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Studies on Tetrahydroisoquinolines. XXVI.[1] A Biomimetic Synthesis of 5-Oxygenated 1,2,3,4-Tetrahydroisoquinolines[2]

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Treatment with acetic anhydride–conc. sulufuric acid of *o*-quinol acetates (**7**, **11**,**18**, **19**, **20**, **28** and **34**), which were derived from the corresponding 6-hydroxy-7-methoxytetrahydroisoquinolines (**6**, **12**, **15**, **16**, **17**, **27** and **31**), gave the 5,6-diacetates (**8**, **13**, **21**, **22**, **23**, **29** and **33**, respectively). The diacetates were transformed into the corresponding 5,6,7-trimethoxytetrahydroisoquinolines (**10**, **14**, **24**, **25**, **26**, **30** and **32**) by hydrolysis and subsequent methylation.

Keywords——biomimetic methoxylation; lead tetraacetate oxidation; tetrahydroisoquinoline; regioselective methoxylation; *o*-quinol acetate

Some benzyltetrahydroisoquinolines such as thalifendrine (**1**) might be biogenetically derived from the corresponding guiacol-type tetrahydroisoquinolines. Namely, the *p*-quinonoid cation (**2**) is considered to be a key intermediate.[3]

In the course of our studies on the isolable *o*-quinol acetates (**3**),[4] we have become convinced that the reactive species must be an *o*-quinonoid cation (**4**), which is essentially equivalent to the cation (**2**). Therefore, it seemed possible that the speculative biogenetic route might be mimicked *in vitro* by the use of the *o*-quinol acetates. On the other hand, we have already succeeded in the introduction of the chloride anion at the C-5 position of **4** to prepare the chlorinated phenol (**5**).[4] Here we wish to report the introduction of the acetate anion by this methodology.

Isocorypalline (**6**) was oxidized with lead tetraacetate (LTA) to give the *o*-quinol acetate (**7**), the structure of which was supported by the spectral data. Namely, the signal at δ 3.38 (3H, s) in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum was assigned to aliphatic methoxy protons, and the absorption bands at 1730 and 1675 cm^{-1} in the infrared (IR) spectrum were assigned to acetate and dienone, respectively.

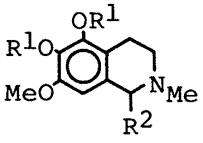
Treatment of the *o*-quinol acetate (**7**) with conc. sulfuric acid (conc. H_2SO_4) in Ac_2O (1 : 10, v/v) afforded an oily 5,6-diacetate (**8**) in 19.4% yield from isocorypalline (**6**). The ^{1}H-NMR spectrum of **8** showed signals of one aromatic proton (δ 6.45) and two acetoxyl protons (δ 2.25, s, 6H), whereas no absorption band due to alkyl acetate was observed on the IR spectral chart. Hydrolysis of **8** with 20% hydrochloric acid (HCl) gave the diol hydrochloride (**9**). Methylation of **9** with diazomethane afforded tehaunine (**10**) as an oil in 22.1% yield from **8**. Tehaunine (**10**) was converted to its hydrochloride [mp 228—229 °C (lit.[5] 229—230 °C)] for characterization.

Similar acid treatment of the *o*-quinol acetate (**11**) derived from (±)-*N*-methylsalsoline (**12**) gave the 5,6-diacetate (**13**), hydrolysis and subsequent methylation of which provided (±)-*O*-methylgigantine (**14**) in a yield of 4% from **12**.

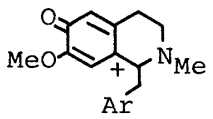
Moreover, the method was applicable to 1-phenyl-(**15**), 1-benzyl-(**16**), and 1-(*p*-

methoxybenzyl)-(**17**) isocorypallines. Acid treatment of the *o*-quinol acetate (**18**, **19** or **20**) obtained from **15**, **16** or **17** gave the 5,6-diacetate (**21**, **22** or **23**, respectively). The substitution position was easily identified; that is, the downfield signal due to the C-5H in the starting phenol (**15**, **16** or **17**) disappeared in the product (**21**, **22** or **23**). The diacetates (**21**, **22** and **23**) were hydrolyzed with 10% HCl–MeOH or 20% HCl aq. and subsequently methylated to give the 5,6,7-trimethoxy derivatives (**24**, **25** and **26**, respectively). The structures of **24** and **25** were determined by ^{1}H-NMR spectral and elemental analyses. Compound **26** was identified as (±)-tetrahydrotakatonine on the basis of a comparison of the physical data with those of Kubota *et al.*[6]

Similarly, one methoxyl group was introduced into the 4- or 12-position of tetrahydroprotoberberines. Namely, (±)-discretine (**27**) was oxidized to give the *o*-quinol acetate (**28**), which was treated analogously to afford the 3,4-diacetate (**29**). The ^{1}H-NMR spectrum of **29** showed three aromatic protons (δ 6.48, 6.58, 6.69) and two acetoxyl protons (δ 2.27, s, 6H),



1 : R^1=Me, R^2=$CH_2C_6H_4OH$ (*p*)
8 : R^1=Ac, R^2=H
10 : R^1=Me, R^2=H
13 : R^1=Ac, R^2=Me
14 : R^1=Me, R^2=Me
21 : R^1=Ac, R^2=Ph
22 : R^1=Ac, R^2=CH_2Ph
23 : R^1=Ac, R^2=$CH_2C_6H_4OMe$ (*p*)
24 : R^1=Me, R^2=Ph
25 : R^1=Me, R^2=CH_2Ph
26 : R^1=Me, R^2=$CH_2C_6H_4OMe$ (*p*)



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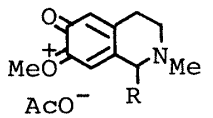

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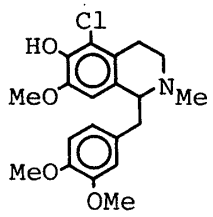

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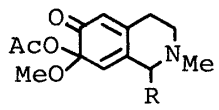
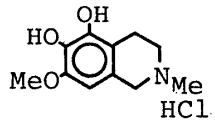


3 : R=veratryl
7 : R=H
11 : R=Me
18 : R=Ph
19 : R=CH_2Ph
20 : R=$CH_2C_6H_4OMe$ (*p*)



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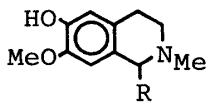
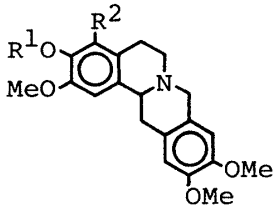
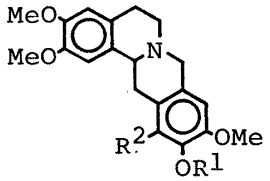


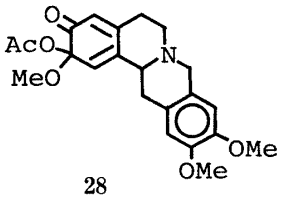
6 : R=H
12 : R=Me
15 : R=Ph
16 : R=CH_2Ph
17 : R=$CH_2C_6H_4OMe$ (*p*)



27 : R^1=R^2=H
29 : R^1=Ac, R^2=OAc
30 : R^1=Me, R^2=OMe



31 : R^1=R^2=H
32 : R^1=Me, R^2=OMe
33 : R^1=Ac, R^2=OAc



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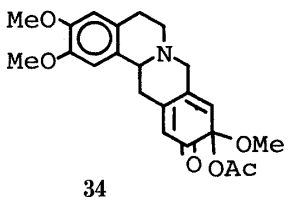

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Fig. 1

TABLE I. Spectral Data for *o*-Quinol Acetates

Compd.	NMR δ (ppm)			IR cm^{-1}	
	Aliph. OMe	OAc	Olef. H	OAc	Dienone
7	3.40	2.05	5.82 (2H, br s)	1730	1675
11[a]	3.36	2.05	5.82 (2H, br s)	1740	1680
18[a]	3.23, 3.37	1.94, 2.01	5.34, 5.46 (1H, each d, J=2 Hz, 8-H), 5.96 (1H, br s, 5-H)	1740	1680, 1660
19[a]	3.16, 3.28	2.00	5.14, 5.47 (1H, each s, 8-H), 5.86 (1H, br s, 5-H)	1740	1680
20[a]	3.23, 3.32	2.01, 2.03	5.49 (1H, br s, 8-H) 5.83 (1H, br s, 5-H)	1745	1690
28[a]	3.42	2.07, 2.09	5.87 (1H, br s), 5.97, 6.07 (1H, each d, J=2 Hz)	1745	1685
34[a]	3.42	2.08	5.92 (2H, br s)	1740	1685

a) A mixture of diastereomers.

confirming the structure. The diacetate (**29**) was subjected to hydrolysis followed by methylation, giving 2,3,4,10,11-pentamethoxytetrahydroprotoberberine (**30**), the physical data of which were consistent with those reported by Kametani *et al.*[7]

A similar sequence of reactions of (±)-corytencine (**31**) gave 2,3,10,11,12-pentamethoxytetrahydroprotoberberine (**32**), the ^{1}H-NMR spectrum of which was superimposable on that of an authentic sample prepared according to Kametani's procedure.[8]

Though the yields of the diacetates were not good, the methodology is of interest as a possible biomimetic reaction.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken with a JEOL JNX-FX-100 (100 MHz) or Hitachi R-24B instrument in $CDCl_3$ solution, unless otherwise noted, with Me_4Si as an internal standard. IR spectra were run on a Hitachi model 260 spectrometer in $CHCl_3$ solution. Preparative thin-layer chromatography (TLC) was performed on precoated Silica gel 60 F_{254} plates (Merck) 2.0 mm thick.

General Procedure for Preparation of the Diacetates (8, 13, 21, 22, 23, 29 and 33)——LTA (1.2 eq) was added into an ice-cooled solution of a phenolic base (**6**,[9] **12**,[9] **15**,[9] **16**,[9] **17**,[10] **27**[11] or **31**[11]) (100 mg) in CH_2Cl_2 (5—20 ml), and the mixture was stirred at the same temperature for 1 min. The resulting precipitate was removed by filtration and a few drops of water were added to the filtrate with stirring. The filtrate was dried over K_2CO_3, and the solvent was removed under reduced pressure below 30 °C to give the *o*-quinol acetate (**7**, **11**, **18**, **19**, **20**, **28** or **34**). Spectral data of the *o*-quinol acetates are listed in Table I. Without purification, each *o*-quinol acetate was dissolved in Ac_2O (2 ml), and a mixture of Ac_2O (2 ml) and conc. H_2SO_4 (0.4 ml) was added to the ice-cooled solution. The mixture was stirred at room temperature for 1 h. Usual work-up gave an oily product, which was purified by preparative TLC[12] to afford the corresponding diacetate.

5,6-Diacetoxy-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (**8**): An oil (19.2%). IR cm^{-1}: 1770 (OAc). ^{1}H-NMR δ: 2.25 (6H, s, 2×OAc), 2.40 (3H, s, NMe), 2.60 (4H, s, 3-, 4-H), 3.50 (2H, s, 1-H), 3.72 (3H, s, OMe), 6.45 (1H, s, 8-H).

5,6-Diacetoxy-1,2,3,4-tetrahydro-7-methoxy-1,2-dimethylisoquinoline (**13**): An oil (19.6%). IR cm^{-1}: 1770 (OAc). ^{1}H-NMR δ: 1.38 (3H, d, J=7 Hz, 1-Me), 2.25 (6H, s, 2×OAc), 2.42 (3H, s, NMe), 3.75 (3H, s, OMe), 6.52 (1H, s, 8-H).

5,6-Diacetoxy-1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenylisoquinoline (**21**): An oil (41.7%). IR cm^{-1}: 1780 (OAc). ^{1}H-NMR δ: 2.18, 2.21 (each 3H, s, OAc), 2.27 (3H, s, NMe), 3.45 (3H, s, OMe), 4.15 (1H, s, 1-H), 6.04 (1H, s, 8-H), 7.18 (5H, s, PhH). Picrate: mp 199—200 °C (iso-PrOH). *Anal.* Calcd for $C_{21}H_{23}NO_5 \cdot C_6H_3N_3O_7$: C, 54.18; H, 4.38; N, 9.36. Found: C, 54.22; H, 4.22; N, 9.41.

5,6-Diacetoxy-1-benzyl-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (**22**): Colorless needles (56.7%). mp 139.5—140.5 °C (*n*-hexane). IR cm^{-1}: 1780 (OAc). ^{1}H-NMR δ: 2.22, 2.24 (each 3H, s, OAc), 2.46 (3H, s, NMe), 3.42

(3H, s, OMe), 5.92 (1H, s, 8-H), 7.10 (5H, br s, PhH). *Anal.* Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.72; H, 6.68; N, 3.71.

5,6-Diacetoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (**23**): An oil (2.7%). IR cm^{-1}: 1770 (OAc). ^{1}H-NMR δ: 2.20, 2.25 (each 3H, s, OAc), 2.45 (3H, s, NMe), 3.45, 3.70 (each 3H, s, OMe), 5.90 (1H, s, 8-H), 6.62, 6.90 (each 2H, d, J=8 Hz, 3′-, 5′-H, and 2′-, 6′-H).

3,4-Diacetoxy-2,10,11-trimethoxytetrahydroprotoberberine (**29**): An oil (65.6%). IR cm^{-1}: 1780 (OAc). ^{1}H-NMR δ: 2.27 (6H, s, 2×OAc), 3.80 (9H, s, 3×OMe), 6.48, 6.58, 6.69 (each 1H, s, ArH).

11,12-Diacetoxy-2,3,10-trimethoxytetrahydroprotoberberine (**33**): An oil (47.2%). IR cm^{-1}: 1780 (OAc). ^{1}H-NMR δ: 2.26 (6H, s, 2×OAc), 3.77 (3H, s, OMe), 3.82 (6H, s, 2×OMe), 6.55 (2H, s, ArH), 6.62 (1H, s, ArH).

General Procedure for Preparation of the 5,6,7-Trimethoxy Compounds (10, 14, 24, 25, 26, 30 and 32)——A solution (7 ml) in conc. HCl–MeOH (2 : 5) was added to a diacetate (250—350 mg), and the mixture was stirred at 50 °C for 1—2 h. Evaporation of the solvent gave a wet residue, from which water was removed as the benzene azeotrope, affording the corresponding diol hydrochloride. Without purification,[13] the diol was methylated in MeOH with diazomethane–ether solution (excess) to give the crude methylated compound, which was purified by preparative TLC.[12]

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methylisoquinoline (Tehaunine) (**10**): An oil (22.1%). ^{1}H-NMR δ: 2.40 (3H, s, NMe), 2.60—2.80 (4H, m, 3-, 4-H), 3.45 (2H, s, 1-H), 3.80 (9H, s, 3×OMe), 6.25 (1H, s, 8-H). Hydrochloride (benzene–$CHCl_3$): mp 228—229 °C (lit.[5] 229—230 °C). The hydrochloride was identical with an authentic sample, which was prepared by a usual procedure from 2,3,4-trimethoxyphenethylamine.

(±)-1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1,2-dimethylisoquinoline [(±)-*O*-Methylgigantine] (**14**): An oil (22.2%). ^{1}H-NMR δ: 1.35 (3H, d, J=7 Hz, 1-Me), 2.45 (3H, s, NMe), 3.80 (9H, s, 3×OMe), 6.35 (1H, s, 8-H). Methopicrate (MeOH): mp 200—201 °C. The methopicrate was identical with an authentic sample, which was prepared by a usual procedure from 2,3,4-trimethoxyphenethylamine.

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methyl-1-phenylisoquinoline (**24**): An oil (42.2%). ^{1}H-NMR δ: 2.22 (3H, s, NMe), 3.54, 3.84, 3.88 (each 3H, s, OMe), 6.89 (1H, s, 8-H), 7.24 (5H, s, PhH). Styphnate (iso-PrOH): mp 154—155.5 °C. *Anal.* Calcd for $C_{19}H_{23}NO_3 \cdot C_6H_3N_3O_8$: C, 53.76; H, 4.69; N, 10.03. Found: C, 53.80; H, 4.81; N, 9.96.

1-Benzyl-1,2,3,4-tetrahydro-5,6,7-trimethoxy-2-methylisoquinoline (**25**): An oil (42.4%). ^{1}H-NMR δ: 2.56 (3H, s, NMe), 3.52, 3.86, 3.88 (each 3H, s, OMe), 5.82 (1H, s, 8-H), 7.22 (5H, m, PhH). Styphnate (iso-PrOH): mp 136.5—138 °C. *Anal.* Calcd for $C_{20}H_{25}NO_3 \cdot C_6H_3N_3O_8$: C, 54.54; H, 4.93; N, 9.79. Found: C, 54.64; H, 5.07; N, 9.77.

(±)-1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-5,6,7-trimethoxy-2-methylisoquinoline [(±)-Tetrahydrotakatonine] (**26**): An oil (17.6%). ^{1}H-NMR (CD_3OD) δ: 2.96 (3H, s, NMe), 3.47 (4H, s, 3-, 4-H), 3.78 (9H, s, 3×OMe), 3.89 (3H, s, OMe), 5.78 (1H, s, 8-H), 6.86, 7.06 (each 2H, d, J=10 Hz, 3′-, 5′-H, and 2′-, 6′-H). Hydrochloride (ether–iso-PrOH): mp 185—187 °C (lit.[6] 188—192 °C). Compound **26** was identical with an authentic sample, which was prepared according to Kubota's procedure.[6]

2,3,4,10,11-Pentamethoxytetrahydroprotoberberine (**30**): Colorless needles (44.3%). mp 125—125.5 °C (*n*-hexane) (lit.[7] 135—136 °C). *Anal.* Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.81; H, 7.03; N, 3.64. ^{1}H-NMR δ: 3.90, 3.92, 3.93 (each 3H, s, OMe), 3.91 (6H, s, 2×OMe), 6.60 (2H, s, ArH), 6.68 (1H, s, ArH).

2,3,10,11,12-Pentamethoxytetrahydroprotoberberine (**32**): Pale yellow prisms (16.4%). mp 117—119 °C (ether). ^{1}H-NMR δ: 3.88, 3.90, 3.91, 3.92, 3.94 (each 3H, s, OMe), 6.44, 6.64, 6.82 (each 1H, s, ArH). The methyl ether (**32**) was identical with an authentic sample, which was prepared according to Kametani's procedure.[8]

Preparation of the Authentic Sample of Tehaunine (10)——A mixture of 2,3,4-trimethoxyphenethylamine (2 g) and 37% formalin (850 mg) was heated on a water bath for 30 min, and 23% HCl (3.5 ml) was added to the reaction mixture. The whole was heated for a further 5 min. After cooling, the mixture was made alkaline with 10% NH_4OH and the product was extracted with $CHCl_3$. Usual work-up gave 5,6,7-trimethoxytetrahydroisoquinoline (1.9 g, 89.6%) as an oil. Without purification, the cyclic amine was reacted with 37% formalin (1.38 g) in MeOH (50 ml) at room temperature for 1.5 h. $NaBH_4$ (0.6 g) was added in portions to the stirred reaction mixture under ice-cooling, and the whole was stirred at room temperature for 1 h. Work-up as usual gave an oily product (1.9 g), which was purified by column chromatography (SiO_2; eluent, $CHCl_3$) to afford tehaunine (10), colorless needles (40.1 %), mp 228—229 °C (benzene–$CHCl_3$) (lit.[5] 229—230 °C).

Preparation of the Authentic Sample of (±)-*O*-Methylgigantine (14)——A mixture of 2,3,4-trimethoxyphenethylamine (10.8 g) and acetic anhydride (64.8 ml) was allowed to stand overnight, and the reaction mixture was poured into ice-cold water. The whole was stirred for 30 min and made alkaline with sat. $NaHCO_3$. The product was extracted with benzene, and usual work-up gave the acetoamide (10.3 g, 79.3%) as an oil. A mixture of the amide (4.8 g) and $POCl_3$ (4 ml) in benzene (70 ml) was refluxed for 5.5 h, and work-up as usual gave 3,4-dihydro-5,6,7-trimethoxy-1-methylisoquinoline (4.0 g, 88.9%) as an oil. $NaBH_4$ (1.4 g) was added portionwise to an ice-cold MeOH (50 ml) solution of the dihydroisoquinoline (4.0 g), and the whole was stirred at room temperature for 45 min. The solvent was evaporated off, and usual work-up afforded 5,6,7-trimethoxy-1-methyl-tetrahydroisoquinoline quantitatively as an oil. A mixture of the tetrahydroisoquinoline (3.7 g) and 37% formalin (1 ml) in MeOH (60 ml) was stirred at room temperature for 1.5 h, then $NaBH_4$ (1.3 g) was added to the stirred reaction mixture under ice-cooling. The whole was stirred at room temperature for 30 min. Usual work-up gave a brown oil (3.6 g), which was purified by

column chromatography [SiO_2; eluent, benzene–MeOH (100 : 1)] to afford (±)-*O*-methylgigantine (**14**) (an oil, 1.2 g). Methopicrate: mp 201 °C. *Anal.* Calcd for $C_{21}H_{26}N_4O_{10}$: C, 51.01; H, 5.31; N, 11.33. Found: C, 51.02; H, 5.22; N, 11.33.

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