

[Chem. Pharm. Bull.]
34(5)1946—1949(1986)

**Studies on Tetrahydroisoquinolines. XXVIII.¹⁾ Syntheses of
(±)-*N*-Methyllaurotetanine, (±)-Cassythicine, (±)-9-
Hydroxy-1,2,3,10-tetramethoxyaporphine, (±)-
Dicentrine, and (±)-Thalicsimidine²⁾**

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(Received September 18, 1985)

The skeleton of the title aporphines was synthesized by use of the lead tetraacetate oxidation of 1-(3-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolines.

Keywords—9-hydroxyaporphine; lead tetraacetate oxidation; *o*-quinol acetate; cyclization; vinylogous retro-Mannich reaction

The synthesis of (±)-*N*-methyllaurotetanine (1) by our methodology³⁾ is tedious because the protection of the hydroxy group, which is later located at the C-9 position of 1, during the oxidation (and thus its deprotection in the final stage) is necessary. To improve the method, we tried direct lead tetraacetate oxidation of the 1-(3-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolines (6, 7, and 8) and found that this method provided a new route to the 9-hydroxyaporphines.²⁾

This paper deals with syntheses of (±)-*N*-methyllaurotetanine (1), (±)-cassythicine (2), and (±)-9-hydroxy-1,2,3,10-tetramethoxyaporphine (3) by the above methodology, as well as of (±)-dicentrine (4) and (±)-thalicsimidine (5) by methylation of 2 and 3, respectively.

The starting phenols 6 [(±)-laudanin], 7, and 8 were prepared as usual.¹⁾ Namely, heating of the corresponding phenethylamines and 3-benzyloxy-4-methoxyphenylacetic acid gave the amides, which were subjected to Bischler–Napieralski cyclization in methylene chloride to give the 3,4-dihydroisoquinoline hydrochlorides. Reduction of the hydrochlorides with NaBH₄ gave the 1,2,3,4-tetrahydroisoquinolines, *N*-methylation of which with formalin and NaBH₄, followed by debenzoylation by hydrogenolysis, afforded 6, 7, and 8.

The lead tetraacetate oxidation of (±)-laudanin (6) was carried out in methylene chloride as usual⁴⁾ to give the *o*-quinol acetate (9) [infrared (IR) cm⁻¹: 1725 (OAc), 1665 (dienone); proton nuclear magnetic resonance (¹H-NMR) spectrum: δ 2.05 (3H, s, OAc), 3.37 (3H, s, aliph. OMe)], treatment of which with trifluoroacetic acid (TFA) furnished two products, crystalline A and oily B in a ratio of 1:3.3. Product A was identified as (±)-*N*-methyl-laurotetanine (1) as described in the experimental section. In the hope of improving the ratio in favor of product A, the oxidation was carried out in the presence of TFA to give again two products A and B in a ratio of 1:1.4. Thus, the yield of 1 was much improved. At this point, we turned our attention to the structure of product B. The spectroscopic evidence presented below strongly suggested a carbinol amine structure (10). As expected, the hydrogenolysis of product B gave *O*-methyl-corypalline (11).⁵⁾ The fragmentation of 9 *via* a vinylogous retro-Mannich reaction seemed to be responsible for the formation of 10 as depicted in the scheme.

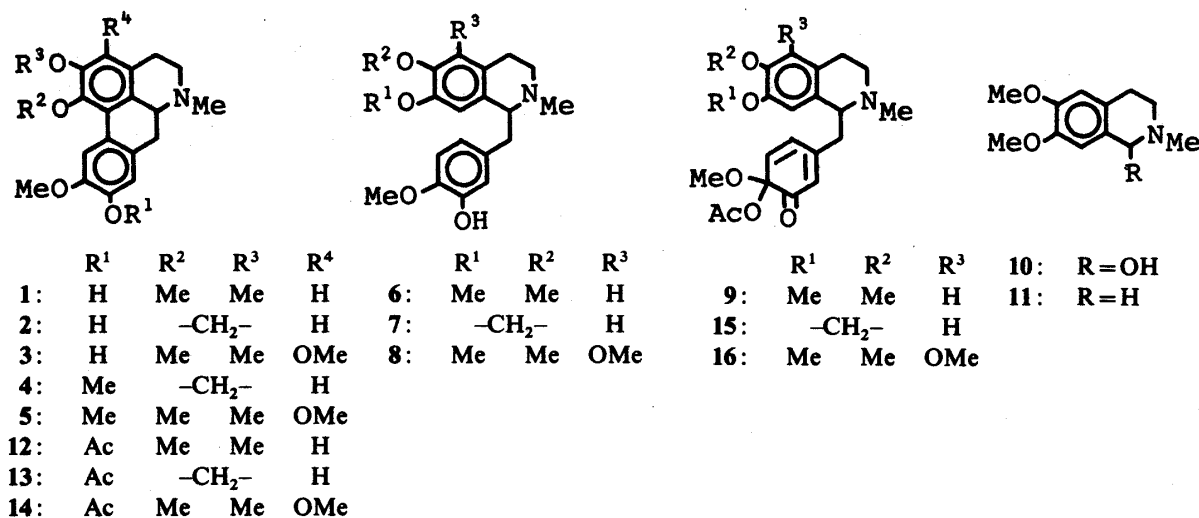


Fig. 1

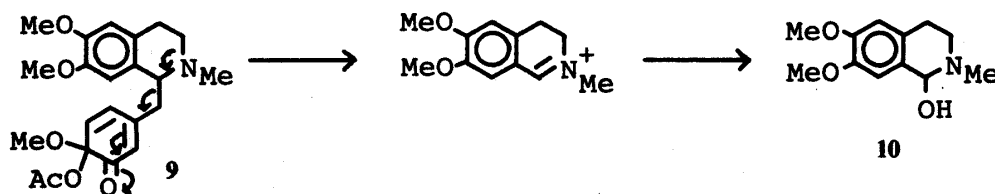


Chart 1

Since the nitrogen atom in **9** would be protonated more effectively by a strong acid such as sulfuric acid than by TFA, movement of its lone pair electrons in favor of the above fragmentation would be greatly hampered, improving the yield of **1**. Actually, employment of conc. sulfuric acid-acetic anhydride as the acid for cyclization was successful. Thus, ($\pm$)-*O*-acetyl-*N*-methyllaurotetanine (**12**) was formed from **6** in 37% yield. Hydrolysis of **12** proceeded smoothly to give **1**.

Analogously, ($\pm$)-*O*-acetylcassythicine (**13**) and ($\pm$)-9-acetoxy-1,2,3,10-tetramethoxyaporphine (**14**) were formed from **7** and **8** in yields of 45% and 80%, respectively, via the *o*-quinol acetates **15** [IR cm^{-1} : 1735 (OAc), 1670 (dienone); $^1\text{H-NMR}$ δ : 2.04 (OAc), 3.32 (aliph. OMe)] and **16** [IR cm^{-1} : 1735 (OAc), 1675 (dienone); $^1\text{H-NMR}$ δ : 2.02 (OAc), 3.30 (aliph. OMe)]. Hydrolysis of **13** and **14** gave ($\pm$)-cassythicine (**2**) and the aporphine (**3**). The structure of the former was confirmed by its melting point⁶ and spectral data,⁷ while that of the latter was established by elemental analysis and by *O*-methylation leading to ($\pm$)-thalicsimidine (**5**). *O*-Methylation of **2** or **13** and of **3** gave ($\pm$)-dicentrine (**4**) and ($\pm$)-thalicsimidine (**5**). The spectral data⁷ of the former and melting point⁸ of the latter (as the perchlorate) were identical with those in the literature.

Thus, the present modification was proved to be useful for the preparation of 9-hydroxyaporphines.

Experimental

All melting points were measured on a Büchi melting point apparatus, and are uncorrected. $^1\text{H-NMR}$ spectra were taken with a JEOL model JNM-FX-100 (100 MHz) for most of the samples or with a Hitachi model R-24B (60 MHz) instrument for all *o*-quinol acetates in CDCl_3 solution, with Me_4Si as an internal standard. IR spectra were run on a Hitachi model 260 spectrometer in CHCl_3 solution. Mass spectra (MS) were run on a Hitachi RMU-7M mass spectrometer. Preparative thin layer chromatography (TLC) was performed on Silica gel 60 F₂₅₄ plates (Merck), 2.0 mm thick.

(±)-Laudanine (6), (±)-1-(3-Hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (7), and (±)-1-(3-Hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-5,6,7-trimethoxy-2-methylisoquinoline (8)—Hydrogenolysis of (±)-*O*-benzyl-laudanine (941 mg; *Anal.* Calcd for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.81; H, 7.25; N, 3.40.) with 17% Pd-C (62 mg) gave 6, 737 mg (99%), mp 169–171 °C (MeOH; lit.⁹ mp 164–165 °C): 1H -NMR δ : 2.46 (3H, s, NMe), 3.51 (3H, s, OMe), 3.76 (3H, s, 2 $\times$ OMe), 5.95 (1H, s, 8-H), 6.40–6.70 (4H, m, ArH). IR cm^{-1} : 3510 (OH). 7: mp 123–124 °C (MeOH). *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.64; H, 6.67; N, 4.28. 1H -NMR δ : 2.36 (3H, s, NMe), 3.68 (3H, s, OMe), 5.63 (2H, s, OCH_2O), 6.05 (1H, s, 8-H), 6.32 (1H, s, 5-H), 6.38–6.55 (3H, m, ArH). IR cm^{-1} : 3500 (OH). 8: mp 111–113 °C (ether; lit.¹⁰ mp 110–111 °C).

(±)-*N*-Methylaurotetanine (1) and 1-Hydroxy-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (10)—i) Trifluoroacetic Acid Treatment of the *o*-Quinol Acetate (9): The usual oxidation⁴ of 6 (49 mg) with lead tetraacetate (1.2 eq) in CH_2Cl_2 (5 ml) gave 9, which was treated with TFA (0.5 ml) to give an oil (56 mg). Separation of the oil by preparative TLC [developing solvent: $CHCl_3$ -MeOH (10:1)] afforded crystalline 1 [8.3 mg (17%), mp 143–144 °C (ether-acetone; lit.³ mp 144–145 °C)] and oily 10 [18 mg (56%); IR cm^{-1} : 3560 (OH). 1H -NMR δ : 3.70–3.85 (6H, brs, 2 $\times$ OMe), 4.40 (1H, s, 1-H), 6.35, 6.46 (each 1H, s, ArH)].

ii) Lead Tetraacetate Oxidation in the Presence of Trifluoroacetic Acid: Two batches of the reaction products [one batch: 6 (100 mg), TFA (1 ml), lead tetraacetate (144 mg), CH_2Cl_2 (5 ml)] gave an oil (236 mg), which was purified by preparative TLC [developing solvent: $CHCl_3$ -MeOH (10:1)] to give 1 [46 mg (23%)] and oily 10 [63 mg (32%)].

O-Methylcorypalline (11) from 10—Hydrogenolysis of 10 (63 mg) with 10% Pd-C (40 mg) in MeOH (15 ml) gave, after usual work-up, an oil (51 mg). The oil was purified by preparative TLC [developing solvent: $CHCl_3$ -MeOH (10:1)] to afford crystalline 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (11: *O*-methylcorypalline), mp 69–71 °C (ether), which was identical with an authentic sample [mp 69.5–70.5 °C (ether) (lit.⁵ mp 75–77 °C)].

(±)-*N*-Methylaurotetanine (1), (±)-Cassythicine (2), and (±)-9-Hydroxy-1,2,3,4-tetramethoxyaporphine (3) via the *O*-Acetates, 12, 13, and 14, Obtained by Acetic Anhydride-conc. Sulfuric Acid Treatment of the *o*-Quinol Acetates 9, 15, and 16—A Typical Procedure: The phenolic amine (6) (50 mg) was oxidized with lead tetraacetate (1.2 eq) in CH_2Cl_2 (3 ml) at 0 °C for 1 min. Usual work-up⁴ and evaporation of the solvent under reduced pressure below 30 °C gave the *o*-quinol acetate (9). A mixture of Ac_2O (1 ml) and conc. H_2SO_4 (0.2 ml) was added to a solution of the crude *o*-quinol acetate in Ac_2O (1 ml) at 0 °C and the whole was stirred at room temperature for 30 min. Usual work-up and subsequent purification by preparative TLC gave the *O*-acetylporphine (12). Amounts (6, 7, and 8), developing solvents, yields (12, 13, and 14) from 6, 7, 8, spectral data (12, 13, and 14), and analytical data, when available, are given below. 6 (50 mg): $CHCl_3$ -MeOH (10:1); oily 12, 21 mg (37%). IR cm^{-1} : 1750 (OAc). 1H -NMR δ : 2.34 (3H, s, OAc), 2.53 (3H, s, NMe), 3.66, 3.84, 3.88 (each 3H, s, OMe), 6.60, 6.92, 8.14 (each 1H, s, ArH). 12 $\cdot CH_3I$: mp 210–213 °C (decomp.) (MeOH): *Anal.* Calcd for $C_{23}H_{28}NO_5$: C, 52.58; H, 5.37; N, 2.66. Found: C, 52.74; H, 5.38; N, 2.60. 7 (200 mg): $CHCl_3$ -MeOH (15:1); oily 13, 101.5 mg (43%). IR cm^{-1} : 1750 (OAc). 1H -NMR δ : 2.33 (3H, s, OAc), 2.56 (3H, s, NMe), 3.87 (3H, s, OMe), 5.90, 6.06 (each 1H, d, $J=1.7$ Hz, OCH_2O), 6.52, 6.91, 7.69 (each 1H, s, ArH). 13 $\cdot CH_3I$: mp 179–181 °C (MeOH): *Anal.* Calcd for $C_{22}H_{24}NO_5 \cdot 1.5H_2O$: C, 49.26; H, 5.07; N, 2.61. Found: C, 49.39; H, 4.83; N, 2.62. 8 (50 mg): $CHCl_3$ -MeOH (20:1); oily 14, 45 mg (80 mg). IR cm^{-1} : 1760 (OAc). 1H -NMR δ : 2.34 (3H, s, OAc), 2.52 (3H, s, NMe), 3.72, 3.86, 3.96 (each 3H, s, OMe), 6.89, 7.99 (each 1H, s, ArH). 14 $\cdot CH_3I$: mp 160–163 °C (MeOH). *Anal.* Calcd for $C_{24}H_{30}NO_6 \cdot 0.5H_2O$: C, 51.07; H, 5.54; N, 2.48. Found: C, 51.31; H, 5.60; N, 2.24.

Hydrolysis of 12, 13, and 14 was effected with 5% potassium hydroxide in MeOH at room temperature. 1 (91%). 2 (96%): mp 112–114 °C (MeOH, lit.⁶ 111–113 °C). IR cm^{-1} : 3530 (OH). 1H -NMR δ : 2.54 (3H, s, NMe), 3.93 (3H, s, OMe), 5.88, 6.04 (each 1H, d, $J=1.7$ Hz, OCH_2O), 6.47, 6.77, 7.59 (each 1H, s, ArH). 3 (83%): mp 142–144 °C (MeOH, lit.¹⁰ mp 206–207 °C). *Anal.* Calcd for $C_{21}H_{25}NO_5 \cdot 0.25H_2O$: C, 67.09; H, 6.84; N, 3.73. Found: C, 67.12; H, 6.87; N, 3.61. MS m/z : 371 (M^+), 328 ($M^+ - 43$). IR (KBr): 3440 (OH) cm^{-1} . 1H -NMR δ : 2.53 (3H, s, NMe), 3.77, 3.88, 3.92, 3.96 (each 3H, s, OMe), 6.77, 7.89 (each 1H, s, ArH).

(±)-Dicentrine (4) and (±)-Thalicsimidine (5)—Methylation of 2 and 3 was performed with CH_3N_2 - Et_2O in MeOH at room temperature for 2 d. 4: mp 176–177 °C (acetone), 8.8 mg [43%, after purification by preparative TLC [developing solvent: $CHCl_3$ -MeOH (15:1)] from 2 (20 mg)]. *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.97; H, 6.23; N, 4.10. 1H -NMR⁷ δ : 2.42 (3H, s, NMe), 3.75 (6H, s, 2 $\times$ OMe), 5.56, 5.80 (each 1H, d, $J=1.6$ Hz, OCH_2O), 6.21, 6.48, 7.31 (each 1H, s, ArH). 5: Crystals, 75 mg (90%) from 3 (80 mg), mp 121–122 °C (lit.⁸ syrup). *Anal.* Calcd for $C_{22}H_{27}NO_5 \cdot 0.25H_2O$: C, 67.75; H, 7.10; N, 3.59. Found: C, 67.50; H, 7.25; N, 3.36. 1H -NMR δ : 2.57 (3H, s, NMe), 3.76, 3.92, 3.99 (each 3H, s, OMe), 3.96 (6H, s, 2 $\times$ OMe), 6.81, 8.00 (each 1H, s, ArH). 5 $\cdot HClO_4$: mp 219–222 °C (MeOH-ether, lit.⁸ mp 220–225 °C). Similar treatment of 13 (74 mg) gave 4, 35 mg (52%) after purification of the product by preparative TLC [developing solvent: $CHCl_3$ -MeOH (20:1)].

Acknowledgements The authors gratefully acknowledge the financial support of this work by a Grant-in-Aid for Scientific Research (No. 58570890) from The Ministry of Education, Science and Culture, Japan. They are

indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for providing vanillin. Thanks are also due to Miss Y. Yamaguchi for her technical assistance, to Sankyo Co., Ltd. for elemental analyses, and to Miss N. Sawabe and Mrs. N. Yamatani, of this Faculty for NMR and mass spectral measurements.

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