Studies on the Alkaloids of Menispermaceous Plants. Part CCXLIX.[1] Total Synthesis of Optically Active Natural Isotetrandrine, Phaeanthine, and Tetrandrine[2]

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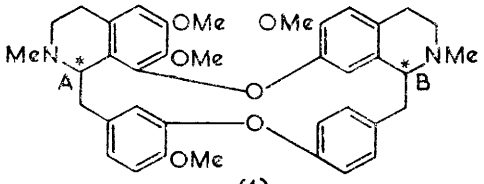
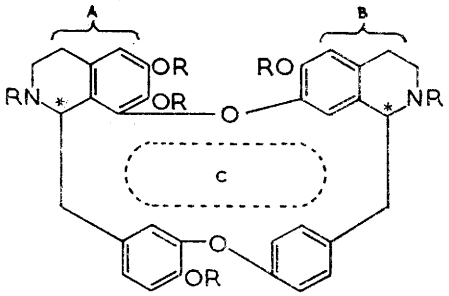
Natural phaeanthine (1a), isotetrandrine (1b), and tetrandrine (1c), belonging to the oxyacanthine–berbamine series of the bisbenzylisoquinoline alkaloids, have been synthesised by a stepwise route. One of the benzylisoquinoline nuclei was constructed initially, and joined by the Ullmann method through ether linkages to protected phenethylamine and phenylacetic acid units. The phenylacetic acid portion was activated by formation of its nitrophenyl ester and condensed with the phenethylamine unit (protected by a t-butoxycarbonyl group) to form a macrocyclic amide. The latter was converted by Bischler-Napieralski cyclisation and reduction into the desired alkaloids without formation of any structural isomers.

THE bisbenzylisoquinoline alkaloids possessing two diphenyl ether linkages have been classified into two groups: the oxyacanthine–berbamine series, to which the title alkaloids belong, and the isochondodendrine series.



(1)

a; (AR,BR) Phaeanthine
b; (AR,BS) Isotetrandrine
c; (AS,BS) Tetrandrine



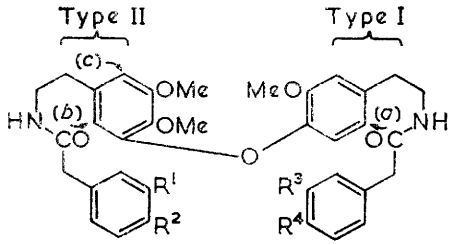
R = H or Me
* Asymmetric centre

SCHEME 1

The total synthesis of optically active natural alkaloids of the former series has not hitherto been achieved. We now report the stepwise synthesis of phaeanthine (1a), isotetrandrine (1b), and tetrandrine (1c).

In the design of suitable synthetic schemes, the following aspects were considered.

(i) *Construction of the macro-ring* c. Two different methods have been employed; in the first, two appropriately substituted coclaurine units are simultaneously coupled by an Ullmann condensation.[3] This route, however, is less satisfactory in this case since, depending on the direction of coupling, it may lead to either a berbamine or an isochondodendrine type of alkaloid. In the second method, two appropriately substituted diphenyl ethers are first synthesised, one containing two carboxymethyl groups and the other two 2-amino ethyl groups. The two ethers are then combined *via* amide linkages, and two isoquinoline rings are then formed by a dual Bischler-Napieralski reaction.[4] This route, however, is still equivocal at the stage of the cyclobisamide formation: either of the isomeric cyclobisamides [*e.g.* (2a) and (2b) in Scheme 2] may be formed. However, stepwise amide formation may be effected by use of the technique employed in peptide synthesis and successfully used in the synthesis of (±)-cepharanthine[5] and (±)-cycleanine.[6] This route, however, still leaves the final stage equivocal, *i.e.* the direction of the Bischler-Napieralski ring closure is not controlled.



(2)

a; $R^1 = H$, $R^2 + R^3 = \cdot O \cdot$, $R^4 = OMe$
b; $R^1 + R^4 = \cdot O \cdot$, $R^2 = OMe$, $R^3 = H$

SCHEME 2

(ii) *Formation of the two isoquinoline rings* A *and* B (Scheme 1). It is known that Bischler-Napieralski cyclisation of amides of type I (Scheme 2) occurs nearly exclusively in the (*a*) direction,[7] whereas that of the

[1] Part CCXLVIII, M. Tomita, M. Ju-ichi, and H. Furukawa, *J. Pharm. Soc. Japan*, 1967, **87**, 1560.
[2] Preliminary communication, Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *Tetrahedron Letters*, 1968, 3399.
[3] M. Tomita, K. Fujitani, and T. Kishimoto, *J. Pharm. Soc. Japan*, 1962, **82**, 1148.
[4] T. Kametani, O. Kusama, and K. Fukumoto, *Chem. Comm.*, 1967, 1212.
[5] M. Tomita, K. Fujitani, Y. Aoyagi, and Y. Kajita, *Tetrahedron Letters*, 1967, 1201; *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 217.
[6] M. Tomita, K. Fujitani, and Y. Aoyagi, *Tetrahedron Letters*, 1966, 4243; *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 62.
[7] W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, 81; W. J. Genster, Heterocyclic Compounds, ed. by R. C. Elderfield, vol. 4, Wiley, New York, 1952, p. 351; M. Tomita and H. Watanabe, *J. Pharm. Soc. Japan*, 1938, **58**, 783; K. Fujitani, T. Kishimoto, and S. Niimura, *J. Pharm. Soc. Japan*, 1963, **83**, 412.

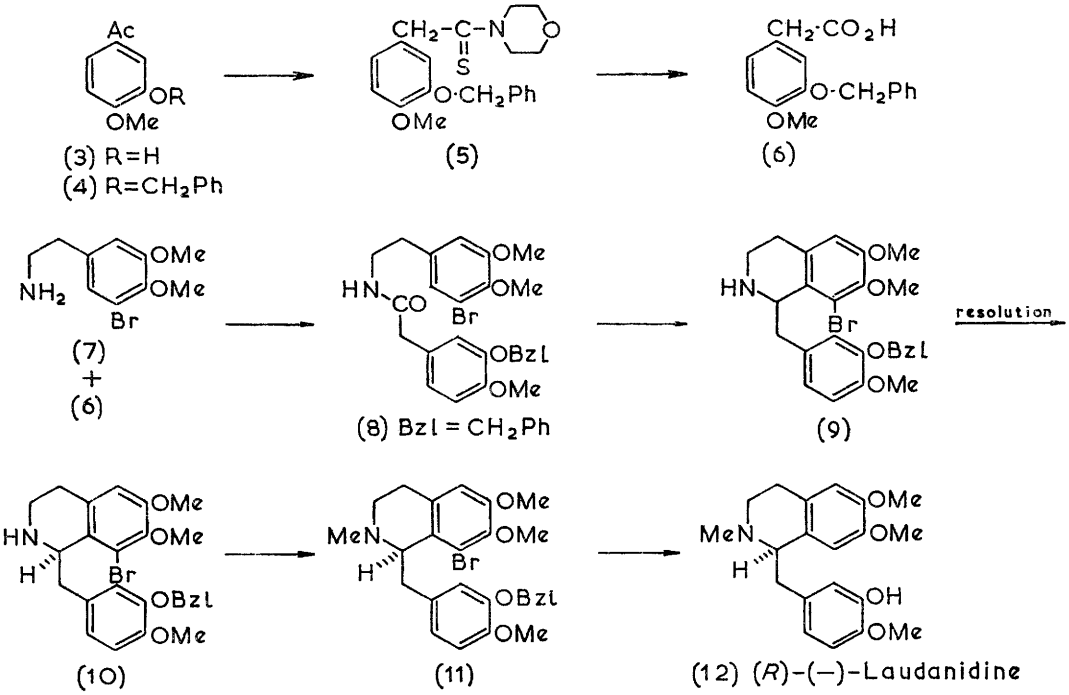
amides of type II occurs simultaneously in two directions, (*b*) and (*c*).[5,6] Consequently, in the construction of ring B, cyclisation would be expected to occur exclusively in the desired direction when the reaction is applied to either the cycloamide intermediate or the earlier intermediate (for example the amide which gives the coclaurine-type compound). However, ring A would have to be constructed before the formation of the macro-ring C.

(iii) *Production of two asymmetric centres.* Reduction of epistephanine, which is an oxyacanthine type alkaloid and possesses one asymmetric centre and one C=N group, proceeds stereoselectively with sodium borohydride in methanol.[8] Thus if one asymmetric centre is introduced at an early stage in the synthesis, the second could be produced stereoselectively by a similar reduction.

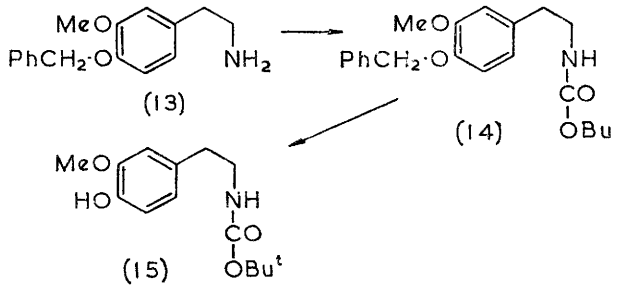
On the basis of the foregoing considerations, the total synthesis of the title alkaloids has now been accomplished as follows.

The intermediate (*R*)-(—)-*O*-benzyl-8-bromolaudanidine (11) was synthesised *via* *O*-benzyl-8-bromo-*N*-norlaudanine (9) from *O*-benzylisohomovanillic acid (3-benzyloxy-4-methoxyphenylacetic acid) (6)[9] and 3-bromo-4,5-dimethoxy-phenethylamine (7)[10] as shown in Scheme 3. Compound (9) was resolved *via* its (+)-tartaric acid salt, and the absolute configuration and optical purity of the resolved free base (10) were confirmed by conversion into (*R*)-(—)-laudanidine (12),[11] of established absolute configuration.

The resolved base (11) was then condensed with 4-hydroxy-3-methoxy-phenethylamine, protected with a t-butoxycarbonyl group[12] because of its instability under the Ullmann reaction conditions. The ease of removal of the protecting group under mild acid conditions and its resistance towards hydrogenolysis and cleavage by alkali are of great advantage in subsequent stages, especially in the formation of the second diphenyl ether linkage. The protected phenolic compound (15) was synthesised as shown in Scheme 4.



SCHEME 3



SCHEME 4

Ullmann condensation of the resolved base (11) with the phenol (15) afforded compound (16) (50%), which showed one spot on t.l.c. Hydrogenolysis over palladium–charcoal then gave compound (17) (84%), the

[8] M. Tomita and Y. Watanabe, *Chem. and Pharm. Bull. (Japan)*, 1956, **4**, 124; Y. Watanabe, *J. Pharm. Soc. Japan*, 1960, **80**, 166; H. Furukawa, *ibid.*, 1966, **86**, 253.

[9] R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 1931, 3163; C. Schöpf, *Annalen*, 1940, **544**, 62.

[10] M. Tomita, Y. Aoyagi, Y. Sakatani, and K. Fujitani, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 1996.

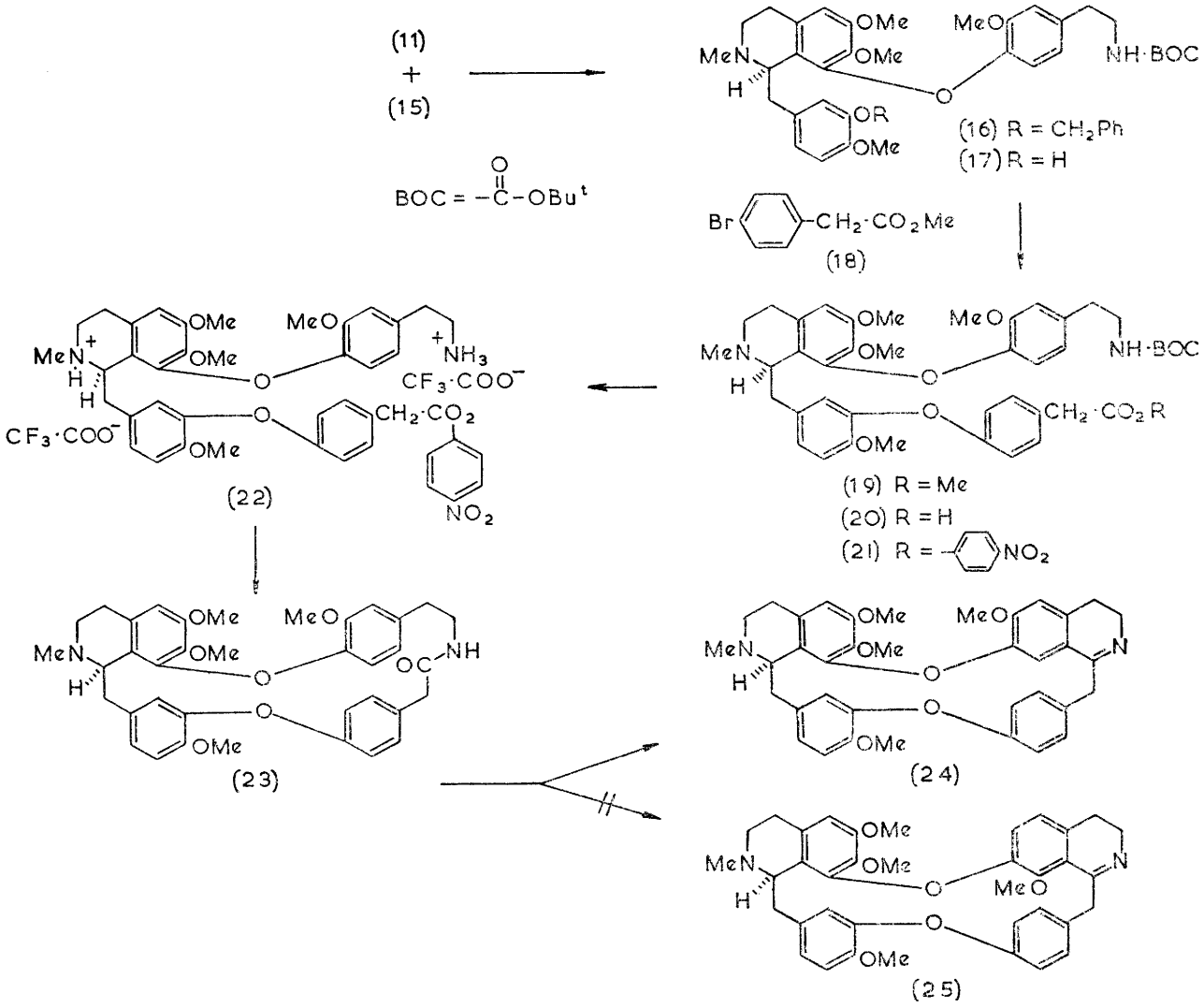
[11] O. Hesse, *Annalen*, 1894, **282**, 208; M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan*, 1962, **82**, 734.

[12] R. A. Boissonnas, *Adv. Org. Chem.*, 1963, **3**, 159.

structures of compounds (16) and (17) were confirmed by their i.r. and n.m.r. spectra. Ullmann condensation of compound (17) with methyl *p*-bromophenylacetate (18) gave compound (19) (48%), shown to be homogeneous by t.l.c. Its n.m.r. spectrum agreed with the structure assigned (19).

Next, the amide linkage was formed by the *p*-nitrophenyl ester method. The methoxycarbonyl group of (19) was hydrolysed with alkali to give the free acid (20), which, without purification, was converted into the *p*-nitrophenyl ester (21) with *p*-nitrophenol and dicyclohexylcarbodi-imide. The t-butoxycarbonyl group was then removed with trifluoroacetic acid, to give the *p*-nitrophenyl ester-phenethylammonium trifluoroacetate (22), which was cyclised to the amide (23) by adding a solution of the former in anhydrous dimethylformamide to pyridine at 70°. Chromatography of the product on alumina afforded the amide (23) [54% from compound (19)]; its i.r. and n.m.r. spectra confirmed its structure. That this amide is not oligomeric (oligomers are occasionally formed in the peptide synthesis [13]) was confirmed by the appearance of the molecular ion peak at *m/e* 624 in the mass spectrum.

Bischer-Napieralski cyclisation of the amide (23) gave the 3,4-dihydroisoquinoline (24) (87%), m.p. 148—150°, $[\alpha]_D$ +82° (in chloroform), *m/e* 606 (M^+) and 303 (M^{2+}). Its i.r. spectrum showed the disappearance of the amide bands (3410 and 1660 cm.$^{-1}$) due to compound (23), and a new band due to C=N at 1620 cm.$^{-1}$. The analytical data corresponded to the formula $C_{37}H_{38}N_2O_6$. Thus the dihydroisoquinoline must be (24) or (25). However, the latter seems unlikely in view of the preferred direction of cyclisation of amides of type I (see previously). This ambiguity was ultimately settled by identification of the final products of the synthesis with isotetrandrine and phaeanthine.



SCHEME 5

[13] E. Schröder and K. Lübke, ' The Peptide,' vol. 1, Academic Press, New York and London, 1965, p. 271.

The n.m.r. spectra of the 3,4-dihydroisoquinoline (24) showed some interesting features. In deuteriochloroform or deuteriopyridine at room temperature the compound exhibited a complex signal pattern such as expected for a mixture of two structural isomers. This was interpreted as indicating the presence of several conformers, and supporting evidence for this was obtained from the spectrum of a solution in deuteriopyridine at 100° (Figure 1), which revealed a simpler signal pattern, as expected for a single compound.

Three different sets of conditions were investigated for stereospecific (or stereoselective) reduction of the 3,4-dihydroisoquinoline (24): (*a*) sodium borohydride in methanol at room temperature; (*b*) zinc in ethanol–20% aqueous sulphuric acid (5 : 4) under reflux; and (*c*) catalytic hydrogenation over platinum oxide in ethanol containing a trace of concentrated hydrochloric acid. For the sake of economy of material, racemic 3,4-dihydroisoquinoline (24), obtained from racemic (11) was employed for these examinations. The product was expected to be a diastereomeric mixture consisting of two kinds of racemates: (±)-*N*-norisotetrandrine (26) and its mirror image, and (±)-*N*-nortetrandrine [(±)-*N*-norphaeanthine] (27) and its mirror image. The n.m.r. spectra of natural isotetrandrine and phaeanthine, show differences in the chemical shifts of the four highest-field methyl signals (Figure 3).[14] In the spectrum of the *N*-nor-type alkaloid, an analogous situation is expected, so the ratio of two diastereomers in the reaction products could be estimated from the relative intensities of the high-field methyl signals. The spectra of the products obtained by the three different methods (Figure 2) show that reduction by method (*c*) is not stereoselective but that by the other two methods is so to some extent. Thus, the ratio of (±)-*N*-norisotetrandrine (26) to (±)-*N*-nortetrandrine [(±)-*N*-norphaeanthine] (27) in the product from the method (*a*) was estimated as 3 : 2 and that in the product obtained by method (*b*) as 1 : 4.

The product from the method (*a*), without purification, was *N*-methylated; t.l.c. of the mixture of *N*-methyl derivatives showed only one spot, and the n.m.r. spectrum (Figure 3) showed that the ratio of (±)-isotetrandrine to (±)-phaeanthine was 3 : 2. The product from the method (*b*), when recrystallised, gave only compound (27) (and its mirror image) which was then *N*-methylated. The n.m.r. and i.r. spectra of the product were identical with those of authentic (±)-tetrandrine [(1c) and mirror image]. Since (±)-tetrandrine has been isolated from the natural source and resolved into its optically active forms,[15] the present synthesis amounts to a total synthesis of optically active natural tetrandrine. The above results show that for a total synthesis of isotetrandrine, reduction of the 3,4-dihydroisoquinoline (24) by the method (*a*) is preferable.

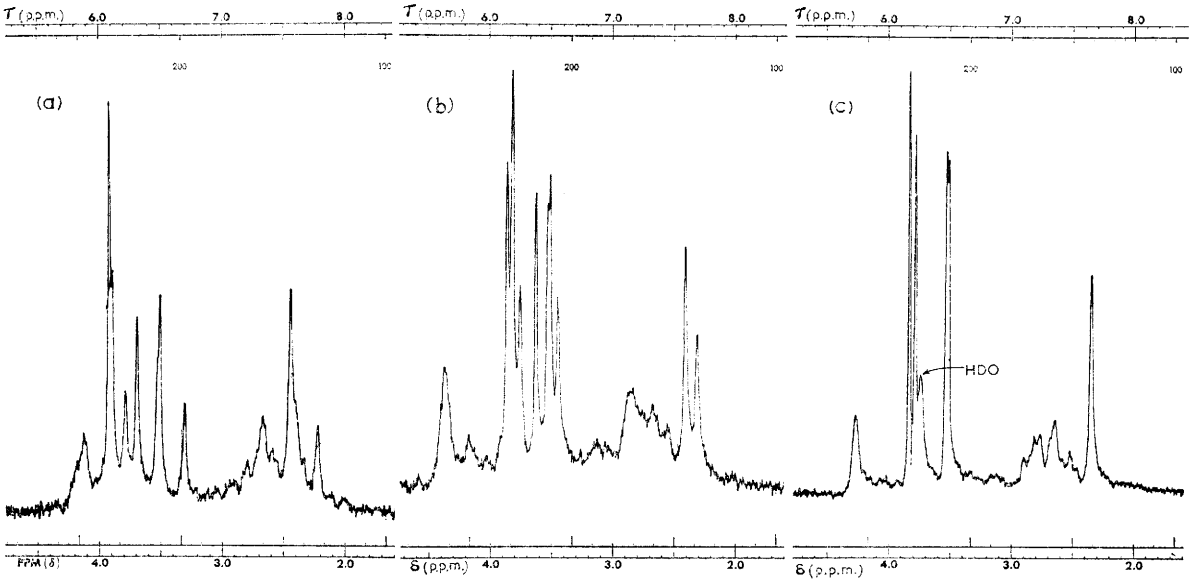


FIGURE 1 Signals for OMe and NMe in the n.m.r. spectra of the 3,4-dihydroisoquinoline (24): (a) in $CDCl_3$ at room temperature, (b) in [^{2}H]pyridine at room temperature, and (c) in [^{2}H]pyridine at 100°

Separation of each diastereomer from the mixture of isotetandrine (1b) and phaeanthine (1a) obtained *via* method (*a*) was effected by fractional crystallisation of the mixture of picrates. The less soluble phaeanthine picrate was identical with natural phaeanthine picrate, derived from limacine,[16] in all respects, including specific rotation. The free base, m.p. 152°, was identical with a

[14] Celebration Publication for the Retirement of Professor Masao Tomita, 1926—1967, Hirokawa Publishing Co., Tokyo, Japan, 1967, p. 44.

[15] S. M. Kupchan, N. Yokoyama, and B. S. Thyagarajan, *J. Pharm. Sci.*, 1961, **50**, 164.

[16] M. Tomita, H. Furukawa, and K. Fukagawa, *J. Pharm. Soc. Japan*, 1967, **87**, 793.

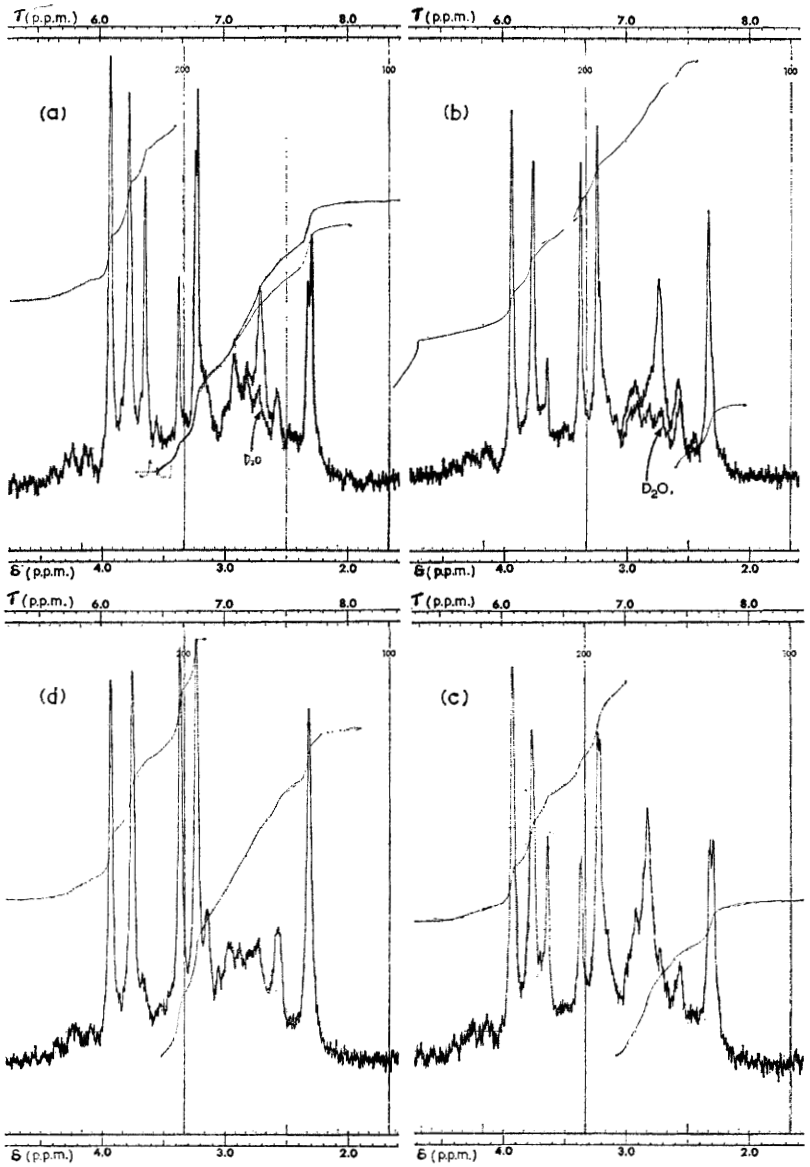


FIGURE 2 Signals for OMe and NMe in the n.m.r. spectra ($CDCl_3$) of *N*-nor-bases formed by reduction of the macrocyclic dihydroisoquinoline (**24**) (a) with sodium borohydride in methanol, (b) with zinc in ethanol–20% aqueous sulphuric acid (5 : 4), and (c) by catalytic hydrogenation in ethanolic HCl; (d) (±)-*N*-nortetrandrine (**27**; racemate)

sample of natural phaenanthine [17,18] (i.r. and n.m.r. spectra and mixed m.p.). Similarly the synthetic isotetrandrine, was identical with natural isotetrandrine [18,19] in all respects, including specific rotation.

The synthetic schemes described seem to offer promise of a general synthetic route to the oxyacanthine–berbamine-type alkaloids.

EXPERIMENTAL

M.p.s were determined with a microscopic hot-stage apparatus. Unless otherwise stated, n.m.r. spectra were taken with a Varian A-60 spectrometer for solutions in deuteriochloroform, with tetramethylsilane as internal reference, and i.r. spectra were measured for solutions in chloroform. Mass spectral determinations were performed with a Hitachi RMU-6D mass spectrometer with a direct heated-inlet system. T.l.c. was carried out on silica gel G (Merck) in methanol–acetone (1 : 1 v/v) and chloroform–acetone (1 : 1 v/v) and on alumina G (Merck) in chloroform and chloroform–acetone (1 : 1 v/v); plates were developed with iodine vapour or Dragendorff's reagent. Column chromatography was performed with Brockmann neutral alumina, activity II—III.

O-Benzylisoacetovanillone (*3-Benzyloxy-4-methoxyacetophenone*) (4).—To a mixture of isoacetovanillone [20]

[17] A. C. Santos, *Rev. Filipina Med. y. Farm.*, 1931, **22**, 11; H. Kondo and I. Keimatsu, *Ber.*, 1935, **68**, *B*, 1503; D. A. A. Kidd and J. Walker, *J. Chem. Soc.*, 1954, 669.

[18] M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan*, 1962, **82**, 741.

[19] H. Kondo and I. Keimatsu, *J. Pharm. Soc. Japan*, 1935, **55**, 234, 894; M. Tomita, E. Fujita, and F. Murai, *ibid.*, 1951, **71**, 226, 1035.

[20] W. Schneider and E. Kraft, *Ber.*, 1922, **55**, 1892.

(3-hydroxy-4-methoxyacetophenone) (89 g.), anhydrous potassium carbonate (35 g.), and dimethylformamide, benzyl chloride (70 g.) was added dropwise under reflux during *ca.* 30 min. with stirring. After a further 3 hr. under reflux with stirring, the mixture was poured into ice–water and extracted with ether. The extract was washed with dilute sodium hydroxide solution and dried (K_2CO_3). Evaporation of the solvent left the crude product, which gave *prisms* (104 g.), m.p. 76° (from methanol) (Found: C, 75·3; H, 6·3. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%), $\nu_{max.}$ 1670 cm.$^{-1}$, τ (CCl_4) 7·62 (3H, s, Ac), 6·22 (3H, s, OMe), and 5·00 (2H, s, PhCH_2).

N-[(3-*Benzyloxy*-4-*methoxyphenyl*)*thioacetyl*]*morpholine* (5).—A mixture of *O*-benzylisoacetovanillone (4) (70 g.), sulphur (40 g.), and morpholine (125 g.) was heated gradually with stirring until the bath temperature reached 140° and then stirred for 5 min. The mixture was then cooled and extracted with benzene, and the extract was successively washed with dilute hydrochloric acid and dilute sodium hydroxide and dried (K_2CO_3). Evaporation of the solvent under reduced pressure left an oily product (115 g.) which slowly crystallised and gave *needles*, m.p. 70—71° (from methanol) (Found: C, 67·0; H, 6·5. $C_{20}H_{23}O_3NS$ requires C, 67·2; H, 6·5%), τ 6·13 (3H, s, OMe), 5·78 (s, PhCH_2·CS), and 4·83 (2H, s, PhCH_2·O).

O-*Benzylisohomovanillic Acid* (3-*Benzyloxy*-4-*methoxyphenylacetic Acid*) (6).—A mixture of the crude thioamide (5) (130 g.), ethanol (125 ml.), and 20% sodium hydroxide (600 ml.) was heated under reflux with stirring for 10 hr. Ethanol was evaporated off under reduced pressure and the remaining aqueous layer was acidified with concentrated hydrochloric acid and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. The residue gave crystals (55 g.), m.p. 122° (from benzene), identical with an authentic sample of *O*-benzylisohomovanillic acid [9] (m.p. mixed m.p. and i.r. spectra).

3-*Benzyloxy*-N-(3-*bromo*-4,5-*dimethoxyphenethyl*)-4-*methoxyphenylacetamide* (8).—A mixture of 3-bromo-4,5-dimeth-

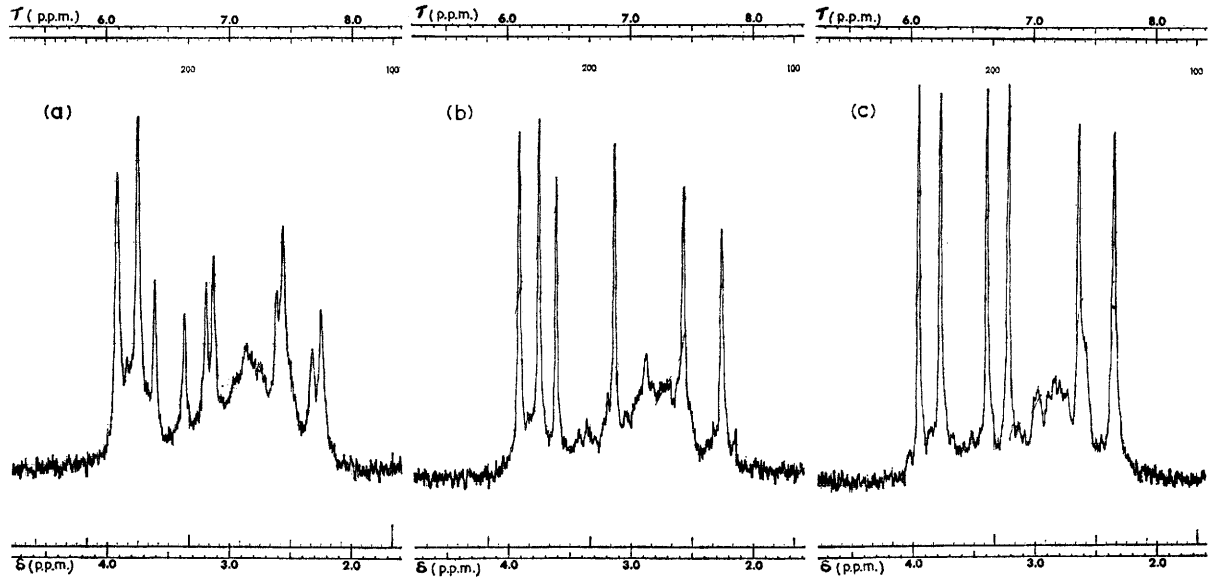
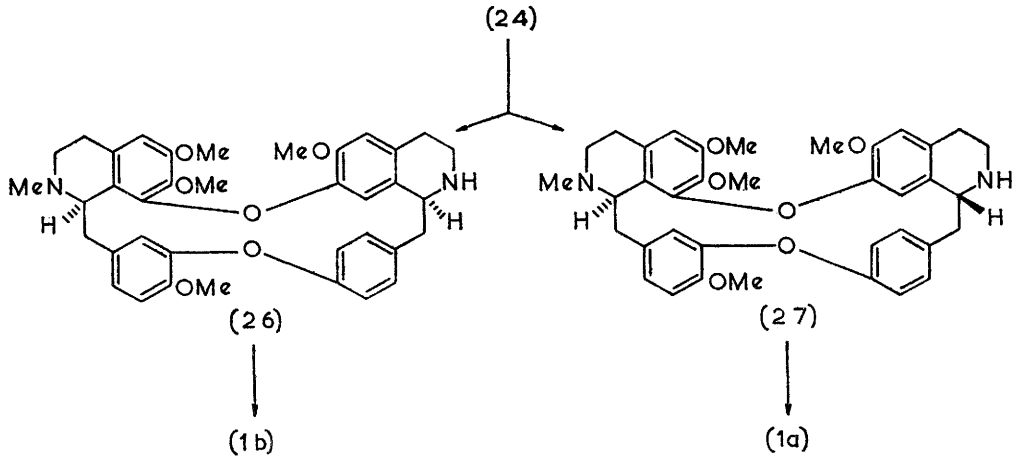


FIGURE 3 Signals for OMe and NMe in the n.m.r. spectra ($CDCl_3$) of berbamine-type alkaloids: (a) synthetic product (diastereomeric mixture), (b) natural isotetrandrine (1b), and (c) natural phaeanthine (1a)



SCHEME 6

oxyphenethylamine [10] (15 g.), *O*-benzylisohomovanillic acid (6) (15 g.) and decalin (100 ml.) was heated under reflux for 1·5 hr. Decalin was discarded by decantation and a solution of the residue in chloroform was successively washed with dilute sodium hydroxide and dilute hydrochloric acid and dried ($MgSO_4$). Evaporation left a residue which gave *needles* (18 g.), m.p. 126—127° (from methanol) (Found: C, 59·4; H, 5·5; N, 2·4. $C_{26}H_{28}BrNO_5,CH_3OH$ requires C, 59·6; H, 5·9; N, 2·6%), $\nu_{max.}$ 3410 and 1660 $cm.^{-1}$.

(±)-1-(3-*Benzyloxy*-4-*methoxybenzyl*)-8-*bromo*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (9) (O-*Benzyl*-8-*bromo*-N-*norlaudanine*).—A mixture of the amide (8) (15 g.), phosphoryl chloride (30 g.), and anhydrous chloroform (150 ml.) which had been treated with phosphorus pentoxide, was heated under reflux for 4 hr. Chloroform and phosphoryl chloride were removed under reduced pressure, and the mixture was triturated with dilute hydrochloric acid and ether. The ethereal layer was discarded and the crude 1-(3-benzyloxy-4-methoxybenzyl)-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride was collected and washed with water. The crude hydrochloride, sparingly soluble in water, was then dissolved in methanol (150 ml.) and reduced with sodium borohydride (3 g.) at room temperature with stirring. The mixture was worked up as usual and a non-phenolic base was extracted with ether. The dried (K_2CO_3) extract was evaporated and the residue gave *prisms* (8 g.), m.p. 115—116° (from methanol) (Found: C, 62·5; H, 5·6. $C_{26}H_{28}BrNO_4$ requires C, 62·7; H, 5·7%), τ 6·17 (6H, s, two OMe), 6·12 (3H, s, OMe), 4·82 (2H, s, $PhCH_2$), and 3·15 (3H, s, aromatic).

(±)-1-(3-*Benzyloxy*-4-*methoxybenzyl*)-8-*bromo*-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (11; *racemate*) (O-*Benzyl*-8-*bromolaudanine*).—A solution of *O*-benzyl-8-bromo-*N*-norlaudanine (9) (18 g.) in methanol (150 ml.) and chloroform (30 ml.) was treated with formalin (3·5 g.) and sodium borohydride (2 g.) at room temperature. The mixture was worked up as usual and a non-phenolic base was extracted with ether. The dried (K_2CO_3) extract was evaporated and the residue gave *prisms* (15 g.), m.p. 127—128° (from methanol) (Found: C, 63·5; H, 5·9. $C_{27}H_{30}BrNO_4$ requires C, 63·3; H, 5·9%), τ 7·70 (3H, s, NMe), 6·13 (6H, s, two OMe), 6·11 (3H, s, OMe), and 4·81 (2H, s, $PhCH_2$).

Resolution of O-*Benzyl*-8-*bromo*-N-*norlaudanine* (9).—To a solution of *O*-benzyl-8-bromo-*N*-norlaudanine (9) (10 g.) in methanol (150 ml.) was added a solution of L-(+)-tartaric acid (1·51 g.) in methanol (15 ml.); the mixture was set aside for 2 days at room temperature and the deposited tartaric acid salt was repeatedly recrystallised from methanol. (R)-(−)-O-*Benzyl*-8-*bromo*-N-*norlaudanidine* (10) L-(+)-*tartrate* (2·7 g.) had m.p. 179°, $[\alpha]_D^{24}$ −29° (*c* 1 in chloroform) (Found: C, 58·8; H, 5·5. $C_{26}H_{28}BrNO_4,1/2C_4H_6O_6$ requires C, 58·6; H, 5·4%). The salt (16 g.) was dissolved in chloroform and shaken with dilute sodium hydroxide. The chloroform layer was dried (K_2CO_3) and evaporated to yield the free base as *needles* (14 g.), m.p. 99—102° (from methanol), $[\alpha]_D^{18}$ −38° (*c* 2 in chloroform) (Found: C, 62·4; H, 5·6; N, 2·8. $C_{26}H_{28}BrNO_4$ requires C, 62·7; H, 5·7; N, 2·8%), i.r. and n.m.r. spectra identical with those of the racemic base.

(R)-(−)-O-*Benzyl*-8-*bromolaudanidine* (11).—A solution of (*R*)-(−)-*O*-benzyl-8-bromo-*N*-norlaudanidine (14 g.) in methanol (100 ml.) and chloroform (10 ml.) was treated with formalin (2·8 g.) and sodium borohydride (1·5 g.) at room temperature and the mixture was worked up as usual. The non-phenolic base was extracted with chloroform and the dried (K_2CO_3) extract was evaporated. The residue gave prisms (13 g.), m.p. 90° (from methanol), $[\alpha]_D^{23}$ −27° (*c* 2 in chloroform) (Found: C, 63·6; H, 5·9; N, 2·8. $C_{27}H_{30}BrNO_4$ requires C, 63·3; H, 5·9; N, 2·7%), i.r. and n.m.r. spectra identical with those of the racemic base.

Conversion of (R)-(−)-O-*Benzyl*-8-*bromolaudanidine* (11) *into* (R)-(−)-*Laudanidine* (12).—To a solution of (*R*)-(−)-*O*-benzyl-8-bromolaudanidine (11) (220 mg.) in methanol (15 ml.) and ethyl acetate (10 ml.) was added 1% palladium chloride solution (1·5 ml.) and active charcoal (Darco G 60; 150 mg.). The mixture was stirred under hydrogen at room temperature and atmospheric pressure. After absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in dilute hydrochloric acid and washed with ether. The acidic aqueous layer was made alkaline with dilute sodium hydroxide and washed with ether; ammonium chloride was then added and the solution was extracted with ether. The extract was dried (K_2CO_3) and evaporated and the residue gave prisms (70 mg.), m.p. 184° (from ethanol), $[\alpha]_D^{19}$ −80° (*c* 1·5 in chloroform) [lit.,[11] m.p. 184—185°, $[\alpha]_D^{25}$ −86·3° (in chloroform)] (Found: C, 70·1; H, 7·4. Calc. for $C_{20}H_{25}NO_4$: C, 70·0; H, 7·3%), τ 7·47 (3H, s, NMe), and 6·42, 6·17, and 6·15 (9H, three s, three OMe). Its i.r. and n.m.r. spectra were identical with those of an authentic sample of *R*-(−)-laudanidine.[11]

4-*Benzyloxy*-3-*methoxyphenethylamine* (13).—This compound has been prepared previously by lithium aluminium hydride reduction [21] or electrolytic reduction [7] of the corresponding β-nitrostyrene. We obtained it by a modified Clemmensen reduction. To a suspension of zinc amalgam [from mercuric chloride (10 g.) and zinc powder (100 g.) in methanol (200 ml.)] in an ice–water bath, concentrated hydrochloric acid (140 ml.) and a solution of 4-benzyloxy-3-methoxy-β-nitrostyrene [7] (20 g.) in tetrahydrofuran (200 ml.) were alternately added, dropwise, with vigorous stirring. The temperature of the mixture was kept below 20° during the reaction. The mixture was then stirred for a further 30 min., and filtered; the filtrate was neutralised with sodium carbonate (*ca.* 80 g.), with vigorous stirring, and the precipitate was filtered off. The filtrate was concentrated to *ca.* 150 ml. under reduced pressure, made alkaline with ammonia, and extracted with ether. The extract was washed with 2% sodium hydroxide, dried (K_2CO_3), and evaporated to leave the oily amine (13) (17 g.), i.r. spectrum identical with that of an authentic sample; [7] its formate gave plates, m.p. 149° (from ethanol) (lit.,[7] 146—149°).

4-*Benzyloxy*-N-*t*-*butoxycarbonyl*-3-*methoxyphenethylamine* (14).—To a solution of the phenethylamine (13) (25 g.) and triethylamine (10 g.) in ethyl acetate (150 ml.), t-butyl azidoformate [22] (14 g.) was added dropwise with stirring at room temperature, and the mixture was stirred for 20 hr. at 40—50°. It was then extracted with ethyl acetate, and the extract was successively washed with water, 5% aqueous citric acid, and 2% sodium hydrogen carbonate solution. Evaporation of the dried organic phase and recrystallisation of the residue from cyclohexane gave *prisms* (24 g.), m.p.

[21] M. Tomita, K. Fujitani, Y. Masaki, and Kuo-Hsuing Lee, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 251.

[22] L. A. Carpino, *J. Amer. Chem. Soc.*, 1957, **79**, 98; L. A. Carpino, C. A. Giza, and B. A. Carpino, *ibid.*, 1959, **81**, 955; R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, 1959, **42**, 2622; H. Yajima and H. Kawatani, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 182.

68—70° (Found: C, 70·6; H, 7·7. $C_{21}H_{27}NO_4$ requires C, 70·5; H, 7·6%), $\nu_{max.}$ 3450 and 1703 cm.$^{-1}$, τ 8·57 (9H, s, Bu^t), 6·12 (3H, s, OMe) and 4·88 (2H, s, PhCH_2).

N-t-Butoxycarbonyl-4-hydroxy-3-methoxyphenethylamine (15).—A solution of 4-benzyloxy-*N*-t-butoxycarbonyl-3-methoxyphenethylamine (14) (24 g.) in ethanol (400 ml.) was hydrogenolysed over 5% palladised charcoal (3 g.) at atmospheric pressure and room temperature. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residue, dissolved in ether, was shaken with 2% sodium hydroxide solution and the aqueous layer (a phenolic fraction) was acidified with citric acid and extracted with ether. The extract was washed with water saturated with sodium chloride, dried ($MgSO_4$), and evaporated. The residue gave *prisms* (8 g.), m.p. 115° (from benzene) (Found: C, 62·9; H, 7·7. $C_{14}H_{21}NO_4$ requires C, 62·9; H, 7·9%), $\nu_{max.}$ 3450, 3450, and 1703 cm.$^{-1}$, τ 8·57 (9H, s, Bu^t) and 6·15 (3H, s, OMe). The original ethereal solution gave more phenolic product, m.p. 115° (total yield 14 g.).

(R)-(−)-1-(3-*Benzyloxy*-4-*methoxybenzyl*)-8-(4-*butoxycarbonylaminoethyl*-2-*methoxyphenoxy*)-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (16).—A mixture of (*R*)-(−)-*O*-benzyl-8-bromolaudanidine (11) (15 g.), *N*-t-butoxycarbonyl-4-hydroxy-3-methoxyphenethylamine (15) (8 g.), anhydrous potassium carbonate (10 g.), and dry pyridine (60 ml.) was heated slowly to 130° under nitrogen with stirring, then cupric oxide (5 g.) was added. The mixture was stirred for 16 hr. at 145—150° under nitrogen, cooled, and extracted with chloroform (Soxhlet). The extract was evaporated to dryness under reduced pressure and the residue was extracted with benzene; the extract was washed with 2% sodium hydroxide and 5% aqueous citric acid solution. The aqueous acidic layer gave a crystalline base (220 mg.), which gave needles, m.p. 104° (from methanol, $[\alpha]_D^{24}$ −57° (*c* 1 in chloroform) (negative Beilstein test) and was identified as (R)-(−)-O-*benzyl-laudanidine* [benzyl ether of (12)] (Found: C, 74·7; H, 7·1. $C_{27}H_{31}O_4N$ requires C, 74·8; H, 7·2%), τ 7·52 (3H, s, NMe), 6·43, 6·18, and 6·17 (9H, three s, three OMe), and 4·95 (2H, s, PhCH_2).

The benzene layer was dried (K_2CO_3) and evaporated; and the residue was chromatographed on an alumina column in benzene containing increasing concentrations of chloroform to give fraction A (2·5 g.) and fraction B (8·5 g.), each of which was homogeneous on t.l.c. Fraction A crystallised on trituration with methanol and gave colourless prisms, m.p. 90° (from methanol), of starting material (11). Fraction B gave an oily *compound* (16) which resisted attempts at crystallisation (Found: C, 70·0; H, 7·1; N, 3·9. $C_{41}H_{50}N_2O_8$ requires C, 70·5; H, 7·2; N, 4·0%), $[\alpha]_D^{18}$ −12° (*c* 5 in chloroform), $\nu_{max.}$ 3450 and 1703 cm.$^{-1}$, τ 8·58 (9H, s, Bu^t), 7·82 (3H, s, NMe), 6·33, 6·19, 6·17 and 6·11 (12H, four s, four OMe), and 5·00 (2H, s, PhCH_2), *m/e* 471 [M − $CH_2{\cdot}C_6H_3$(O·CH_2Ph) (OMe)], 415, 397, 371, and 227.

(R)-(−)-8-(4-*t-Butoxycarbonylaminoethyl*-2-*methoxyphenoxy*)-1-(3-*hydroxy*-4-*methoxybenzyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (17).—A solution of the benzyloxy-base (16) (6·5 g.) in ethanol (250 ml.) was hydrogenolysed over 5% palladised charcoal (1 g.) in the presence of 1% palladium chloride solution (10 ml.) at room temperature and atmospheric pressure. The reaction was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 5% aqueous citric acid and washed with ether, and the acidic aqueous layer was made alkaline with dilute sodium hydroxide solution and washed again with ether. Ammonium chloride was then added to the alkaline aqueous layer, and the product was extracted with ether by the salting-out technique. The extract was dried (K_2CO_3) and evaporated to leave an oily base (17) (5·5 g.). It could not be crystallised but it was homogenous on t.l.c. and its n.m.r. spectrum showed no impurity signals; $[\alpha]_D^{18}$ −24° (*c* 2 in chloroform), $\nu_{max.}$ 3500, 3410, and 1700 cm.$^{-1}$, τ 8·57 (9H, s, Bu^t), 7·77 (3H, s, NMe), and 6·30, 6·20, 6·15, and 6·07 (12H, four s, four OMe) (Found: C, 66·5; H, 7·5. $C_{34}H_{44}N_2O_8$ requires C, 67·1; H, 7·3%), *m/e* 471 [M − $CH_2{\cdot}C_6H_3$(OH)(OMe)], 415, 397, 371, and 137.

(R)-(−)-8-(4-*t-Butoxycarbonylaminoethyl*-2-*methoxyphenoxy*)-6,7-*dimethoxy*-1-[4-*methoxy*-3-(4-*methoxycarbonylmethylphenoxy*)*benzyl*]-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (19).—A mixture of the hydroxy-base (17) (5·8 g.), methyl 4-bromophenylacetate [23] (18) (3·5 g.), and anhydrous potassium carbonate (2·5 g.), in dry pyridine (30 ml.) was heated slowly to 120° under nitrogen with stirring, and then cupric oxide (1 g.) was added. The mixture was heated under reflux for 5 hr. at 145—155° with stirring under nitrogen, then extracted with benzene. The extract was washed with 5% aqueous citric acid solution and dried (K_2CO_3). Evaporation left a gum containing a little starting material along with the product. The gum was chromatographed on alumina in benzene containing increasing concentrations of chloroform to give a homogeneous amorphous *compound* (19) (3·5 g.), which resisted attempts at crystallisation; $[\alpha]_D^{17}$ +25° (*c* 0·5 in chloroform), $\nu_{max.}$ 3450, 1727, and 1702 cm.$^{-1}$, τ 8·58 (9H, s, Bu^t), 7·75 (3H, s, NMe), 6·42 (2H, s, PhCH_2), and 6·33, 6·31, 6·25, 6·22, and 6·16 (15H, five s, five OMe) (Found: C, 67·9; H, 6·8; N, 3·6. $C_{43}H_{52}N_2O_{10}$ requires C, 68·2; H, 6·9; N, 3·7%), *m/e* 471 [M − $CH_2{\cdot}C_6H_3$-(OMe) (O·$C_6H_4{\cdot}CH_2{\cdot}CO_2$Me)], 415, 397, 371, and 285.

The 3,4-dihydroisoquinoline (24) *from Compound* (19) via *the Cycloamide* (23).—The ester (19) (2·93 g.) in methanol was hydrolysed with 10% aqueous sodium hydroxide (20 ml.) for 6 hr. at room temperature with stirring. The mixture was made weakly acidic with crystalline citric acid, and then methanol was removed under reduced pressure. The residue was dissolved in 1% aqueous sodium hydroxide and washed with ether, and the aqueous layer was acidified with crystalline citric acid and extracted with chloroform. The dried extract was evaporated to give the crude carboxylic acid (20) (2·81 g.). To a solution of the acid (20) in ethyl acetate (50 ml.) was added *p*-nitrophenol (550 mg.). Then dicyclohexylcarbodi-imide (800 mg.) was added little by little with stirring at 0—5°, and the mixture was kept for a further 30 min. at the same temperature, then for 1 hr. at room temperature.[24] Dicyclohexylurea was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was washed with light petroleum to remove excess of dicyclohexylcarbodi-imide. The crude *p*-nitrophenyl ester (21) (3·01 g.), was mixed with trifluoroacetic acid (25 g.) at room temperature, and the mixture was kept for 1 hr. at the same temperature. Excess of trifluoroacetic acid was removed under reduced pressure at 30—40° (bath) and the residue was washed with ether

[23] T. Kametani, K. Fukumoto, and M. Ro, *J. Pharm. Soc. Japan*, 1964, **84**, 532.

[24] M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, 1959, **81**, 5688; R. Schwyzer and B. Gorup, *Helv. Chim. Acta*, 1958, **41**, 2199; H. Brockmann and V. Graef, *Naturwiss.*, 1962, **49**, 540.

to leave the crude phenethylamine trifluoroacetate (22) (3·10 g.) as an amorphous powder. A solution of the acetate in anhydrous dimethylformamide (25 ml.) was added dropwise to dry pyridine, preheated at 70—80° (bath), with stirring during 6 hr. After the addition was complete, the mixture was stirred for an additional 1 hr. Pyridine and dimethylformamide were then removed under reduced pressure and the residual oil was extracted with benzene. The extract was washed with 2% aqueous sodium hydroxide solution, dried, and evaporated to leave an oil which was chromatographed on an alumina column in benzene containing increasing concentrations of chloroform to give the pure amorphous cycloamide (23) (1·31 g.), $[\alpha]_D^{17}$ −153° (*c* 1 in chloroform), $\nu_{max.}$ 3410 and 1658 cm.$^{-1}$, τ 7·82 (3H, s, NMe), 6·49 (2H, s, PhCH_2), and 6·34, 6·18, and 6·16 (9H, three s, three OMe), *m/e* 624 (M^+), 609, 594, 312 (M^{++}), and 206. A mixture of the cycloamide (23) (1·02 g.) and phosphoryl chloride (3 g.) in anhydrous chloroform (25 ml.) was heated under reflux for 1 hr. Evaporation of the chloroform and phosphoryl chloride under reduced pressure left a solid, which was dissolved in dilute hydrochloric acid and successively washed with ether and chloroform. The chloroform layer was washed with water. The acidic aqueous layer and aqueous washings were combined, made alkaline with ammonia, and extracted with ether. Evaporation of the dried ether extract left crystals which gave *prisms* (600 mg.), m.p. 148—150° (from ethanol), $[\alpha]_D^{21}$ +82° (*c* 1 in chloroform), (Found: C, 73·5; H, 6·3. $C_{37}H_{38}N_2O_6$ requires C, 73·2; H, 6·3%), $\nu_{max.}$ 1620 cm.$^{-1}$, τ (in deuteriopyridine at 100°) 7·65 (3H, s, NMe), 6·50, 6·48, 6·22, and 6·17 (12H, four s, four OMe), and 5·73 (2H, s, PhCH_2·C:N) (see Figure 1 c), *m/e* 606 (M^+, 100%) and 303 (M^{++}). From the chloroform layer, starting material (350 mg.) was recovered.

The Racemic 3,4-*Dihydroisoquinoline* (24; *racemate*).—This was prepared *via* the same route as the optically active (*R*)-compound; the racemic intermediates were all amorphous powders, and their homogeneity and structures were confirmed by comparison (t.l.c. and i.r. and n.m.r. spectra) with the corresponding optically active compounds. Racemic 3,4-dihydroisoquinoline formed prisms, m.p. 221—223°.

Reduction of the Racemic 3,4-*Dihydroisoquinoline* (24; *racemate*).—(a) *Sodium borohydride.* To a solution of the racemic 3,4-dihydroisoquinoline (200 mg.) in methanol (20 ml.) was added sodium borohydride (100 mg.) in small portions at room temperature with stirring. Stirring was then continued for 30 min. at the same temperature. The mixture was worked up as usual, and a non-phenolic base [a mixture of diastereomeric racemates of (26) and (27)] (170 mg.) was obtained in an amorphous state, and showed one spot on t.l.c. Its n.m.r. spectrum is shown in Figure 2a.

(b) *Zinc and dilute sulphuric acid in ethanol.* A mixture of the racemic 3,4-dihydroisoquinoline (300 mg.), 20% (w/v) sulphuric acid (12 ml.), zinc powder (1 g.), and ethanol (15 ml.) was heated under reflux for 5 hr. with stirring. The mixture was filtered to remove excess of zinc powder and the filtrate was concentrated under reduced pressure. The residue was shaken with dilute sulphuric acid and ether. The aqueous layer was made alkaline with ammonia and extracted with chloroform. The dried extract was evaporated to yield a crude oily base (a diastereomeric mixture) (300 mg.) which showed the same t.l.c. R_F value as the product from (a); its n.m.r. spectrum is shown in Figure 2b. It crystallised when triturated with methanol and gave *prisms* of (27; racemate) [(±)-*N*-nortetrandrine] (180 mg.), m.p. 215—216° (from methanol) (Found: C, 73·1; H, 6·4; N, 4·9. $C_{37}H_{40}N_2O_6$ requires C, 73·0; H, 6·6; N, 4·6%). Its n.m.r. spectrum is shown in Figure 2d.

(c) *Catalytic hydrogenation.* The racemic 3,4-dihydroisoquinoline (50 mg.) was hydrogenated over platinum dioxide (10 mg.) in ethanol containing a trace of hydrochloric acid at room temperature and atmospheric pressure. The mixture was worked up as usual and a non-phenolic basic fraction was obtained as an amorphous solid which was a mixture of product and starting material (t.l.c.). This fraction was chromatographed on alumina in chloroform to give starting material (11 mg.) and a product (a diastereomeric mixture) (10 mg.) which showed the same t.l.c. R_F value as the product from (9); its n.m.r. spectrum is shown in Figure 2c.

(±)-*Tetrandrine* (1c: *racemate*) *and* (±)-*Isotetrandrine* (1b: *racemate*).—(*a*) The crude amorphous tetrahydroisoquinoline [a mixture of diastereomeric racemates of (26) and (27)] (130 mg.) obtained by reduction by method (a) was *N*-methylated in the usual way. An amorphous non-phenolic base (110 mg.) isolated in the usual manner, showed the same R_F value as tetrandrine and isotetrandrine, but its n.m.r. spectrum corresponded to a mixture of (±)-tetrandrine (1c : racemate) and (±)-isotetrandrine (1b : racemate) (2 : 3) as shown in Figure 3a. This mixture was separated into (±)-tetrandrine (20 mg.) and (±)-isotetrandrine (50 mg.) by fractional crystallisation of their picrates. (±)-Tetrandrine had m.p. 252° (lit.,[15] 252°) and its i.r., n.m.r., and mass spectra were identical with those of a sample of natural tetrandrine.[25] The i.r., n.m.r., and mass spectra of (±)-isotetrandrine, m.p. 166—168° were identical with those of a sample of natural isotetrandrine.[19]

(*b*) The crystalline tetrahydroisoquinoline (27 : racemate) [(±)-*N*-nortetrandrine] (170 mg.) obtained by method (b) was *N*-methylated. The crude crystals (170 mg.) gave prisms, m.p. 252° (from ethanol), identified as (±)-tetrandrine (1c : racemate).

Phaeanthine (1a) *and Isotetrandrine* (1b).—The 3,4-dihydroisoquinoline (24) (120 mg.) in methanol (10 ml.) was reduced with sodium borohydride (60 mg.) as before [method (a)]. The product [a mixture of (26) and (27)] (100 mg.) showed one spot on t.l.c. and was obtained in an amorphous state; $[\alpha]_D^{17}$ −14° (*c* 1 in chloroform). This mixture in methanol (6 ml.) was treated with formalin (200 mg.) and sodium borohydride (200 mg.) at room temperature. The *N*-methylated product] was obtained as an amorphous powder, which was found to be a mixture of isotetrandrine (1b) and phaeanthine (1a) (3 : 2 by n.m.r. spectrometry). The R_F value of the product was identical with that of authentic samples of isotetrandrine and phaeanthine. To a solution of the diastereomeric mixture [(1a) and (1b)] in acetone was added a saturated solution of picric acid in acetone; the crystalline picrate (30 mg.) deposited had m.p. 245—250° (decomp.), $[\alpha]_D^{17}$ −98° (*c* 0·3 in pyridine), and was identical with an authentic sample of phaeanthine (1a) picrate [m.p., specific rotation, and i.r. spectrum (Nujol)]. The free base (1a) had m.p. 152° (from acetone), $[\alpha]_D^{18}$ −238° (*c* 0·5 in chloroform) and was identical with an authentic specimen of phaeanthine (1a) derived from limacine as described below (mixed m.p., and i.r. and n.m.r. spectra). The mother liquor from the phaeanthine picrate was made alkaline with ammonia and

[25] M. Tomita and H. Furukawa, *J. Pharm. Soc. Japan*, 1963, **83**, 190.

extracted with ether. The extract was dried and evaporated and the residue gave prisms (35 mg.), m.p. 179—181° (from acetone), $[\alpha]_D^{18}$ +136° (*c* 1 in chloroform), identical with an authentic specimen of isotetrandrine (1b) mixed m.p. and i.r. and n.m.r. spectra).

Conversion of Limacine into Phaeanthine (1a) .—To a solution of limacine [16] (120 mg.) in ether (10 ml.) and methanol (1 ml.) was added an excess of ethereal diazomethane, and the mixture was kept at room temperature overnight. It was worked up as usual and the non-phenolic base (100 mg.) was obtained as *prisms*, m.p. 152° (from acetone), $[\alpha]_D^{18}$ −257° (*c* 0·35 in chloroform) (Found: C, 73·2; H, 6·7; N, 4·6. $C_{38}H_{42}O_6N_2$ requires C, 73·3; H, 6·8; N, 4·5%). The i.r. and n.m.r. spectra of the base were identical with those of an authentic sample of tetrandrine (1c).[25] After prolonged heating at 150° under reduced pressure, its m.p. was changed to 210° and the m.p. of a mixture of this specimen with an authentic sample of phaeanthine,[17] m.p. 210°, was not depressed. Phaeanthine picrate had m.p. 245—250° (decomp.), $[\alpha]_D^{18}$ −116° (*c* 0·5 in pyridine).

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