[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 (±)-Thalicsimidine[2]

HIROSHI HARA, FUMIAKI HASHIMOTO, OSAMU HOSHINO, and BUNSUKE UMEZAWA*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, 12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

(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

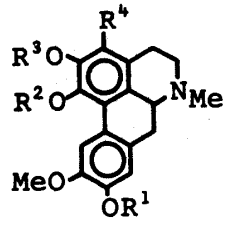
The synthesis of (±)-*N*-methyllaurotetanine (**1**) by our methodology[3] is tedious because the protection of the hydroxy group, which is later located at the C-9 position of **1**, during the oxidation (and thus its deprotection in the final stage) is necessary. To improve the method, we tried direct 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.

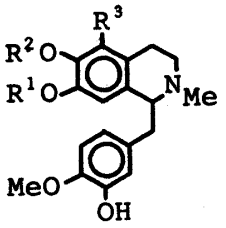
The starting phenols **6** [(±)-laudanine], **7**, and **8** were prepared as usual.[1] Namely, heating of the corresponding phenethylamines and 3-benzyloxy-4-methoxyphenylacetic acid gave the amides, which were subjected to Bischler–Napieralski cyclization in methylene chloride to give the 3,4-dihydroisoquinoline hydrochlorides. Reduction of the hydrochlorides with $NaBH_4$ gave the 1,2,3,4-tetrahydroisoquinolines, *N*-methylation of which with formalin and $NaBH_4$, followed by debenzylation by hydrogenolysis, afforded **6**, **7**, and **8**.

The lead tetraacetate oxidation of (±)-laudanine (**6**) was carried out in methylene chloride as usual[4] to give the *o*-quinol acetate (**9**) [infrared (IR) cm^{-1}: 1725 (OAc), 1665 (dienone); proton nuclear magnetic resonance (^{1}H-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.

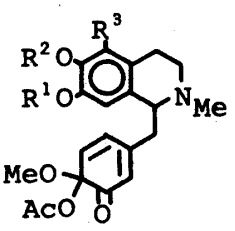
NII-Electronic Library Service



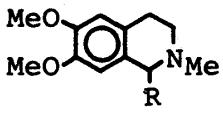
	R^1	R^2	R^3	R^4
1:	H	Me	Me	H
2:	H	$-CH_2-$		H
3:	H	Me	Me	OMe
4:	Me	$-CH_2-$		H
5:	Me	Me	Me	OMe
12:	Ac	Me	Me	H
13:	Ac	$-CH_2-$		H
14:	Ac	Me	Me	OMe



	R^1	R^2	R^3
6:	Me	Me	H
7:	$-CH_2-$		H
8:	Me	Me	OMe



	R^1	R^2	R^3
9:	Me	Me	H
15:	$-CH_2-$		H
16:	Me	Me	OMe



10: R=OH
11: R=H

Fig. 1

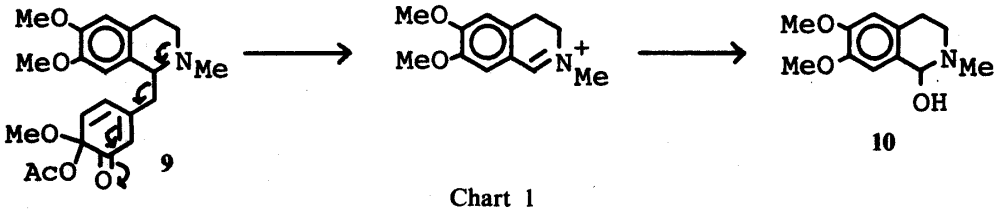


Chart 1

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, (±)-*O*-acetyl-*N*-methyllaurotetanine (**12**) was formed from **6** in 37% yield. Hydrolysis of **12** proceeded smoothly to give **1**.

Analogously, (±)-*O*-acetylcassythicine (**13**) and (±)-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}H-NMR δ: 2.04 (OAc), 3.32 (aliph. OMe)] and **16** [IR cm^{-1}: 1735 (OAc), 1675 (dienone); ^{1}H-NMR δ: 2.02 (OAc), 3.30 (aliph. OMe)]. Hydrolysis of **13** and **14** gave (±)-cassythicine (**2**) and the aporphine (**3**). The structure of the former was confirmed by its melting point[6] and spectral data,[7] while that of the latter was established by elemental analysis and by *O*-methylation leading to (±)-thalicsimidine (**5**). *O*-Methylation of **2** or **13** and of **3** gave (±)-dicentrine (**4**) and (±)-thalicsimidine (**5**). The spectral data[7] of the former and melting point[8] 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}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 F_{254} plates (Merck), 2.0 mm thick.

NII-Electronic Library Service

(±)-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): ^{1}H-NMR δ: 2.46 (3H, s, NMe), 3.51 (3H, s, OMe), 3.76 (3H, s, 2×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. ^{1}H-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*-Methyllaurotetanine (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 oxidation[4] 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). ^{1}H-NMR δ: 3.70—3.85 (6H, br s, 2×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*-Methyllaurotetanine (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-up[4] 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*-acetylaporphine (**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). ^{1}H-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**·CH_3I: mp 210—213 °C (decomp.) (MeOH): *Anal.* Calcd for $C_{23}H_{28}NO_5I$: 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). ^{1}H-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**·CH_3I: mp 179—181 °C (MeOH): *Anal.* Calcd for $C_{22}H_{24}NO_5I \cdot 1.5H_2O$: 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). ^{1}H-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**·CH_3I: mp 160—163 °C (MeOH). *Anal.* Calcd for $C_{24}H_{30}NO_6I \cdot 0.5H_2O$: 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). ^{1}H-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}. ^{1}H-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_2N_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. ^{1}H-NMR[7] δ: 2.42 (3H, s, NMe), 3.75 (6H, s, 2×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. ^{1}H-NMR δ: 2.57 (3H, s, NMe), 3.76, 3.92, 3.99 (each 3H, s, OMe), 3.96 (6H, s, 2×OMe), 6.81, 8.00 (each 1H, s, ArH). **5**·$HClO_4$: 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

NII-Electronic Library Service

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.

References

1) Part XXVII: H. Hara, H. Shinoki, T. Komatsu, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **34**, 1924 (1986).
2) Preliminary report: see H. Hara, F. Hashimoto, O. Hoshino, and B. Umezawa, *Tetrahedron Lett.*, **25**, 3615 (1984).
3) H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **24**, 1921 (1976).
4) H. Hara, A. Tsunashima, H. Shinoki, T. Akiba, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **34**, 66 (1986).
5) J. S. Buck, *J. Am. Chem. Soc.*, **56**, 1769 (1934).
6) M. Tomita and I. Kikkawa, *Yakugaku Zasshi*, **77**, 1011 (1957).
7) T. Kametani, T. Sugahara, and K. Fukumoto, *Chem. Ind.* (London), 833 (1969).
8) T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 1032.
9) B. Frydman, R. Bendisch, and V. Deulofeu, *Tetrahedron*, **4**, 342 (1958).
10) R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *J. Org. Chem.*, **36**, 2409 (1971).

NII-Electronic Library Service