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Synthesis of Trilobine, Isotrilobine, and Obaberine[1]

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Bisbenzylisoquinoline alkaloids, trilobine (**2**: R–H) possessing a dibenzo-*p*-dioxin nucleus and obaberine (**3**) were synthesized.

dl-O-Benzyl-8-bromo-N-norarmepavine (**10**: R=H) synthesized through an established route was resolved and N-benzoylation of the resolved free base, followed by condensation with the amine (**12**) gave the diphenyl ether (**13a**). Debenzylation of **13a**, followed by condensation with the compound (**14**) gave the ester (**15a**) which was cyclized to the cycloamide (**17**) *via* the phenethylammonium trifluoroacetate (**16**). Bischler-Napieralski reaction of the amide (**17**) and reduction of the imine (**18**), followed by N-methylation afforded the compound (**19b**) and (**5**) in a 2: 5 ratio.

Successive treatments of the compound (**19b**) with $LiAlH_4$–$AlCl_3$, hydrogen on Pd-C catalyst and HCHO–$NaBH_4$ afforded obaberine (**3**).

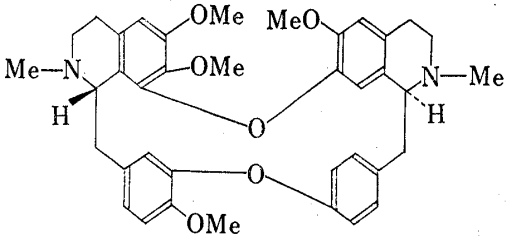
On the other hand, the N-benzyl base (**19c**) from the compound (**5**) was demethylated to give the demethyl base (**20**) which was heated in a saturated aqueous HBr solution to provide the compound (**21**). Finally, treatment of the compound (**21**) with CH_2N_2, followed by hydrogenolysis on Pd-C catalyst gave trilobine (**2**: R=H).

Keywords——bisbenzylisoquinoline synthesis; dibenzo-*p*-dioxin; Ullmann reaction; asymmetric reduction; trilobine; obaberine; isotrilobine; butoxycarbonyl amino protective group

The significant tumor-inhibitory activity of bisbenzylisoquinoline alkaloids such as thalidasine,[3] thalicarpine,[3] tetrandrine[3] (**1**) and cepharanthine[4,5] have been reported. Most recently, studies on the antitumor effects of 23 bisbenzylisoquinoline alkaloids have been made by Tomita, *et al.*[6] and they reported that isotrilobine (**2**: R=CH_3) possessing a dibenzo-*p*-dioxin nucleus exerted remarkable effects against HeLa and HeLa-S_3 cells, Ehrlich ascites carcinoma (ascites tumor) and Sarcoma-180 (solid tumor) in the same extent of effect as that of tetrandrine. The antitumor effect of these alkaloids has stimulated to interest in synthetic approaches to these alkaloids. A variety of sequences have been developed for the synthesis of alkaloids[3,7] containing one or two diphenyl ether linkages but synthesis of the alkaloid containing three diphenyl ether linkages to which isotrilobine and trilobine belong, has not yet been reported. In a previous paper,[8] we reported synthesis of optically active tetrandrine (**1**), isotetrandrine, and phaeanthine possessing two diphenyl ether linkages, and the authors now wish to report total synthesis of trilobine (**2**: R=H),[9] isotrilobine (**2**: R=CH_3)[9] as well as obaberine (**3**).[10]

1) A preliminary communication appeared in *Tetrahedron Lett.*, **1976**, 2857.
2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
3) S.M. Kupchan and H.W. Altland, *J. Med. Chem.*, **16**, 913 (1973) and references cited therein.
4) E.J. Gralla, G.L. Coleman, and A.M. Jonas, *Cancer Chemother. Rep.*, Part 3, **5**, 79 (1974).
5) K. Nomoto, R. Makidono, and K. Takeya, *Nippon Rinsho* (Tokyo), **31**, 3548 (1973).
6) H. Kuroda, S. Nakazawa, K. Katagiri, O. Shiratori, M. Kozuka, K. Fujitani, and M. Tomita, *Chem. Pharm. Bull.* (Tokyo), **24**, 2413 (1976).
7) M.C.-Rodostamo, "The Alkaloids," Vol. XIII, ed. by R.H.F. Manske, Academic Press, New York and London, 1971, p. 303; M.P. Cava and A. Afzali, *J. Org. Chem.*, **40**, 1553 (1975); E. Fujita, A. Sumi, and Y. Yoshimura, *Chem. Pharm. Bull.* (Tokyo), **20**, 368 (1972).
8) Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *J. Chem. Soc.* (*C*), **1969**, 1547.
9) H. Kondo and T. Nakazato, *Yakugaku Zasshi*, **44**, 691 (1924); H. Kondo and M. Tomita, *ibid.*, **47**, 265 (1927); Y. Inubushi and K. Nomura, *Tetrahedron Lett.*, **1962**, 1133.
10) M. Tomita and T. Kugo, *Yakugaku Zasshi*, **79**, 317 (1959).

The structural feature of trilobine and isotrilobine is that both alkaloids possess a dibenzo-*p*-dioxin nucleus. Dibenzo-*p*-dioxin derivatives are generally obtained by Ullmann condensation reactions of suitably substituted *o*-bromophenols but the yield of this type of reactions is usually very low, especially in unsymmetrically substituted derivatives. This disadvantage will be avoided by the following facts. Thus, O-demethylated oxyacanthine-berbamine type alkaloids provided the trilobine type alkaloids[11,12,13] in a considerable yield when heated in an aqueous saturated hydrobromic acid solution. Accordingly, the compound (**5**) type alkaloid, in which the absolute configurations of two asymmetric centers are the same as those of trilobine, is chosen as the first synthetic target molecule in the present synthesis. Another problem is the introduction of two asymmetric centers in the course of the synthesis. It has been reported that reduction of epistephanine (**4**) with sodium borohydride proceeds stereoselectively.[14] Consequently, if one asymmetric center is introduced, the second could be produced stereoselectively by a similar asymmetric reduction. Furthermore, if one asymmetric center is introduced at an early stage in the synthesis and the



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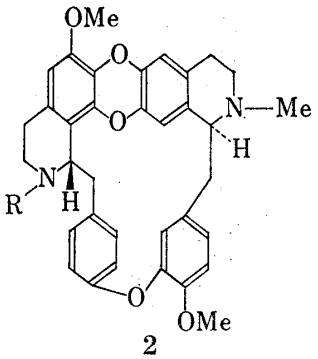

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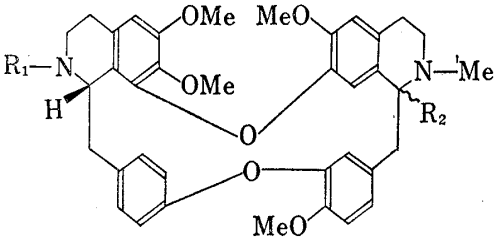
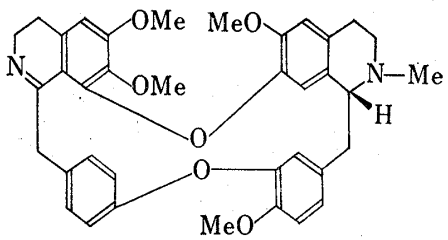


3 : $R_1=CH_3$, $R_2=\beta H$
5 : $R_1=COC_6H_5$, $R_2=\alpha H$



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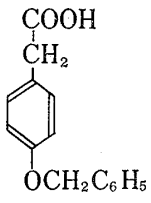

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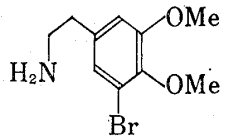

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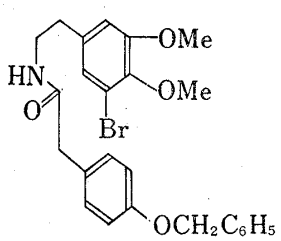

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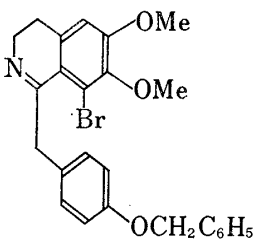
Chart 1

11) Y. Inubushi, *Pharm. Bull.* (Tokyo), **2**, 1 (1954).
12) M. Tomita, Y. Inubushi, and M. Kozuka, *Pharm. Bull.* (Tokyo), **1**, 360 (1953).
13) M. Tomita and H. Furukawa, *Yakugaku Zasshi*, **83**, 760 (1963); *idem*, *ibid.*, **84**, 1027 (1964).
14) M. Tomita and Y. Watanabe, *Pharm. Bull.* (Tokyo), **4**, 124 (1956).

resulting racemate is then resolved, the diastereoisomeric mixture arising from the introduction of the second asymmetric center in the subsequent synthetic stage, will be readily separable as having been known in the tetrandrine synthesis previously reported by the authors.[8] On the other hand, trilobine possesses two different nitrogen functions, thus one is an N-CH_3 group and the other an NH group. The benzyl group as a protecting group of an NH function will be available for the dibenzo-*p*-dioxin nucleus formation since the N-benzyl group is known to be stable under the acidic condition.[15]

Taking these considerations into account, synthesis of trilobine and isotrilobine was attempted.

We started on synthesis of the compound (**5**) and this synthesis was accomplished through the analogous synthetic route to that of tetrandrine synthesis.[8] Condensation of *p*-benzyloxyphenylacetic acid (**6**)[16] and 3-bromo-4,5-dimethoxy-β-phenethylamine (**7**)[17,18] gave the amide (**8**) which was subjected to the Bischler-Napieralski cyclization to provide the 3,4-dihydroisoquinoline derivative (**9**). Sodium borohydride reduction of **9** gave *dl*-O-benzyl-8-bromo-N-norarmepavine (**10**: R=H, racemate) which was resolved *via* its N-acetyl-L-leucine salt. In order to confirm the absolute configuration and optical purity of the resolved free base, the compound (**10**: R=H) was converted into (*S*)-armepavine (**11**), mp 140—142°, $[\alpha]_D$ +96° ($CHCl_3$) of established absolute configuration[19] by hydrogenolysis and N-methylation.



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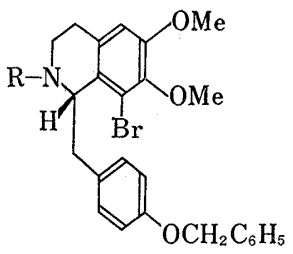

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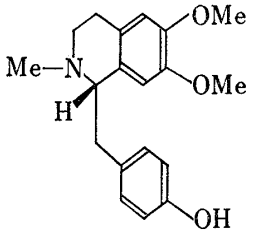

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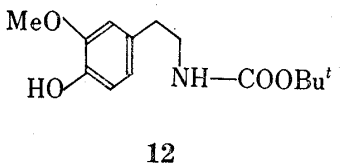

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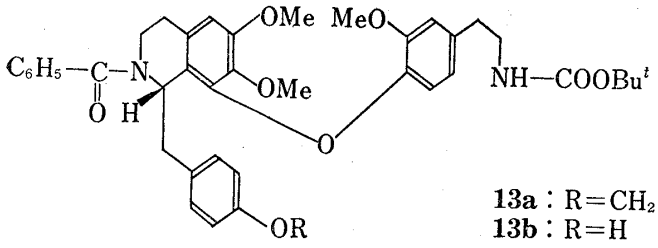


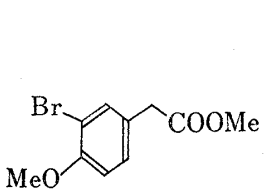
13a : R=$CH_2C_6H_5$
13b : R=H

Chart 2

N-Benzoylation of the resolved base (**10**: R=H) afforded the N-benzoyl compound (**10**: R=CO–C_6H_5). In this stage of synthesis, the benzyl group as an NH protecting group is inadequate because, if this group were employed, it would be essential to differentiate between the O-benzyl group and N-benzyl group in the subsequent second stage Ullmann reaction. The N-benzoyl compound (**10**: R=CO–C_6H_5) was condensed with the amine (**12**), protected with a *t*-butoxycarbonyl (*t*.-BOC) group, because of its instability under the Ullmann reaction condition to yield the compound (**13a**). The ease of removal of the *t*.-BOC group under a mild acidic condition and its resistance towards hydrogenolysis and cleavage by alkali are

15) G. Grethe, V. Toome, H.L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, 33, 504 (1968).
16) M. Tomita, K. Nakaguchi, and S. Takagi, *Yakugaku Zasshi*, **71**, 1046 (1951).
17) K. Fujitani, T. Kishimoto, and S. Niimura, *Yakugaku Zasshi*, **83**, 412 (1963).
18) M. Tomita, Y. Aoyagi, Y. Sakatani, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **15**, 1996 (1967).
19) M. Tomita, T.-H. Yang, and S.-T. Lu, *Yakugaku Zasshi*, **83**, 15 (1963).

of great advantage in subsequent synthetic steps, especially in the step of the second diphenyl ether formation. Hydrogenolysis of the O-benzyl group of the product (**13a**) geve the phenol (**13b**) and Ullmann condensation of **13b** with methyl 3-bromo-4-methoxyphenylacetate (**14**)[20] afforded the compound (**15a**) in 34% yield.



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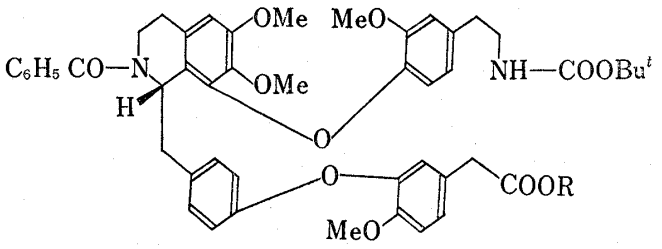

15a : R=CH_3
15b : R=H
15c : R= —C_6H_4—NO_2

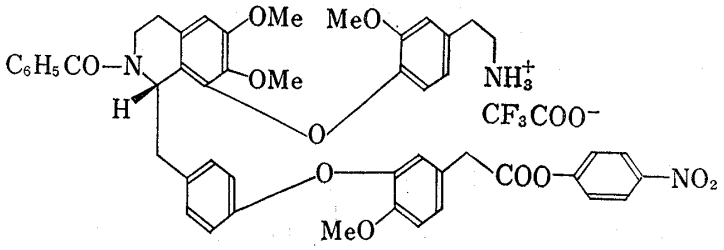

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Chart 3

Next step is the formation of the macroring amide linkage and this was accomplished by the activated ester method. Thus, the methoxycarbonyl group of **15a** was hydrolyzed by alkali to give the free acid (**15b**) which was converted into its *p*-nitrophenyl ester (**15c**) with *p*-nitrophenol and dicyclohexylcarbodiimide (DCC). The *t*.-BOC group of **15c** was then removed with trifluoroacetic acid to give the *p*-nitrophenyl ester phenethylammonium trifluoroacetate(**16**).

The compound (**16**) was cyclized to the macroring amide by a high dilution manner. Thus, a solution of **16** in anhydrous dimethylformamide was added dropwise to preheated pyridine at 80° to afford the cycloamide (**17**) in 36% yield from **15a**. That this amide is not oligomeric (oligomers are occasionally formed in the peptide synthesis[21]) was confirmed by the appearance of the molecular ion peak at *m/e* 714.2950 in the mass spectrum.

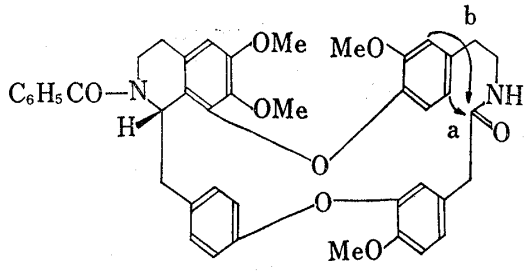
Bischler-Napieralski cyclization of the amide (**17**) gave regioselectively the 3,4-dihydroisoquinoline (**18**) as a sole product in 77.3% yield. In this cyclization reaction, two directions, a or b as shown by an arrow, are possible. However, the latter seems unlikely in view of the preferred direction of cyclization of this type of amides.[8] This ambiguity was ultimately settled by identification of the final products of the synthesis with obaberine and trilobine. Sodium borohydride reduction of the compound (**18**) gave the diastereoisomeric mixture (**19a**) in 90% yield. Without separation, the mixture was N-methylated in the usual manner to give the N-methylated mixture. The preparative thin-layer chromatography (TLC) of the mixture provided the compound (**5**) and (**19b**), respectively. The ratio of **5** and **19b**

20) H. Kondo and S. Uyeo, *Yakugaku Zasshi*, **53**, 557 (1933).
21) M. Bodanszky, *Nature*, **175**, 685 (1955); M. Bodanszky, M.A. Ondetti, S.D. Levine, and N.J. Williams, *J. Am. Chem. Soc.*, **89**, 6753 (1967); E. Schröder and K. Lübke, "The Peptide," Vol. 1, Academic Press, New York and London, 1965, p. 271.

was 5: 2. This result indicates that asymmetric reduction of the prochiral center of **18**, a C=N function, took place.[14]

In order to establish the absolute configuration of an asymmetric center newly introduced at a right-hand hydroisoquinoline moiety, the compound (**19b**) was derived into obaberine of established absolute configurations. Thus, reduction of the compound (**19b**) with AlH_3 gave the N-benzyl compound (**19d**) which was hydrogenated over Pd-C catalyst to give the compound (**19e**). N-Methylation of the compound (**19e**) with formalin-$NaBH_4$ gave obaberine, a sample of which was identical with an authentic sample of natural obaberine in all respects including its optical rotation. Thus, the absolute configuration of an asymmetric center at a right-hand hydroisoquinoline moiety of the compound (**19b**) was established as *R*, thus the hydrogen is *β*. Consequently, the absolute configuration of that of the compound (**5**) is *S* and is a correct one for the trilobine synthesis. It was favorable for the present synthesis that the generation of the desired isomer (**5**) was superior to that of another isomer (**19b**) as mentioned earlier.

Reduction of **5** with AlH_3 gave the N-benzyl compound (**19c**) which was treated with BBr_3 in CH_2Cl_2 at 0° to give the per-O-demethylated compound (**20**). Next stage is the construction of the dibenzo-*p*-dioxin nucleus. A solution of the compound (**20**) in a saturated aqueous HBr solution was heated in a sealed tube at 140° for 3 hr to afford the compound (**21**). Methylation of **21** with diazomethane provided N-benzyltrilobine (**2**: R=



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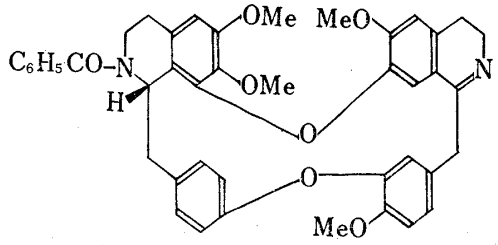

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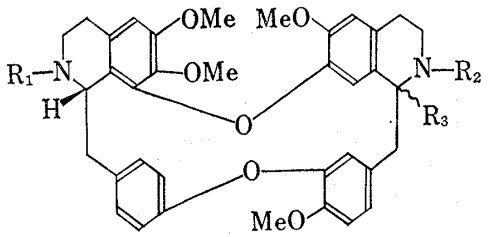
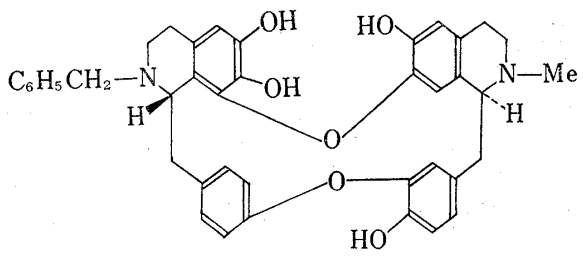


19a : R_1=COC_6H_5, R_2=H, R_3=H
19b : R_1=COC_6H_5, R_2=CH_3, R_3=*β*H
19c : R_1=$CH_2C_6H_5$, R_2=CH_3, R_3=*α*H
19d : R_1=$CH_2C_6H_5$, R_2=CH_3, R_3=*β*H
19e : R_1=H, R_2=CH_3, R_3=*β*H



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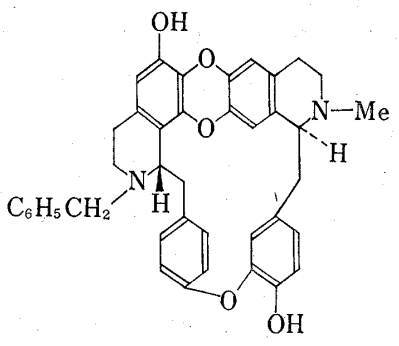

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Chart 4

$CH_2C_6H_5$). Finally, hydrogenolysis of **2** ($R=CH_2C_6H_5$) over Pd-C catalyst gave trilobine, a sample of which was identical with an authentic sample of natural trilobine (**2**: R=H) in all respects including its optical rotation.

Moreover, the present synthesis amounts to synthesis of isotrilobine (**2**: $R=CH_3$) since trilobine was transformed into isotrilobine by N-methylation.[22]

Experimental

Melting points were determined on a Yanagimoto micro mp apparatus and uncorrected. The infrared (IR) spectra were taken on a Hitachi model EPI-S spectrometer, nuclear magnetic resonance (NMR) spectra on a Varian A-60, HA-100D and a Hitachi R-22 spectrometer, using tetramethylsilane (TMS) as internal standard, and high resolution mass spectra on a Nihondenshi JMS-01SG-2 mass spectrometer using a direct heated-inlet system. Specific rotations were measured with a Union PM-101 type automatic digital polarimeter. Brockmann neutral alumina (activity II—III) and silica gel G (Merck) were used for column chromatography, and aluminum oxide PF_{254} (Type T, Merck) and silica gel PF_{254} were used for preparative thin-layer chromatography (TLC).

N-(3-Bromo-4,5-dimethoxyphenethyl)-2-(*p*-benzyloxyphenyl)acetamide (**8**)——A mixture of 3-bromo-4,5-dimethoxyphenethylamine[17,18] (**7**, 134 g), *p*-benzyloxyphenylacetic acid[16] (**6**, 125 g) and decalin (700 ml) was refluxed for 2 hr. Decalin was discarded by decantation and a solution of the residue in $CHCl_3$ was washed successively with 3% HCl, 5% NaOH and H_2O, and then dried over $MgSO_4$. Evaporation of the solvent gave the crystalline residue which was recrystallized from acetone to afford the amide (**8**, 161 g) as colorless pillars, mp 104—105°. *Anal.* Calcd. for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41. Found: C, 61.69; H, 5.48.

1-(4-Benzyloxybenzyl)-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline (**9**)——A mixture of the amide (**8**, 100 g), freshly distilled phosphorus oxychloride (200 g) and anhydrous benzene (1000 ml) was refluxed for 2 hr. Benzene and excess phosphorus oxychloride were removed under reduced pressure. To the residue was added 5% HCl little by little at 0° and the acidic aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give the crystalline residue. Recrystallization from acetone gave hydrochloride of the compound (**9**) as colorless needles (85 g), mp 171—173°. *Anal.* Calcd. for $C_{25}H_{24}BrNO_3 \cdot HCl \cdot 1/2H_2O$: C, 58.66; H, 5.12; N, 2.74. Found: C, 58.93; H, 4.90; N, 2.74.

***dl*-O-Benzyl-8-bromo-N-norarmepavine** (**10**: **R=H, Racemate**)——To the stirred solution of 1-(4-benzyloxybenzyl)-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**9**, 70 g) in MeOH (350 ml) was added $NaBH_4$ (12 g) little by little at 0°. The reaction mixture was stirred for a further 30 min at the same temperature. The solvent was removed under reduced pressure and the residue was mixed with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent gave the crystalline residue which was recrystallized from acetone to afford *dl*-O-benzyl-8-bromo-N-norarmepavine (**10**: R=H, racemate, 60 g) as prisms, mp 139°. *Anal.* Calcd. for $C_{25}H_{26}BrNO_3$: C, 64.11; H, 5.60; N, 2.99. Found: C, 64.02; H, 5.57; N, 3.23.

Resolution of *dl*-O-Benzyl-8-bromo-N-norarmepavine (**10**: **R=H Racemate**)——To a solution of *dl*-O-benzyl-8-bromo-N-norarmepavine (**10**: R=H, racemate, 9.5 g) in acetone (250 ml) was added N-acetyl-L-leucine (3.56 g). The mixture was allowed to stand overnight at room temperature and the crystalline precipitates were collected by filtration. Repeated recrystallizations from acetone gave (*S*)-O-benzyl-8-bromo-N-norarmepavine N-acetyl-L-leucinate (2.5 g), mp 169—172°, $[\alpha]_D^{18}$ +14.0° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{26}BrNO_3 \cdot C_8H_{15}NO_3$: C, 61.77; H, 6.44; N, 4.37. Found: C, 61.54; H, 6.15; N, 4.49. The solution of the salt (2.5 g) in $CHCl_3$ was shaken with conc. NH_4OH. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to leave (*S*)-O-benzyl-8-bromo-N-norarmepavine (**10**: R=H, 1.6 g) as needles, mp 122°, $[\alpha]_D^{23}$ +22.2° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{26}BrNO_3$: C, 64.11; H, 5.60; N, 2.99. Found: C, 64.10; H, 5.51; N, 3.13. NMR ($CDCl_3$) δ: 3.84 (6H, s, $2\times OCH_3$), 5.07 (2H, s, $-OC\underline{H}_2Ph$).

Conversion of (*S*)-O-Benzyl-8-bromo-N-norarmepavine (**10**: **R=H**) **into (*S*)-Armepavine** (**11**)——To a solution of (*S*)-O-benzyl-8-bromo-N-norarmepavine (**10**: R=H, 200 mg) in EtOH (15 ml) were added 1% palladium chloride solution (1 ml) and active charcoal (Darco G 60; 100 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 HCl solution and washed with ether. The acidic aqueous layer was made alkaline with a dilute NaOH solution and washed with ether. The acidic aqueous layer was saturated with NH_4Cl and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give crystals (115 mg). To a solution of above crystals (90 mg) in MeOH (10 ml) was added dropwise formalin (50 mg) at room temperature and the mixture was stirred for a further 30 min at the same temperature. To this mixture was added $NaBH_4$ (50 mg) in small portions and stirring was continued for a further 30 min. The solvent was

22) M. Tomita and Y. Inubushi, *Pharm. Bull.* (Tokyo), **3**, 7 (1955).

removed under reduced pressure and the residue was mixed with water and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated. The crystalline residue was recrystallized from acetone to give pillars (**11**: 40 mg), mp 140—142°, $[\alpha]_D^{22}$ +96.0° (c=1.0, $CHCl_3$), a sample of which was identified with an authentic sample of (*S*)-armepavine [lit.,[19] mp 144—145°, $[\alpha]_D$ +92.76° ($CHCl_3$)] by comparisons of IR and NMR spectra.

(*S*)-N-Benzoyl-O-benzyl-8-bromo-N-norarmepavine (10: R=COC_6H_5)——To a solution of (*S*)-O-benzyl-8-bromo-N-norarmepavine (**10**: R=H, 5 g) in $CHCl_3$ (30 ml) was added pyridine (4 ml). Benzoyl chloride (3 ml) was then added dropwise with stirring during 5 min at 0° and stirring was continued for a further 1.5 hr at the same temperature. The reaction mixture was poured into ice-water and the $CHCl_3$ layer was successively washed with dilute HCl solution, dilute NaOH solution and water, and dried over $MgSO_4$. Evaporation of the solvent left the residue which on trituration with acetone gave crystals. Crystals were collected by filtration and recrystallizations from acetone afforded colorless needles (**10**: R=COC_6H_5, racemate, 0.28 g), mp 185—187°, $[\alpha]_D^{20}$ 0° (c=1.0, $CHCl_3$). After removal of this contaminated racemate, the filtrate and the mother liquor from recrystallizations were combined and concentrated. On trituration with ether, the residue gave crystals which were recrystallized from ether to provide 5.5 g of colorless prisms (**10**: R=COC_6H_5), mp 120—122°, $[\alpha]_D^{21}$ +162° (c=1.0, $CHCl_3$) in 90% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1616 (>N–CO–Ph). NMR ($CDCl_3$) δ: 3.86 (6H, s, 2×OCH_3), 5.09 (2H, s, –OCH_2Ph), 6.92 (5H, s, –Ph), and 7.40 (5H, s, –COPh). *Anal.* Calcd. for $C_{32}H_{30}BrNO_4$: C, 67.13; H, 5.29; N, 2.46. Found: C, 67.32; H, 5.47; N, 2.51.

(*S*)-2-Benzoyl-1-(4-benzyloxybenzyl)-8-(4-*t*-butoxycarbonylaminoethyl-2-methoxyphenoxy)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13a)——To a solution of (*S*)-N-benzoyl-O-benzyl-8-bromo-N-norarmepavine (**10**: R=COC_6H_5, 13 g) and N-*t*-butoxycarbonyl-4-hydroxy-3-methoxy-β-phenylethylamine[8] (**12**, 6 g) in dry pyridine (200 ml) were added anhydrous K_2CO_3 (4 g) and CuO (4 g). The temperature of the reaction mixture rose slowly to 148° (bath temperature) under argon atmosphere with stirring and heating was continued for 15 hr. After cooling, the precipitates were filtered off through a short Al_2O_3 column, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$–benzene (1: 4) mixture and successively washed with dilute NaOH solution, dilute citric acid solution, and water. After drying over $MgSO_4$, the solvent was evaporated under reduced pressure to leave an oily residue. The oil in benzene was chromatographed on an alumina column and the column was eluted successively with benzene and the benzene–$CHCl_3$ mixture to give a pale yellow oil (**13a**, 8.16 g) in 47.4% yield. $[\alpha]_D^{20}$ +82.3° (c=2.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (>NH), 1703 (–NH–COOBu^t) and 1620 (>N–COPh). NMR ($CDCl_3$) δ: 1.44 (9H, s, Bu^t), 3.69, 3.82 3.86 (9H, each s, 3×OCH_3), 5.05 (2H, s, –OCH_2Ph), 6.82 (5H, s, Ph), 7.37 (5H, s, COPh). MS m/e: 561.2572 (M−$C_{14}H_{13}O$) and no M^+ peak was observed.

(*S*)-2-Benzoyl-8-(4-*t*-butoxycarbonylaminoethyl-2-methoxyphenoxy)-1-(4-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13b)——A solution of the compound (**13a**, 6.6 g) in MeOH (80 ml) was hydrogenated over 10% palladized charcoal (800 mg) at room temperature and atmospheric pressure. After absorption of hydrogen had ceased, the reaction mixture was filtered and the filtrate was made alkaline with dilute $NaHCO_3$ solution and concentrated under reduced pressure. The residue was mixed with 5% aqueous citric acid solution and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated to leave an amorphous powder (**13b**, 5.45 g) in 94% yield. $[\alpha]_D^{20}$ +99.9° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (>NH), 1704 (–NH–COOBu^t), 1610 (>N–COPh), NMR ($CDCl_3$) δ: 1.45 (9H, s, Bu^t), 3.72, 3.78, 3.88 (9H, each s, 3×OCH_3). MS m/e: 595.2433 (M−C_4H_9O) and no M^+ peak was observed.

(*S*)-2-Benzoyl-8-(4-*t*-butoxycarbonylaminoethyl-2-methoxyphenoxy)-6,7-dimethoxy-1-[4-(2-methoxy-5-methoxycarbonylmethylphenoxy)benzyl]-1,2,3,4-tetrahydroisoquinoline (15a)——To a solution of the compound (**13b**, 5.3 g), methyl 3-bromo-4-methoxyphenylacetate[20] (**14**, 3.49 g) in dry pyridine (15 ml) were added anhydrous K_2CO_3 (1.5 g) and CuO (1.5 g). The temperature of the reaction mixture rose slowly to 140° (bath temperature) and heating was continued for 20 hr with stirring under argon atmosphere. The reaction mixture was filtered off through a short silica gel column and the column was eluted with 5% MeOH in $CHCl_3$. The eluate was concentrated under reduced pressure and the residue was dissolved in benzene–$CHCl_3$ (4: 1) mixture. The solution was then washed with dilute NaOH solution, dilute aqueous citric acid solution and water. The organic layer was dried over $MgSO_4$ and evaporated to give an oily residue which was chromatographed on a silica gel column in $CHCl_3$ and elution of the column was continued with 5% MeOH in $CHCl_3$. The MeOH–$CHCl_3$ eluents were concentrated to leave the methyl ester (**15a**) as an amorphous powder (**15a**, 2.3 g) in 34% yield. $[\alpha]_D^{20}$ +71.6° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (>NH), 1730 (COOMe), 1705 (>N–COOBu^t), 1620 (>N–COPh), NMR ($CDCl_3$) δ: 1.44 (9H, s, Bu^t), 3.65, 3.70, 3.80, 3.80, 3.87 (15H, each s, 5×OCH_3). MS m/e: 561.2613 (M−$C_{17}H_{17}O_4$), and no M^+ peak was observed.

Cycloamide (17)——A solution of the ester (**15a**, 2.5 g) in MeOH (100 ml) was hydrolyzed with 10% aqueous NaOH solution (20 ml) overnight at room temperature with stirring. The reaction mixture was acidified faintly with crystalline citric acid and MeOH was removed under reduced pressure. The residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated to afford the crude carboxylic acid (**15b**, 2.3 g) as a pale yellow amorphous powder. For an analytical sample, the crude acid was purified by preparative TLC on alumina using 20% acetone in benzene as a developing solvent. $[\alpha]_D^{20}$ +99.7° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (>NH), 1710 (COOH), 1705 (–NH–COOBu^t), 1610 (>N–COPh). NMR ($CDCl_3$) δ: 1.43 (9H, s, Bu^t), 3.69, 3.77, 3.77, 3.87 (12H, each s, 4×OCH_3). MS

m/e: 714.2929 ($M-C_5H_{10}O_3$) and no M^+ peak was observed. To a solution of the acid (**15b**, 2.3 g) in ethyl acetate (45 ml) was added *p*-nitrophenol (420 mg). To this solution was added dicyclohexylcarbodiimide (620 mg) little by little with stirring at 0—5°, and the mixture was stirred for a further 1 hr at room temperature. The precipitated dicyclohexylurea was filtered off and the filtrate was evaporated under reduced pressure. For an analytical sample, the product was purified by preparative TLC on silica gel using 5% acetone in $CHCl_3$ as a developing solvent to afford an amorphous powder (**15c**, 1.7 g), $[\alpha]_D^{20}$ +80.7° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (>NH), 1762 (COOPh), 1709 (-NH-COOBu^t), 1620 (>N-COPh), NMR ($CDCl_3$) δ: 1.45 (9H, s, Bu^t), 3.70, 3.82, 3.83, 3.88 (12H, each s, 4×OCH_3). MS *m/e*: 714.2960 ($M-C_{11}H_{13}NO_5$), and no M^+ peak was observed. The crude *p*-nitrophenyl ester (**15c**, 1.7 g) was mixed with trifluoroacetic acid (25 g) at room temperature, and the mixture was allowed to stand for 1 hr at the same temperature. Excess of trifluoroacetic acid was removed under reduced pressure at 30—40° (bath temperature) to leave the crude phenethylamine trifluoroacetate (**16**, 1.1 g). A solution of the compound (**16**, 1.1 g) in anhydrous dimethylformamide (25 ml) was added dropwise to preheated pyridine at 70—80° with stirring during 5 hr. After the addition was completed, the mixture was stirred at the same temperature for an additional 1 hr. Pyridine and dimethylformamide were then removed under reduced pressure and the residual oil was extracted with $CHCl_3$. The extract was washed with dilute HCl solution and water, and then dried over $MgSO_4$. Evaporation of the solvent afforded a brown oily substance which was chromatographed on silica gel in $CHCl_3$ and the column was eluted with the MeOH-$CHCl_3$ (1:49) mixture. The MeOH-$CHCl_3$ eluents were concentrated to give the crude cycloamide (**17**). The crude product was purified by preparative TLC on silica gel using 5% acetone in $CHCl_3$ as a developing solvent to give a pale yellow amorphous powder (0.76 g; 35.9% yield from (**15a**)). $[\alpha]_D^{20}$ +95.0° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (>NH), 1662 (-CO-NH), 1630 (>NCO-Ph), NMR ($CDCl_3$) δ: 3.90 (9H, s, 3×OCH_3), 4.05 (3H, s, OCH_3); ($CDCl_3$-pyridine-d_5 [2:1]) δ: 3.80, 3.83, 3.88, 3.95 (12H, each s, 4×OCH_3). MS *m/e*: 714.2950 (M^+).

3,4-Dihydroisoquinoline (18)——A mixture of the cycloamide (**17**, 208 mg) and freshly distilled phosphorous oxychloride (1 ml) in $CHCl_3$ (20 ml) was refluxed for 2.5 hr. Excess of phosphorous oxychloride and $CHCl_3$ were removed under reduced pressure. The residue was made alkaline with conc. NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated. The oily residue was purified by preparative TLC on alumina using 6% acetone in benzene as a developing solvent to afford the 3,4-dihydroisoquinoline (**18**, 157 mg) as an amorphous powder in 77.3% yield. $[\alpha]_D^{20}$ −6.7° (c=1.3, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1623 (>N-COPh), NMR ($CDCl_3$) δ: 3.59 (6H, s, 2×OCH_3), 3.80, 3.89 (6H, each s, 2×OCH_3), 7.45 (5H, s, COPh), MS *m/e*: 696.2824 (M^+).

The Compound (5) and (19b)——To a solution of the 3,4-dihydroisoquinoline (**18**, 157 mg) in MeOH (18 ml) was added sodium borohydride (148 mg) in small portions at room temperature with stirring. The reaction mixture was stirred at the same temperature for a further 30 min. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a mixture of diastereoisomers (**19a**, 142 mg) as a pale yellow oil. To a solution of this mixture (**19a**, 142 mg) in MeOH (20 ml) was added 37% formalin (4.5 ml), and the reaction mixture was stirred for 1 hr at room temperature. Sodium borohydride (1.2 g) was then added in small portions at room temperature and the reaction mixture was stirred at the same temperature for a further 30 min. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water and dried over $MgSO_4$. Evaporation of the solvent afforded a mixture of N-methylated diastereoisomers (**5**+**19b**) as a pale yellow oil. Each of diastereoisomers was isolated by preparative TLC on alumina using 6% acetone in benzene as a developing solvent. The upper zone on the chromatoplate gave a pale yellow oil corresponding to the compound (**19b**, 28 mg) and the lower zone afforded a pale yellow oil corresponding to the compound (**5**, 69 mg). The compound (**19b**) showed $[\alpha]_D^{20}$ +101.3° (c=1.3, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 (>N-COPh), NMR ($CDCl_3$) δ: 2.55 (3H, s, N-CH_3), 3.20, 3.63, 3.80, 3.89 (12H, each s, 4×OCH_3), 7.45 (5H, s, COPh), MS *m/e*: 712.3157 (M^+). The compound (**5**) showed $[\alpha]_D^{20}$ −127.0° (c=1.5, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 (>N-COPh), NMR ($CDCl_3$) δ: 2.55 (3H, s, N-CH_3), 3.03, 3.53, 3.77, 3.93 (12H, each s, 4×OCH_3) 7.45 (5H, s, COPh), MS *m/e*: 712.3171 (M^+).

Synthesis of Obaberine (3) from the Compound (19b)——To a suspension of $LiAlH_4$ (110 mg) in dry ether (10 ml) was added $AlCl_3$ (140 mg) little by little at 0° with stirring and stirring was continued for 30 min at room temperature. To this mixture was dropwise added a solution of the compound (**19b**, 27 mg) in THF (2 ml) with stirring at room temperature. The reaction mixture was refluxed for 5.5 hr with stirring. After destroying excess of AlH_3 by adding wet ether at 0°, the reaction mixture was filtered and the filtrate was washed with water, dried over $MgSO_4$ and evaporated. The crude product was purified by preparative TLC on alumina using 6% acetone in benzene as a developing solvent to afford the N-benzyl compound (**19d**) as a pale yellow oil (19 mg). $[\alpha]_D^{20}$ +162° (c=0.33, $CHCl_3$), NMR ($CDCl_3$) δ: 2.55 (3H, s, -NCH_3), 3.23, 3.63, 3.79, 3.88 (12H, each s, 4×OCH_3), MS *m/e*: 698.3345 (M^+).

A solution of the N-benzyl compound (**19d**, 150 mg) in AcOH (6 ml) was hydrogenated over Pd-C catalyst (prepared from Darco G, 100 mg and 3 ml of 1% $PdCl_2$ solution) at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was made alkaline with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a pale yellow oily substance which was purified by preparative TLC on alumina using 10% acetone in

benzene as a developing solvent to afford the compound (**19e**) as a pale yellow oil (63 mg). $[\alpha]_D^{20}$ +294.2° (c=0.2, $CHCl_3$), NMR ($CDCl_3$) δ: 2.55 (3H, s, N-CH_3), 3.20, 3.65, 3.77, 3.88 (12H, each s, 4×OCH_3).

To a solution of the compound (**19e**, 50 mg) in MeOH (20 ml) was added 37% formalin (1 ml) at room temperature and the reaction mixture was stirred for 30 min at the same temperature. Then, sodium borohydride (1 g) was added little by little and the mixture was stirred for a further 30 min. The solvent was removed under reduced pressure and the residue was mixed with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by preparative TLC on alumina using 6% acetone in benzene as a developing solvent to afford obaberine (**3**) as a pale yellow oil (32 mg) which was crystallized on trituration with ether. Recrystallizations from ether gave needles, mp 142—144°, $[\alpha]_D^{20}$ +240.7° (c=0.6, $CHCl_3$), a sample of which was identified with an authentic sample of obaberine (**3**) by comparisons of IR and NMR spectra. NMR ($CDCl_3$) δ: 2.56 (3H, s, N-CH_3), 2.63 (3H, s, N-CH_3), 3.19, 3.61, 3.77, 3.88 (12H, each s, 4×OCH_3), MS m/e: 622.3043 (M^+).

The Compound (19c)——To a suspension of $LiAlH_4$ (110 mg) in dry ether (10 ml) was added $AlCl_3$ (140 mg) little by little at 0° with stirring and the mixture was stirred for 30 min at room temperature. To this suspension was dropwise added a solution of the compound (**5**, 30 mg) in THF (2 ml) at room temperature and the reaction mixture was refluxed for 5.5 hr with stirring. After destroying excess AlH_3 by adding wet ether at 0°, the reaction mixture was filtered and the filtrate was washed with water, dried over $MgSO_4$ and evaporated. The residue gave a pale yellow oil (30 mg) which was purified by preparative TLC on alumina using 6% acetone in benzene as a developing solvent. When triturated with MeOH, this oil gave crystals which were recrystallized from MeOH to afford colorless plates (**19c**, 8 mg), mp 139—141°, $[\alpha]_D^{20}$ −88.5° (c=0.52, $CHCl_3$), NMR ($CDCl_3$) δ: 2.53 (3H, s, N-CH_3), 3.02, 3.41, 3.76, 3.94 (12H, each s, 4×OCH_3), *Anal.* Calcd. for $C_{44}H_{46}N_2O_6$: C, 75.62; H, 6.64; N, 4.01. Found: C, 75.61; H, 6.92; N, 4.26.

N-Benzyltrilobine (2: R=-$CH_2C_6H_5$)——To a solution of the compound (**19c**, 220 mg) in CH_2Cl_2 (10 ml) was dropwise added a solution of borontribromide (2.2 g) in CH_2Cl_2 (2 ml) with stirring at 0°. Stirring was continued for 4 hr at the same temperature and the reaction mixture was then poured into ice-water (20 ml) little by little. The pale yellow precipitates were collected by filtration and dried at 40° under reduced pressure overnight to give the crude demethyl compound (**20**, 200 mg). A solution of the crude demethyl compound in aqueous saturated HBr solution (2 ml) was heated in a sealed tube at 135—140° under argon atmosphere for 3 hr. The reaction mixture was poured into ice-water (20 ml) and the ashy-brown precipitates were collected by filtration to give the crude anhydrodemethyl compound (**21**, brown paste). To a solution of **21** in MeOH (70 ml) was added ethereal diazomethane solution (150 ml) prepared from *p*-toluenesulfonyl-N-methyl-N-nitrosoamide (25 g). Then, the reaction mixture was kept on standing for 3 days at room temperature. The additional ethereal diazomethane solution (100 ml) prepared from *p*-toluenesulfonyl-N-methyl-N-nitrosoamide (25 g) was added. The reaction mixture was allowed to stand for a further one day. To the reaction mixture was then added AcOH (2 ml) at 0° with stirring and the solvent was removed under reduced pressure. The residue was made alkaline with aq. NH_4OH and extracted with the $CHCl_3$–ether (1: 5) mixture and the organic layer was successively washed with 5% NaOH solution, water and dried over $MgSO_4$. Evaporation of the solvent gave the brown oily substance which was purified by preparative TLC on alumina using 6% acetone in benzene as a developing solvent. The eluate showed one spot on alumina thin-layer chromatoplate, but two spots on silica gel thin-layer chromatoplate. This product was purified by repeated preparative TLC on silica gel using 2% MeOH in $CHCl_3$ as a developing solvent to afford a pale yellow oil (**2**: R=$CH_2C_6H_5$, 3 mg). $[\alpha]_D^{20}$ +203.0° (c=0.2, $CHCl_3$), NMR ($CDCl_3$) δ: 2.41 (3H, s, N-CH_3), 3.89, 3.98 (6H, each s, 2×OCH_3). MS m/e: 652.2955 (M^+). These spectroscopic data were identical with those of N-benzyltrilobine derived from natural trilobine (**2**: R=H).

Trilobine (2: R=H)——A solution of N-benzyltrilobine (**2**: R=$CH_2C_6H_5$, 59 mg) in AcOH (5 ml) was hydrogenated over Pd-C catalyst prepared from active charcoal (Darco G, 57 mg) and 1% palladium chloride solution (1.5 ml) at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was made alkaline with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over $MgSO_4$ and evaporated. Trituration of the residue with benzene gave crystals. Recrystallizations from benzene afforded colorless needles (**2**: R=H, 17 mg), mp 242—246°, $[\alpha]_D^{20}$ +304.5° (c=0.66, $CHCl_3$) NMR ($CDCl_3$) δ: 2.42 (3H, s, N-CH_3), 3.80, 3.95 (6H, each s, 2×OCH_3). *Anal.* Calcd. for $C_{35}H_{34}N_2O_5$: C, 74.71; H, 6.09; N, 4.98. Found: C, 75.01; H, 6.03; N, 5.17. A sample of synthetic trilobine was identified with an authentic sample of trilobine by comparisons of IR and NMR spectra.