with tryptamines suitably protected at the N_b function using such oxidants as potassium ferricyanide and manganese dioxide indicated that the electron pair on the indolic nitrogen (N_a) was insufficiently mobilized for radical generation. More specifically N_b-formyl and

* See however a recent synthesis of folicanthine[9-11] (VIIa) which proceeds *via* the 3,3'-bisoxindole (i) obtained from N-methylisatin and N-methyloxindole



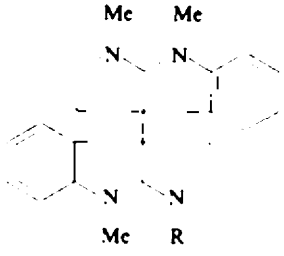
(i)

[10] T. Hino, *Chem and Pharm Bull* **9**, 979, 988 (1961).

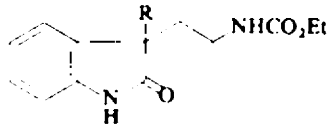
[11] T. Hino and S. Yamada, *Tetrahedron Letters* 1757 (1963).

[12] A. C. Day, F. McCapra and A. I. Scott, unpublished observations.

-carbothoxyl tryptamine were recovered from a series of attempted oxidations.[12] While these experiments were in progress, an elegant synthesis of *rac*-chimonanthine was reported by Hendrickson *et al.*[13] who found conditions for the dehydrogenative



VIIa R = H
VIIb R = Me



VIIIa R = H
VIIIb R =)$_2$

coupling of the oxindole VIIIa to the di-oxindole VIIIb. LAH reduction of the latter then furnished several products including *rac*-chimonanthine (Iγ) and a closely related isomer assigned the *meso*-γ structure (Iγ) on the basis of IR, UV, NMR and mass spectral data. This successful dimerization at the oxindole level in which enhanced activity at the oxindolic-β-position was assured, provided a compelling argument that a search for conditions for the oxidative coupling of unprotected tryptamines should be centred upon the generation of a mesomeric radical (as IV) rather than on a study of a range of oxidants.

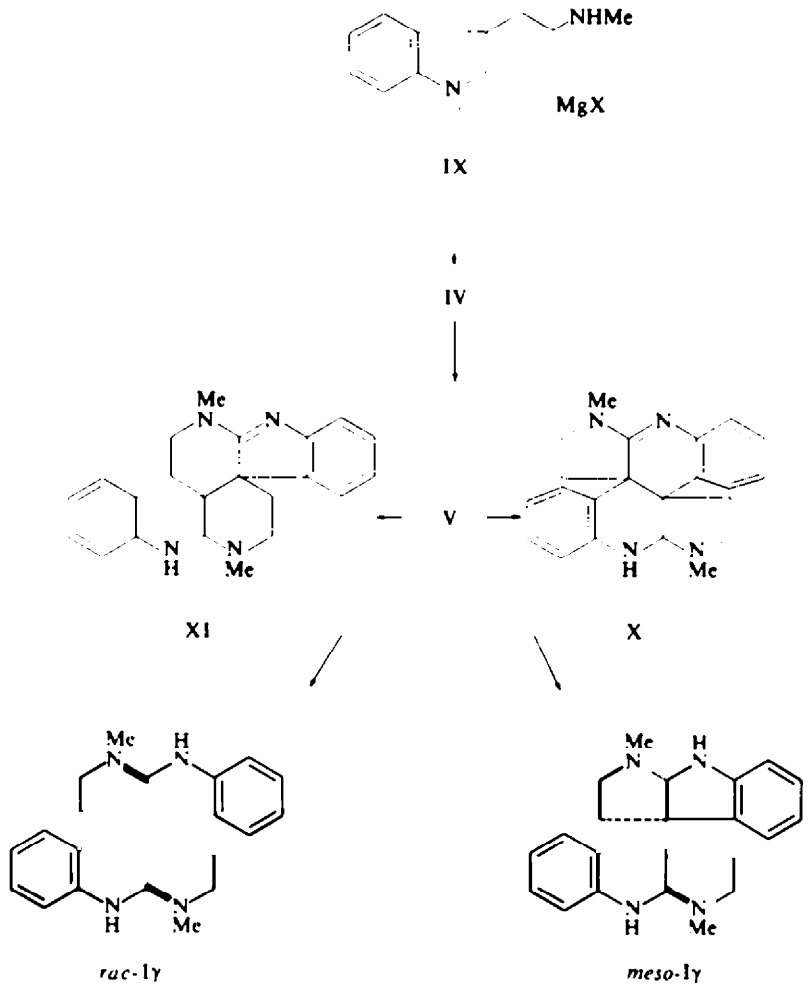
Our attention was therefore next directed to the reactions of indolyl magnesium halides whose alkylation, acylation, and carbonation reactions follow N_a-, β-, and N_a, β-substitution.[14] Taken in conjunction with the recent evidence that in tetrahydrofuran solution indolyl magnesium halides are ionic[15] and that anhydrous ferric chloride oxidation of phenyl magnesium bromide affords diphenyl according to Eq. (1)[16]

$$6PhMgBr + 2FeCl_3 \rightarrow 3Ph.\,Ph + 2Fe + 3MgBr_2 + 3MgCl_2 \qquad (1)$$

it seemed propitious to subject N_b-methyltryptamine to ionization of N_a by formation of the Grignard reagent (IX) and thence to remove the odd electron with ferric chloride to generate the radical IV.

Accordingly N_a-dipteryl magnesium iodide (IX; X = I) was prepared and anhydrous ferric chloride added to its ethereal solution at room temperature. Mild acidic hydrolysis with ammonium chloride furnished a semi-crystalline mixture

[13] J. B. Hendrickson, R. Göschke and R. Rees, *Proc. Chem. Soc.* 383 (1962); *Tetrahedron* **20**, 565 (1964).
[14] B. Oddo, *Gazz. Ital.* **41**, 221 (1911); **63**, 234 (1933). M. S. Kharasch and O. Reimuth *Grignard Reactions of Non-metallic Substances*. Prentice-Hall, New York (1954); A. R. Katritzky and (Sir) R. Robinson, *J. Chem. Soc.* 2481 (1955).
[15] M. G. Reinecke, H. W. Johnson and J. F. Sebastian, *Tetrahedron Letters* 1183 (1963).
[16] G. Champetier, *Bull. Chim. Soc.* **47**, 1131 (1930).



from which unchanged dipterin (30%) was recovered by chromatography over alumina. The remaining fractions from the chromatogram were examined as follows.

Compound A (19%) m.p. 183–185° displayed a typical Ph.N.C.N. chromophore in the UV at 247 and 303 mμ and corresponded in mol wt (346) to a calycanthine isomer, $C_{22}H_{26}N_4$. Of the five isomers (α-ε) only γ chimonanthine shows completely symmetrical fragmentation in the mass spectrum at *m/e* (Fig. 1; a). The mass spectrum of compound A was identical with that of *laevo*-chimonanthine suggesting that the most abundant dimeric material in the oxidation mixture was in fact *rac*-chimonanthine (Iγ). In particular ions due to fragments a (172) and b (130) dominated the spectrum. The 100 mc NMR spectrum of compound A was in accord with this assignment showing at ABCD pattern at τ 2·7 3·7 (8 aromatic protons) a singlet τ 5·62 (R_2-C-H; 2 protons), a broad singlet at τ 7·70 (N-CH_3; 6 protons). The solution IR and UV spectra and the TLC of compound A were identical in every respect with those of *laevo*-chimonanthine and complete confirmation that A was in fact

rac-chimonanthine was forthcoming by direct comparison with a sample of the synthetic racemic alkaloid.[11]

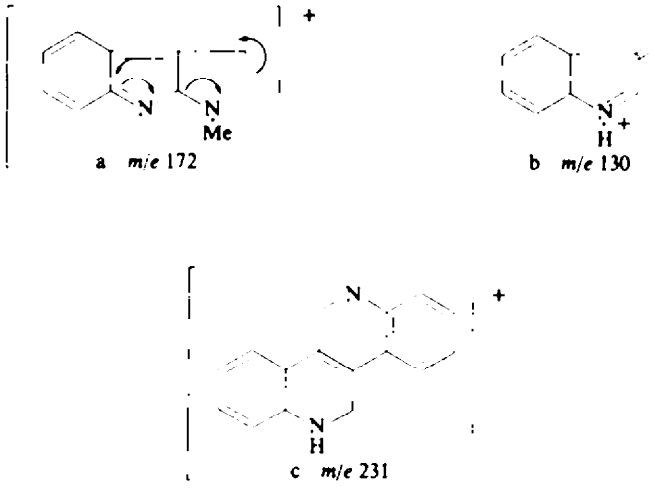


FIG. 1 Principal ions in the mass spectra of chimonanthine and calycanthine.[13, 19]

Compound B m.p. 198–202° formed in 7% yield was isomeric with *rac*-chimonanthine and had almost identical mass and UV spectra. However in the NMR spectrum the N-methyl resonance appeared at τ 7·63 (cf. τ 7·70 for chimonanthine N-Me) reflecting a slight shielding effect by the aromatic rings. The virtual absence of mass spectral fragments between the molecular ion at *m/e* 346 and the base peak at *m/e* 172 (Fig. 1; a) provides compelling evidence that compound B is the *meso*-γ isomer i.e. *meso*-chimonanthine.* Furthermore the properties of compound B are very close to those of Hendrickson's compound B-1 m.p. 203–204° to which the *meso*-γ structure was previously assigned.[13] An unexpected but welcome confirmation of this assignment was however soon forthcoming.

In the course of comparison of natural and synthetic chimonanthine samples, the former material was provided as a semi-purified preparation from *C. floridus* by Dr. G. F. Smith.[6, 7] During the course of extraction of pure *laevo*-chimonanthine from this mixture TLC revealed that the "impurity" corresponded in R_f with synthetic *meso*-chimonanthine. Indeed preparative chromatography afforded several milligrams of a new alkaloid $C_{22}H_{26}N_4$ m.p. 199-202° identical in every respect (mass, UV, IR, NMR spectra; $[\alpha]_D$ 0°) with compound B, i.e. synthetic *meso*-chimonanthine. Thus, the laboratory oxidative coupling of dipterin leads not only to the desired *rac*-chimonanthine in one step, but also to the *meso*-isomer (Iγ) whose isolation from natural sources succeeded its synthetic arrival by several days.

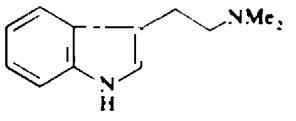
Compound C m.p. 274–275° obtained in 3·5% yield was shown to be a dehydrocalycanthine isomer on the basis of the following evidence. Mass spectral and

* For a detailed discussion of the mass spectral fragmentation of calycanthine and its isomers see references 13 and 19.

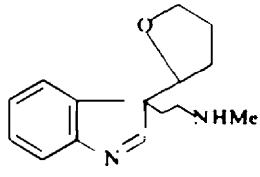
analytical data established the formula $C_{22}H_{24}N_4$. A shoulder at 280 mμ distinguishes *C* from calycanthine and its natural isomers (λ_{max} 247, 303 mμ) yet the mass spectral fragmentation pattern is more reminiscent of calycanthine than of chimonanthine. However the absence of a peak at *m/e* 231 attributed to protonated calycanine (III; Fig. 1; c) by loss of both ethanamine bridges suggests that *C* is in fact a monoamidine of Iβ (X). This formulation is supported by the appearance of *two* N-C$\underline{H}_3$ resonances τ 6·72 and 7·61 and the similarity but non-identity of *C* and Hendrickson's compounds A1 and A2. Since the latter were assigned to the *rac*-series we suggest that the higher melting C is in fact *meso*-dehydro-β-calycanthine (X) formed by over-oxidation. Further evidence is provided by the formation of a *mono* acetate of compound C.

Compound D also obtained in 3·5% yield had m.p. 235° and possessed spectral characteristics very similar to those of (X). On the basis of the presence of one N-$\underline{H}$ and one N—C$\underline{H}$---N< proton in the NMR spectrum of the C$\underline{H}_2$ resonance patterns which closely paralleled those of the ethanamine bridge of calycanthine, and of the acid catalysed conversion of D to C we suggest that D is in fact the isomeric *mono* amidine also in the *meso*-δ series (XI).

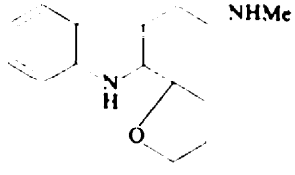
When the solvent for the coupling was changed from ether to tetrahydrofuran the yield of dimeric material was considerably diminished. In fact the major product had a mol wt of 188 corresponding to $C_{12}H_{16}N_2$. The presence of an intact indole chromophore in the UV spectrum indicates that the compound is N_bN_b-dimethyltryptamine (XII) formed by combination of excess methyl iodide with dipterin. A



XII



XIV



XIII

second product also exhibited a monomeric indolic UV spectrum. The absence of an α-indolic proton and the presence of *two* NH protons (exchange with D_2O) were deduced from the NMR spectrum. Taken together with the mol wt of 244 ($C_{15}H_{20}N_2O$) the evidence is in favour of the structure N_b-methyl-α-tetrahydrofuranyltryptamine (XIII) for this compound. Its formation may be rationalized by coupling of an α-indolyl and -tetrahydrofuranyl radicals or by acid-catalysed rearrangement of the ββ-dialkylated indolenine (XIV) formed by β-coupling.

The synthesis of racemic calycanthine was completed by acid catalysed isomerization of synthetic racemic chimonanthine (Iγ). Thus when the latter was heated with dilute acetic acid for 30 hr at 90° a 1:4 mixture of chimonanthine and calycanthine was produced, and in fact a 70% yield of *rac*-calycanthine (Iα) was obtained from this reaction. (cf.[13]) No minor by-products or degradation to N_b-methyltryptamine occurred under these conditions.

Similar treatment of *meso*-chimonanthine (Iγ meso) afforded the high melting *meso*-isomer of calycanthine with a mass spectrum and UV absorption virtually identical with that of the *rac*-alkaloid.

The above experiments thus complete a one-step synthesis of the calycanthaceous alkaloids based on a biogenetic model and yielding *rac*-chimonanthine (19%), and *meso*-chimonanthine (7%) directly, and *rac*-calycanthine (14% overall) after acidic isomerization of *rac*-chimonanthine.

On the basis of the mechanisms involved in these laboratory processes it is tempting to suggest that chimonanthine is the true biological precursor of calycanthine and that N-methyltryptamine is the natural building block for the series of alkaloids.

Recent biosynthetic experiments by O'Donovan and Keogh[17] have shown that 2-^{14}C tryptophan serves as the monomeric unit for folicanthine (VIIa) in *C. floridus*.

EXPERIMENTAL

M.ps were determined on a Kofler hot stage microscope and are uncorrected. UV spectra were taken on a Cary 14 spectrometer, IR spectra on a Perkin-Elmer 137B spectrophotometer, and NMR at 60 and 100 mc on Varian A-60 and HA-100 instruments respectively. Proton resonance positions refer to TMS as internal standard (s = singlet; d = doublet; m = multiplet). Mass spectra were recorded on Atlas CH4 or MS9 instruments. TLC was carried out on alumina G (prepared according to Stahl) in ether–methanol (50:1) as solvent,[14] the colours being developed by 1% ceric sulphate soln in 35% H_2SO_4. R_f's and colours quoted refer to this system.

N_b-Tosyltryptamine. Tryptamine hydrochloride (20 g; 0·102 moles) was suspended in benzene (150 ml) and treated with *p*-toluenesulphonyl chloride (21·4 g; 0·112 moles) followed by KOH (17 g; 0·3 moles) in water (150 ml). After warming until transparent a two phase system resulted and the mixture was allowed to cool with occasional shaking. Acidification with dil HCl and cooling to 5° precipitated the crude tosylate. Recrystallization from EtOH gave 30 g (90%) of tosylate m.p. 114–115° (lit. m.p. 115–116°).[15]

*N_a-Methyl-N_b-tosyltryptamine.** The tosylate (29·8 g, 0·095 moles) was suspended in EtOH (50 ml) and warmed in 50% NaOH aq (20 ml, w/w) to complete soln. Then MeI (16·8 g, 0·118 moles) was added and the soln stored at room temp overnight. After chilling, the resultant crystalline material was filtered, washed with EtOH and crystallized from a minimum of the same solvent. Dil NaOH aq was added to the first filtrate and a further quantity of crystalline material obtained. The yield of recrystallized N_a-methyl-N_b-tosyltryptamine was 20·4 g (67%), m.p. 118–119° (lit. 116–117°).[15]

N-methyltryptamine (Diptérin; III). N_b-methyl-N_b-tosyltryptamine (20 g, 0·064 moles) was dissolved in THF (350 ml) and added with stirring to liquid ammonia (1·5 l.) cooled in Dry Ice–acetone. Na was added until the deep blue colour persisted for 10 min. The reaction was completed by addition of NH_4Cl (until the blue colour disappeared) and the NH_3 allowed to evaporate at room temp. The residue was heated with dil NaOH aq and extracted with ether (3 × 100 ml). The basic product was extracted into

* This preparation, a modification of the method of Hoshino and Kobayashi[16] was devised by Dr A. C. Day to whom we express our best thanks.

[17] D. G. O'Donovan and M. F. Keogh, *J. Chem. Soc.* 1570 (1966C); cf. H. R. Schutte and B. Maier, *Arch. Pharm* **298**, 459 (1965).

[18] T. Hoshino and T. Kobayashi, *Liebigs Ann* **520**, 11 (1935).

[19] E. Clayton, R. I. Reed and J. M. Wilson, *Tetrahedron* **18**, 1495 (1962).

1N HCl; 3 × 50 ml) and recovered with ether in the usual way. N_b-Methyltryptamine was crystallized from ether under N_2 m.p. 88–89° (9·8 g, 93°,) λ_{max} 274, 282, 291 mμ; ε 7000, 7200, 6000. NMR ($CDCl_3$) τ 2·60 and 2·98 (*m*; aromatic H; NH) 3·28 (*s*; α indolic H) 7·12 (*m*; 4 methylene protons) 7·65 (*s*; N CH_3). Mass spectrum *m/e* 174 (M^+, 8°,), 144 (M-31; 7°,) 131 ([M-43]; 100°,)

Oxidation of N-methyltryptamine

Synthesis of the alkaloids. MeMgI was prepared from Mg turnings (1·96 g; 0·805 moles) and MeI (11·4 g; 0·805 moles) in ether (500 ml) under N_2. A soln of N_b-methyltryptamine (14 g; 0·805 moles) in ether (700 ml) was added dropwise in 1 hr to the stirred soln of Grignard reagent. The resultant suspension was stirred vigorously for a further 2 hr then a soln of anhyd FeCl, (15 g, 0·92 moles) in ether (400 ml) added dropwise. The blue-black mixture was stirred for 18 hr and then treated with NH_4Cl aq (1500 ml). After separation of ether and $CHCl_3$ soluble materials, the pH of the aqueous layer was adjusted to pH 10 with 6N NaOH while agitating with $CHCl_3$. Sufficient powdered cellulose was added to absorb the green gelatinous ppt of $Fe(OH)_2$, and the solids removed by filtration and extracted with boiling $CHCl_3$ until the washings were colourless. This extract was combined with several $CHCl_3$ extracts of the aqueous layer, dried ($MgSO_4$) and evaporated to give a crude semi-crystalline mixture (11 g, 80 °, recovery)

TLC analysis revealed 5 major components. In descending order of abundance these were N_b-methyltryptamine (R_f 0·10, yellow) A (R_f 0·30 red → blue → yellow)*; B (R_f 0·50 red → blue → green yellow); C (R_f 0·68 purple, fading) and D (R_f 0·58 brown only after warming to 80°). In the same system *laevo*-chimonanthine had R_f 0·30 (red → blue → yellow)

The total product mixture (11 g) was dissolved in benzene and chromatographed on neutral alumina (Grade 1, 400 g). Compound C (0·25 g) was eluted with benzene (2·5 l) and compound D (0·26 g) with benzene 2°, ether (1 l.). Elution with benzene : ether (4 : 1) gave a mixture consisting mainly of compounds A and B (2·25 g) together with a trace of C and D. Benzene : ether (1 : 1; 500 ml) eluted compound A (1·05 g). A further elution with this solvent mixture afforded N-methyltryptamine (1·22 g). Finally ether–MeOH mixtures eluted a further quantity of N-methyltryptamine (5·2 g). The compounds A–D were further purified by rechromatography and examined as follows (yields are based on 30°, recovery of N-methyltryptamine)

Compound A. *rac-Chimonanthine* (Iγ) recrystallized from benzene, formed prisms m.p. 183–185° (yield 19°,). Complete identity of spectral data and m.p. behaviour (alone and mixed) with a sample of synthetic *rac*-chimonanthine† was established. *UV spectrum* λ_{max}^{EtOH} 247, 303 mμ ε 13600, 5600 shifted to 239, 294 m in 0·1N HCl–EtOH. *IR spectrum* ν^{CHCl_3} 3440 (w) 2920 (s) 2850 (m) 2800 (m) 1615 (s) 1480 (s) 1460 (s) 1395 (m) 1350 (m) 1310 (m) 1240 (w) 1150 (m) 1120 (m) 1050 (w) 1055 (w) 1022 (m) 904 (w) cm^{-1}. *NMR spectrum* (in $CDCl_3$) at 100 mc τ 2·7–3·7 (Ar-H; 8H; *m*), 5·62 (R_3C-H; 2H; *s*) 5·75 (R_2N-H; 2H; *s*) 7·2–8·2 (–CH_2–; 8H; *m*) 7·70 (N-CH_3; 6H; *s*). *Mass spectrum m/e* 346 (M^+; 12°,) 347 (M + 1; 1°,) 172 M-174, 100°,) 173 (M-173, 33°,) 157 (2°,) 144 (2°,) 130 (26°,).

Compound B. *meso*-Chimonanthine (Iγ) was recrystallized from benzene m.p. 198–202° (7°,). *UV spectrum* λ_{max}^{EtOH} 248, 305 mμ 13000, 4900, shifting in 0·1N HCl–EtOH to λ_{max} 239, 294 mμ. *IR spectrum* ν^{CHCl_3} 3440, 2920, 2850, 2800, 1615, 1480, 1460, 1395, 1340, 1310, 1240, 1150, 1120, 1022, 994, 935, 908 cm^{-1}. *NMR spectrum* (in $CDCl_3$) τ 2·7–4·0 (Ar-H; 8H; *m*) 5·35 (R_2N-H, 2H; *s*) 6·15 (R_3C-H; 2H; *s*) 7·0–8·3 (CH_2; 8H, *m*); 7·63 (N-CH_3; 6H; *s*). *Mass spectrum m/e* 346 (M^+, 7°,) 172 (M-174, 100°,) 173 (M-173; 25°,) 157 (2°,) 144 (2°,) and 130 (10°,).

These data are in close accord with those published for Hendrickson's compound B-1. Identical data were obtained for natural *meso*-chimonanthine isolated as described below

Compound C. Compound X was recrystallized from $CHCl_3$ m.p. 274–275°, 3·5°,. (Found: C, 76·30; H, 7·45; N, 15·80. $C_{22}H_{24}N_4$ requires: C, 76·70; H, 7·0; N, 16·25°,) *UV spectrum* λ_{max}^{EtOH} 249, 276 *sh*, 283, 304 *sh* mμ ε 7100, 7000, 7200, 4500 $\lambda_{max}^{EtOH\ 1\ HCl}$ 239 *sh*, 264, 271 *sh*, 290 *sh* mμ ε 6000, 5300, 5000, 3800 *IR spectrum* ν^{CHCl_3} 3440, 2930, 2850, 2790, 1640, 1590, 1580 cm^{-1} *NMR spectrum* (in $CDCl_3$) τ 2·95 and 3·45 (Ar-H; 8H, *m*) 5·34 (NH; 1H, *s*) 5·80 (R_3CH; 1H; *s*) 6·4–8·1 (CH_2 *m*) 6·72 (R_2NCH_3; 3H, *s*) and 7·61 (R_2NCH_3, 3H; *s*). *Mass spectrum m/e* 344 (M^+) 345 (M + 1, 100°,) 346 (M + 2, 23°,) 329 (M-15, 12°,), 300 (M-44; 10°,) 286 (M-158, 4°,), 209 (M-135; 5°,) 197 (M-147; 4°,) 172 (M-172, 10°,) 130 (4°,)

The compound was recovered unchanged from attempted catalytic and borohydride reduction experiments. Treatment of compound C (20 mg) with Ac_2O (0·5 ml) and pyridine (5 ml) afforded an amorphous

* Red → blue → etc refer to colour changes within 10 min of spraying with ceric sulphate soln

† Kindly supplied by Professor J. B. Hendrickson

monoacetate λ_{max} 250, 273, 280 whose integrated NMR spectrum revealed the presence of *one* $-OCOCH_3$ function

Compound D. Compound XI m.p. 235–240° (from benzene) was isolated in 3·5% yield. (Found: C, 76·55; H, 7·10; N, 16·10 $C_{22}H_{24}N_4$ requires: C, 76·70; H, 7·00; N, 16·25%) *UV spectrum* λ_{max}^{EtOH} 274, 283, 310 mμ 10,080, 10,100, 6500 $\lambda_{max}^{EtOH-HCl}$ 267, 276, 293 mμ 7600, 7000, 5900 *IR spectrum* ν^{CHCl_3} 3440, 3200, 2950, 2830, 1630, 1580, 1450 cm^{-1}. *NMR spectrum* (in $CDCl_3$) τ 2·21 (Ar-H; 1H; *d*) 3·30 (Ar-H; 7H; *m*) 5·50, 5·70 ($R_3C\underline{H}$ and $R_2N\underline{H}$; 2H; doublets) 6·1–6·65 (CH_2; 2H; *m*) 7·0–8·1 (CH_2; 5H; *m*) 8·84 ($C\underline{H}$ of CH_2; 1H; *m*) 6·78 (N-CH_3; 3H; *s*) 7·42 (N-CH_3; 3H; *s*). *Mass spectrum m e* 344 (M^+) 345 (M + 1; 20%) 346 (M + 2; 10%) 343 (M-1; 45%) 299 (M-45; 22%) 288 (M-56; 20%) 231 (M-113; 4%) 172 (M-172; 23%) 159 (16%) 143 (10%) 130 (16%). Treatment of D with HCl afforded C (TLC, mixed m.p.)

Oxidation of N_b-methyltryptamine in tetrahydrofuran solution

To a soln of MeMgI (from Mg [0·28 g] and MeI [1·63 g]) in THF (60 ml) was added a soln of N_b-methyltryptamine (1·5 g) in THF (50 ml). Addition (as above) of $FeCl_3$ (1·4 g) in THF (50 ml) gave a black soln which was stirred overnight under N_2. Worked up as before yielded after chromatography on alumina:

(i) *N_bN_b-Demethyltryptamine* (15%; XII) had m.p. 45–49°, lit. m.p. 49–50°. (Found: C, 76·75; H, 8·70; N, 14·30. Calc. for $C_{12}H_{16}N_2$: C, 76·55; H, 8·60; N, 14·9%). *UV spectrum* λ_{max} 277 *sh*, 283, 292 mμ ε 6600, 7000, 6200 (unchanged in dilute acid). *IR spectrum* ν^{CHCl_3} 3500, 2950, 2870, 2840, 2790. *NMR spectrum* ($CDCl_3$) τ 2·4 (Ar$\underline{H}$); 1H; *m*) 2·9 (ArH; 3H; *m*) 3·27 (α-indolic H; 1$\underline{H}$; *d*; *J* = 1·8 c s) 7·21 (CH_2; 4H; *m*) 7·61 (NCH_3; 6H; *s*). *Mass spectrum m e* 188 (M^+; 100%), 143 (M-45; 45%) 130 (M-58; 85%) 115 (40%) 58 (M-130) 44%.

(ii) *2-(α-Tetrahydrofuranyl)tryptamine* (5%; XIII) was crystallized from ether, m.p. 134–147°. (Found: C, 73·10; H, 8·20; N, 11·70 $C_{15}H_{20}N_2O$ requires: C, 73·73; H, 8·25; N, 11·47%; M, 244. *UV spectrum* λ_{max}^{EtOH} 276 *sh*, 283, 290 mμ (unchanged in dilute acid). *IR spectrum* ν^{CHCl_3} ε 3500, 2910, 2850, 2700, 1670, 1630, 1010, 990, 975, 956 cm^{-1}. *NMR spectrum* ($CDCl_3$) τ 0·96 (N$\underline{H}$ exchanges with D_2O, 1H) 2·3, 3·1 (Ar$\underline{H}$; 4H; *m*) 3·53 (N-$\underline{H}$ exchanged with D_2O; 1H; *s*) 6·39 ( ; 3H; *m*) 7·12 ($C\underline{H}_2C\underline{H}_2N$; 4$\underline{H}$; *m*) 7·44 (N-$C\underline{H}_3$; 3$\underline{H}$; *s*) 8·22 [$CH(C\underline{H}_2)_2$; 4H; *d*]. *Mass spectrum m e* 244 (M^+ 10%) 198 (M-45; 1%) 185 (M-59; 100%) 172 (M-72; 3%) 156, 144 and 130

Isolation of natural mesochimonanthine

A sample (83 mg) of crude chimonanthine ex. *C. floridus* was chromatographed on alumina. The fraction eluted with benzene–ether (9:1) yielded colourless prisms (20 mg) m.p. 199–202° after several recrystallizations from benzene $[\alpha]_D$ 0·0° (*c*, 2·0 in $CHCl_3$). The spectra data and TLC behaviour of this compound were identical in every respect with those of the synthetic *meso*-isomer (see above for details). There was no depression on mixed m.p. with a sample of synthetic *meso*-chimonanthine (m.p. 198–202°).

Isomerization of rac-chimonanthine

Synthesis of rac-calycanthine (Ix). *rac*-Chimonanthine (30 mg) was dissolved in water (5 ml) containing AcOH (5 drops) and heated on the steam bath for 30 hr under N_2. The recovered material (27 mg) was separated by chromatography to give *rac*-calycanthine (20 mg) m.p. 244–247° (from benzene). The TLC characteristics (R_f 0·80; red → green → mauve) and soln IR, UV, NMR and mass spectral data were identical in every respect with the corresponding data for *dextro*-calycanthine. *UV spectrum* λ_{max}^{EtOH} 250, 309 mμ ε 19,000, 6300. *IR spectrum* ν^{CHCl_3} 3480, 2960, 2820, 1607, 1585, 1490, 1450, 1378, 1315, 1303, 1287, 1268, 1240, 1190, 1167, 1157, 1118, 1107, 1067, 1040, 1025, 975, 958, 886, 865 cm^{-1}. *NMR spectrum* (in $CDCl_3$) τ 2·90–3·90 (Ar-$\underline{H}$; 8H; *m*) 5·52 ($R_2N\underline{H}$; exchanges D_2O; 2H; *s*) 5·72 (N-$C\underline{H}$-N; 2H; *s*) 6·85 (CH_2; 2H; *m*) 7·2–8·1 (CH_2; 4H; *m*) 7·62 (NCH_3; 6H; *s*). *Mass spectrum m e* 346 (M^+; 100%) 347 (M + 1; 25%) 302 (M-44; 12%) 288 (M-58; 17%) 259 (6%) 245 (10%) 231 (M-115; 25%) 172 (M-174; 10%) and 130 (6%) The remaining (7 mg) of isomerization mixture consisted of *rac*-chimonanthine (TLC; m.p.)

Isomerization of meso*-chimonanthine*

meso-*Calycanthine* (meso-Ix). *meso*-Chimonanthine (10 mg) was treated with aqueous AcOH as above to give a 1:2 mixture of *meso*-chimonanthine and *meso*-calycanthine. The latter had m.p. 265–268°; λ_{max}

245 and 307 mμ and a mass spectrum almost identical with that of *dextro*-calycanthine with major peaks at *m e* 346 (M^+; 100%) 347 (M + 1; 25%) 302, 288, 259, 245, 231, 172 and 130

Acknowledgements—We warmly thank Dr. A. Brossi (Hoffmann La Roche, Nutley) for a very generous gift of tryptamine, N.R.C. for financial support and the Roche Anniversary Foundation for a Fellowship (to A.I.S.)