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Studies on Tetrahydroisoquinolines. XIX.[1] Synthesis of (±)-Isothebaine, (±)-1-Hydroxy-2,9-dimethoxy-, (±)-1-Hydroxy-2,10-dimethoxy-, and (±)-2,10-Dimethoxy-aporphines, (±)-2,6-Dimethoxyhomomorphinandienone, and (±)-1-Hydroxy-2,10-dimethoxyhomoaporphine

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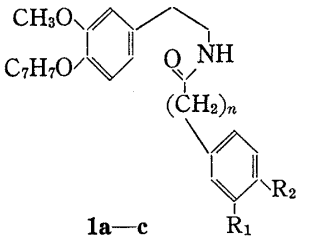
The title alkaloids and two related aporphines have been prepared in considerable yields by trifluoroacetic acid treatment of the corresponding *p*-quinol acetates.

Keywords——oxidation; lead tetraacetate; *p*-quinol acetate; lirinine; trifluoroacetic acid; cyclization; nuclear magnetic resonance; aporphines; homoaporphine; homomorphinandienone

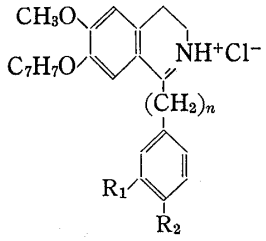
In continuation of our work on aporphine synthesis,[2] we have been interested in the synthesis of aporphines carrying a monomethoxylated D-ring and in that of so-called lirinine,[3] the originally proposed structure of which was recently claimed to be erroneous on the basis of its nuclear magnetic resonance (NMR) spectral data. Here we wish to report the results of trifluoroacetic acid (TFA) treatment of *p*-quinol acetates (**6a**—**c**) and a synthetic confirmation of Chen's reconsideration[4] of the structure of lirinine.

When considered logically, the presence of a methoxyl or similar group *papa* or *ortho* to the cyclizing site in the benzene ring seems to be indispensable for the synthesis of aporphines with a monomethoxylated D-ring. Therefore, we first planned to cyclize 1-(3-methoxybenzyl) (**5a**)- and 1-(3-methoxyphenethyl) (**5b**)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolines, and obtained the following results.

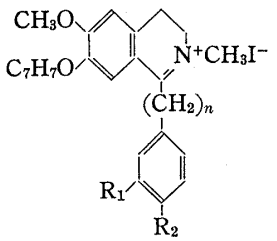


1a—c

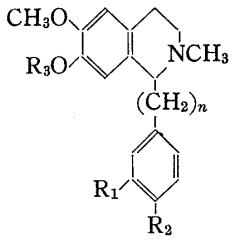
1a: $n=1$, $R_1=OCH_3$, $R_2=H$
1b: $n=2$, $R_1=OCH_3$, $R_2=H$
1c: $n=1$, $R_1=OC_6H_5$, $R_2=OCH_3$



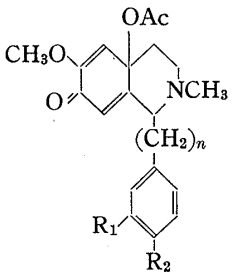
2a—c



3a—c



4a—c: $R_3=C_7H_7$
5a—c: $R_3=H$

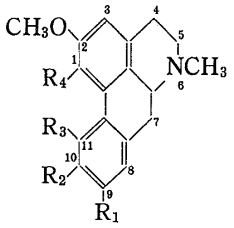


6a—c

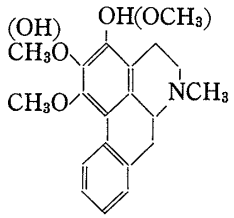
Chart 1

Bishler-Napieralsky cyclization[5] of N-(4-benzyloxy-3-methoxyphenethyl)-3-methoxyphenylacetamide (**1a**) and N-(4-benzyloxy-3-methoxyphenethyl)-3-methoxypropionamide (**1b**) gave the 3,4-dihydroisoquinolinium salts **2a** and **2b**, conversion of which to the metho salts **3a** and **3b** and subsequent reduction with sodium borohydride followed by debenzylation produced the starting isoquinolines **5a** and **5b**.

Oxidation of **5a** and **5b** with lead tetraacetate gave quantitatively the *p*-quinol acetates **6a** and **6b**, which showed the characteristic infrared (IR) absorption bands at 1740, 1675, 1650, and 1630 cm^{-1}. TFA treatment of **6a** furnished, after separation by preparative thin-layer chromatography (TLC), (±)-isothebaine[6] (**7**) and (±)-1-hydroxy-2,9-dimethoxyaporphine[7]



	R_1	R_2	R_3	R_4
7	H	H	OCH_3	OH
8	OCH_3	H	H	OH
11	OC_6H_5	OCH_3	H	OH
12	H	OCH_3	H	OH
13	OCH_3	H	H	OCH_3
14	OC_6H_5	OCH_3	H	OCH_3
15	H	OCH_3	H	OCH_3
16	H	OCH_3	H	H



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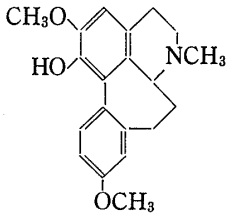

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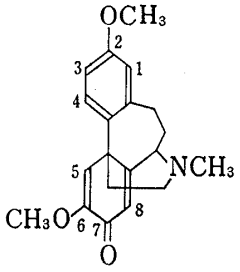

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Chart 2

TABLE 1. Microanalytical Data for New Compounds

Compound	Formula	Molecular weight	Analysis (%) Calcd C	H	N	Found C	H	N
1a	$C_{25}H_{27}NO_4$	405.47	74.05	6.71	3.45	73.95	6.50	3.77
1b	$C_{26}H_{29}NO_4$	419.50	74.44	6.97	3.34	74.67	7.06	3.44
1c	$C_{31}H_{31}NO_5$	497.6	74.83	6.28	2.82	74.89	6.28	2.83
2a	$C_{25}H_{25}NO_3 \cdot HCl$	423.93	70.83	6.18	3.30	71.19	6.25	3.58
2b	$C_{32}H_{30}N_4O_{10}$[a]	630.59	60.95	4.80	8.89	60.85	4.73	8.94
2c	$C_{31}H_{29}NO_4 \cdot HCl \cdot 0.5H_2O$	525.02	70.91	5.95	2.67	71.23	5.99	2.41
3a	$C_{26}H_{28}NO_3I \cdot 0.5H_2O$	538.41	57.80	5.43	2.60	57.94	5.27	2.76
3b	$C_{27}H_{30}NO_3I$	543.43	59.67	5.56	2.58	59.86	5.51	2.69
3c	$C_{32}H_{32}NO_4I \cdot H_2O$	639.5	60.04	5.31	2.19	59.98	4.87	1.81
4a	$C_{26}H_{29}NO_3$	403.5	77.39	7.24	3.47	77.22	7.18	3.43
4b	$C_{27}H_{32}NO_3 \cdot HCl$	454.0	71.43	7.11	3.09	71.26	7.04	3.14
5a	$C_{19}H_{23}NO_3$	313.38	72.82	7.40	4.47	72.50	7.36	4.73
5c	$C_{25}H_{27}NO_4$	405.5	74.05	6.71	3.45	74.18	6.71	3.49
8	$C_{19}H_{21}NO_3$	311.37	73.29	6.80	4.50	73.62	6.80	4.50
10	$C_{21}H_{26}NO_3I \cdot 0.5H_2O$	476.35	52.91	5.67	2.94	52.57	5.52	2.63
11	$C_{25}H_{24}NO_4$	403.5	74.42	6.25	3.47	74.37	6.26	3.40
12	$C_{19}H_{21}NO_3$	311.38	73.29	6.80	4.50	73.12	6.86	4.58
13	$C_{21}H_{26}NO_3I$[b]	467.34	53.97	5.61	3.00	53.84	5.73	2.85
14	$C_{26}H_{27}NO_4$	417.51	74.80	6.52	3.36	74.75	6.49	3.21
17	$C_{20}H_{23}NO_3$	325.39	73.82	7.12	4.30	74.20	6.99	4.34

a) Picrate. b) Methiodide.

(**8**) in 22 and 53% yields, respectively. The structure of the latter was substantiated especially by the presence of one proton doublet at δ 8.26 (J=8 Hz) assignable to the C_{11} hydrogen atom of aporphine in the NMR spectrum. Since non-identity of **8** with the natural lirinine had been confirmed by Yunusov,[8] Chen's suggestion for the correct structure, 2-hydroxy-1,3-dimethoxy- or 3-hydroxy-1,2-dimethoxy-aporphine (**9**) was strongly supported.

Similar treatment of **6b** gave 2,6-dimethoxyhomomorphinandienone (**17**) and 1-hydroxy-2, 10-dimethoxyhomoaporphine[9] (**10**) in 45 and 11% yields, respectively. The structures of the products were assigned on the basis of spectroscopic evidence [for **17**: IR bands at 1663, 1635, and 1607 cm^{-1}. For **10**: NMR signal of one proton doublet at δ 7.47 (J=9.5 Hz)].

Table II. IR ($CHCl_3$) and NMR Spectral Data for Tetrahydroisoquinoline

Compound	IR (cm^{-1}) OH	NMR (δ) NMe	OMe	OCH_2Ph	8-H	5-H
4a		2.48	3.68, 3.78	4.75	6.07	6.53
4b		2.40	3.69, 3.78	5.02		
4c		2.33	3.62, 3.67	4.74	6.21	6.41
5a	3550	2.41	3.68, 3.77		6.32	6.47
5b	3400	2.41	3.72, 3.77			
5c	3550	2.30	3.59, 3.60		6.23	6.35

Table III. IR ($CHCl_3$) and NMR Spectral Data for Aporphines

Compound	IR(cm^{-1}) OH	NMR (δ)(J in Hz) NMe	OMe	3-H	8-H	9-H	11-H	Others
7	3250	2.53	3.86, 3.93	6.64				6.70—7.40(3H, m)
8	3505	2.51	3.78, 3.81	6.46			8.26(d) (8)	6.70—6.90(2H, m)
11	3540	2.56	3.84, 3.88	6.55	6.81		8.17	
12	3520	2.59	3.84, 3.89	6.58	7.16(d) (8)	6.77(dd) (3, 8)	8.01(d) (3)	
13[a]		2.47	3.58, 3.77, 3.80	6.50			8.24(d) (9)	6.71—6.86(2H, m)
14		2.51	3.73, 3.88, 3.90	6.63	6.83		8.20	
15		2.57	3.69, 3.84, 3.89	6.64	7.16(d) (8)	6.80(dd) (3, 8)	8.03(d) (3)	
16		2.63	3.86, 3.87	6.64(d) (3)				

a) Run on a Hitachi model R-24B (60 MHz) spectrometer.

In order to widen the scope of our aporphine synthesis, the applicability of the phenoxyl group for effective cyclization was explored, with the following results.

A similar sequence of reactions on N-(4-benzyloxy-3-methoxyphenethyl)-4-methoxy-3-phenoxyphenylacetamide (**1c**) gave the 7-phenolic 1,2,3,4-tetrahydroisoquinoline (**5c**), the oxidation of which quantitatively afforded the *p*-quinol acetate (**6c**) (IR bands at 1740, 1690, 1660, and 1640 cm^{-1}) as usual. Treatment of **6c** with TFA produced 1-hydroxy-2,10-dimethoxy-9-phenoxyaporphine (**11**) in 49% yield. Its structure was confirmed by the presence of one proton singlet at δ 8.17 in the NMR spectrum. Thus, the phenoxyl group was also proved to be suitable for the aporphine cyclization.

By using the known reductive dephenoxylation,[10] the preparation of an aporphine bearing a monomethoxylated D-ring was expected to be possible. As expected, treatment of **11** with sodium in liquid ammonia ensured removal of the phenoxyl group, leading to 1-hydroxy-2,10-dimethoxyaporphine (**12**) in 91% yield.

Methylation of **8**, **11**, and **12** with diazomethane gave 1,2,9-trimethoxy (**13**)-, 1,2,10-trimethoxy-9-phenoxy (**14**)-, and 1,2,10-trimethoxy[11] (**15**)-aporphines. Dephenoxylation of **14** as described above led to 2,10-dimethoxyaporphine[12] (**16**).

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. NMR spectra were taken a JEOL model JNR-4H-100 (100 MHz) spectrometer in $CDCl_3$ solution with Me_4Si as an internal standard, and IR spectra were run on a Hitachi model 215 ($CHCl_3$) or 225 (KBr) spectrometer. Unless otherwise noted, preparative TLC and column chromatography were performed on silica gel HF_{254} (Merck) and silica gel (>100 mesh, Kanto Chemical Co., Inc.,), respectively. Microanalytical data for all new compounds and spectral data for tetrahydroisoquinolines and aporphines are listed in Table I, II, and III, respectively.

General Procedure[13] for the Synthesis of 7-Phenolic 1,2,3,4-Tetrahydroisoquinolines 5a, 5b, and 5c——A mixture of 4-benzyloxy-3-methoxyphenethylamine and an appropriate acid or ester was heated for several hours to give the corresponding amides (**1a**, **1b**, and **1c**), Bishler-Napieralsky reaction of which afforded the 3,4-dihydroisoquinoline hydrochlorides (**2a**, **2b**, and **2c**). Quaternization of the free bases with methyl iodide gave the metho salts (**3a**, **3b**, and **3c**), sodium borohydride reduction of which yielded 7-benzyloxy-1,2,3,4-tetrahydroisoquinolines (**4a**, **4b**, and **4c**). Hydrogenolysis of the bases with palladium on carbon gave **5a**, **5b**, and **5c**. Yields and physical data are as follows. **1a**: 72%, mp 115—116° (MeOH); IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1634 (C=O). **1b**: 73%, mp 95—96°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1640 (C=O). **1c**: 91%, mp 115—116° (AcOEt); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 1660 (C=O). **2a**: 100%, mp 227—228° (MeOH); IR ν_{max}^{KBr} cm^{-1}: 1636 ($C=\overset{+}{N}H$). **2b**: 87%, mp 150—151° (iso-PrOH); IR ν_{max}^{KBr} cm^{-1}: 1640 ($C=\overset{+}{N}H$) [picrate, mp 145—146° (MeOH)]. **2c**: 85%, mp 216—217° (abs. EtOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 ($C=\overset{+}{N}H$). **3a**: 72%, mp 183—184° (acetone–MeOH); IR ν_{max}^{KBr} cm^{-1}: 1624 ($C=\overset{+}{N}<$. **3b**: 76%, mp 138—139° (MeOH); IR ν_{max}^{KBr} cm^{-1}: 1640 ($C=\overset{+}{N}<$). **3c**: 93%, mp 178—179° (iso-PrOH); IR ν_{max}^{KBr} cm^{-1}: 1630 ($C=\overset{+}{N}<$). **4a**: 85%, mp 67—68° (*n*-hexane). **4b**: 98%, oil (HCl salt, mp 215°). **4c**: 96%, oil. **5a**: 80%, mp 100.5—101.5° (iso-PrOH). **5b**: 76%, oil. **5c**: 82%, mp 145—146° (ether).

Syntheses of 7, 8, 10, 11, and 17——$Pb(OAc)_4$ oxidation and subsequent treatment with CF_3CO_2H were carried out as described previously.[5] The amounts of the starting phenols, methods of purification, melting points and yields of the products, and spectroscopic data for **10** and **17** are shown below. **5a** (200 mg): preparative TLC (development with $CHCl_3$: MeOH=8: 1, mobility **7**>**8**), **7** [mp 163—164° (*n*-hexane), 22%] and **8** [mp 155—156.5° (acetone–ether), 53%]. **5b** (165 mg): preparative TLC (development with $CHCl_3$: MeOH=20: 1, mobility **17**>**10**), **10** [mp 107—109°, 11%; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 2.40 (3H, s, NMe), 3.83, 3.88 (each 3H, s, 2×OMe), 7.47 (1H, d, J=9.5 Hz, 12-H)] and **17** [mp 121—122° (ether), 45%; IR ν_{max}^{KBr} cm^{-1}: 1663, 1635, 1607. NMR δ: 2.35 (3H, s, NMe), 3.63, 3.76 (each 3H, s, 2×OMe), 6.07, 6.32 (each 1H, s, 5- and 8-H), 6.53 (1H, d, J=2.5 Hz, 1-H), 6.81 (1H, dd, J=2.5, 9 Hz, 3-H), 7.36 (1H, d, J=9 Hz, 4-H)]. **5c** (400 mg): silica gel chromatography (elution with $CHCl_3$: MeOH=100: 1), **11**, mp 147—148° (ether), 49%.

Dephenoxylation of 11 and 14——Sodium (115 mg, 4.3 eq) and a solution of **11** (245 mg) in toluene (15 ml) were added alternately to stirred liquid ammonia (50 ml) at −78° under argon at intervals sufficient to maintain the blue color of the solution. The reaction required 4 hr for completion, when the color persisted for 15 min. Ammonia was evaporated off and the residue was shaken with a mixture of 5% HCl and ether. The ether layer was washed with H_2O and the combined acidic layer and washings were basified with conc. NH_4OH. The product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave **12** [mp 178—179° (MeOH), 182 mg (91%)].

When similarly treated, **14** (125 mg) was transformed, after purification by preparative TLC, to oily **16** [11 mg (12%); HCl salt, mp 243—244° (MeOH)].

Methylation of 8, 11, and 12——Usual methylation[5] led to oily **13** [95%; methiodide, mp 212—132° (MeOH)], **14** [mp 145—146° (ether), 100%], and oily **15** [37%; picrate, 184—185° (THF)]. The oily **13** and **15** were purified by neutral Al_2O_3 (Woelm) column chromatography and preparative TLC, respectively.

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