Chem. Pharm. Bull. 23(11)2878—2890(1975)

UDC 547.943.057 : 542.942.4 : 581.192

Synthetic Studies on Isoquinoline Alkaloids. II.*,[1] Selective Conversion of 3,9,10-Substituted Tetrahydroprotoberberines into 3,9,10-Substituted 14-Deoxoprotopines. Total Synthesis of 3,9,10-Substituted 5,6,7,8,13,14-Hexahydrodibenz(c,g)azecines[2]

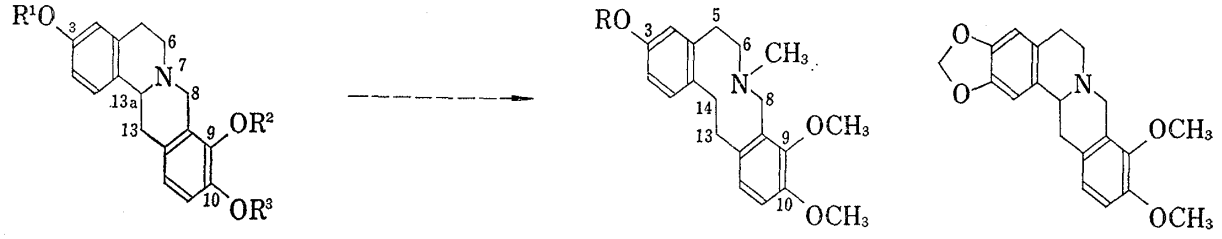
Wataru Nagata, Kyo Okada, Hiroshi Itazaki, and Shoichiro Uyeo

Shionogi Research Laboratory, Shionogi & Co., Ltd.[3]

(Received May 2, 1975)

An efficient method for highly selective conversion of 3,9,10-trisubstituted tetrahydroprotoberberines into the corresponding 3,9,10-substituted 5,6,7,8,13,14-hexahydrodibenz(c,g)azecines was established as exemplified by high yield conversions of **13** into **15** and **1g** into **29**. The method involves Emde reduction (Birch modification) of the methiodide **14** or **28**, in which the C_9-phenolic function is specifically protected by the benzyl group enabling selective reductive fission at the C_{13a}-N bond. By application of this method combined with the method newly developed in our laboratory[1] for synthesis of 9,10-substituted tetrahydroprotoberberines, a straight-forward and sophisticated total synthesis of 9,10-dimethoxy-3-hydroxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g)-azecine (**2a**) was achieved as illustrated in Chart 8. The cyclopropylmethyl group was newly introduced as a very useful protecting group for a phenolic function.

In the previous paper[1] we described a very efficient and straight-forward synthesis of 3-benzyloxy-9,10-dimethoxy-tetrahydroprotoberberines (**1a**) by applying a new and general method for *ortho*-(α-hydroxy)alkylation of phenols using benzeneboronic acid. The purpose of the present work was to convert these synthesized compounds **1** into 9,10-dimethoxy-3-hydroxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (**2a**), a synthetic analogue of protopine alkaloids which has potent, non-narcotic analgesic activity,[1] in an efficient and straight-forward manner. The conversion required regio-selective cleavage of **1** at the C_{13a}-N



1a : $R^1=PhCH_2$, $R^2=R^3=CH_3$
1b : $R^1=H$, $R^2=R^3=CH_3$
1c : $R^1=p\text{-}CH_3OC_6H_4CH_2$, $R^2=R^3=CH_3$
1d : $R^1=3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$, $R^2=R^3=CH_3$
1e : $R^1=R^2=R^3=CH_3$
1f : $R^1=CH_3OCH_2$, $R^2=R^3=CH_3$
1g : $R^1=$ ▷—CH_2, $R^2=PhCH_2$, $R^3=CH_3$

2a : R=H
2b : $R=PhCH_2$
2c : $R=CH_3OCH_2$
2d : R= ▷—CH_2

3

Ph=phenyl

Chart 1

bond and, thus, involved a difficult problem. Solution of this problem was the major subject of the present study.

* Dedicated to the memory of Prof. Eiji Ochiai.

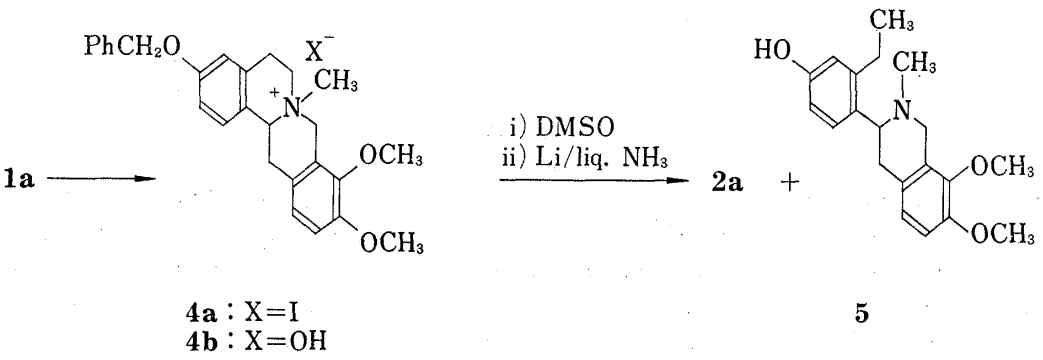
1) Part I: W. Nagata, H. Itazaki, K. Okada, T. Wakabayashi, Y. Shibata, and N. Tokutake, *Chem. Pharm. Bull.* (Tokyo), **23**, 2867 (1975).

2) This work was presented by W.N. during his Pacific Coast Lecture (U.S.A.) tour in October 1974.

3) Location: *Sagisu, Fukushima-ku, Osaka, 553, Japan.*

A priori, conventional methods for degradation of the quinolizine ring system were expected to give two or three cleavage products depending upon the mode of reaction involved. Thus, Hofmann degradation would give rise to cleavage at both C_{13a}-N and C_6-N bonds, Emde reduction would occur at the two benzylic C_{13a}-N and C_8-N bonds, and von Braun cyanogen bromide degradation would take place at the three possible C_{13a}-N, C_8-N, C_6-N bonds. In fact Sawa and Maeda[4] were unable to control the direction of cleavage in their attempted Hofmann and Emde degradations of methiodide of canadine (tetrahydroberberine, **3**). Two possible cleavage products were actually formed in the Hofmann degradation and four in the Emde reduction. Apart from the results of Sawa and Maeda, many other examples of non-selective degradation of such a quinolizine system were available in literature.[5]

With this information in mind, we carried out degradations of the tetrahydroprotoberberine derivative **1a** with the hope that it might be selectively transformed into the target compound **2a**. First, we attempted Hofmann degradation, although this was thought less promising. The methiodide (**4a**) was converted into the quaternary hydroxide (**4b**) in the usual way, which on treatment with dimethylsulfoxide (DMSO) underwent Hofmann degradation followed by Birch reduction giving the desired **2a** and the C_6-N seco isomer (**5**) in a ratio



4a : X=I
4b : X=OH

5

Chart 2

of approximately 1 : 1. The result was worse than the case of a similar degradation of canadine (**3**) performed by Sawa, *et al.*,[4] where the desired C_{13a}-N seco-compound was formed in 52% yield. Attempted hydrogenolyses of **4a** with either Raney Ni or platinum oxide under atmospheric or high pressure were also unsuccessful, resulting in only recovery of **4a** or its debenzylated product.

We next investigated a route *via* von Braun cyanogen bromide degradation. For this purpose, we applied a method recently reported by Rönsch.[6] In his procedure, the reaction was cleverly performed under solvolytic conditions giving the C_{13a}-Nseco-compound as a sole product. To our knowledge, this method was the only means to effect selective cleavage of this type of compound at the C_{13a}-N bond. The reaction turned out to proceed excellently with our compounds **1a** and **1f** giving the C_{13a}-N seco cyanamides **6a** and **6f** in 85 and 88% yield, respectively. These intermediates seemed to us to be easily convertible into the deoxy derivative (**7**) by removal of the benzylic hydroxyl at the C_{14}-position. Contrary to our expectation, this was not always successful, principally because of an unusually high tendency of these ten-membered ring intermediates (**6**) to recyclize into the tetracyclic precursors (**1**). Thus, attempts to remove the C_{14}-hydroxyl in **6a**, for example, by chlorination, dehydration

4) Unpublished data of Y. Sawa and S. Maeda of this laboratory, and Japan Unexamined 49-41386, 49-41387, and 49-51290 (1974).
5) *a*) M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N.Y., 1972, p. 268; *b*) R.M. Sotelo and D. Giacopello, *Australian J. Chem.*, **25**, 385 (1972); *c*) I. Sallay and R.H. Ayers, *Tetrahedron*, **19**, 1397 (1963).
6) H. Rönsch, *J. Prakt. Chem.*, **314**, 382 (1972).

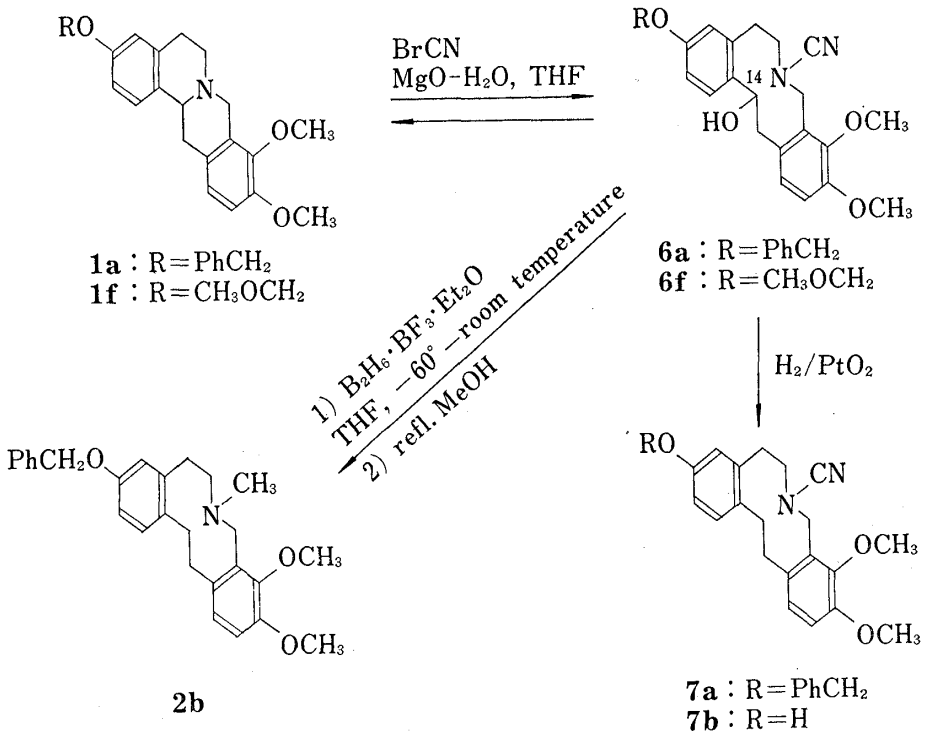


Chart 3

and direct reduction with stannous chloride or a combination of lithium aluminum hydride and aluminum chloride, resulted mostly in recyclization to **1a**. Such a high tendency of recyclization is not understandable in view of the reduced nucleophilicity of the nitrogen by substitution with the cyano group and ascribable to the fact that molecule **6** most likely takes a conformation in which the C_{14}-carbon and the nitrogen are in close proximity, facilitating the transannular reactions. Some other attempts were, however, partly successful. For example, hydrogenolysis using Adams catalyst afforded about 20% of an oily product which seemingly has the desired structure, **7b**, together with a mixture of other products which contained the recyclized product **1a** and over-hydrogenated products. A more acceptable result was obtained when **6a** was subjected to reduction with a combination reagent[7] of borane and borontrifluoride etherate at a low temperature. The reagent first afforded an amine-borane complex which was decomposed in refluxing methanol giving **2b** and the recyclized **1a** in 42 and 20% isolated yield, respectively. An advantage of this conversion was that reduction of the cyano group to the methyl group occurred simultaneously. Since the only by-product **1a** can be recycled, the sequence of solvolytic cyanogen bromide degradation and subsequent B_2H_6-BF_3·Et_2O reduction provides a useful synthetic route to **2**.

We finally turned our attention to Emde reduction of the methiodide **4a** hoping that reductive cleavage might occur mainly at the C_{13a}-N bond. However, disappointingly, the sole product obtained in high yield by reduction of **4a** under Birch conditions was the undesired C_8-N seco compound (**8**) resulting from cleavage at the C_8-N bond benzylic to the D aromatic ring. The result was in contrast to that obtained by an analogous reduction of the methiodide of canadine (**3**) in which reductive fission occurred equally at both the C_8-N and C_{13a}-N bonds.[4] Obviously, the direction of the bond cleavage was affected by the A-ring substitution and it was not very difficult to deduce why product **8** was solely formed in the reduction of **4a**. In this reduction, initial attack of electrons was assumed to take place at the least substituted benzene ring, *i.e.*, the protecting benzyl benzene in **4a**, resulting in formation of the A ring phenoxide (**9**) as a primary product as illustrated in Chart 4. The electron then attacked

7) E. Breuer, *Tetrahedron Letters.*, **1967**, 1849.

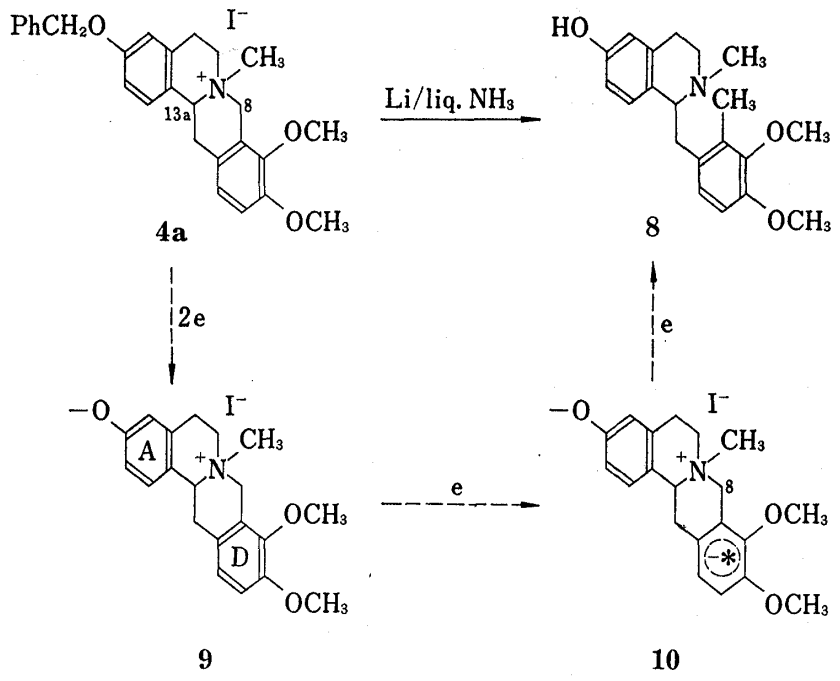
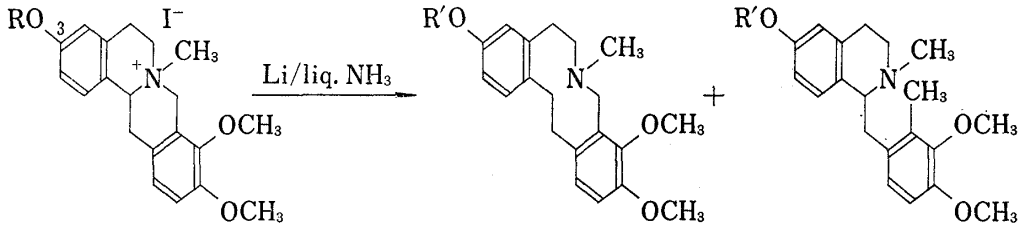


Chart 4

the D aromatic ring in phenoxide as indicated, (**10**), avoiding the negatively charged A ring, thus resulting in selective cleavage of the C_8-N bond and exclusive formation of product **8**. Now, if this argument was correct, two ways existed to solve the problem of selective C_{13a}-N bond reduction. The one was to devise a suitable protecting group for the C_3-phenolic function which would cause preferential electron attack at the A ring. The other was to change one of the two methoxy groups on the D ring to a benzyl group which would give rise to formation of a D ring phenoxide and consequently cause preferential attack of the electron at the A ring accompanied by exclusive cleavage at the C_{13a}-N bond.

We first examined a variety of protecting groups for the C_3-phenolic function. Our results, summarized in Table I showed that the free phenol and the *p*-methoxybenzyloxy group exhibit-

TABLE I. C_3-Substituent Effect in Emde Reduction (Birch Modification) of **4**



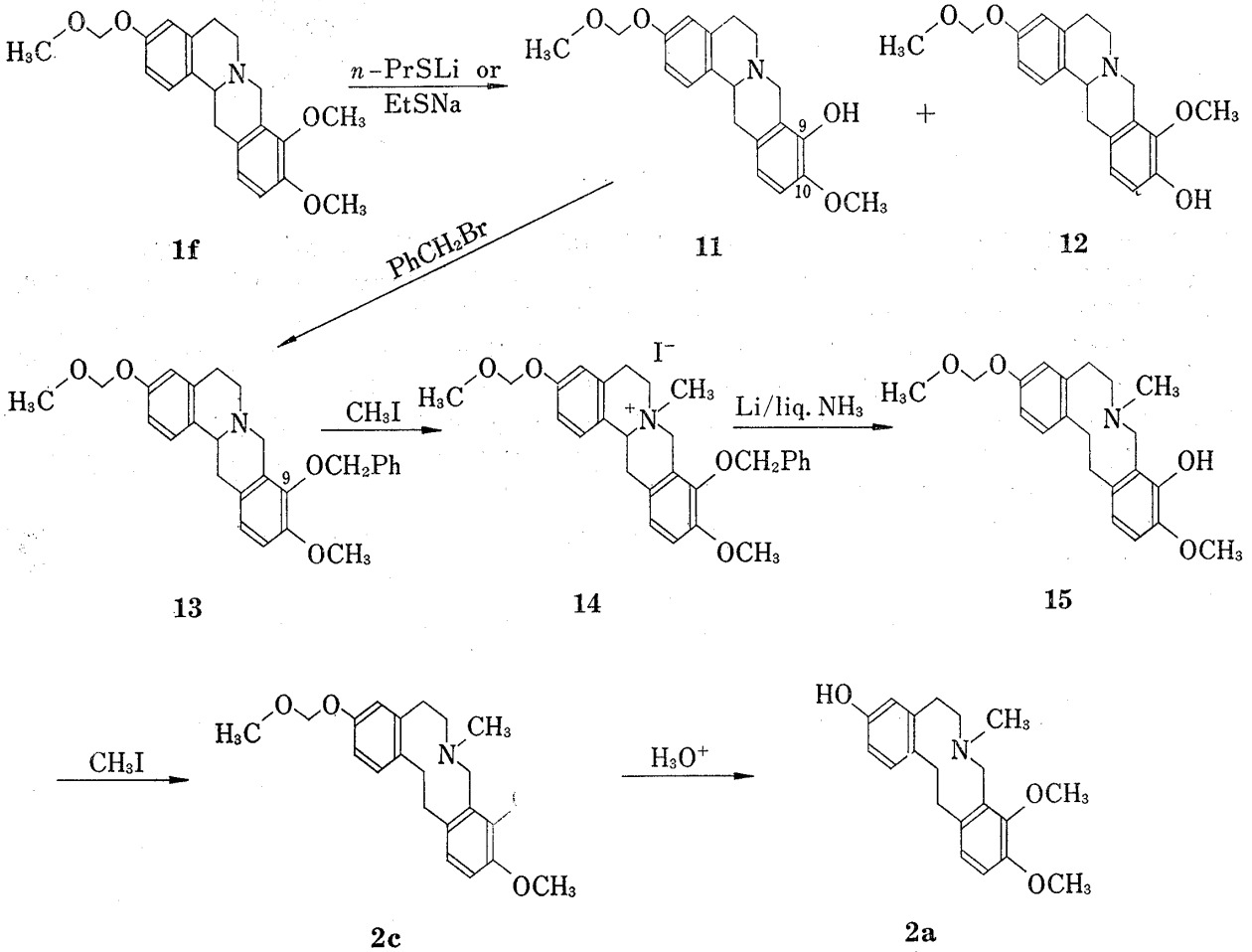
4 **2** **8**

Entry	R	R′	Yield or ratio **2** : **8**
1	H	H	0 : —70%
2	$PhCH_2$	H	trace : —90%
3	p-$CH_3OC_6H_4CH_2$	H	trace : —90%
4	3,4,5-$(CH_3O)_3C_6H_2CH_2$	H	1 : 2 — 3
5	CH_3	CH_3	1 : 2.5
6	CH_3OCH_2	CH_3OCH_2	2 : 1

Ph=phenyl

ed almost the same effect as the benzyloxy, resulting in almost exclusive formation of the undesired product **8**. The 3,4,5-trimethoxybenzyloxy and methoxy groups gave a mixture of the desired **2** and the undesired **8** in a ratio of 1: 2—3, which was disappointing. However, the methoxymethyl group gave a 2: 1 mixture of **2** and **8** from which the desired **2c** was isolated in 50% yield. For rationalization of the remarkable directing effect of the methoxymethoxy group, we can only suggest its inductive effect which would enable the predominant attack of electrons at the A aromatic ring.

As we thus failed to find a suitable protecting group for the C_3-phenolic function, the other method, namely, changing one of the two methoxy groups to a benzyloxy group on the D aromatic ring and subsequently having it undergo Emde reduction, was investigated, although this change would require additional steps. The compound suitable for this purpose was thought to be the 3-methoxymethoxy derivative (**13**), since the C_3-substituent could stand Birch reduction and could be easily hydrolyzed afterwards. Compound **13** was temporally prepared from **1f** as follows (Chart 5). Demethylation of **1f** with lithium *n*-propylmer-



1f **11** **12**

13 **14** **15**

2c **2a**

Chart 5

captide[8] or sodium ethylmercaptide[9] in basic aprotic polar solvents such as hexamethylphosphoryl triamide (HMPT) or dimethyl formamide (DMF) gave two phenolic products, **11** and **12**, with **11** being predominant. In this conversion, the C_3-methoxymethyl protecting group was not eliminated as expected. Structural assignment of the products **11** and **12** was based upon the fact that in general the methyl group at the more congested C_9-position was

8) P.A. Bartlett and W.S. Johnson, *Tetrahedron Letters.*, **1970**, 4459.
9) G.I. Feutrill and R.N. Mirrington, *Australian J. Chem.*, **25**, 1719 (1972).

eliminated more easily[5a] leading to the unequivocal transformation of **15** into 3-hydroxy-10-methoxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g) azecine.[4] Compound (**11**) after benzylation (**13**), was converted into the methiodide (**14**) which was then subjected to Birch reduction. Gratifyingly, the reduction proceeded uniformly giving the desired 13a,7-seco compound (**15**) as a sole product in 71% yield. This compound led to the target compound **2a** *via* **2c** by methylation followed by acid hydrolysis.

At this stage, we converged on the problem of synthesizing the key intermediate **13** more directly from smaller fragments according to our method for 9,10-substituted tetrahydroprotoberberine derivatives described in the previous paper.[1] Thus, 3-methoxymethoxyphenethylamine (**19**) prepared from *m*-hydroxybenzaldehyde (**16**) *via* **17** and **18**, as illustrated in Chart 6, was condensed with the 8-benzyloxy isochromanone (**20**)[1] to give the amide (**21**). Unfortuately, attempted Bischler-Napieralski cyclization followed by sodium borohydride

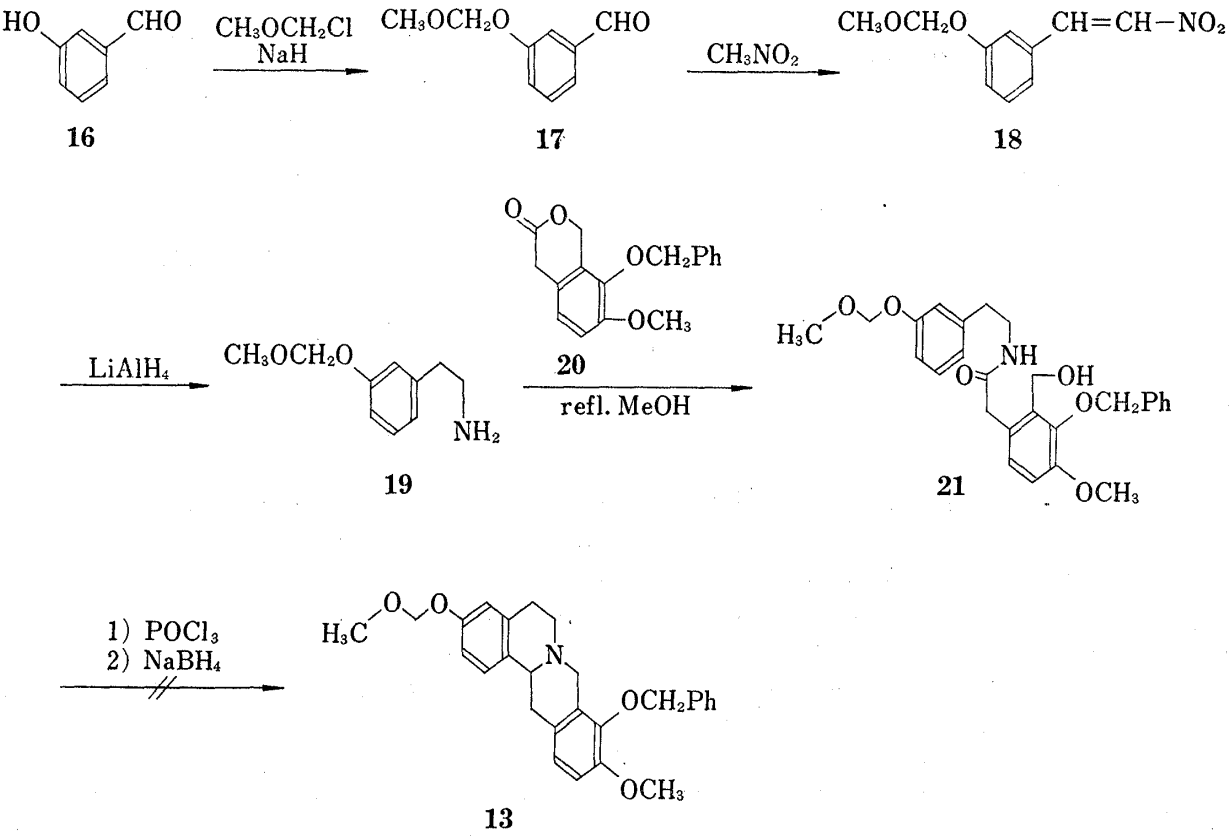


Chart 6

reduction of this compound failed under the usual and even milder conditions, probably owing to its sensitivity to the acidic reagent, phosphoroxychloride. Obviously, the sensitivity was due to the C_3-methoxymethyl protecting group and, thus, another suitable protecting group had to be introduced.

Considering the nature of the reactions which were to be involved in the over-all reaction sequence, including the synthesis of the tetrahydroprotoberberines (**1**), the following criteria had to be taken into account for a C_3-phenol protecting group to be newly introduced. The protecting group R^1 in **1** had to be, first, other than benzyl or methyl, since these groups were already assigned to R^2 and R^3, respectively; second, unaffected by complex metal hydride reduction, catalytic hydrogenation, Birch reduction and Bischler-Napieralski condensation; and, third, easily and selectively removable. Among several candidates, we selected cyclopropylmethyl as the most suitable group for this purpose, since cyclopropyl stabilizes the

adjacent carbonium ion better than phenyl, but does not transmit a substituent effect well[10] and appeared to satisfy above criteria.

Chart 7 shows a successful synthesis of 3-cyclopropylmethoxyphenethylamine (**25**) starting from **16**. Cyclopropylmethylation of **16** with cyclopropyl methylbromide[11] was effected with potassium *tert*-butoxide or sodium hydride in DMF giving 79% of 3-cyclopropylmethoxybenzaldehyde (**22**). This compound was transformed into either the β-nitrostyrene derivative (**23**) or the cyanohydrin ethyl carbonate (**24**) by condensation with nitromethane[12] or hydro-

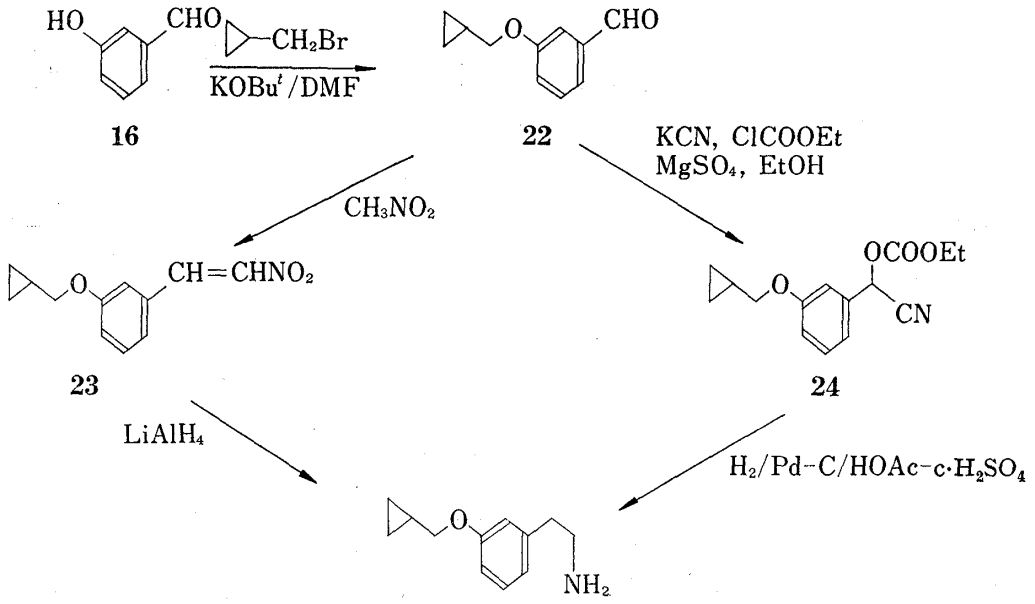


Chart 7

cyanation followed by carbethoxylation[13] as illustrated. The phenethyl amine **25** was prepared from either **23** or **24** by lithium aluminum hydride reduction[14] or hydrogenation[15] using palladium-charcoal as catalyst. The route *via* **24** gave a better over-all yield of 67%. Fortunately, 3-cyclopropylmethoxy group could stand lithium aluminum hydride reduction and also catalytic hydrogenation using palladium, as expected.

The synthesis of 9-benzyloxy-3-cyclopropylmethoxy-10-methoxy-tetrahydroprotoberberine (**1g**) and its transformation into the target compound **2a** are illustrated in Chart 8. Thus, the phenethylamine **25** was condensed with 8-benzyloxy-7-methoxy-isochromanone (**26**), the synthesis of which is described in the previous paper,[1] giving the amide (**27**) in 80% yield. Next, this compound underwent Bischler-Napieralski condensation under mild conditions followed by sodium borohydride reduction giving in 88% yield the tetrahydroprotoberberine intermediate **1g**, which after conversion into the methiodide (**28**), was subjected to Birch reduction affording the desired ten-membered ring amine (**29**) in as high as 91% yield. Gratifyingly, the C_3-cyclopropylmethoxy group was also able to bear Bischler-Napieralski condensation as well as Birch reduction. Compound (**29**), after selective methylation to **2d** with trimethylanilinium methoxide,[16] was hydrolyzed with aqueous hydrochloric acid to the target 9,10-dimethoxy-3-hydroxy-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (**2a**) in 74% over-all yield.

10) *cf.* C.F. Wilcox, L.M. Loew, and R. Hofmann, *J. Am. Chem. Soc.*, **95**, 8192 (1973).
11) L.I. Smith and S. McKenzie, *J. Org. Chem.*, **15**, 74 (1950).
12) I. Baxter, L.T. Allen, and G.A. Swan, *J. Chem. Soc.*, **1965**, 3645.
13) *cf.* K. Kindler and K. Schrader, *Arch. Pharm.*, **283**, 190 (1950).
14) M.S. Gibson, G.W. Preuton, and J.M. Walthew, *J. Chem. Soc.*, **1970**, 2234.
15) *cf.* K. Kindler, H.G. Helling, and F. Sussner, *Ann. Chem.*, **605**, 200 (1959).
16) W. Rodionow, *Bull. Soc. Chim. France*, **39**, 305 (1926).

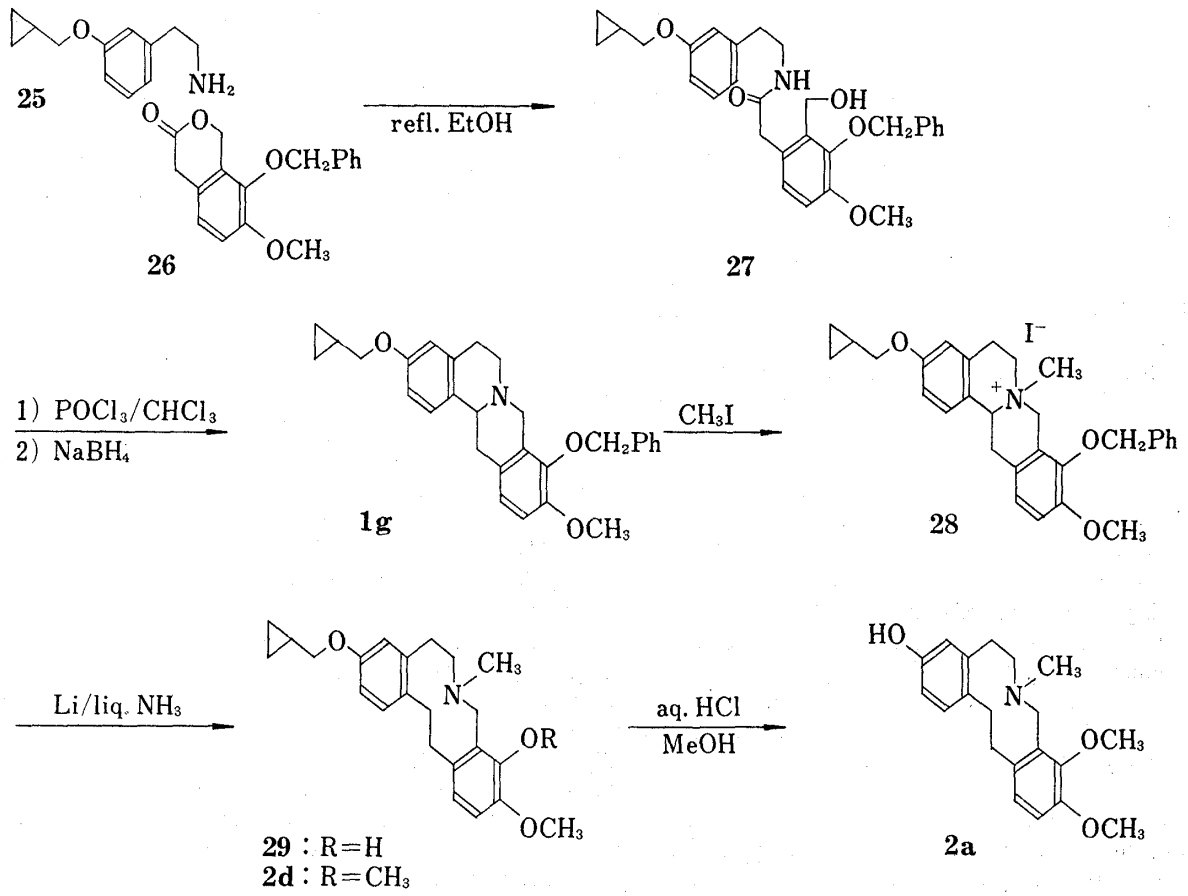


Chart 8

In this way, we succeeded in converting the tetrahydroprotoberberine derivative **1g** into **2a** in a highly selective manner. The conversion involves the completely selective Emde reduction of the methiodide **28** and represents a four-step synthesis of 53% over-all yield. The synthetic route may be useful more generally for conversion of protoberberine into protopine alkaloids. Moreover, the present success provides a straight-forward and sophisticated total synthesis of 3,9,10-substituted 5,6,7,8,13,14-hexahydrodibenz(c,g)azecine derivatives or 3,9,10-substituted 14-deoxoprotopine alkaloids, since the 3,9,10-substituted tetrahydroprotoberberine (**1g**) was also synthesized in a straight-forward manner according to the method described in the previous paper.[1] Methodologically, we introduced for the first time the cyclopropyl methyl group as a new and useful protecting group for a phenolic function.

Experimental

All melting points are uncorrected and were taken on a Yanagimoto micro melting point apparatus. Infrared (IR) spectra were recorded on a Hitachi spectrophotometer Model EPI-G3 or a JASCO Model IR-S. Nuclear magnetic resonance (NMR) spectra were measured with a Varian A-60 or Varian T-60 spectrometer using $(CH_3)_4Si$ as an internal standard. Solvents were removed with a rotary evaporator under water-aspirator pressure. Extracts were dried over sodium sulfate or magnesium sulfate.

Hoffman Degradation of 4a——A mixture of 3-benzyloxy derivatives (**1a**, 100 mg), methyl iodide (0.4 ml), dry MeOH (1.5 ml) and dry benzene (1 ml) was allowed to stand overnight at room temperature, then concentrated *in vacuo* to dryness. The residue was dissolved in MeOH (1.5 ml) and treated with silver oxide prepared from silver nitrate (85 mg), with refluxing for 20 min. The precipitate was filtered off and washed with MeOH. The filtrate was evaporated to dryness and dry DMSO (1 ml) was added. The mixture was allowed to stand for 20 min at room temperature, poured into ice water, and extracted with benzene and CH_2Cl_2 to give a residue (102 mg). A solution of the residue in dry THF (2 ml) and dry *t*-BuOH (0.2 ml) was added to liquid ammonia (12 ml) containing lithium (60 mg) at −73° and the mixture was stirred for 1.5 hr. Evaporation of ammonia, addition of NH_4Cl solution and extraction with CH_2Cl_2 gave a crude

product (66 mg). Separation of the product by preparative TLC gave crude **2a** (23 mg, 36%) and crude **5** (24.5 mg, 39%).

3-Benzyloxy-9,10-dimethoxy-14-hydroxy-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine-7-carbonitrile (6a)——A mixture of quinolizine **6a** (400 mg, 1 mmole), BrCN (227 mg, 2.14 mmoles), MgO (86 mg, 2.14 mmoles), THF (30 ml), and H_2O (10 ml) was heated to 40—45° with stirring. After 3 hr, BrCN (222 mg, 2.09 mmoles) and MgO (84 mg, 2.09 mmoles) were added to the mixture, which was heated at 40—45° for a further 2 hr until **1a** had disappeared on TLC. After cooling, a solid was filtered off and washed well with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2. A usual work-up gave a crystalline residue (440 mg). Recrystallization from ether–acetone gave crystals (372 mg, 84%), mp 176—177°. *Anal.* Calcd. for $C_{27}H_{28}O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 73.00; H, 6.30; N, 6.37. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2240 (CN), 1610, 1585. NMR δ ($CDCl_3$): 3.83, 3.90 (each 3H, s, OCH_3), 4.63, 4.87 (1H, d, C_{14}–H), 5.03 (2H, s, $-CH_2Ph$), 7.33 (5H, s, $-CH_2C_6H_5$).

9,10-Dimethoxy-3-methoxymethoxy-14-hydroxy-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine-7-carbonitrile (6f)——A mixture of **1f** (5.00 g, 14.1 mmoles), BrCN (5.253 g, 49.56 mmoles) and MgO (2.06 g, 49.56 mmoles), THF (260 ml), and H_2O (170 ml) was warmed with stirring to 40—50°. After 3 hr, BrCN (2.573 g, 25 mmoles) and MgO (0.98, 25 mmoles) were added to the mixture, and heating was continued for 1 hr. Work-up as described above afforded a crystalline residue, which was recrystallized from ether–acetone to give crystals (4.75 g, 88%), mp 153—155°. *Anal.* Calcd. for $C_{22}H_{26}O_5N_2$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.02; H, 6.52; N, 7.29. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2425 (CN), 1610, 1585. NMR δ ($CDCl_3$): 3.40 (3H, s, CH_2OCH_3), 3.77, 3.82 (each 3H, s, OCH_3), 4.67, 4.88 (1H, d, C_{14}–H), 3.07 (2H, s, OCH_2OCH_3).

Hydrogenolysis of Compound (6a)——A solution of **6a** (80 mg) in AcOH (10 ml) and conc. HCl (1ml)was hydrogenated over PtO_2 (80 mg) for 7 hr at atmospheric pressure. After **6a** had disappeared on thin-layer chromatography (TLC) (silica gel/CH_2Cl_2: MeOH=9: 1), CH_2Cl_2 was added to the reaction mixture, and the resulting precipitate was filtered off and washed well with CH_2Cl_2. The filtrate and the washing were combined, washed with water, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to give a residue (60 mg), which was subjected to preparative TLC (silica gel/CH_2Cl_2: MeOH=9: 1). Two main factors were separated. The less polar fraction was an oil (15 mg), the structure of which was assumed to be a compound reduced on an aromatic ring, because of the presence of many methylene protons in the NMR spectrum and no hydroxyl group in the IR spectrum. The more polar fraction was also an oil (22 mg); its IR spectrum indicated the presence of the hydroxyl group. To a solution of this polar fraction (22 mg), in dry DMF, a 50% NaH dispersion (8 mg) and $PhCH_2Br$ (30 mg) were added. The mixture was allowed to stand overnight at room temperature with stirring. The usual work-up afforded a residue (40 mg), which was separated into two fractions by preparative TLC (silica gel/CH_2Cl_2 only). A less polar substance was obtained as an oil (15 mg), which was assumed to be **7a**. A more polar one was also obtained as an oil (80 mg), the structure of which was not determined.

Diborane Reduction of 6a——A 1M solution of diborane in dry tetrahydrofuran (THF) (1.5 ml, 1.5 mmoles) was added to a mixture of the N-CN compound **6a** (444 mg, 1 mmole) in dry THF (8 ml) at −60°, followed by dropwise addition of a solution of boron trifluoride etherate (426 mg) in dry THF (2 ml). After stirring for 2.5 hr, a diborane-THF solution (1.5 ml, 1.5 mmoles) was added. The reaction mixture was stirred for 3.5 hr while the reaction temperature was slowly raised from −60° to room temperature. The THF was removed and the residual mixture was treated with boiling MeOH (5 ml) for 2 hr, neutralized with aqueous ammonia and extracted with CH_2Cl_2 to give a crude product (416 mg) which was purified by silica gel chromatography. The fraction (174 mg, 41.73%) from benzene was recrystallized from ether to give the N-CH_3 compound **2b** (132 mg), mp 99—104°, which was identified by IR, NMR, and TLC with an authentic sample (mp 102—104°). The fraction (82 mg, 20.45%) from benzene–CH_2Cl_2 was recrystallized from ether to give **1a** (64 mg), mp 152—155°.

Hydrolysis of 3-Benzyloxy Compound (2b)——A solution of the 3-benzyloxy compound **2b** (126 mg, 0.3 mmole) in conc. HCl–MeOH (1: 1, 6 ml) was refluxed for 1 hr, followed by cooling, addition of aqueous ammonia, and extraction with CH_2Cl_2. The residue from the extracts was recrystallized from ether to obtain **2a** (90 mg, 91.8%), mp 136—138°.

3-Benzyloxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo(a,g)quinolizine N-Methiodide (4a)——A mixture of the 3-benzyloxy compound **1a** (1.002 g, 2.5 mmoles), methyl iodide (3 ml), and dry MeOH (20 ml) was refluxed for 2 hr. Removal of methyl iodide and MeOH gave the residue, which was recrystallized from MeOH to give N-methiodide **4a** (1.263 g, 93%), mp 212—215°. *Anal.* Calcd. for $C_{27}H_{30}O_3NI$: C, 59.67; H, 5.56; N, 2.58; I, 23.36. Found: C, 59.43; H, 5.62; N, 2.52; I, 23.34.

6-Hydroxy-2-methyl-1-(6-methyl-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (8)——To a suspension of methiodide **4a** (99 mg, 0.2 mmoles) in liquid ammonia (20 ml), a mixture of 50% NaH dispersion (10 mg) and dry THF (4 ml) was added. Lithium (28 mg, 4 mmoles) was added over a period of 30 min at −78°. After addition of NH_4Cl and evaporation of ammonia, the reaction mixture was extracted with CH_2Cl_2 in the usual way. The resulting product was crystallized from AcOEt to give an isoquinoline derivative **8** (52 mg, 80%), mp 147—148°, which was identified with an authentic sample (mp 151—154°) by IR and TLC.

9,10-Dimethoxy-3-methoxymethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo(a,g)quinolizine (1f)——The hydrogen chloride salt of the 3-hydroxy derivative **1b** (1.391 g, 4 mmoles) was added slowly to a suspension of 50% NaH dispersion (480 mg, 10 mmoles) in dry DMF (6 ml) and the resulting mixture was stirred for 30 min at room temperature. Methoxymethyl chloride (484 mg, 6 mmoles) in dry THF (5 ml) was added dropwise with ice-cooling. The reaction mixture was stirred for 1.5 hr at room temperature, treated with ice to dceompose the excess NaH, and extracted with ether. The ether extracts were washed with an alkaline solution and water, dried, and evaporated. The residue was crystallized from ether to give the 3-methoxymethyloxy derivative **1f** (1.34 g, 95.32%), mp 110—112°. NMR δ ($CDCl_3$): 3.47 (3H, s, $-CH_2OCH_3$), 3.83 (6H, s, $OCH_3\times 2$), 5.13 (2H, s, $-OCH_2-$). *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.58; H, 7.21; N, 3.72.

N-Methiodide of Compound (1f)——This methiodide was prepared in the same way as the 3-benzyloxy derivative **4a**, in 92.06% yield, mp 210—225°. *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.12; H, 5.67; N, 2.82; I, 25.51. Found: C, 52.85; H, 5.46; N, 2.56; I, 25.65.

Lithium-liquid Ammonia Reduction of N-Methiodide 4f——Lithium (70 mg, 10 mmoles) was dissolved in a mixture of liquid ammonia (45 ml) and dry THF (3 ml) at −78°, powdered compound **1f** (500 mg, 1 mmole) was added, and the reaction mixture was stirred for 15 min. After addition of NH_4Cl and evaporation of ammonia, the residue was extracted with ether. The usual work-up gave an oil (367 mg), which was heated with 5% HCl solution (20 ml) at 70° for 1 hr. After being neutralized with aqueous ammonia, the mixture was extracted with CH_2Cl_2, followed by the usual work-up, to give a brown oil (335 mg), which was separated by SiO_2 chromatography. The fraction (167 mg, 51.07%) from benzene–AcOEt (9: 1) was converted to the HCl salt of (165 mg, 45.33%), mp 228—234° (decomp.), and identified with an authentic sample of the HCl of salt of **2a** by IR, NMR, and TLC. The fraction (87 mg, 26.6%) from benzene–AcOEt (3: 2) was recrystallized from ether to obtain **8** (81 mg, 24.78%), mp 148—150°, which was identified with an authentic sample by IR.

9,10-Dimethoxy-3-methoxymethoxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (2c)——The above reduction was performed on **4f** and the reaction mixture was purified by preparative TLC without treated with 5% HCl to give the 3-methoxymethoxy compound **2c** (57 mg, 51.35%), mp 98—98.5°. NMR δ ($CDCl_3$): 2.07 (3H, s, $N-CH_3$), 3.42 (3H, s, $-CH_2OCH_3$), 5.08 (2H, s, $-OCH_2O-$), 3.77 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.90 (2H, s, $-N-CH_2-Ar$). *Anal.* Calcd. for $C_{22}H_{29}O_4N$: C, 71.13; H, 7.87; N,3.77. Found: C, 70.13; H, 7.69; N, 3.80.

Demethylation of 1f——Method A (by lithium *n*-propylmercaptide): An HMPT solution (8 ml) of lithium *n*-propylmercaptide (0.489 mmole, 1 ml) prepared as described in literature,[8] was added to a solution of **1f** (711 mg, 2 mmoles) in dry THF (8 ml). The reaction mixture was heated at 100° for 6 hr, cooled, mixed with NH_4Cl and extracted with ether. Evaporation gave a brown oil which was separated by preparative TLC to yield 448 mg (57.07%) of the 9-hydroxy compound **11** and 96 mg (12.23%) of the 10-hydroxy compound **12**.

9-Hydroxy-3-methoxymethoxy-10-methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo(a,g)quinolizine (11)——mp 125—128°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3535, NMR δ ($CDCl_3$): 3.47 (3H, s, $-OCH_2OCH_3$), 3.83 (3H, s, $-OCH_3$), 5.13(2H,s, $-OCH_2O-$). *Anal.* Calcd. for $C_{20}H_{23}ON_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.39; H, 6.70; N, 3.99.

10-Hydroxy-3-methoxymethoxy-9-methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo(a,g)quinolizine (12)——mp 142—146°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3535. NMR δ ($CDCl_3$): 3.47 (3H, s, $-OCH_2OCH_3$), 3.76 (3H, s, $-OCH_3$), 5.13 (2H, s, $-OCH_2O-$). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.74; N, 4.48. Found: C, 70.29; H, 6.74; N, 4.48.

Method B (by sodium ethylmercaptide): Ethanethiol (625 mg, 10 mmoles) dissolved in dry DMF (10 ml) was added to a suspension of 50% NaH dispersion (480 mg, 10 mmoles) in dry DMF (5 ml) under an atmosphere of nitrogen. The mixture was stirred for 5 min before a solution of **1f** (658 mg, 1.85 mmoles) in dry DMF (5 ml) was added. The resulting solution was then heated at 100° for 3 hr, cooled, treated with aqueous NH_4Cl solution, and extracted with ether. The ether solution was washed with water, dried, and evaporated to give a brown oil (604 mg), which was separated by preparative TLC to yield 410 mg (64.87%) of the 9-hydroxy compound **11** and 41 mg (6.94%) of the 10-hydroxy compound **12**.

9-Benzyloxy-3-methoxymethoxy-10-methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo(a,g)quinolizine N-Methiodide (14)——A solution of the 9-hydroxy compound **11** (409 mg, 1.2 mmoles) in dry DMF (2 ml) was added to a suspension of 50% NaH dispersion (75 mg, 1.5 mmoles) in dry DMF (2 ml). The reaction mixture was stirred for 15 min before a solution of benzyl bromide (257 mg, 1.5 mmoles) in dry THF (1 ml) was added with ice-cooling. The mixture was stirred for 3 hr at room temperature. The excess NaH was decomposed and extraction with ether in the usual manner gave 496 mg of a yellowish oil, NMR δ ($CDCl_3$): 3.47 (3H, s, $-OCH_2-OCH_3$), 3.83 (3H, s, OCH_3), 5.00 (2H, s, OCH_2Ar), 5.13 (2H, s, $-OCH_2O-$). A solution of this oil (302 mg, 0.7 mmole) and methyl iodide (2 ml) in MeOH (4 ml) was refluxed for 2 hr. Treatment by the usual method and recrystallization from ether gave 353 mg (88.03%) of pure N-methiodide **14**, mp 139—159° (decomp.). *Anal.* Calcd. for $C_{23}H_{32}O_4NI$: C, 58.64; H, 5.62; N, 2.44; I, 22.13. Found: C, 58.32; H, 5.70; N, 2.48; I, 22.89.

9-Hydroxy-3-methoxymethoxy-7-methyl-10-methoxy-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (15)——Lithium (28 mg, 4 mmoles) was dissolved into a stirred mixture of dry THF (4 ml) and distilled liquid ammonia

(20 ml) at −78°. Powdered N-methiodide (229 mg, 0.4 mmole) was added at once. The reaction mixture was stirred for 15 min, and treated with NH_4Cl. The ammonia evaporated and the residue was extracted with CH_2Cl_2 in the usual way. The crude product was chromatographed to remove colored materials and recrystallized from ether to give 101 mg (70.63%) of pure 9-hydroxy compound **15**, mp 98—99°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3535. NMR ($CDCl_3$) δ ppm: 2.40 (3H, s, N-CH_3), 2.78 (4H, bs), 3.03 (4H, bs), 3.43 (3H, s, -OCH_2-OCH_3), 3.77 (3H, s, OCH_3), 3.87 (2H, s, -NCH_2Ar), 5.07 (2H, s, -OCH_2O-). This compound **15** was identified with an authentic sample whose structure was confirmed by another member of our laboratory, as described in the following Chart 9.

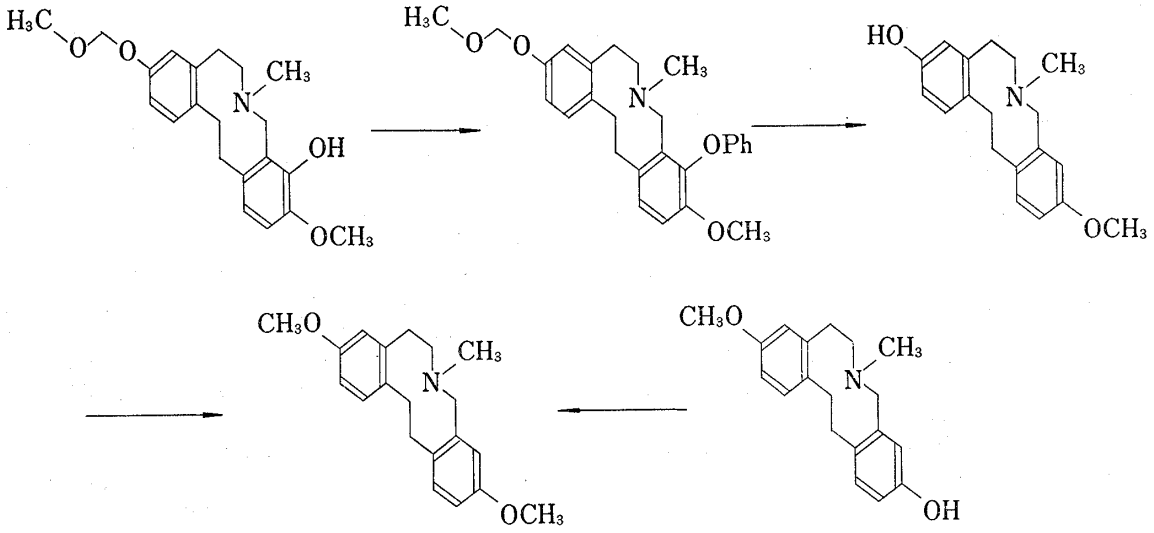


Chart 9

9,10-Dimethoxy-3-methoxymethoxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (2c)——The 9-hydroxy compound **15** (89 mg, 0.25 mmole) was added to a suspension of 50% NaH dispersion (15 mg, 0.3 mmole) in dry DMF (2 ml). After stirring for 15 min, a solution of methyl iodide (43 mg, 0.3 mmole) in dry THF (1 ml) was added dropwise and the stirring was continued for 1 hr at room temperature. Extraction with ether in the usual way and crystallization of a crude product (85 mg) from ether gave the 9,10-dimethoxy compound **2c** (78 mg, 83.87%), mp 98—99°, which was identified by IR, NMR, and TLC with an authentic sample obtained from **4f**.

Hydrolysis of the 3-Methoxymethoxy Derivative 2c——A solution of the 3-methoxymethyloxy compound **2c** (93 mg, 0.25 mmole) in 5% HCl–MeOH (10 ml) was refluxed for 2 hr. The reaction mixture was extracted with CH_2Cl_2 after adding aqueous ammonia. The CH_2Cl_2 extract was crystallized from ether to obtain the target **2a**, 74 mg (88.1%), mp 136—138°.

3-Methoxymethoxy-benzaldehyde (17)——A solution of *m*-hydroxybenzaldehyde (10 g, 0.082 mole) in dry DMF (70 ml) was added to 50% NaH-oil (7.86 g, 0.164 mole), the oil being removed by washing twice with petroleum ether, and the mixture was stirred at room temperature for 1 hr. A solution of $ClCH_2OCH_3$ (13.12 g, 0.164 mole) in dry THF (30 ml) was added dropwise to the mixture over a period of 1 hr. The reaction was carried out at room temperature with stirring for 1 hr, then the mixture was diluted with water and extracted with ether. The ether extract was washed with water and dried. Evaporation of the solvent *in vacuo* yielded a crude product which was purified by distillation. Yield of **17** (10 g, 70%), bp 88—90°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1595, 1705.

3-Methoxymethoxy-β-nitrostylene (18)——A mixture of **17** (16 g), $AcONH_4$ (4.0 g), CH_3NO_2 (32 ml) and abs. EtOH (200 ml) was refluxed with stirring for 1 hr. The mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried. Evaporation of the solvent *in vacuo* yielded a crude product which was purified by preparative TLC to give a pure oil **18** (3.55 g).

3-Methoxymethoxy-β-phenethylamine (19)——To a mixture of $LiAlH_4$ (2 g) and dry THF (30 ml), a solution of **18** (3.5 g) in dry THF (15 ml) was added with stirring under ice-bath cooling, then the mixture was refluxed with stirring for 1.5 hr. After cooling, the excess $LiAlH_4$ was decomposed by adding water, and the mixture was diluted with CH_2Cl_2. The resulting solid was filtered off and washed well with CH_2Cl_2. The filtrate and CH_2Cl_2 washings were combined and washed with 2N NaOH and H_2O and dried. Evaporation of the solvent *in vacuo* yielded a crude oil (3.0 g) which was purified by distillation to give **19** (1.38 g, 45%), bp 100—103°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1590. NMR δ ($CDCl_3$): 1.27 (2H, s, -NH_2), 2.53—3.18 (4H, m, -CH_2-CH_2N-), 3.50 (3H, s, OCH_3), 5.18 (2H, s, CH_2OCH_3), 6.90 (4H, broad, aromatic proton).

N-(3-Methoxymethoxyphenethyl)-3-benzyloxy-2-hydroxymethyl-4-methoxyphenylacetamide (21)——A solution of lactone **20** (1.800 g, 6.34 mmoles) and amine **19** (1.34 g, 7.61 mmoles) in abs. MeOH (12 ml) was

refluxed with stirring for 19 hr. The reaction was monitored by TLC (silica gel/CH_2Cl_2=97: 3). After the MeOH had been evaporated *in vacuo*, the resulting residue was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed twice with water, and dried over anhyd. Na_2SO_4. Evaporation of the solvent *in vacuo* yielded a crude oily product which was purified by preparative TLC (silica gel/CH_2Cl_2: MeOH=95: 5) to give **21** as an oil (1.95 g). The oil was directly subjected to Bischler-Napieralski reaction, but a cyclic product **13** was not obtained.

3-Cyclopropylmethoxy-benzaldehyde (**22**)——To a suspension of *t*-BuOK (11.22 g, 0.1 mole) in dry DMF (40 ml), benzaldehyde (**16**; 12.21 g, 0.1 mole) in dry THF (100 ml) was added with ice-water cooling over a period of 20 min. After stirring for an addition 10 min, cyclopropylmethyl bromide 14.85 g (0.11 mole) in dry THF (5 ml) was added over a period of 20 min at room temperature. The mixture was heated at 40—45° with stirring for 3 hr. Next, an additional portion of bromide (2.70 g, 0.02 mole) was added, and heating at 40—45° with stirring was continued for 3 hr.

The reaction mixture was treated with ice-water and extracted with ether. The ether extracts were washed with 2N KOH solution and water, dried, then the solvent was removed. The residual oil was distilled through a 15-cm Vigreux column to give 12.96 g (78.9%) of **22**, bp 103—107°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2750, 1700, NMR δ ($CDCl_3$): 0.6 (4H, m), 1.13 (1H, m), 3.93 (2H, d, J=7 Hz), 9.97 (1H, s, –CHO).

3-Cyclopropylmethoxynitrostylene (**23**)——A mixture of benzaldehyde **22** (0.03 g, 0.055 mole), ammonium acetate (4.625 g, 0.06 mole), nitromethane (27 ml), and acetic acid (36 ml) was refluxed for 1.5 hr. The reaction mixture was mixed with water and extracted with CH_2Cl_2. The extracts were washed with water, dried, and concentrated *in vacuo* leaving an oily product. Recrystallization from boiling ethanol gave 8.21 g (68.15%) of pure nitrostylene **23**, mp 60—61°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1580, 1345. NMR δ ($CDCl_3$): 0.73 (4H, m), 1.27 (1H, m), 3.83 (2H, d, J=7 Hz), 7.50, 7.97 (2H, ABq, J=14 Hz). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.98; H, 6.02; N, 6.37.

3-Cyclopropylmethoxyphenethylamine (**25**)——A solution of nitrostylene **23** (7.892 g, 0.036 mole) in 40 ml of dry THF was added dropwise to a stirred suspension of $LiAlH_4$ (4.099 g, 0.108 mole) in dry THF (120 ml) over a period of 1 hr. The mixture was then stirred for 1.5 hr, refluxed for 1 hr and cooled. The excess $LiAlH_4$ was decomposed by cautious addition of wet THF to form a filterable cake. This was filtered off and washed well with dry ether. The combined filtrate and washing was concentrated to 50 ml. After addition of water and extraction with CH_2Cl_2. The CH_2Cl_2 extracts were washed, dried and evaporated to obtain an oil. To a solution of this oil in dry EtOH (10 ml), an anhydrous saturated hydrogen chloride–ether solution was added with ice-cooling. The precipitate was collected washed with dry ether, and dried over KOH pellets to give the amine hydrochloride **25** 4.177 g (50.95%), mp 160—161°.

3-Cyclopropylmethoxymandelonitrile Ethyl Carbonate Ester (**24**)——To a stirred mixture of benzaldehyde (1.76 g), EtOH (10 ml), ethyl chloroformate (1.357 g), $MgSO_4$ (1.504 g), and water (5 ml), KCN (0.98 g) in water (2.5 ml) was added at 0°. After stirring for 3 hr at 0°, water was added and the mixture was extracted with ether. The ether extracts were washed with water, 10% NaOH solution, 30% $NaHSO_3$ solution, then water. Drying and removal of the solvent gave 2.73 g of crude carboethoxymandelonitrile **24**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750.

Catalytic Reduction of 24——To a solution of **24** (413 mg) in AcOH (2 ml), 5% Pd-C (300 mg) and conc. H_2SO_4 (0.12 ml) in acetic acid (3 ml) were added.

Hydrogen gas was applied under 2—3 atm over a period of 2 hr. The filtrate was acidified with 50% KOH and K_2SO_4 was filtered off. The filtrate was concentrated *in vacuo*, made alkaline with aqueous ammonia and then extracted with ether. The extracts were dried, concentrated to a half volume, and saturated with dry hydrogen chloride at 0°. Evaporation of the ether gave a residue, which was treated with acetone to yield 227 mg (66.9%) of amine hydrochloride **25**, mp 160—162°.

N-(3-Cyclopropylmethoxyphenethyl)-3-benzyloxy-2-hydroxymethyl-4-methoxyphenylacetamide (**27**)——A solution of lactone **26** (2.274 g, 8 mmoles) and amine **25** from its hydrochloride (2.05 g) in dry EtOH (6 ml) was refluxed for 18 hr. The EtOH was evaporated and the residue was extracted with CH_2Cl_2. The extracts were washed with 2N HCl nad water, dried, and evaporated to give 3.75 g of crude product. The crude product was purified by short-column chromatography on neutral Al_2O_3, and crystallization from ether to give 3.041 g (79.94%) of acetamide **27**, mp 67—68°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR δ ($CDCl_3$): 0.5 (4H, m), 1.20 (1H, m), 4.60 (2H, bs, $-CH_2OH$), 5.07 (2H, s, $-OCH_2Ar$). *Anal.* Calcd. for $C_{29}H_{33}O_5N$: C, 73.24; H, 7.00; N, 2.95. Found: C, 73.11; H, 6.72; N, 3.05.

9-Benzyloxy-3-cyclopropylmethoxy-10-methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo(a,g)quinolizine N-Methiodide (**28**)——A solution of acetamide **27** (1.902 g, 4 mmoles) and freshly distilled phosphorus oxychloride (0.9 ml, 10 mmoles) in dry $CHCl_3$ (20 ml) was heated under reflux for 3 hr. The reaction mixture was concentrated below 40° to 60 ml, mixed with MeOH (50 ml), and neutralized with aqueous ammonia under ice-cooling. $NaBH_4$ (6.054 g, 0.16 mole) was added during 15 min to the above reaction mixture. The resulting mixture was stirred for 5 hr at room temperature. After addition of water and filtration of the inorganic salt, the filtrate was extracted with CH_2Cl_2. The extracts were washed with water, dried, and evaporated to give 1.701 g of an oily product. Purification by short-column chromatography gave 1.553 g (87.94%) of liquid **1g**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2760 (Bohlmann band).

A mixture of 1.325 g (3 mmoles) of this compound **1g**, methyl iodide (6 ml), and MeOH (14 ml) was refluxed for 2.5 hr. Removal of methanol and methyl iodide, and crystallization from MeOH–ether gave 1.260 g (72%) of N-methiodide **28**, mp 196—198° (decomp.). *Anal.* Calcd. for $C_{30}H_{34}O_3NI$: C, 61.75; H, 5.87; N, 2.40; I, 21.75. Found: C, 61.53; H, 5.92; N, 2.60; I, 21.77.

3-Cyclopropylmethoxy-9-hydroxy-7-methyl-10-methoxy-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (29)——Lithium (70 mg, 10 mmoles) was added to a stirred solution of 10 ml of dry THF and distilled liquid ammonia (50 ml) at −78°. Powdered N-methiodide **28** (583 mg, 1 mmole) was added at once and the reaction mixture was stirred for 2.5 hr. Excess lithium was decomposed by adding NH_4Cl. Evaporation of the ammonia, extraction with CH_2Cl_2, and removal of the solvent gave a solid, which was recrystallized from ether to yield 334 mg (91%) of the 9-hydroxy derivative **29**, mp 118—119°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3525 (OH); NMR δ ($CDCl_3$): 2.43 (3H, s, N–CH_3), 2.80 (4H, bs), 3.07 (4H, bs), 3.70 (2H, s, –N$\underline{CH_2}$Ar), 3.83 (3H, s, –OCH_3), 3.87 (2H, d, J=7 Hz, –OCH_2–◁). *Anal.* Calcd. for $C_{23}H_{29}O_3N$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.91; H, 7.84; N, 4.11.

3-Cyclopropylmethoxy-9,10-dimethoxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (2d)——Trimethyl anilinium tosylate (768 mg, 2.5 mmoles) in MeOH (1 ml) was added to a sodium methoxide solution prepared from sodium (58 mg, 2.5 mmoles) and dry MeOH (1 ml). The reaction mixture was stirred for 1 hr at room temperature, cooled, and mixed with dry toluene (2 ml); the precipitate was collected. The filtrate was added to a solution of 440 mg (1.2 mmoles) of **29** in dry toluene (10 ml). MeOH was removed by distillation at 63—110°. The resulting mixture was refluxed for 2.5 hr, poured into water, and extracted with CH_2Cl_2. The extracts were washed with water, dried and evaporated. The resulting oil was mixed with EtOH and concentrated to remove dimethylaniline completely. Recrystallization from *n*-pentane gave 362 mg (79.04%) of pure dimethoxy compound **2d**, mp 106—109°. NMR δ ($CDCl_3$): 0.5 (4H, m), 1.27 (1H, m), 2.07 (3H, s, N–CH_3), 2.77 (4H, m), 2.93 (4H, m), 3.80 (8H, –CH_2–◁, –OCH_3×2). *Anal.* Calcd. for $C_{24}H_{31}O_3N$: C, 75.56; H, 8.19; N, 3.67. Found: C, 74.51; H, 7.93; N, 3.85.

9,10-Dimethoxy-3-hydroxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g)azecine (2a)——A solution of the 3-cyclopropylmethoxy derivative **2d** (191 mg, 0.5 mmole) in 8 ml of conc. HCl–MeOH (1: 1) was refluxed for 2 hr. The reaction mixture was extracted with CH_2Cl_2 after addition of aqueous ammonia. The resulting residue was crystallized from ether to obtain 154 mg (93.9%) of **2a**, which was identified with an authentic sample by TLC, IR, NMR, and mixed mp (137—138°).