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Synthetic Studies on Isoquinoline Alkaloids. I.* An Efficient Synthesis of 9,10-Substituted Protoberberine Alkaloids[1]

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Three synthetic routes leading to the 9,10-disubstituted tetrahydroprotoberberine derivative (**4a**) were investigated. The third route involving a four-step reaction sequence starting from homoisovanillinic acid (**13b**) afforded 3-benzyloxy-9,10-dimethoxy-tetrahydroprotoberberine (**4a**) in 65% over-all yield providing the most efficient and general synthesis of the hitherto not easily available 9,10-disubstituted protoberberine alkaloids. The key step in this synthesis was effective conversion of **13b** into the 7,8-disubstituted isochromanone derivative (**28b**) which required specific introduction of hydroxymethyl into the position *ortho* to the phenolic function in **13b**. This was nicely effected our newly discovered general method for *ortho*-(α-hydroxy)-alkylation of phenols using benzeneboronic acid.

In the course of degradation studies of protoberberine alkaloids, Sawa and his collaborators of this laboratory found that a series of the compounds derived from berberine hydrochloride (**1**) showed analgesic activity.[3] All of these pharmacologically active compounds were further shown to have a common skeleton of the hexahydrodibenzoazecine ring system, the skeleton corresponding to that involved in naturally occurring protopine alkaloids (**2**). Among these compounds, 9.10-dimethoxy-3-hydroxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz(c,g) azecine (**3**) was found to be most potent and of low toxicity. While its potency is as high as that of codeine according to tests by various assay methods including the hot plate, Haffner and

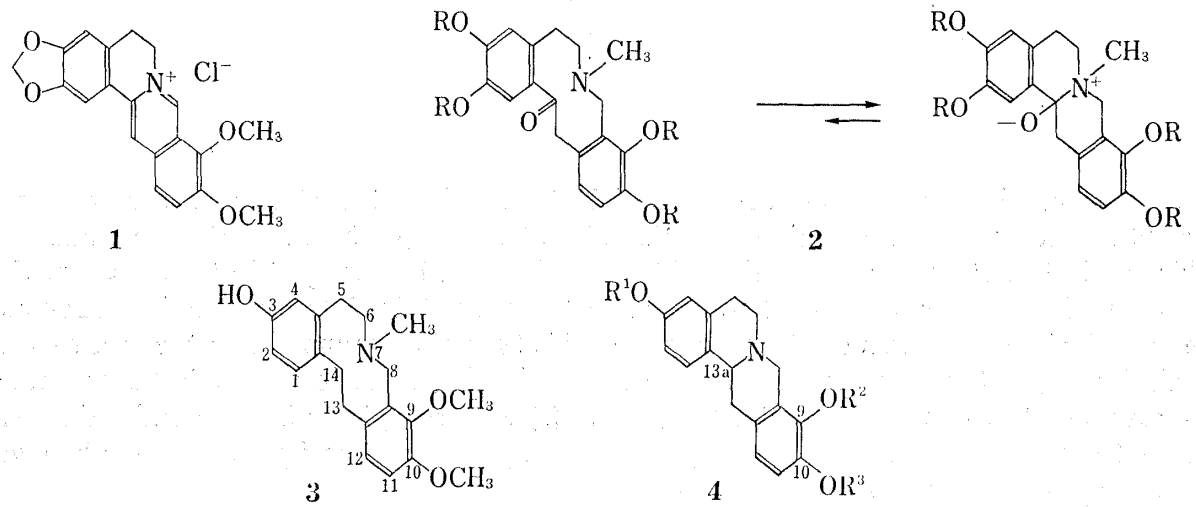

Chart 1

* Dedicated to the memory of Prof. Eiji Ochiai.

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

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3) Y. Sawa and S. Maeda, Japan Unexamined Patent 49-41386 and 49-41387 (1974).

Writhing methods, this compound was found to be non-narcotic as evidenced by almost no symptoms of addiction in the tested monkeys. Thus compound (3) has a possibility of being a unique non-narcotic analgesic based upon criteria of structure-pharmacological relations. In view of the failure of Sawa and his collaborators to find a straight-forward route to 3 starting from abundantly available berberine hydrochloride (1),[3] we decided to undertake a total synthetic study to enable us to reach the target compound (3) in a straight-forward and highly selective manner.

A broadly performed literature investigation and subsequent intensive speculative work led us to formulate the following synthetic schemes as general synthetic plans. In these formulations the 9,10-substituted tetrahydroprotoberberine derivative (4) was selected as a com-

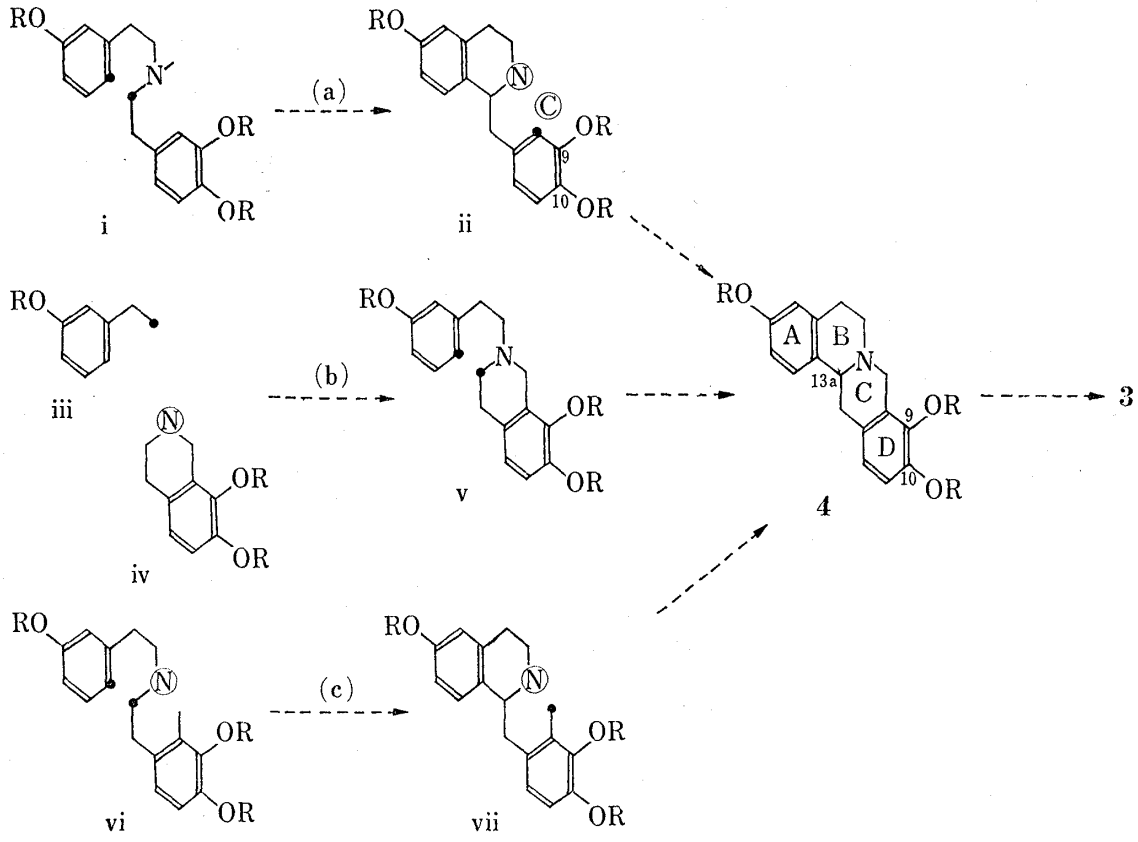


Chart 2

mon and major intermediate, although we anticipated that in further elaboration some difficulty would be encountered in selective reduction of 4 at the C_{13a}-N bond. Later we found that this was in fact the case and solution of this problem will be a subject in the accompanying paper.[4] Despite this difficulty, 4 was thought to be a suitable intermediate since abundant information[5] accumulated on the chemistry of this type of compounds over the past century make its preparation very easy; a number of routes leading to the intermediate 4 are recorded in literature.[5] Among these routes (a), (b) and (c) were thought to be most rational for the present purpose and worthy of investigation, although some *a priori* problems were involved commonly in these routes as discussed below.

The principal problem was how to introduce the four substituents *ortho* to each other on the future D ring of the starting material, *i.e.*, how to introduce one carbon fragment at the *ortho* position to the C_9–OR group in (ii), or how to selectively synthesize the C/D ring

4) W. Nagata, K. Okada, H. Itazaki, and S. Uyeo, *Chem. Pharm. Bull.* (Tokyo), 23 2878 (1975).
5) See for example, M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N.Y., 1972, p. 268.

moiety in the intermediate (iv) or (vi) from appropriate starting materials such as homoisovanillinic acid or *ortho*-vanillin. Literature inspection revealed that, in view of the abundant occurrence of 9,10-substituted protoberberines in nature, this problem had already been intensively tackled by many authors but still remained only incompletely solved.[5] For example, Battersby and his students[6] and, a little later, Kametani and his school[7] reported that product ratios in Pictet-Spengler cyclization of the type (ii) compound giving 9,10- and 10,11-substituted tetrahydroprotoberberine derivatives varied with varying pH of the medium, when the C_9-substituent is a free phenol. Thus, norreticuline (**5**) afforded scoulerine

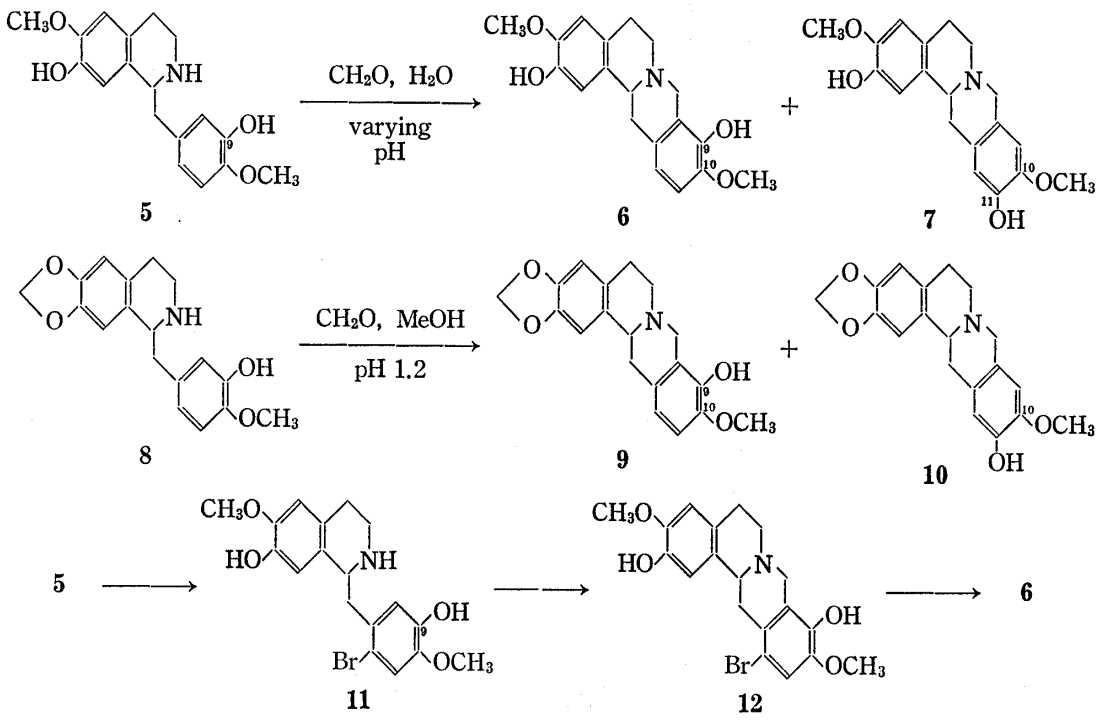


Chart 3

(**6**) and coreximine (**7**) in the ratio of 2:1 at pH 6.3, while it gave coreximine (**7**) as a sole product at pH 7. Furthermore, Kametani and his collaborators[8] showed that in the Pictet-Spengler reaction of **8** as much as 71% of nandinine (**9**) was obtained when the pH of the reaction medium was adjusted to 1.2. Thus, considerable improvement was achieved in controlling the product ratio, but this achievement was thought to be still unsatisfactory particularly because tedious chromatographical separation from the accompanying isomer (**10**) was necessary.

Another device for avoiding the non-selectivity in the Pictet-Spengler cyclozation was reported by Kametani and his students.[9] Norreticuline (**5**) was first brominated selectively at the *para* position to the C_9–OH group yielding the bromophenol intermediate (**11**), which was subjected to Pictet-Spengler cyclization giving the single product (**12**). Removal of the bromine by lithium aluminum hydride reduction yielded the desired 9,10-substituted product, scoulerine (**6**). Although this route required an additional two steps, it seemed to us that a similar elaboration was worth following if each step proceeds smoothly. In the following we describe the preliminary results of work performed along this line (route a).

6) A.R. Battersby, R. Southgate, J. Staunton, and M. Hirst, *J. Chem. Soc.* (*C*), **1966**, 1052.
7) T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.*, (*C*), **1968**, 112.
8) T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi, *J. Chem. Soc.* (*C*), **1971**, 2709.
9) T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), **1967**, 530.

Methyl homoisovanillinate (**13a**) prepared by the known method[10] was first brominated to give the bromophenol **14** which underwent condensation of *m*-benzyloxyphenethylamine (**15**) giving the amide (**16a**) in 53% yield. This compound after benzoylation (**16b**) was subjected to Bischler-Napieralski condensation followed by sodium borohydride reduction giving tetrahydroisoquinoline (**17a**), which after alkali hydrolysis to (**17b**) underwent Pictet-Spengler cyclization yielding the tetracyclic intermediate (**18a**). This compound after methylation

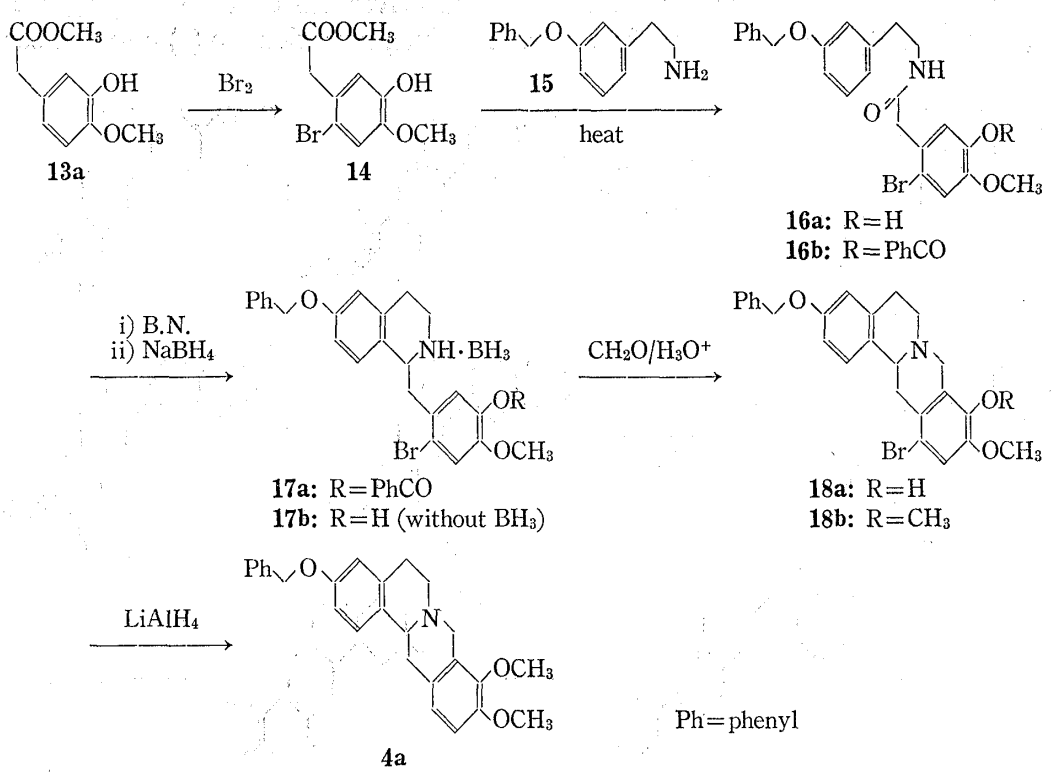


Chart 4

with diazomethane was debrominated with lithium aluminum hydride to give the final product (**4a**). As expected, this synthesis afforded no isomeric product in the Pictet-Spengler step, but unfortunately the over-all yield of **18a** was only 13% from the benzoylated amide (**16b**). This poor result was by no means satisfactory and may be ascribed to the alkali-sensitive bromophenol function involved in each intermediate. This approach was therefore abandoned and we turned to the second approach, *i.e.*, route (b).

Very recently, Schlademan and Partch[11] reported a unique synthesis of tetrahydroisoquinoline derivative. The method was based upon intramolecular Friedel-Crafts condensation of the N-tosylated acid chloride (**19**). The reaction was carried out specifically at low temperature in methylene chloride, giving the cyclized product (**20**) in almost quantitative yield. We transferred this technique to our synthesis as described next.

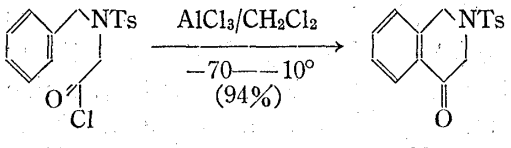


Chart 5

According to the method of Quitt, *et al.*,[12] *o*-vanillin methyl ether (**21**) was subjected to condensation with glycine followed by reduction with sodium borohydride giving the amino acid (**22a**) in 86% yield. This compound was then treated with tosylchloride under Schottenbauman conditions giving the tosylamide (**22b**)

10) R. Grewe and H. Fischer, *Chem. Ber.*, **96**, 1520 (1963).
11) J. Schlademan and R. Partch, *J. Chem. Soc., C*, **1972**, 213.
12) P. Quitt, J. Hellerbach, and K. Vogler, *Helv. Chim. Acta*, **46**, 327 (1963).

also in a high yield of 84%. This acid after chlorination with thionyl chloride underwent Friedel-Crafts condensation at −70° in methylene chloride, affording the desired tetrahydroisoquinolone derivative (**23**) in a yield as high as 86%, as expected. Treatment of this

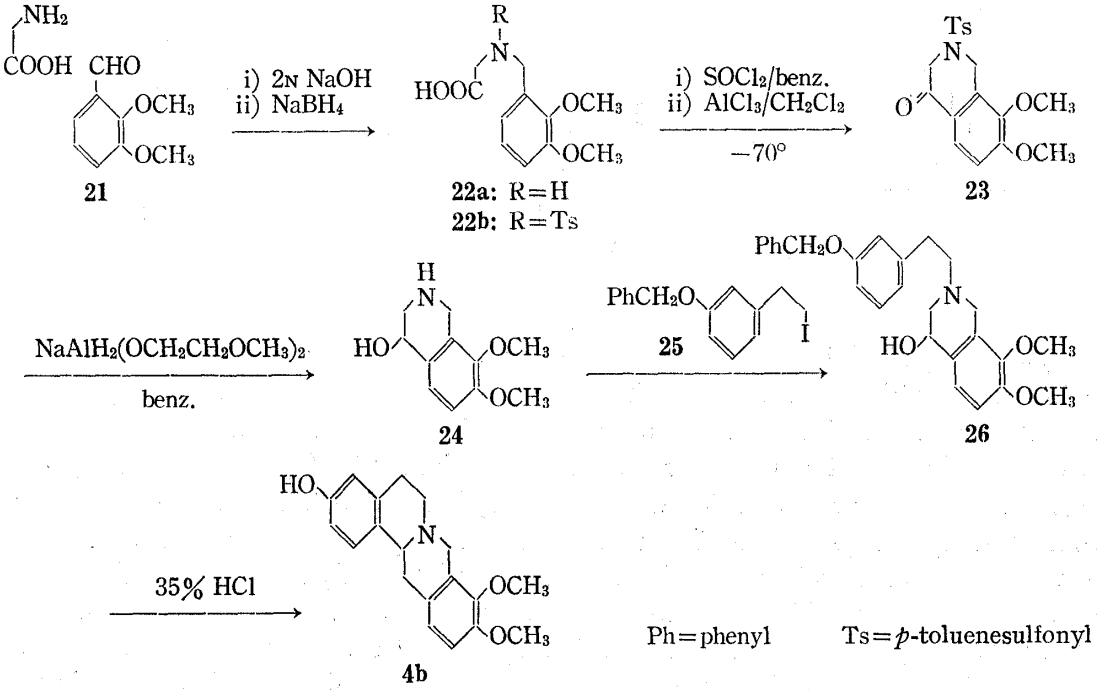


Chart 6

product with sodium bis-methoxyethoxyaluminum dihydride (Vitride) in benzene resulted in simultaneous reduction of both the tosylamide and the keto group giving the imino alcohol (**24**) in good yield. Selective phenethylation at the nitrogen was then carried out successfully with *m*-benzyloxyphenethyl iodide giving 84% of the intermediate (**26**). Finally, cyclization of this intermediate to the desired tetrahydroprotoberberine intermediate was effected by treatment with conc. hydrochloric acid after some unsuccessful attempts. It is noteworthy that this synthesis provided a new and useful synthetic route to protoberberine alkaloids generally. However, the yield of 30% in the final crucial step was low, although improvement of this step might be possible by optimizing the reaction conditions.

Before discussing the third route (route c) to the 9,10-substituted tetrahydroprotoberberine intermediate **4**, some methodological successes which enabled us to establish the most efficient synthesis of the present target molecule and more generally 9,10-substituted protoberberine alkaloids, should be referred to briefly.

In 1966, Battersby, *et al.*[6] published a notable synthesis of scoulerine which corresponds to route c in our general synthetic plan and is illustrated in Chart 7. The synthesis similarly involved a tricky step requiring *ortho*-arrangement of the four substituents in the future D ring. However, these authors wisely set this tricky step early in the synthesis in conformance to a general principle for total syntheses of complex natural products. Thus in their synthesis, 7-methoxy-8-hydroxyisochromanone (**28a**), the crucial intermediate, was first synthesized though in a poor yield of 15% by applying a sequence of two reactions, *i.e.*, Reimer-Tiemann formylation followed by sodium borohydride reduction. Application of the Reimer-Tiemann reaction for introduction of one carbon fragment specifically at the *ortho* position to the free hydroxy in **13b** was presumably due to the fact that the Mannich reaction frequently used for hydroxymethylation usually gives to *para*-substitution. Clearly, compound (**28a**) was recognized as a crucial intermediate, since 9,10-substitution was secured on the D ring of the derived tetrahydroprotoberberine. The subsequent conversions, *i.e.*, condensation with the

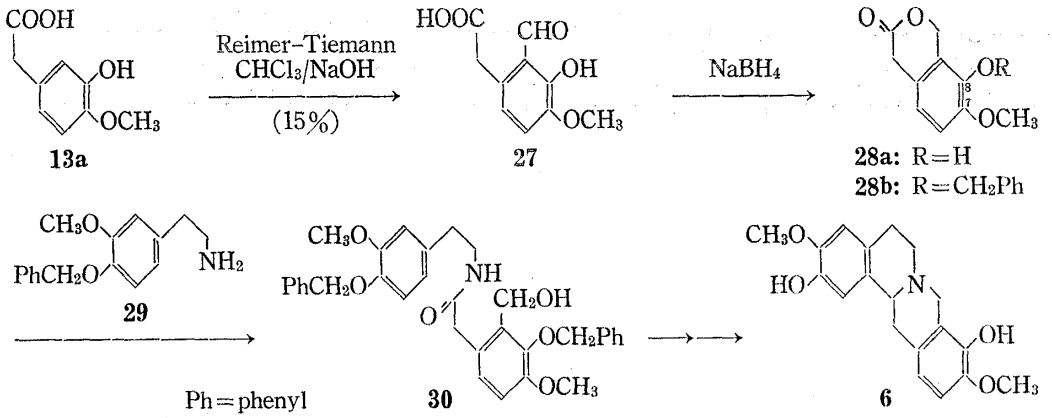


Chart 7

phenethylamine (**29**) giving the amide (**30**) and its Bischler-Napieralski cyclization followed by sodium borohydride reduction yielding scoulerine (**6**) proceeded well. Thus, the sequence of the reactions provided an efficient synthesis of this kind of alkaloid. However, their synthesis as it stands did not suit our purpose, since the yield of 15% in the first Reimer-Tiemann step was too low. Our investigation was, therefore, directed at finding a new efficient method for *ortho*-hydroxymethylation of **13b** and more generally a veriety of phenols.

Investigation of literature revealed that there existed only few methods for introducing one carbon fragment specifically *ortho* to a phenolic function. Among these, an attempted *ortho*-hydroxymethylation of phenol reported by Peer[13] drew our attention. The method involved reaction of phenol with formaldehyde in the presence of boric acid in refluxing benzene with azeotropic removal of the water giving saligenol (**32**) without any concomitant formation of *para*-substituted or *o,p*- bis- or tri-substituted products. In this reaction, Peer suggested an intermediary of the chelate transition state (**30**) which attained the state of the stable conjugate acid (**31**) as illustrated in Chart 8. Although the reaction was thus interesting mecha-

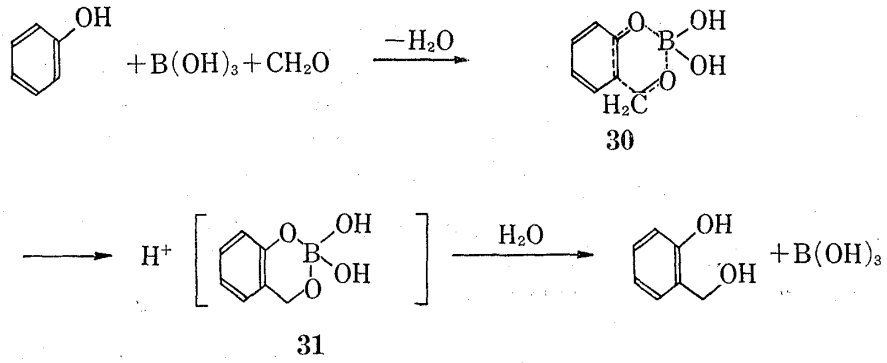
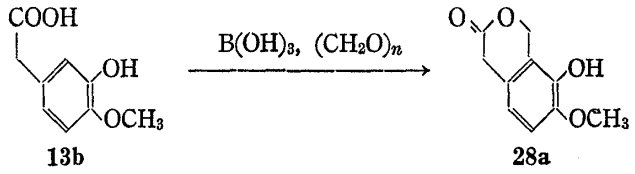


Chart 8

nistically, the yield of only 4% was by no means acceptable. Later, some variants increasing the yield of saligenol were reported in patent literature.[14] A yield of 65%, though with a low quality of the product, was obtained by changing the solvent from benzene to toluene[14a] and one of 50% by using ethylene glycol as a co-reagent.[14b] However, the procedures were essentially the same as that originally reported and there were no examples other than phenol. Therefore, applicability of these methods to more complex phenols was not known. In fact, when these procedures were applied to homoisovanillic acid, the yield of the expected (**28a**),

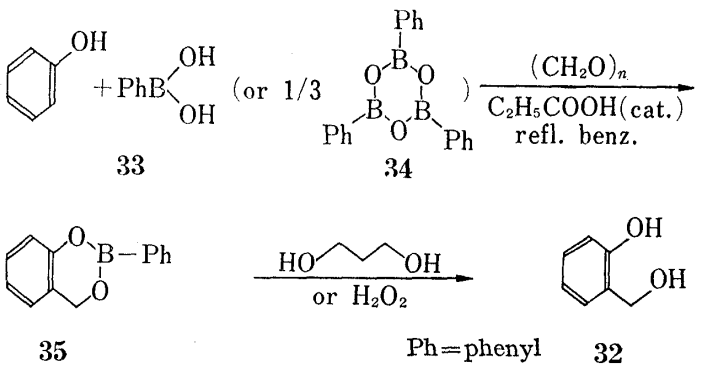
13) H.G. Peer, *Rec. Trav. Chim.*, **79**, 825 (1960).
14) *a*) P. Marchand and J.B. Grenet, Fr. Patent 1328945 (1963) [*C.A.* **60** P 2831e (1964)]; *b*) S. Kitamura, Japan Patent 47-34346 (1972) [*C.A.* **78** P 15773p (1973)].

which was actually formed gratifyingly by using toluene as solvent, never exceeded 15% even on several attempts. Needless to say, the yield was too low to pursue the synthesis further. Faced to this difficulty we had to improve the procedure substantially. In this situation, use of benzeneboronic acid instead of boric acid as a co-reagent seemed to be favorable, since benzeneboronic acid had higher Lewis acidity and higher solublity in aromatic hydrocarbons than boric acid and, moreover, a product like 2-phenyl-1,3,2-benzodioxaborin (**35**) would be stable towards further reactions. In fact, benzeneboronic acid was very effective when phenol was reacted with it and *para*-formaldehyde in the presence of a catalytic amount (0.1 mole) of propionic acid in refluxing benzene with simultaneous removal of the water formed. The product (**35**) was obtained in nearly quantitative yield. It should be pointed out that the reaction was extremely slow in the absence of propionic acid and the primary product formed in this case was phenylboroxine (**34**), which could be used as a co-reagent in the presence of propionic acid as well. Next, **35** was converted in an excellent yield of over 90% either by exchange reaction with propylene glycol or by oxidation with hydrogen peroxide. Further investigation determining the scope and limitation of this reaction showed that it works out very nicely with a number of substituted phenols and also a variety of aldehydes, regardless of their being aliphatic or aromatic. In this way, we succeeded in providing a new general method for *ortho*-(α-hydroxy)alkylation of phenols which we believe is very useful practically. The details of this method, scope and limitation and the probable reaction mechanism will be published elsewhere.



13b **28a**

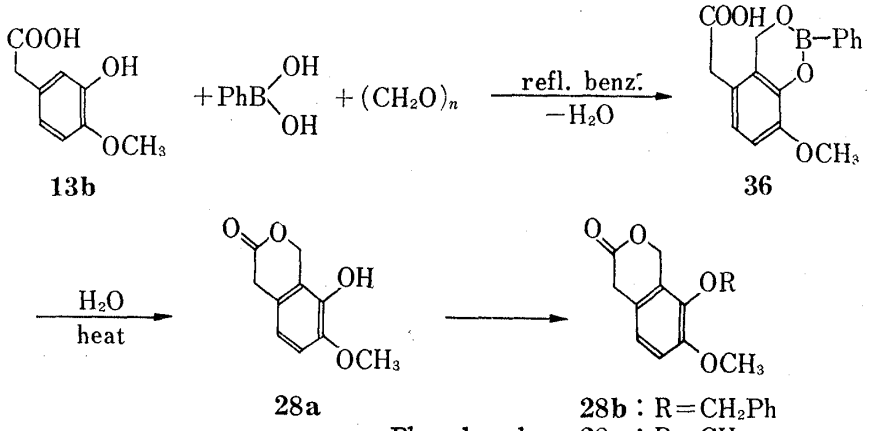
Chart 9



33 **34** **35** Ph=phenyl **32**

Chart 10

The new method was next applied to homoisovanillinic acid (**13b**). The reaction proceeded very efficiently even in the absence of propionic acid giving the expected product (**36**) in an excellent yield, which without isolation was treated with warm water to obtain **28a**. The over-all yield of **28a** was 83%. That no propionic acid was necessary in this case is easily



13b **36** **28a** Ph=phenyl **28b** : R=CH_2Ph **28c** : R=CH_3

Chart 11

understandable because homoisovanillic acid itself contains a carboxylic acid function. Next, **28a** was benzylated or methylated by conventional method to the corresponding ethers (**28b**) and (**28c**) in almost quantitative yield.

The final stage of the present synthesis was performed analogously to Battersby's synthesis.[6] The isochromanone dimethylether (**28c**) was condensed with *m*-benzyloxyphenethylamine in refluxing ethanol to give the amide (**37**) quantitatively, which then underwent Bischler-Napieralski cyclization followed by sodium borohydride reduction to give 3-benzyloxy-9,10-dimethoxytetrahydroprotoberberine (**4a**) in 82% yield. The over-all yield of this compound was now as high as 65% starting from homoisovanillinic acid (**13b**) *via* four steps. We believe that the sequence of reactions shown in Chart 11 and 12 provides the most efficient synthetic route yet to the hitherto not easily available 9,10-disubstituted tetrahydroprotoberberine alkaloids generally, which occur very widely in nature.

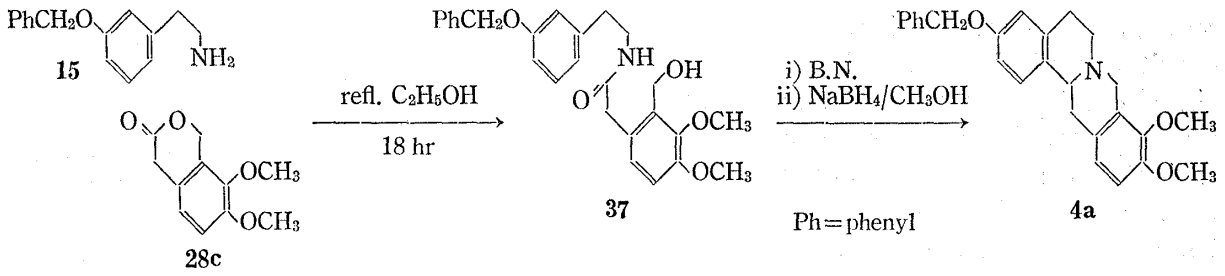


Chart 12

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. Removal of solvents was performed using a rotary evaporator under water-aspirator pressure. Extracts were dried over sodium sulfate or magnesium sulfate.

Methyl 2-Bromo-5-hydroxy-4-methoxyphenylacetate (14)——A mixture of carboxylic acid **13b** (10 g), 1,2-dichloroethane (30 ml), conc. H_2SO_4 (0.3 ml), and MeOH (12 ml) was refluxed for 4 hr. After cooling, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with saturated sodium bicarbonate solution, dried and evaporated. The residue (11.03 g) was dissolved in AcOH (130 ml), and a solution of bromine (3.3 ml) in AcOH (30 ml) was added dropwise over 4 hr at 13°. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with 2N NaOH solution, dried and evaporated. A part of the residue was recrystallized from ether–*n*-pentane to give a pure crystal (**14**), mp 97—99°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3536 (OH), 1738 ($-COOCH_3$). *Anal.* Calcd. for $C_{10}H_{11}O_4Br$: C, 43.66; H, 4.03. Found: C, 43.52; H, 3.85.

N-(3-Benzyloxyphenethyl)-3-hydroxy-6-bromo-4-methoxyphenylacetamide (16a)——Phenethylamine (870 mg, 3.84 mmoles) and bromoester (1.150 g, 4.18 mmoles) were heated at 120° for 4 hr. After cooling, the reaction mixture was mixed with $CHCl_3$, and washed with 2N HCl and 2N NaOH solution. The resulting residue (1.3 g) from the $CHCl_3$ layer was recrystallized from CH_2Cl_2–ether to give crystals (670 mg). A crude material from the mother liquor was purified by SiO_2 chromatography to obtain pure crystals (240 mg). The total yield of the crystals was 53%, mp 124—125°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3536 (OH), 3430 (NHCO), 1664 (NHCO). *Anal.* Calcd. for $C_{24}H_{24}O_4NBr$: C, 61.28; H, 5.14; N, 2.98. Found: C, 62.89; H, 5.34; N, 3.16.

N-(3-Benzyloxyphenethyl)-3-benzoyloxy-6-bromo-4-methoxy-phenylacetamide (16b)——A mixture of amide **16a** (240 mg), benzoyl chloride (88 μl) and dry pyridine (2 ml) was allowed to stand overnight. The reaction mixture was treated with five drops of water, allowed to stand for 2.5 hr, then extracted with ether–CH_2Cl_2 (2: 1). The extracts were washed with 2N HCl, water, 2N NaOH, and water, then dried and evaporated. The product was recrystallized from ether–CH_2Cl_2 to give pure crystals (271 mg, 92%), mp 117—119°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3433 (NHCO), 1745 (OCOPh), 1667 (NHCO).

3-Benzyloxy-9,10-dimethoxy-tetrahydroprotoberberine (4a)——A mixture of amide **16b** (320 mg), $POCl_3$ (0.4 ml), and dry benzene (8 ml) was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, made alkaline with saturated $NaHCO_3$ solution and extracted with ether–CH_2Cl_2 (2: 1). The residue (368 mg) was dissolved in a mixture of tetrahydrofuran (THF) (10 ml) and water (0.5 ml), then $NaBH_4$ (180 mg) was added over 1 hr. The resulting mixture was allowed to stand overnight, concentrated at room temperature extracted with CH_2Cl_2 in the usual way, then evaporated to obtain compound (**17a**) (326 mg). A mixture of this compound, 2N NaOH (2.5 ml), and MeOH (10 ml) was refluxed for 2 hr, concentrated *in vacuo*, made

alkaline with saturated NH_4Cl solution, and extracted with $CHCl_3$–MeOH (9: 1) to give combound **17b** (270 mg). A mixture of crude **17b** (260 mg), 37% formalin (5 ml), water (5 ml), and conc. HCl (one drop) was refluxed for 3.5 hr. After addition of 2N NaOH (3 ml), the reaction mixture was extracted with $CHCl_3$ to give crude **18a** (240 mg). A part of this compound (120 mg) was treated with CH_2N_2 in THF (5 ml) and MeOH (1 ml) to yield crude **18b** (133 mg), which was purified by preparative thin-layer chromatography (TLC) to obtain pure **18b** (40 mg). To a solution of pure **18b** in dry THF (3 ml), $LiAlH_4$ (50 mg) was added. The reaction mixture was refluxed for 2 hr, decomposed with water, mixed with saturated NH_4Cl solution, and extracted with CH_2Cl_2–MeOH (9: 1) to give a crude product (24 mg). This material was purified by preparative TLC and recrystallization from acetone to yield a pure product **4a** (17 mg), mp 182—184°, which was identified with an authentic sample.

3-Benzyloxy-12-bromo-9-hydroxy-10-methoxy-tetrahydroprotoberberine (18a)——A mixture of amide **16b** (970 mg), $POCl_3$ (0.85 ml) and dry benzene (20 ml) was refluxed for 1 hr as described in the above experiment, followed by reduction with $NaBH_4$ (200 mg) in THF (30 ml) and water (2 ml) to give crude (**17a**) (960 mg). A mixture of MeOH (12 ml), $KHCO_3$ (2 g), crude **17a**, and water (3 ml) was refluxed for 1 hr. The reaction mixture was extracted with $CHCl_3$–MeOH (9: 1) after being mixed with saturated NH_4Cl solution to yield crude (**17b**) (660 mg). A solution of crude **17b** (580 mg), 30% formalin (5 ml), water (5 ml), conc. HCl (two drops), and MeOH (2 ml) was refluxed for 3.5 hr and extracted with $CHCl_3$ after being made alkaline with $NaHCO_3$ solution to give crude (**18a**) (458 mg), which was purified by preparative TLC to yield pure (**18a**) (157 mg). Recrystallization from EtOH gave pure crystals (104 mg, 13% from **16b**), mp 155—156°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 2838, 2806, 2761 (Bohlmann band), 1612. *Anal.* Calcd. for $C_{25}H_{24}O_3NBr$: C, 64.38; H, 5.19; N, 3.00. Found: C, 64.38; H, 5.45; N, 2.78.

N-(2,3-Dimethoxybenzyl)glycine (22a)——To a solution of glycine (3.0 g) in 2N NaOH (20 ml), 2,3-dimethoxybenzaldehyde (5.64 g) and MeOH (10 ml) were added, and the mixture was stirred at room temperature for 3 hr. $NaBH_4$ (2.28 g) was added with stirring under ice-cooling over a period of 45 min, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was extracted with ether to remove the neutral portion (2,3-dimethoxybenzyl alcohol) and adjusted to approximately pH 3 by dropwise addition of conc. HCl. Water was evaporated *in vacuo*, and the residue was extracted with MeOH to separate the inorganic material. The MeOH extract was concentrated, and the resulting residue was crystallized from EtOH to give colorless crystals (5.5 g, 81.5% yield), mp 196—197° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3030—2380, 1635, 1590, 1275, 1225, 1075, 1000, 790, 750.

N-(2,3-Dimethoxybenzyl)-N-(*p*-toluenesulfonyl)glycine (22b)——To a solution of N-(2,3-dimethoxybenzyl)glycine (**22a**, 3.05 g) in 2N NaOH (20.3 ml), a solution of *p*-TsCl (5.2 g) in ether (27 ml) was added, and the mixture was stirred for 4 hr under ice-cooling. Then 2N NaOH (14 ml), *p*-TsCl (2.66 g) and ether (10 ml) were added and the mixture was stirred for 1 hr. Next, 2N NaOH (10 ml), *p*-TsCl (1.33 g) and ether (8 ml) were added, followed by stirring. After 3 hr the reaction was terminated. The ether layer was separated and extracted with 2N NaOH, which was combined with the aqueous layer. The aqueous layer was neutralized with conc. HCl and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated to dryness. The resulting crude crystals were recrystallized from EtOAc–*n*-hexane to give colorless crystals (4.23 g, 84% yield), mp 103—106°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—2400, 1735, 1603, 1595, 1485, 1160, 1090, 1065, 1010. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1725, 1600, 1590, 1485, 1277, 1230, 1163, 1085, 1075, 1005, 935.

7,8-Dimethoxy-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-4-isoquinolone (23)——To a suspension of N-(2,3-dimethoxybenzyl)-N-(*p*-toluenesulfonyl)glycone (**22b**, 3.0 g) in benzene (7 ml), $SOCl_2$ (2.0 ml) was added and the mixture was refluxed for 2 hr. Benzene was distilled off *in vacuo* to give a reddish oily residue. This was dissolved in anhydrous CH_2Cl_2 (75 ml, passed through a column of Al_2O_3), cooled to −70°, and then $AlCl_3$ (3.4 g, purified by sublimation) was added in one portion. The reaction temperature was slowly raised up to −13° with stirring over a period of 4.5 hr. The reaction mixture was then poured into ice-conc. HCl, and the CH_2Cl_2 layer was washed with sat. $NaHCO_3$ and sat. NaCl successively, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The resulting crude crystals were recrystallized from CH_2Cl_2–EtOH to give light yellow prisms (2.46 g, 86% yield), mp 147—149°. IR ν_{max}^{Nujol} cm^{-1}: 1695, 1600, 1490, 1295, 1280, 1160, 1060, 950. NMR δ ($CDCl_3$): 2.40 (3H, s), 3.95 and 4.00 (8H, two s), 4.55 (2H, s), 6.90 and 7.35 (2H, AB-type d), 7.35 and 7.70 (4H, AB-type d). *Anal.* Calcd. for $C_{18}H_{19}O_5NS$: C, 59.81; H, 5.30; N, 3.88; S, 8.87. Found: C, 60.05; H, 5.09; N, 3.85; S, 8.89.

7,8-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (24)——To a solution of 7,8-dimethoxy-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydro-4-isoquinolone (**23**, 339 mg) in dry benzene (2 ml), a benzene solution of $NaAlH_2(OCH_2CH_2OMe)_2$ (2.6 ml, Vitride, Kodak Co.) was added and the mixture was refluxed overnight. Water was added under ice-cooling to kill excess reagent, and the mixture was then dried over Na_2CO_3, filtered, and evaporated to dryness. The residue was dissolved in 2N HCl and extracted with $CHCl_3$ to remove the neutral and acidic portions. The HCl layer was neutralized with 50% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a crystalline residue (164 mg), which on recrystallization from CH_2Cl_2–benzene gave pure crystals (117 mg, 62.5% yield), mp 142—145.5°. IR ν_{max}^{Nujol} cm^{-1}: 3280, 3125, 1608, 1583, 1495, 1283, 1054, 1007, 820.

2-(3-Benzyloxy)-phenethyl-7,8-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**26**)——A solution of 3-benzyloxyphenethyl iodide (282 mg) and 7,8-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (175 mg) in MeOH (2 ml) was refluxed overnight in N_2 atmosphere. MeOH was distilled off *in vacuo*, and the residue was dissolved in $CHCl_3$ and washed with 5% HCl and sat. Na_2CO_3, dried over $MgSO_4$, and evaporated to dryness to give a light yellow viscous material (300 mg, 86% yield). This showed approximately one spot on TLC. IR ν_{max}^{film} cm^{-1}: 3570, 3300—3400, 1600, 1585, 1500, 1285, 1115, 1080, 1030.

9,10-Dimethoxy-3-hydroxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (**4b**)——2-(3-Benzyloxy)-phenethyl-7,8-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**26**, 395 mg) was allowed to stand in 35% HCl (8 ml) at room temperature with occasional swirling for 3 days. Ice pieces (20 g) were added to the reaction mixture which was extracted with $CHCl_3$. The aqueous layer was adjusted to pH 9 with aqueous Na_2CO_3, and extracted with $CHCl_3$–MeOH (9: 1). The extract was dried and evaporated to give a residue (53 mg), which was crystallized from MeOH to give crystals identical with an authentic specimen.

On the other hand, the $CHCl_3$ layer, when allowed to stand, gave crystals as a precipitate, which was collected by filtration and treated with Na_2CO_3 to give the free base. This was confirmed to be identical with an authentic specimen by TLC, and recrystallized from acetone to give crystals, mp 173°. The IR spectrum was identical with that of an authentic specimen. The $CHCl_3$ layer was then washed with aqueous Na_2CO_3 was water, dried, and evaporated to give a residue, which was crystallized from MeOH–ether to give crystals (90 mg) identical with an authentic specimen on TLC.

8-Hydroxy-7-methoxy-isochromanone (**28a**)——A suspension of homoisovanillinic acid (**13b**, 3.64 g) and powdered boric acid (1.49 g) in dry toluene (80 ml) was refluxed for 2 hr with azeotropic removal of water. A suspension of 0.66 g of paraformaldehyde in toluene (25 ml) was added and refluxing was continued for 1 hr. The toluene was removed *in vacuo*, 40 ml of MeOH was added, and the resulting mixture was heated at 40° for 10 min and evaporated to dryness. After this treatment had been repeated twice, the residue was dissolved in EtOAc and washed with 5% $NaHCO_3$ solution. From the EtOAc layer, crude crystals (**28a**) (0.58 g, 15%) were obtained. The starting material (3.10 g) was recovered from the aqueous layer. Recrystallization from acetone–hexane gave pure crystals of **28a**, mp 176.5—177.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1728 (CO), NMR δ (d_6-DMSO): 3.65 (2H, s), 3.80 (3H, s), 5.32 (2H, s), 6.70, 6.90 (2H, ABq, J=8.0 Hz), 8.07 (1H, s, disappeared with D_2O). *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.70; H, 5.17.

2-Phenyl-1,3,2-benzodioxaborin (**35**)——A solution of phenol (1.882 g, 0.02 mole), benzeneboronic acid (2.43 g, 0.02 mole) and EtCOOH (148 mg, 2 mmoles) in dry benzene (50 ml) was refluxed with azeotropic removal of water. During refluxing, paraformaldehyde (1 g) was added at intervals of 1.5 hr. A 0.488 g (4 mmoles) portion of $PhB(OH)_2$ was added after 3 hr and refluxing was continued for 10 hr (total). The cooled reaction mixture was concentrated *in vacuo* and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried and evaporated to give a crude product (4.114 g). Distillation at 114—118°/1—0.5 mmHg yielded pure borin **35**, mp 36—38°. NMR δ ($CDCl_3$): 5.15 (2H, s), 7.06 (4H, m), 8.0 (2H, m). *Anal.* Calcd. for $C_{13}H_{11}O_2B$: C, 74.34; H, 5.28. Found: C, 74.49; H, 5.34.

2-Hydroxy-benzylalcohol (**32**)——A mixture of borin (**35**) (1.05 g, 5 mmoles), propyleneglycol (7.6 g, 0.1 mole), and dry benzene (8 ml) was refluxed for 2 hr. Benzene was evaporated and the resulting residue was extracted with *n*-pentane to remove boronic ester. A lower layer was extracted with ether efficiently. The ether extracts were dried and concentrated *in vacuo* to give crude product **32**, which was crystallized from *n*-pentane to yield pure crystals **32**, (559 mg, 90%) identical with an authentic sample by TLC, IR, NMR, and mp (86—87°) data.

8-Hydroxy-7-methoxy-isochromanone (**28a**)——A mixture of homoisovanillic acid **13b** (11.0 g) and benzeneboronic acid (14.0 g) in benzene (550 ml) was stirred under refluxing for about 1 hr with azeotropic removal of water.

The azeotropic removal was continued for a total period of 20 hr, while a 2—3 g portion of paraformaldehyde was added at intervals of two or three hours and benzeneboronic acid (**1.0** g) was added after 9 hr. The reaction was monitored by TLC (silica gel/CH_2Cl_2: $(CH_3)_2CO$: AcOH=7: 2: 0.5). After removal of the solvent *in vacuo*, water (150 ml) was added to the oily residue, and the mixture was heated to 90—100° (oil bath) with stirring for 1.5 hr. The mixture became homogeneous after 30 min, a solid appeared again and gradually increased. After cooling at room temperature, the solid that formed was filtered off and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried over anhyd. Na_2SO_4 and the solvent was evaporated *in vacuo* to give a crystalline residue (10.0 g). Recrystallization from $(CH_3)_2CO$–ether afforded lactone **28a** (9.7 g, 83%), mp 183—185°.

7,8-Dimethoxy-isochromanone (**28c**)——A mixture of lactone **28a** (24.9 g, 0.128 mole), K_2CO_3 (39.0 g, 0.282 mole) and $(CH_3O)_2SO_2$ (24 ml, 0.257 mole) was refluxed with stirring for 2 hr until **28a** had disappeared on the TLC (silica gel/CH_2Cl_2: $(CH_3)_2CO$: AcOH=7: 2: 0.5). After cooling of the mixture, a solid (inorganic compound) was removed by filtration and washed well with $(CH_3)_2CO$. The filtrate and the washing were combined and evaporated *in vacuo* to dryness to give a crystalline residue, which was extracted with CH_2Cl_2. The CH_2Cl_2 extract was worked up in the usual way to give a residue (30 g). Recrystallization from ether–petroleum ether gave dimethoxy lactone (25.5 g, 94%), mp 98—100°. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.38; H, 5.85. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O), 1590 (aromatic).

7-Benzyloxy-8-methoxy-isochromanone (28b)——A mixture of lactone **28a** (3.00 g), K_2CO_3 (4.71 g) and $PhCH_2Br$ (5.28 g) in $(CH_3)_2CO$ (150 mg) was refluxed for 2 hr with stirring until lactone **28a** had disappeared on the TLC. Working up as described above gave a residue, which was recrystallized from petroleum ether to give a crystal (4.0 g, 92%), mp 80—81°. *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.59; H, 5.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O). NMR ($CDCl_3$): 3.53 (2H, s, $-O-\overset{O}{\overset{\|}{C}}-CH_2-$), 3.88 (3H, s, OCH_3), 5.03 (2H, s, $-O-CH_2-$aromatic), 5.08 (2H, s, $-O-CH_2-$aromatic).

N-(3-Benzyloxyphenethyl)-3,4-dimethoxy-2-hydroxymethyl phenylacetamide (37)——A solution of lactone **28c** (15.5 g, 0.0745 mole) and 3-benzyloxy-β-phenethylamine (20.5 g, 0.09 mole) in abs. EtOH (80 ml) was refluxed with stirring for 18 hr under N_2 atmosphere until lactone **28c** had disappeared on the TLC. The EtOH was removed *in vacuo* and the resulting residue was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed twice with 2N HCl and twice with water and dried. The solvent was evaporated *in vacuo* to give a crystalline residue (32.2 g). Recrystallization from $(CH_3)_2CO$–ether–petroleum ether afforded phenylacetamide **37** (31.5 g, 97%), mp 119—120°. *Anal.* Calcd. for $C_{26}H_{29}O_5N$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.70; H, 6.70; N, 3.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3330, 1658, 1600, 1580.

3-Benzyloxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (4a)——To a solution of phenylacetamide **37** (30.0 g, 68.9 mmoles) in dry toluene (300 ml), $POCl_3$ (65 ml, 710 mmoles) was added and the mixture was refluxed with stirring for 3 hr. After removal of the solvent and the excess reagent *in vacuo*, the resulting oily residue was dissolved in MeOH (1 liter). The solution was stirred in an ice bath, and $NaBH_4$ (56 g) was gradually added for 1 hr. The mixture was allowed to stand overnight with stirring at room temperature, diluted with water (350 ml), then stirred for 20 min, poured into water (2 liters), and extracted with CH_2Cl_2. The emulsified CH_2Cl_2 extract was washed twice with sat. NaCl, dried, and evaporated *in vacuo* to give an oily residue, which contained a CH_2Cl_2–insoluble material. Therefore the residue was mixed with CH_2Cl_2, and the mixture was filtered through celite to give a clear solution. Removal of the solvent *in vacuo* gave a residue (28.0 g), which was recrystallized from $(CH_3)_2CO$–ether to afford the first crop (22.20 g), mp 155—157°, and the second crop (0.42 g), mp 150—155°. Yield: 82%. *Anal.* Calcd. for $C_{26}H_{27}O_3N$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.67; H, 6.78; N, 3.55. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2795, 2770, 1613, 1587. NMR δ ($CDCl_3$): 3.80, 3.83 (each 3H, s, CH_3), 5.02 (2H, s, CH_2Ph), 6.72, 7.30 (5H, broad, aromatic H), 7.35 (5H, s, CH_2Ph).