UDC 547.837.07

160. Yoshiro K. Sawa, Kazuhiko Kawasaki, and Shin Mayeda: Studies on Morphinan Derivatives. I. By-products in the Synthesis of 3-Methoxy-N-methylmorphinan.

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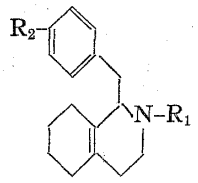
A well-known and convenient reaction which has so far been developed for the synthesis of N-methylmorphinans (II) is the treatment of 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinolines (I) with hydrobromic or phosphoric acid. Some workers[1~5] reported several by-products, having the same composition as that of the objective N-methylmorphinan, in this reaction. Physical constants of those substances are shown in Table I. Among those compounds, the by-product B-I (picrate, m.p. 203°) (cf. Table I), which had been obtained by Grewe, *et al.*,[1] was later identified as N-methylisomorphinan (IIIa) by Gates and his collaborators,[6] who had achieved a unique synthesis of N-methylisomorphinan. This is the only case where the isolation of isomorphinan derivative from this reaction mixture was reported. N-Methylisomorphinan has a *trans*-configuration at the B-C ring juncture in contrast to N-methylmorphinan (IIa), which has *cis*-configuration at this juncture just as in the case of natural morphine.[7]

Table I. By-products Reported in Past Literature



			Reagent	m.p. of by-products	Types, reportedly confirmed	Ref.
B-I B-II	±	$R_1=CH_3$, $R_2=H$	$C\cdot H_3PO_4$	Picrate A, m.p. 203° Picrate B, m.p. 201°	Isomorphinan	1
B-III	±	$R_1=CH_3$, $R_2=OCH_3$, oxalate	$C\cdot H_3PO_4$	m.p. 202~203°		2
B-IV	±	$R_1=CH_3$, $R_2=OCH_3$	48% HBr	m.p. 197~198°		3
B-V	−	$R_1=CH_2\cdot$  , $R_2=OH$	99% H_3PO_4	salicylate, m.p. 226~227°	Aporphine	4
B-VI	+	$R_1=CH_3$, $R_2=OCH_3$	H_3PO_4	m.p. 209~210°	〃	5
B-VII	+	$R_1=CH_2\cdot CH=CH_2$, $R_2=OCH_3$	H_3PO_4	m.p. 158~159°	〃	5

In 1956, Grüssner, *et al.*[5] had successfully revealed that the by-product (B-VI in Table I), m.p. 209~210°, obtained in this morphinan synthesis using (+)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (Ic), has an apomorphine-type structure (IVc), *i.e.* (+)-10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine by the method shown in Chart 1. According to their result, (+)-3-methoxy-N-methylmorphinan (IIc) gave 3-methoxyphenanthrene (VIII), whereas (+)-10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine (IVc) gave 1-ethyl-6-methoxyphenanthrene. On applying this method, the by-products (B-V, B-VII) (in Table I) obtained in their previous works[4,5] were also proved to have the hexahydroaporphine structure from the degradation products.

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1) R. Grewe, A. Mondon: Ber., **81**, 279(1948).
2) O. Schnider, J. Hellerbach: Helv. Chim. Acta, **33**, 1437(1950).
3) H. Henecka: Ann., **583**, 110(1953).
4) J. Hellerbach, A. Grüssner, O. Schnider: Helv. Chim. Acta, **39**, 429(1956).
5) A. Grüssner, J. Hellerbach, A. Brossi, O. Schnider: *Ibid.*, **39**, 1371(1956).
6) M. Gates, R. B. Woodward, W. F. Newhall, R. Künzli: J. Am. Chem. Soc., **72**, 1141(1950).
7) H. Corrodi, J. Hellerbach, A. Züst, E. Hardegger, O. Schnider: Helv. Chim. Acta, **42**, 212(1959).

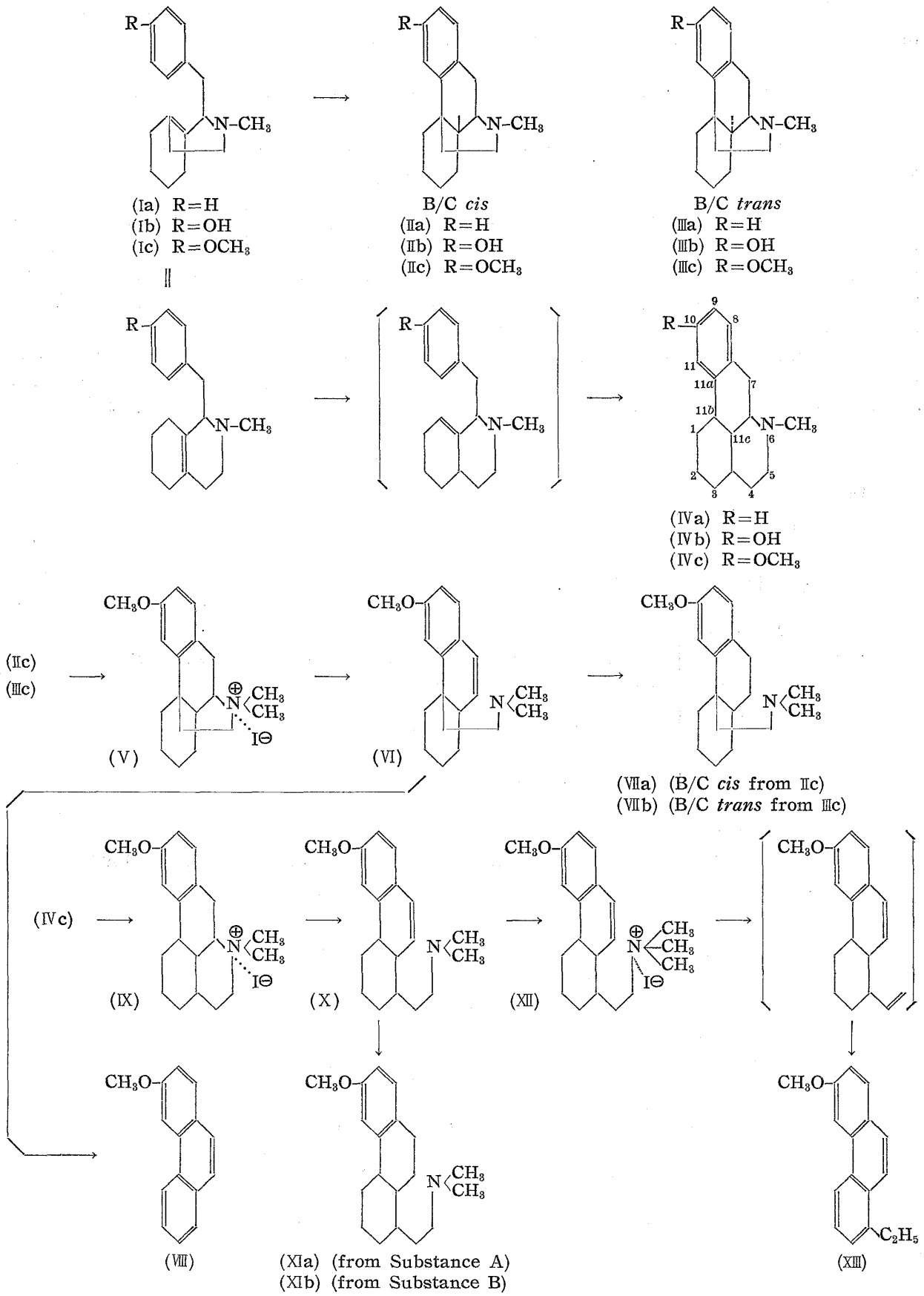


Chart 1.

Thus, an excellent procedure for distinguishing between the two types of the products, morphinans and hexahydroaporphines, has been established.

Even though the inspection of molecular models shows that at least three steresisomers are possible for hexahydroaporphine compounds, steric relationship among those compounds has never been elucidated.

Some other by-products (B-II, B-III, and B-IV in Table I) have reportedly been obtained in this reaction, but nothing has been commented on the structures of these substances.

In the synthesis of (+)-3-methoxy-N-methylmorphinan (IIc) from (+)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (Ic), attempt was made to isolate as many by-products as possible from the reaction mixture, and degradations of these substances to the corresponding phenanthrene derivatives were carried out for the elucidation of their structures.

Thus, (+)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (Ic) was heated with 48% hydrobromic acid or phosphoric acid according to the method described in the literature[1,3] and the reaction mixture was worked up as shown in Chart 2. When

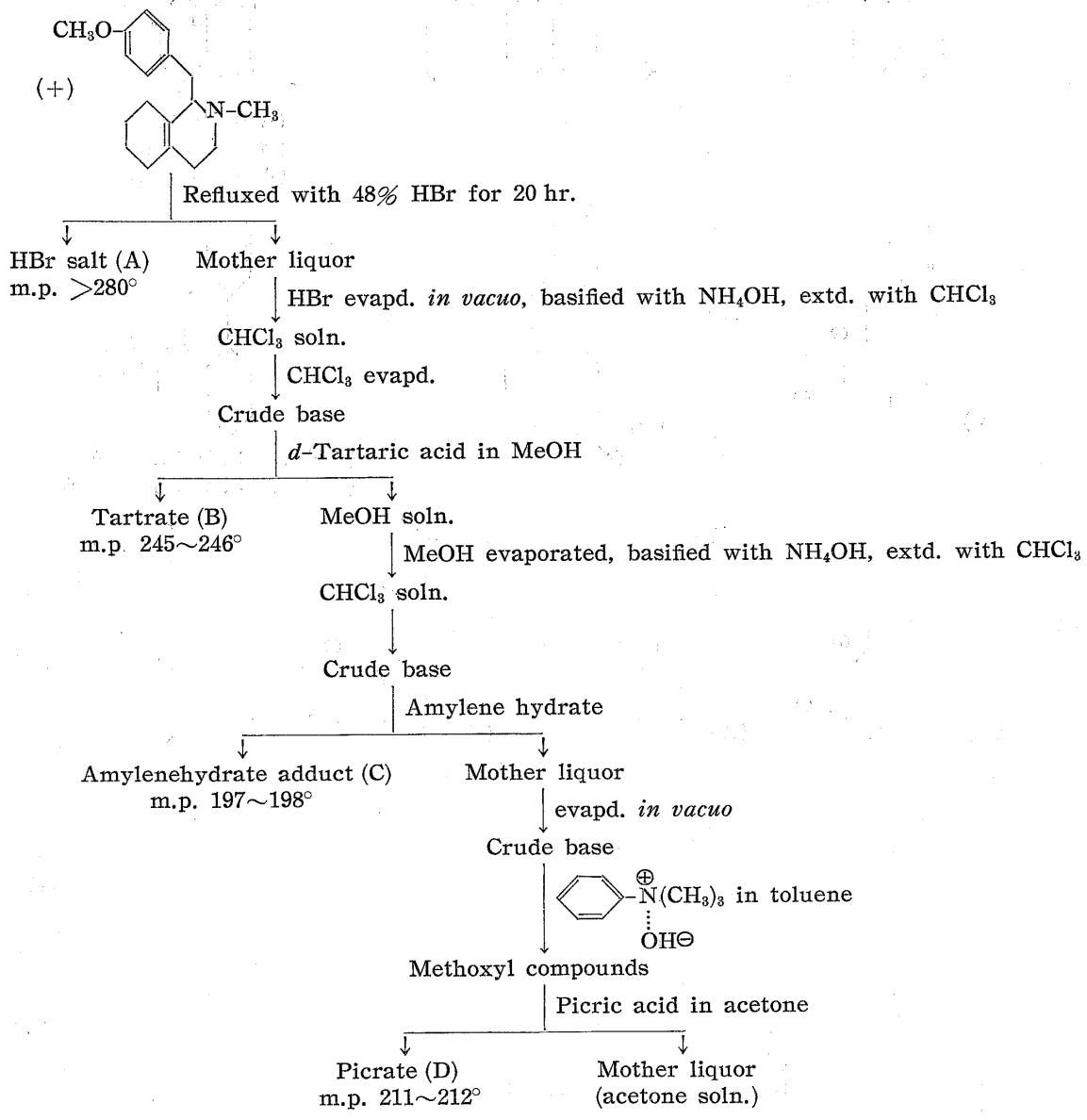
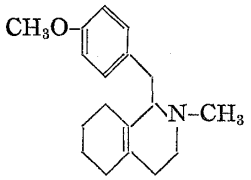


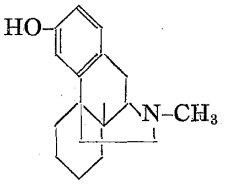
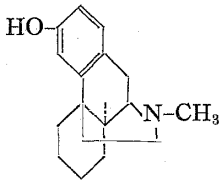
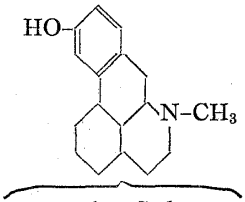
Chart 2.

phosphoric acid was used, the crude hydroxyl base was heated with 48% hydrobromic acid for an hour after separation from phosphoric acid. By this treatment methoxyl compounds were converted to hydroxyl compounds.

The yields of the isolated by-products are shown in Table II.

Table II. Yield of By-products



	Reaction conditions	 Substance C (Morphinan)	 Substance D (Isomorphinan)	 Substance A isolated as hydrobromide	Substance B isolated as *d*-tartrate
(+)	48% HBr 20 hr.[a]	39%	5.5%	2.8%	35%
(+)	85% H_3PO_4 70 hr.[b]	60.2%	2.9%	0.4%	11.8%
(−)	48% HBr 20 hr.[a]	36%	3.2%	3.6%	24%

a) reflux *b*) 140~150°

Among these substances (A, B, C, and D), (C) is the amylenehydrate adduct of (+)-3-hydroxy-N-methylmorphinan (IIb) and the physical data of this compound and the methylated substance are all identical with those of the authentic samples.

Substance (A) was isolated in the form of hydrobromide, m.p. >280°, as shown in Chart 2. The free base, m.p. 206~207°, $C_{17}H_{23}ON$, was methylated with phenyltrimethylammonium hydroxide and this methoxyl compound afforded 1-ethyl-6-methoxyphenanthrene (XIII) through Hofmann degradation and successive dehydrogenation as described in the Experimental part. From this result, substance (A) was concluded to have a hexahydroaporphine structure (IV).

The tartrate of substance (B) melts at 245~246°, and its free base, m.p. 209~210°, was methylated and degradated as above to give the very same 1-ethyl-6-methoxyphenanthrene. Thus, this substance also has the hexahydroaporphine structure. According to Grüssner, *et al.*,[5] they had also obtained a by-product which showed the same melting point, 209~210°, as this substance (B) and 1-ethyl-6-methoxyphenanthrene was given as its degradation product.

Substance (D) (picrate, m.p. 211~212°) gave an oily base and degradations of this compound in a similar way afforded 3-methoxyphenanthrene (VIII). Demethylation of the methoxyl compound by heating with 48% hydrobromic acid yielded a hydroxyl compound which melted at 172~173°, and this value is identical with that of (+)-3-hydroxy-N-methylisomorphinan described in the report of Gates, *et al.*[8] It may reasonably be deduced that the substance (D) is a picrate of (+)-3-methoxy-N-methylisomorphinan (IIIc).

Further (−)-enantiomers of the by-products were obtained from the reaction mixture using corresponding (−)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (Ic) as a starting material, and racemic compounds were prepared from these enantiomers by mixing equal part of (+) and (−) compounds in order to compare with these compounds listed in literature. Physical constants of these substances are tabulated in Tables III, IV, V, and VI.

Considering from these data, it is assumed that the racemic substance, m.p. 197~198° (B-IV in Table I), obtained by Henecka,[3] may be identical with substance (B), m.p. 197~198° (hydrobromide, m.p. 287~288°) (cf. Table VI), obtained in the present experiment,

8) M. Gates, W. G. Weff: J. Am. Chem. Soc., **80**, 1186(1958).

Table III. 3-Hydroxy-N-methylmorphinan (Substance C)

	+	−	±
Base, m.p. (°C)	197～198	197～198	252～253
$[\alpha]_D^{20}$ *	+42°±2°	−41.5°±2°	—
Salicylate, m.p. (°C)	220	220～221	212～214

* Amylenehydrate adduct.

Table IV. 3-Hydroxy-N-methylisomorphinan (Substance D)

	+	−	±
Base, m.p. (°C)	172～173	171～173	212～214
$[\alpha]_D^{30(19)}$	^{30} +59.2°±2°	^{19} −60.6°±2°	—
Methiodide, m.p. (°C)	244～245	—	—

Table V. 10-Hydroxy-hexahydroaporphine (Substance A)

	+	−	±
Base, m.p. (°C)	206～207	203.5～205	216～218*
$[\alpha]_D^{20}$	+175.6°±2°	−171.6°±2°	—
Hydrobromide, m.p. (°C)	280	280	>280

* EtOH adduct

Table VI. 10-Hydroxy-hexahydroaporphine (Substance B)

	+	−	±
Base, m.p. (°C)	209～210	209～210	197～198
$[\alpha]_D^{20}$	+111.5°±2°	−114°±2°	—
Picrate, m.p. (°C)	249～250	250～251	243～244
Hydrobromide, m.p. (°C)	—	—	287～288

and this is presumably a stereoisomer of 10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine (IV). Furthermore, a racemic by-product, m.p. 202～203° (hydrobromide, m.p. 282～283°) (B-III in Table I), described in the report of Schnider, *et al.*,[2] may also be considered to be identical with this substance because of the close resemblance of the melting point of both free base and its hydrobromide.

After separating the substance (D) as in Chart 2, acetone solution was evaporated and the residue was decomposed by alkali to a methoxyl base, which was demethylated by refluxing with 48% hydrobromic acid. The two basic substances, (E) and (F), were then separated. Substance (E), m.p. 214～215°, has an empirical formula $C_{17}H_{23}ON$, the same composition as 3-hydroxy-N-methylmorphinan. The yield was 0.05% and the specific rotation of this substance is $[\alpha]_D^{26}$ +79.2° (c=1.0 in EtOH). It showed a remarkable depression on admixture with the free base of substances (A) and (B). The substance (F), m.p. 86～88°, was optically inactive and its empirical formula is $(C_9H_{11}N)_2$ from analysis and molecular weight determination by the Rast method. The yield was 0.1.%. It formed a picrate, m.p. 189～190°, and a methiodide, m.p. 242～244°.

On these two substances, (E) and (F), detailed examinations were withheld because of insufficient quantity of the materials available.

Experimental*2

Reaction conditions and isolation procedures for the following substances are summarized in Table II and Chart 2.

Degradations of (+)-3-Hydroxy-N-methylmorphinan (IIb) (Substance C)—This compound is the major product and was isolated as the amylene-hydrate adduct as shown in Chart 2. Methylation, Hofmann degradation, and dehydrogenation of this substance were carried out in the same way as described by Grüssner, *et al.*[5] Degradation product was 3-methoxyphenanthrene (VIII), the melting point of its picrate (m.p. 121～122°) and the ultraviolet absorption spectrum were confirmed to be identical with those in the literature. The Hofmann degradation product of (IIc) was hydrogenated in the presence of 30% Pd-C catalyst at atmospheric pressure and a saturated compound, (+)-6-methoxy-4a-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VIIa) was obtained.

*2 All m.p.s are uncorrected.

Hydrochloride : Colorless pillars (from EtOH), m.p. 254~255°, $[\alpha]_D^{20}$ +14.9°±2° (C=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{29}ON \cdot HCl$: C, 70.46; H, 8.71; N, 4.33. Found : C, 69.98; H, 9.45; N, 4.49.
Picrate : Yellow plates (from EtOH), m.p. 173~174°. *Anal.* Calcd. for $C_{19}H_{29}ON \cdot C_6H_3O_7N_3$: C, 58.13; H, 6.24; N, 10.85. Found : C, 58.41; H, 6.51; N, 10.80.

Degradations of (+)-10-Hydroxy-1,2,3,3a,11b,11c-hexahydroaporphine (IVb) (Substance B)—This by-product was already obtained by Grüssner, *et al.*[5] It was isolated as its tartrate, m.p. 245~246° (Chart 2), and afforded 1-ethyl-6-methoxyphenanthrene (XIII) (picrate, m.p. 124~125°), by degradation as described in the literature. Its melting point and ultraviolet absorption spectrum were all identical with those reported. Hofmann degradation product of (IVc) (Substance B) was hydrogenated in the presence of 30% Pd-C catalyst and a saturated compound, (+)-6-methoxy-1-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XIb), was obtained.
Methiodide : Colorless plates (from AcOEt-MeOH), m.p. 214~215°, $[\alpha]_D^{19}$ +4.3°±2° (c = 1.0, MeOH). *Anal.* Calcd. for $C_{20}H_{32}ONI$: C, 55.94; H, 7.51; N, 3.26. Found : C, 55.53; H, 7.78; N, 3.22.

Degradation of Substance A; (+)-10-Hydroxy-1,2,3,3a,11b,11c-hexahydroaporphine (IVb)—This was isolated as in Chart 2, as its hydrobromide of colorless needles (from H_2O), m.p. >280°. *Anal.* Calcd. for $C_{17}H_{23}ON \cdot HBr$: C, 60.83; H, 7.32; N, 4.14; Br, 23.62. Found : C, 59.99; H, 7.36; N, 4.11; Br, 23.72. The free base was recrystallized from Et_2O to colorless cubes, m.p. 206~207°, $[\alpha]_D^{20}$ +175.6°±2° (c=0.5, EtOH).

(+)-10-Methoxy-1,2,3,3a,11b,11c-hexahydroaporphine (IVc)—MeOH solution of phenyltrimethylammonium hydroxide (from 7.8 g. of its tosylate) was added to a solution of the free base of substance A (1.3 g.) in toluene (50 cc.) and MeOH was removed by evaporation. The residual solution was heated under reflux for 4 hr. Toluene was concentrated *in vacuo* to obtain a non-phenolic compound (1.3 g.) as a residue. It was purified as its hydrochloride of needles (from H_2O), m.p. 265~266°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot HCl \cdot \frac{1}{2}H_2O$: C, 68.21; H, 8.59; N, 4.42. Found : C, 68.22; H, 8.61; N, 4.36.
Picrate : Yellow needles (from MeOH), m.p. 179~180°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_6H_3O_7N_3$: C, 57.54; H, 5.63; N, 11.19. Found : C, 58.00; H, 5.93; N, 11.13.
Methiodide (IX) : Colorless plates (from MeOH), m.p. 262~263°, $[\alpha]_D^{23}$ +82°±2° (c=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{28}ONI$: C, 55.21; H, 6.83; N, 3.39; I, 30.71. Found : C, 55.27; H, 6.79; N, 3.29; I, 30.68.

(−)-6-Methoxy-1-(2-dimethylaminoethyl)-1,2,3,4,4a,10a-hexahydrophenanthrene (X)—The methiodide (IX) (4.13 g.) in H_2O (30 cc.) was converted to methohydroxide by heating with fresh Ag_2O (from 4.13 g. of $AgNO_3$) at 50° for 1 hr. Precipitated AgI was filtered off and the filtrate was concentrated *in vacuo* to dryness. The residual oil was extracted with Et_2O. The crude base (2.3 g.) was obtained.
Picrate : Orange rhombics (from EtOH), m.p. 137~138°. *Anal.* Calcd. for $C_{19}H_{27}ON \cdot C_6H_3O_7N_3$: C, 58.36; H, 5.88; N, 10.89. Found : C, 58.39; H, 6.14; N, 10.92.
Methiodide (XII) : White plates (from EtOH), m.p. 243~244°, $[\alpha]_D^{21}$ −126.9°±2° (c=1.0, MeOH). *Anal.* Calcd. for $C_{20}H_{30}ONI$: C, 56.20; H, 7.07; N, 3.28. Found : C, 56.33; H, 7.03; N, 3.73.

(+)-6-Methoxy-1-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XIa)—Hydrogenation of the foregoing base (X) in the presence of 30% Pd-C catalyst resulted in the absorption of about 1 mole of H_2. After evaporation of the solvent, the residue was purified as the hydrochloride of white fine granules (from EtOH), m.p. 212~213°, $[\alpha]_D^{21}$ +54.8°±2° (c = 1.0, MeOH). *Anal.* Calcd for $C_{19}H_{29}ON \cdot HCl$: C, 70.46; H, 9.34; N, 4.33. Found : C, 70.49; H, 9.38; N, 4.29.
Picrate : Orange yellow needles (from EtOH), m.p. 166~167°. *Anal.* Calcd. for $C_{19}H_{29}ON \cdot C_6H_3O_7N_3$: C, 58.13; H, 6.24; N, 10.85. Found : C, 58.08; H, 6.35; N, 11.09.

1-Ethyl-6-methoxyphenanthrene (XIII)—The methiodide (XII) (2.5 g.) in 30% MeOH (150 cc.) was treated with fresh Ag_2O (from 2.5 g. of $AgNO_3$) at 50° for 1 hr. The filtrate was evaporated *in vacuo* and the residue was heated at 120~125° for 2 hr. The reaction mixture was extracted with Et_2O, washed with 5% HCl and H_2O, dried, and evaporated. The residue (0.45 g.) was dehydrogenated with 5% Pd-C (0.1 g.) at 310~315°. The residue was extracted with Et_2O, evaporated, the residual oil (0.34 g.) was dissolved in petr. ether, and chromatographed over alumina. The eluates afforded a pale yellow oil. Its picrate recrystallized from MeOH to red needles, m.p. 127~128°. *Anal.* Calcd. for $C_{17}H_{16}O \cdot C_6H_3O_7N_3$: C, 59.35; H, 4.12; N, 9.03. Found : C, 59.73; H, 4.16; N, 8.72.

Admixture of this picrate with 1-ethyl-6-methoxyphenanthrene picrate, m.p. 124~125°, showed no depression. The aromatic hydrocarbon freed from the picrate was recrystallized from EtOH to colorless plates, m.p. 65~66°.

Degradations of Substance D; (+)-3-Methoxy-N-methylisomorphinan (IIIc)—This compound was isolated as its picrate (Chart 2) of yellow plates (from EtOH), m.p. 211~212°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_6H_3O_7N_3$: C, 57.54; H, 5.63; N, 11.19. Found : C, 57.98; H, 5.73; N, 11.61. The free base did not crystallize.
Methiodide (V) : Colorless plates (from MeOH-Me_2CO), m.p. 245~246°, $[\alpha]_D^{25}$ +13.5°±2° (c=2.0, MeOH). *Anal.* Calcd. for $C_{19}H_{28}ONI$: C, 55.21; H, 6.83; N, 3.39; I, 30.78. Found : C, 55.33; H, 7.15; N, 3.27; I, 30.29.

(+)-6-Methoxy-4a-(2-dimethylaminoethyl)-1,2,3,4,4a,10a-hexahydrophenanthrene (VI)—The fore-

going methiodide (V) (4.1 g.) was treated with Ag_2O (from 4.1 g. of $AgNO_3$) at 50° for 1 hr. The degradation product was extracted with Et_2O and a crude oily base (2.6 g.) was obtained.
Picrate: Yellow rods (from EtOH), m.p. 161~162°. *Anal.* Calcd. for $C_{19}H_{27}ON \cdot C_6H_3O_7N_3$: C, 58.36; H, 5.88; N, 10.89. Found: C, 57.54; H, 5.90; N, 10.70.
Methiodide: Colorless plates (from EtOH), m.p. 217~218°, $[\alpha]_D^{21}$ +144.5°±2° (c=1.0, MeOH). *Anal.* Calcd. for $C_{20}H_{30}ONI$: C, 56.20; H, 7.08; N, 3.28. Found: C, 56.29; H, 7.06; N, 3.10.

(−)-6-Methoxy-4a-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VIIb)—This compound was obtained by hydrogenation of the foregoing base (VI) in the presence of 30% Pd-C catalyst at atmospheric pressure.
Hydrochloride: Colorless needles (from H_2O), m.p. 268~269°, $[\alpha]_D^{20}$ −24.3°±2° (c=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{29}ON \cdot HCl$: C, 70.46; H, 9.34; N, 4.33. Found: C, 70.13; H, 9.40; N, 4.07.
Picrate: Yellow needles (from EtOH), m.p. 164.5~166°. *Anal.* Calcd. for $C_{19}H_{29}ON \cdot C_6H_3O_7N_3$: C, 58.13; H, 6.24; N, 10.85, Found: C, 57.93; H, 6.43; N, 10.83.

3-Methoxyphenanthrene (VIII)—The foregoing base (VI) (2.22 g.) was mixed with 5% Pd-C (0.25 g.) and heated at 300~310° for 3 hr. The reaction mixture was extracted with Et_2O and washed with 5% HCl and H_2O. The residue was dissolved in petr. ether and passed through alumina column. The petr. ether eluates afforded colorless plates, m.p. 95~97°. Admixture with phenanthrene showed no depression.

Benzene eluates afforded an oily product. The picrate of this compound formed red needles, m.p. 119~120°. Admixture with 3-methoxyphenanthrene picrate, m.p. 121~122°, gave no depression.

(+)-3-Hydroxy-N-methylisomorphinan (IIIb)—The base of the methoxyl compound (IIIc) was refluxed with 48% HBr for 1 hr., evaporated to dryness, basified with K_2CO_3, and extracted with Et_2O. This solution was chromatographed over alumina. Fine needles (from Et_2O), m.p. 172~173°, $[\alpha]_D^{30}$ +59.5°±2° (c=2.0, MeOH). *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.68; H, 9.00; N, 5.41.
Methiodide: Colorless cubes (from MeOH-Me_2CO), m.p. 244~245°. *Anal.* Calcd. for $C_{18}H_{26}ONI$: C, 54.14; H, 6.56; N, 3.51. Found: C, 54.32; H, 6.57; N, 4.00.
Picrate: Yellow plates (from EtOH), m.p. 212~213°.

Levorotatory Substances—(−)-1-(*p*-Methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (Ic; *l*-enantiomer) was treated with 48% HBr under reflux for 20 hr. The reaction mixture was worked up as shown in Chart 2.

(−)-10-Hydroxy-1,2,3,3a,11b,11c-hexahydroaporphine (IVb) (Substance A)—Hydrobromide: Colorless needles (from H_2O), m.p. >280°. Base: Colorless cubes (from Et_2O), m.p. 203.5~205° $[\alpha]_D^{20}$ −171.6°±2° (c=0.5, EtOH). *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.33, H, 9.01; N, 5.44. Found: C, 79.22; H, 9.10; N, 5.26.

(−)-10-Hydroxy-1,2,3,3a,11b,11c-hexahydroaporphine (IVb) (Substance B)—*d*-Tartrate: Colorless fine needles (from H_2O), m.p. 210~211°. *Anal.* Calcd. for $C_{17}H_{23}ON \cdot C_4H_6O_6 \cdot H_2O$: C, 59.28; H, 7.34; N, 3.29. Found: C, 59.63; H, 7.49; N, 3.18. Base-MeOH adduct: Colorless cubes (from MeOH), m.p. 209~210° (sint. 120°), $[\alpha]_D^{19}$ −99.85°±2° (c=1.0, MeOH). *Anal.* Calcd. for $C_{17}H_{23}ON \cdot CH_3OH$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.35; H, 9.26; N, 4.90.
MeOH was evaporated at 120° and the base melted at 209~210°, $[\alpha]_D^{20}$ −114°±2° (c=1.0, MeOH). Methoxyl base: Colorless needles (from petr. ether), m.p. 98~99°, $[\alpha]_D^{19}$ −112.5° (c=2.0, EtOH). *Anal.* Calcd. for $C_{18}H_{25}ON$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.85; H, 9.31; N, 5.29.
Oxalate: Colorless plates (from H_2O), m.p. 192~193° (decomp.). *Anal.* Calcd. for $C_{18}H_{25}ON \cdot (COOH)_2$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.11; H, 7.31; N, 3.95.

(−)-3-Hydroxy-N-methylisomorphinan (IIIb) (Substance D)—Free base, fine white needles (from Et_2O), m.p. 171~173°, $[\alpha]_D^{19}$ −60.6°±2° (c=1.0, MeOH). *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.37; H, 8.99; N, 5.20.

Racemic compounds of these substances (A, B, C, and D) were prepared by mixing 0.5 g. of the two enantiomers and recrystallization from MeOH or EtOH. Melting points of these racemates are given in Tables III, IV, V, and VI.

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Summary

In the synthesis of 3-methoxy-N-methylmorphinan from 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, several by-products, i.e. 3-methoxy-N-methylisomorphinan and two stereoisomers of 10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine, were isolated. One of the 10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphines was considered to be identical with that obtained by Grüssner, *et al.* However, steric correlation of these two hexahydroaporphines remains undecided. Racemic compounds were prepared by mixing equal part of (+) and (−) compounds.

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