

A NOVEL SYNTHESIS OF 5- OR 13-OXYGENATED
TETRAHYDROPROTOBERBERINES[§]

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In order to introduce O-functional groups at the 5- or 13-position in tetrahydroprotoberberine, we tried lead tetraacetate oxidation of (\pm)-2-hydroxy-3,10,11-trimethoxy (3)- or (\pm)-10-hydroxy-2,3,11-trimethoxy (12)-tetrahydroprotoberberine, a moiety of which was 1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline convertible to the corresponding 4,7-diacetate via p-quinol acetate.

(\pm)-2-Phenol (3) yielded a p-quinol acetate (4), which was transformed to several 5-oxygenated tetrahydroprotoberberines (6,7,8,9,10, and 11). Similarly, some 13-oxygenated derivatives (14,15, and 16) were prepared from (\pm)-10-phenol (12).

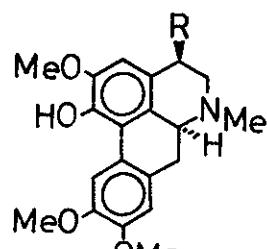
Protoberberine alkaloids carrying a hydroxyl group at the

[§] Dedicated to Emeritus Professor S. Sugashawa of University of Tokyo on the occasion of his eightieth birthday.

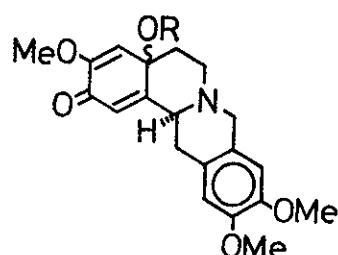
5-¹⁾ or 13-²⁾ position have been known and their syntheses have also been achieved by several methods such as Pomeranz-Fritsch type cyclization leading to 5-hydroxy compounds³⁾, hydroboration-oxidation to a 5-⁴⁾ or 13-⁵⁾-hydroxy compound, and conversion of phthalide isoquinolines⁶⁾, Mannich reaction of α -hydroxybenzylisoquinolines⁷⁾ or hydride reduction of the oxidation products of berberine-acetone^{8a)}, berberine^{8b)}, and dihydroberberine^{2b,8c)} to 13-hydroxy compounds.

Our success that (\pm)-thaliporphine (1) has on oxidation with lead tetraacetate [$Pb(OAc)_4$] been stereospecifically transformed in one step to (\pm)-4 β -acetoxythaliporphine (2)⁹⁾ encouraged us to carry out similar reactions on 2- or 10-phenolic tetrahydroprotoberberine in an anticipation to introduce oxygen functions at the 5- or 13-position. This communication deals with a novel synthesis of the title compounds in a stereoselective manner by use of $Pb(OAc)_4$.

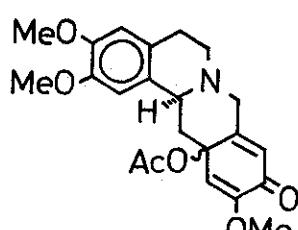
To a solution of (\pm)-2-hydroxy-3,10,11-trimethoxy-tetrahydroprotoberberine (3)¹⁰⁾ (400 mg) in acetic acid (4 ml) was added $Pb(OAc)_4$ (624 mg, 1.1 eq.) in one portion and the whole was stirred for 30 min at room temperature. Contrary to the anticipation, usual work-up¹²⁾ gave a p-quinol acetate (4) [mp 159-161°; IR¹³⁾: 1740 (OCOCH₃), 1670, 1645, 1630 cm⁻¹ (dienone)] (455 mg, quantitative). The p-quinol acetate was by no means a mixture of diastereoisomers because it displayed a sole spot on TLC and a simple pattern consisting of all singlet peaks [NMR¹³⁾ δ : 2.02 (3H, s, NCH₃), 3.66, 3.78, 3.80 (each 3H, s, 3xOCH₃), 5.88, 6.28 (each 1H, s, 2 x olefinic H), 6.50, 6.61 (each 1H, s, 2 x aromatic H)] ascribable to a diastereoisomer. However, attempted hydrolysis of 4 failed to give a p-quinol



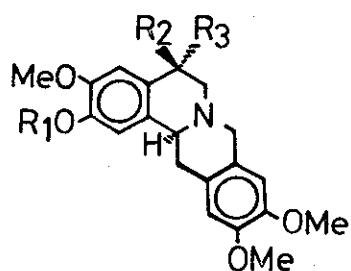
R
1 : H
2 : OAc



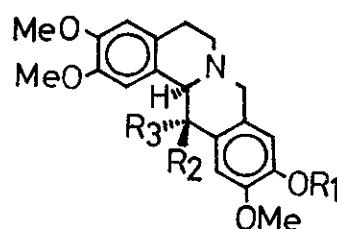
R
4 : Ac
5 : H



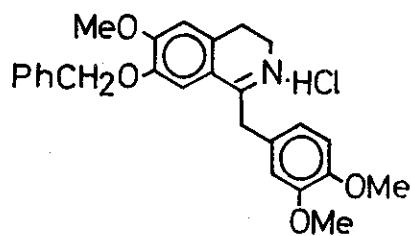
13



R ₁	R ₂	R ₃
3 : H	H	H
6 : Ac	OAc	H
7 : H	OH	H
8 : Me	OH	H
9 : Me	OAc	H
10 : H	H	OMe
11 : H	OMe	H



R ₁	R ₂	R ₃
12 : H	H	H
14 : Ac	OAc	H
15 : Ac	H	OAc
16 : H	H	OMe



17

(5) leaving stereochemistry of $\tilde{\alpha}$ unsolved.

Accordingly, a usual rearrangement technique in this region¹²⁾ was next tried. Namely, to a stirred suspension of the unpurified $\tilde{\alpha}$ (455 mg) in acetic anhydride (4 ml) under ice-cooling, was added conc. sulfuric acid (0.8 ml) drop by drop during 30 sec. The whole was stirred for 1 hr at room temperature and work-up as usual gave stereospecifically (\pm)-2, 5 β -diacetate (6) [IR: 1760, 1725 cm^{-1} ; NMR δ : 6.00 (1H, t, $J=2,5\text{Hz}$)] (468 mg, 91%). Purification on a silica gel short column and repeated recrystallization from acetone-pet. ether yielded colorless fine needles, mp 150-151°. Hydrolysis with conc. hydrochloric acid of $\tilde{\alpha}$ gave (\pm)-2, 5 β -diol (7) [mp 165-170°; IR: 3540 cm^{-1} (OH); NMR (in d_5 -pyridine) δ : 4.84 (1H, t, $J=2.5\text{Hz}$)], re-acetylation of which with acetic anhydride and pyridine led back to $\tilde{\alpha}$. For further confirmation of their structures, two derivatives of the diol (7) were prepared by conventional methods; (\pm)-5 β -hydroxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (8)¹⁴⁾ [mp 189-190° (lit.^{3a)} mp 194-195°)] and (\pm)-5 β -acetate (9)¹⁴⁾ [mp 184-186° (lit.^{3a)} mp 188-189°)].

Treatment¹²⁾ of a suspension of $\tilde{\alpha}$ in MeOH with 5% KOH and purification on preparative TLC¹⁵⁾ (CHCl_3 : MeOH=30:1) gave rise to (\pm)-5 α -methoxy (10)-[mp 179-181° (dec.); IR: 3540 cm^{-1} ; NMR δ : 4.58 (1H, dd, $J=5, 10\text{Hz}$)] and (\pm)-5 β -methoxy (11)-[mp 137.5-138°; IR: 3540 cm^{-1} ; NMR δ : 4.20 (1H, t, $J=2.5\text{Hz}$)] 2-hydroxy-3,10,11-trimethoxytetrahydroprotoberberines in 29% and 35% yield, respectively.

Similarly, $\text{Pb}(\text{OAc})_4$ oxidation of (\pm)-10-hydroxy-2,3,11-trimethoxytetrahydroprotoberberine (12)¹⁶⁾ gave quantitatively an oily p-quinol acetate (13) [IR: 1740, 1675, 1645, 1630 cm^{-1} ,

NMR δ : 2.12 (OCOCH₃), 3.67, 3.83, 3.86 (each 3H, s, 3xOCH₃), 5.87, 6.24 (each 1H, s, 2 x olefinic H), 6.58, 6.59 (each 1H, s, 2 x aromatic H)], stereochemistry of which was unknown though homogeneous. Similar acid treatment with acetic anhydride and conc. sulfuric acid followed by purification on a silica gel column¹⁵⁾ gave (\pm)-10, 13 β -diacetate (\sim)¹⁷⁾ [mp 166-167°; IR: 1765, 1730 cm⁻¹; NMR δ : 6.54 (1H, d, J=2.5Hz)] and (\pm)-10, 13 α -diacetate (\sim)¹⁷⁾ [mp 168.5-169°; IR: 1760, 1730 cm⁻¹; NMR δ : 6.14 (1H, d, J=7.5Hz)] in a ratio of 3:1. This result was consistent with a suggestion on relative steric effect between 13 α - and 13 β -hydroxytetrahydroprotoberberines⁵⁾.

Although attempted hydrolysis of \sim 14 and \sim 15 to their respective diols was futile, reaction with 5% KOH in MeOH of \sim 14 and \sim 15 took place to give solely (\pm)-10-hydroxy-13 α -methoxy-2,3,11-trimethoxytetrahydroprotoberberine (\sim)¹⁶⁾ [mp 146-148°; IR: 3530 cm⁻¹; NMR δ : 4.64 (1H, d, J=9Hz)] in 28% and 27% yield, respectively. However, the reason why the reaction lacked stereoselectivity as observed in the case of the rearrangement of \sim 13 remained unexplained in spite of the common belief that these reactions proceeded through a p-quinone methide¹²⁾.

Thus, 5- and 13-oxygenated tetrahydroprotoberberines were synthesized stereoselectively (partly stereospecifically) starting from 2- and 10-phenolic congeners according to an entirely different method from hitherto known ones. In particular, synthesis of the 13-acetoxytetrahydroprotoberberines in the manner described above could be referred as biomimetic¹⁸⁾. One step synthesis of 5- or 13-acetoxytetrahydroprotoberberine on Pb(OAc)₄ oxidation of 3- or 11-phenolic congener is currently investigated.

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REFERENCES

1. M.M. Nijland, Pharm. Weekbl., 1961, 96, 640 [Chem. Abstr., 1961, 55, 2626371h]; Idem, Pharm. Weekbl., 1963, 98, 301 [Chem. Abstr., 1963, 59, 10142]; M. Shamma and B.S. Dudock, Tetrahedron Letters, 1965, 3825; I. Monkovic and I.D. Spenser, J. Amer. Chem. Soc., 1965, 87, 1137; Idem, Can. J. Chem., 1965, 43, 2017.
2. a) R.H.F. Manske, Can. J. Research, 1939, 17, Sec. B, 51; Idem, ibid., 1942, 20, Sec. B, 57; b) P.W. Jeffs and J.D. Scharver, J. Org. Chem., 1975, 40, 644.
3. a) D.W. Brown, S.F. Dyke, G. Hardy, and M. Sainsbury, Tetrahedron Letters, 1968, 5177; Idem, Tetrahedron, 1971, 27, 3495; b) Idem, J. Chem. Soc. (C), 1971, 3219; S.F. Dyke and E.P. Tiley, Tetrahedron Letters, 1972, 5175; Idem, Tetrahedron, 1972, 31, 561.
4. M. Shamma and L.A. Smeltz, Tetrahedron Letters, 1976, 1415.
5. I.W. Elliott, Jr., J. Heterocyclic Chem., 1967, 4, 639.
6. a) T.R. Govindachari and S. Rajadurai, J. Chem. Soc., 1957, 557; T.R. Govindachari, S. Rajadurai, M. Subramanian, and N. Viswanathan, ibid., 1957, 2943; b) M. Ohta, H. Tani, and S. Morozumi, Tetrahedron Letters, 1963, 859; A.R. Battersby and H. Spencer, J. Chem. Soc., 1965, 1087; M. Shamma and V. St. Georgiev, Tetrahedron, 1976, 32, 211.
7. T. Kametani, H. Matsumoto, Y. Satoh, H. Nemoto, and K. Fukumoto, J. Chem. Soc. Perkin I, 1977, 376.

8. a) T. Takemoto and Y. Kondo, J. Pharm. Soc. Japan, 1962, 82, 1413; Y. Kondo, ibid., 1964, 84, 146; J. Iwasa and S. Naruto, ibid., 1966, 86, 534; b) M. Hanaoka, C. Mukai, and Y. Arata, Heterocycles, 1977, 6, 895; c) Y. Kondo, H. Inoue, and J. Imai, ibid., 1977, 6, 953.
9. O. Hoshino, H. Hara, M. Ogawa, and B. Umezawa, J. Chem. Soc. Chem. Commun., 1975, 306; Idem, Chem. Pharm. Bull. (Tokyo), 1975, 23, 2578.
10. Compound (3) was prepared from 3,4-dihydroisoquinoline hydrochloride (17)¹¹ with NaBH₄ reduction, cyclization (98% HCOOH/37% HCHO) and debenzylation (H₂/Pd-C, MeOH, H^②). All new compounds gave satisfactory analytical data.
11. G. Billek, Monatsh. Chem., 1956, 87, 106; M. Shamma and W.A. Slusachyk, Tetrahedron, 1967, 23, 2563.
12. B. Umezawa and O. Hoshino, Heterocycles, 1975, 3, 1005 and references cited therein.
13. NMR spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in CDCl₃ solution by using (CH₃)₄Si as an internal standard, unless otherwise noted. IR spectra were run on a Hitachi 225 spectrometer in CHCl₃.
14. NMR and IR spectroscopic data of 8 and 9 were consistent with those given in the literature^{3a)}.
15. Preparative TLC was run on silica gel HF₂₅₄ (Merck). Column chromatography was performed on silica gel (Kanto Chemical), eluant: CHCl₃.
16. D.H. Tdeschi, U.S.P., 3272707 [Chem. Abstr., 1966, 63, 20109b]; T. Kametani, T. Honda, and M. Ihara, J. Chem. Soc. (C), 1971, 3318; T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwaki, J. Pharm. Soc. Japan, 1973, 93, 1116;

T. Kametani, S-P. Huang, M. Ihara, and K. Fukumoto, J. Org. Chem., 1976, 41, 2545.

17. Configuration of the 13-acetoxy group was determined by values of the coupling constant of the 13-hydrogen and these were well accordant with those of other models^{2b,6b,8b}.

18. A.R. Battersby, M. Hirst, D.J. McCaldin, R. Southgate, and J. Stauton, J. Chem. Soc. (C), 1968, 2163; P.W. Jeffs and J.D. Scharver, J. Amer. Chem. Soc., 1976, 98, 4301.

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