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Studies on Morphine Derivatives. II.[1] The Stereochemistry of the By-products in the Synthesis of 3-Methoxy-N-methylmorphinan

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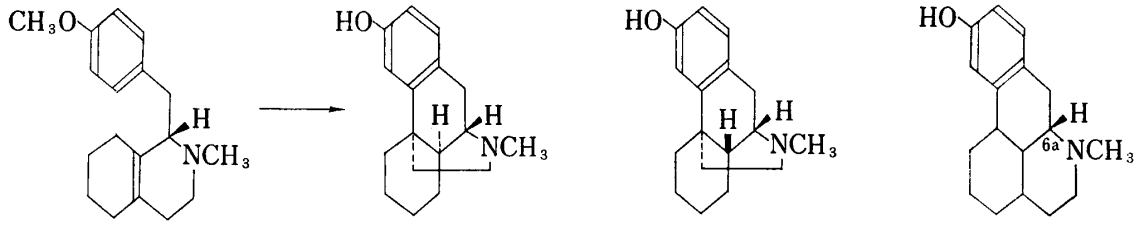
The absolute configuration of (+)-10-hydroxy-1,2,3,3a,11b,11c-hexahydroaporphine A and B (IVa and IVb), which were obtained as by-products on the cyclization of (+)-1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (I) to (+)-3-hydroxy-N-methylmorphinan (II) was established by degradation reaction to 3-alkyl cyclohexane-1,2-dicarboxylic acids.

As described in the previous paper of this series,[1] the cyclization of (+)-1-(4'-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (I)[3] with phosphoric acid or 48% hydrobromic acid afforded (+)-3-hydroxy-N-methylmorphinan(II) along with several by-products, *i.e.* (+)-3-hydroxy-N-methylisomorphinan (III), mp 171—172°, (+)-10-hydroxy-1,2,3,3a, 11b,11c-hexahydroaporphine A (IVa), mp 206—207°, and B (IVb), mp 209—210°.



I II III IVa and b

Chart 1

Among these compounds, (+)-3-hydroxy-N-methylmorphinan (II) and (+)-3-hydroxy-N-methylisomorphinan (III) were proved to be identical with the authentic samples, the latter of which was given by courtesy of M. Gates. The by-product (IVb) was considered to be identical with (+)-10-hydroxyhexahydroaporphine, mp 209—210°, reported by Grüssner, *et al.*[4] because of the close resemblance of the melting point of both free base and its several salts.

However, the absolute configuration of (+) -10-hydroxyhexahydroaporphine A and B (IVa and b) except C_{6a} has remained unsolved.

This paper deals with degradations of these compounds to 3-alkyl cyclohexane-1,2-dicarboxylic acids to elucidate the absolute configuration of these compounds.

The methiodides of the dihydromethines (Va and b)[1] which have been derived from (+)-10-hydroxyhexahydroaporphine A and B (IVa and b), respectively, were converted to the corresponding vinyl compounds (VIa and b) by Hofmann degradation.

1) Part I: Y.K. Sawa, K. Kawasaki, and S. Maeda, *Chem. Pharm. Bull.* (Tokyo), **8**, 960 (1960).
2) Location: *Fukushima-ku, Osaka.*
3) The positive sign of the specific rotation is based on that of its oxalate ($[\alpha]_D^{20}+39°\pm2°$ (MeOH)). The free base was reported to show the negative specific rotation($[\alpha]_D^{21}-78.5°\pm1°$ (ether)) (O. Shnider, A. Brossi, and K. Vogler, *Helv. Chim. Acta*, **37**, 710 (1954)).
4) A. Grüssner, J. Hellerbach, A. Brossi, and O. Schnider, *Helv. Chim. Acta*, **39**, 1371 (1956).

The presence of the vinyl groups was proved by the nuclear magnetic resonance (NMR) signals at 3.9—5.2 τ characteristic of the terminal vinyl group.

Catalytic hydrogenation of these compounds (VIa and b) and the successive oxidation of the resulted ethyl compounds (VIIa and b) with chromium trioxide gave the respective oxo-compounds (VIIIa and b).

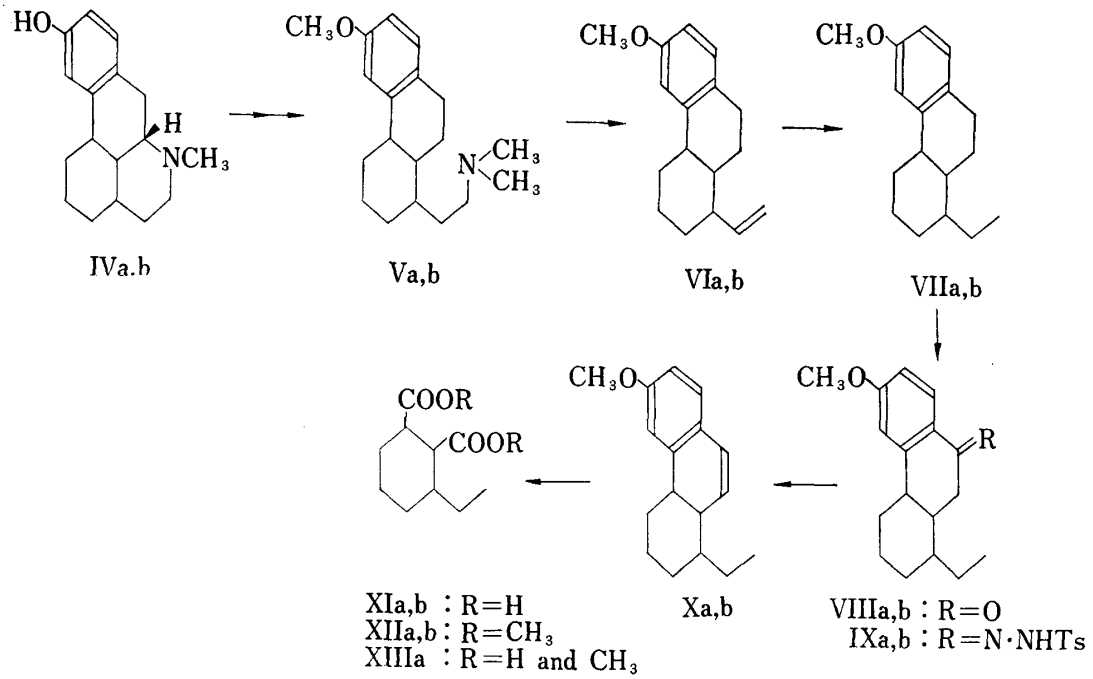


Chart 2

Bamford reaction of the tosylhydrazones (IXa and b) of these compounds led to the hexahydrophenanthrenes (Xa and b), the ultraviolet (UV) spectra of which showed a characteristic absorption maximum of the double bond conjugated to the benzene ring at 273 mμ.

Ozonolysis of Xa and Xb followed by performic acid oxidation gave the respective carboxylic acids, XIa, mp 175—177°, $[\alpha]_D^{25.5}$+2.9° (MeOH) and XIb, mp 127—129°, $[\alpha]_D^{25}$+34.6° (MeOH), the latter of which was purified by distillation of its dimethyl ester (XIIb). Both of these compounds (XIa and b) gave the molecular formula $C_{10}H_{16}O_4$ corresponding to the expected 3-ethylcyclohexane-1,2-dicarboxylic acids.

The infrared (IR) spectrum of the former (XIa) in carbon tetrachloride was in good agreement with that of (±)-*cis*-3-ethylcyclohexane-*cis,trans*-1,2-dicarboxylic acid (XXXVIIIa)[5] except a slight difference in 1300—1250 cm^{-1} region but quite different from those of the other three geometrical isomers, XXXVIIIb, XXXVIIIc, and XXXVIIId.

These four geometrical isomers of (±)3-ethylcyclohexane-1,2-dicarboxylic acid were prepared from 1,3-hexadiene and maleic anhydride or fumaric acid according to the method of Alder, *et al.*[5]

Esterification of the carboxylic acid (XIa) with diazomethane gave the corresponding dimethyl ester (XIIa), the IR spectrum of which was superimposable on that of (±)*cis*-3-ethylcyclohexane-*cis,trans*-1,2-dicarboxylic acid dimethyl ester (XLa) in carbon tetrachloride. The above mentioned slight difference in IR spectra was also observed in IR spectra of the optically active and the racemic *cis*-3-methylcyclohexane-*cis,trans*-1,2-dicarboxylic acid (XXIIa and XXXVIIa) in CCl_4 while the IR spectra of these dimethyl esters (XXIIIa and XXXIXa) were completely consistent with each other.

5) K. Alder and W. Vogt, *Ann.*, **571**, 137 (1951); K. Alder and H. von Bracheel, *ibid*, **608**, 195 (1957).

The optically active compounds (XXIIa and XXIIIa) were derived from (+)-10-hydroxyhexahydroaporphine A (IVa) through the degradation process illustrated in Chart 4 and the racemic compounds (XXXVIIa and XXXIXa) were also prepared by Bussert's[6] method.

The reason why the IR spectra of the above mentioned optically active dicarboxylic acids disagreed with those of the corresponding racemic compounds at about 1300 cm^{-1} has not been cleared.

The IR spectra of the carboxylic acid (XIb) and its dimethylester (XIIb) in carbon tetrachloride were identical with those of (±)*trans*-3-ethylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid (XXXVIIIb) and its dimethyl ester (XLb), respectively.

Treatment of the optically active and the racemic *trans*-3-ethylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid dimethyl esters (XIIb and XLb) with 15% KOH at room temperature gave the original dicarboxylic acids (XIb and XXXVIIIb), whereas on the same saponification the optically active and the racemic *cis*-3-ethylcyclohexane-*cis*,*trans*-1,2-dicarboxylic acid dimethyl esters (XIIa and XLa) gave the corresponding monomethyl esters (XIIIa and XLIIa), the IR spectra of which exactly coincided with each other and showed absortion bands at 1710 and 1738 cm^{-1} due to carboxyl and carbomethoxyl groups.

Although it was not proved which ester grouping was saponified, these monomethyl esters were turned back to the original dimethyl esters respectively by the action of diazomethane.

From these results, the relative configurations of the hydrophenanthrenes derived from (+)-10-hydroxyhexahydroaporphine A and B (IVa and b) should be represented by structures A and B respectively.

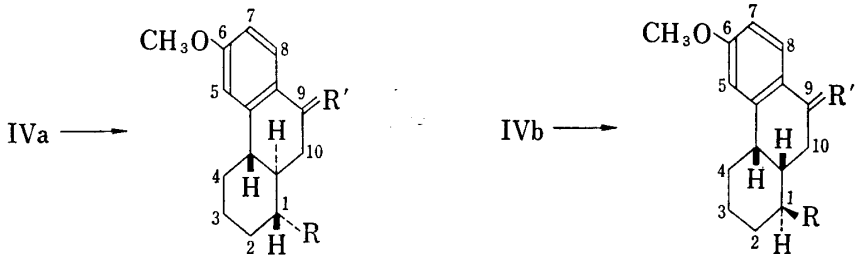


Chart 3

The absolute configuration of the B/C *trans* hydrophenanthrenes (Va—Xa) was also shown by the structure A (Chart 3) based on the comparison of the ORD curves of the oxo compounds VIIIa and XXXI, the latter of which was derived from (−)-3-hydroxy-N-methylisomorphinan (III) according to the Corrodi's degradation method used in the elucidation of the absolute configuration of (−)-3-hydroxy-N-methylmorphinan[7] as shown in Chart 4.

This oxo compound (XXXI) was further transformed into (−)-*trans*-2-methyl-2-carboxylacetic acid (XXXII), mp 144—146°: $[\alpha]_D^{23}$ −122° (acetone)[8] to offer a chemical evidence for the absolute configuration of (−)-3-hydroxy-N-methylisomorphinan (III).

The oxo compounds VIIIa and XXXI exhibited mirror-image dispersion curves in 300—400 mμ region as shown in Fig. 1. This result established that the absolute configuration at the B/C ring juncture of VIIIa was opposite to that of XXXI.

On the other hand the absolute configuration of the B/C *cis* hydrophenanthrenes (Vb—Xb) would be elucidated according to the sign of the Cotton effect in the ORD curve of the oxo compound (VIIIb) if the B/C ring conformation of VIIIb was established.

6) J.F. Bussert, K.W. Greenlee, J.M. Derfer, and C.E. Boord, *J. Am. Chem. Soc.*, **78**, 6076 (1956).
7) H. Corrodi, J. Hellerbach, A. Züst, E. Hardegger, and O. Schnider, *Helv. Chim. Acta*, **42**, 212 (1959).

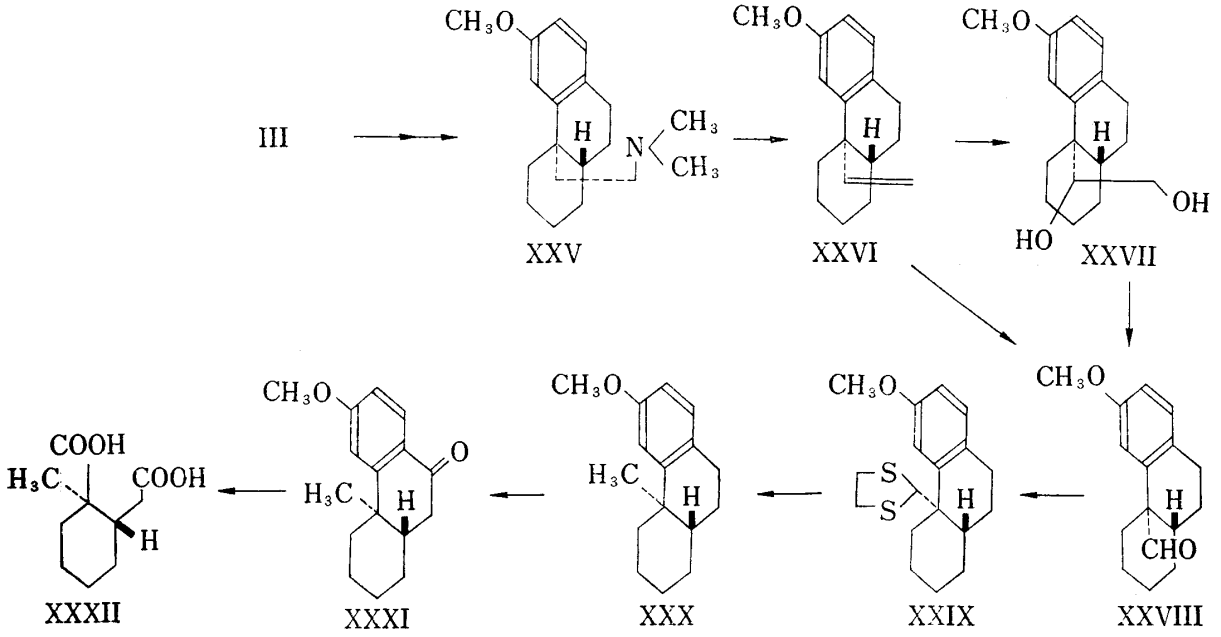


Chart 4

The conformational analysis was carried out by comparison of the chemical shifts of C_5 protons of these compounds with the corresponding chemical shifts of the B/C *trans* hydrophenanthrenes (Va—VIIIa).

In the NMR studies on 7-substituted octahydrophenanthrenes, Nagata, *et al.*[9] reported that the signals of the aromatic C_5-protons in the compounds of type **A** (Chart 5) appeared at the same field as the corresponding signals in compounds of type **B** and at lower fields than the corresponding signals in compounds of type **C** (Chart 5) on account of the steric effect of an equatorial C_4-proton.

According to this result, the chemical shifts of the C_5-protons of the B/C *cis* hydrophenanthrenes (Vb—VIIIb) were expected to be similar as the corresponding chemical shifts of the B/C *trans* hydrophenanthrenes (Va—VIIIa) in the case of the steroidal form

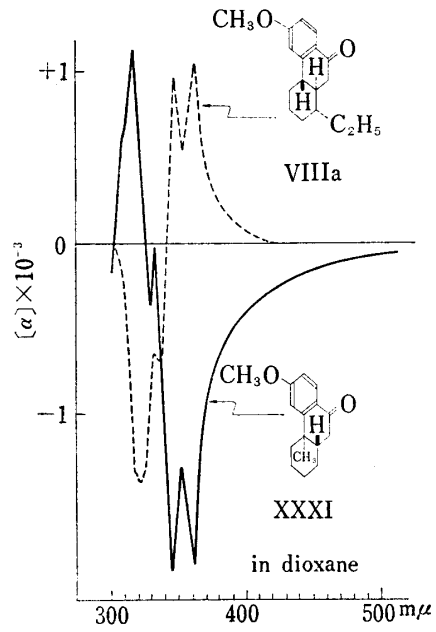


Fig. 1

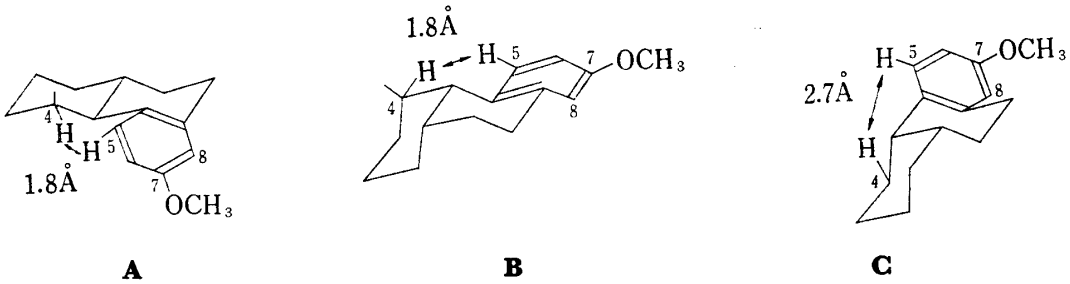


Chart 5

8) B. Rinker, J. Kalvoda, D. Arigoni, A. Füst, O. Jeger, A.M. Gold, and R.B. Woodward, *J. Am. Chem. Soc.*, **76**, 313 (1954).
9) W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3746 (1964).

(type **B**) and to be larger than those of the latter in the case of the nonsteroidal form (type **C**).

As shown in Table I, the signals of the C_5-protons of the B/C *cis* compounds (Vb—VIIIb) were observed at higher fields compared with those of the corresponding B/C *trans* compounds (Va—VIIIa).

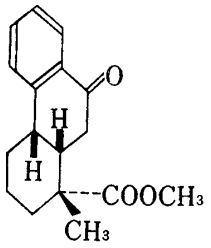
Therefore, the B/C *cis* hydrophenanthrenes would exist in the nonsteroidal form.

Table I. The Chemical Shifts of the C_5 and C_8 Protons (in $CDCl_3$)

Compounds	B/C	C_8–H (τ)	C_5–H (τ)	$\Delta\tau_{5,8}$ (ppm)[a]
Va	*trans*	3.06	3.18	0.12
VIa	*trans*	3.03	3.16	0.13
VIIa	*trans*	3.04	3.16	0.12
VIIIa	*trans*	1.99[b]	3.12	1.13
Vb	*cis*	3.02	3.33	0.31
VIb	*cis*	3.00	3.24	0.24
VIIb	*cis*	3.06	3.30	0.24
VIIIb	*cis*	1.99[b]	3.28	1.29

a) $\Delta\tau_{5,8}$: The difference in the chemical shifts between the C_5 and C_8-protons which was used as an index to the deshielding of the C_5-protons because of the steady chemical shifts of the C_8-protons.
b) The deshielding of this proton was due to the anisotropy of the carbonyl group at C_9.

The absolute configuration of these B/C *cis* hydrophenanthrenes was elucidated by comparison of the Cotton effects of the oxo compound (VIIIb) and methyl 17-nor-9-oxo-deoxy-*enantio*-podocarpate (XIV), the latter of which was derived from abietic acid and was proved to have the nonsteroidal conformation by K. Hirao.[10]

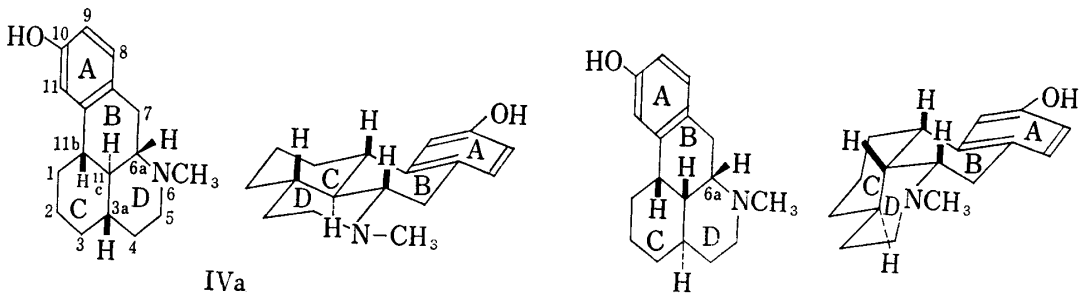


XIV

The ORD curve of the oxo compound (VIIIb) exhibited negative Cotton effects in 300—400 mμ region and the CD curve of XIV[11] was reported to show the same signed Cotton effects in this region.

Therefore, the absolute configuration at the B/C ring juncture of the oxo-compound (VIIIb) was shown to be same as that of XIV and hence the absolute configuration of the hydrophenanthrenes (Vb—Xb) derived from (+)-10-hydroxyhexahydroaporphine B (IVb) was proved to be represented by the structure B (Chart 3).

From these results, the absolute configuration of (+)-10-hydroxyhexahydroaporphine A (IVa) and B (IVb) must be expressed by following structures (Chart 6) since the hydrogen at C_{6a} of these compounds obviously oriented to the β side in these structures.



IVa IVb

Chart 6

10) K. Hirao, Dissertation, University of Hokkaido 1967.
11) Ref. 10: CD of XIV (c=1.14, dioxane) $\Delta\varepsilon^{18}$: 0 (378), −0.38 (364), −0.81 (350), −0.91 (335), −0.81 (322).

The B/C ring of (+)-10-hydroxyhexahydroaporphine B (IVb) is fixed in the steroidal form, and this conformation explained satisfactorily the NMR spectral result that the O-methyl derivative of IVb showed the aromatic C_{11}-proton at the same field (3.15 τ) as the corresponding signal of the O-methyl derivative of IVa having the B/C *trans* conformation. However, this ring conformation was proved to be the nonsteroidal form in the hexahydrophenanthrenes (Vb—Xb).

This suggested the occurrence of the conformational change in the B/C ring system during the cleavage of N-C_{6a} bond of IVb.

In this conformation the 1-β-substituent of the hydrophenanthrenes oriented axially and was expected to be epimerizable to the more stable α-equatorial configuration when this substituent was converted to aldehyde.

On this consideration, the vinyl compound (VIb) was subjected to ozonolysis to yield the aldehyde (XVb) which was isolated as its semicarbazone, mp 213—214°.

On the acid catalyzed epimerization of C_1, the aldehyde (XVb), liberated from the semicarbazone gave a mixture of the aldehyde (XVb) and its epimer (XVc). Since it was not feasible to isolate the aldehydes XVb and XVc, these compounds were converted to the corresponding oxo compounds (XIXb and c) as follows.

The mixture of the aldehydes XVb and XVc, was reduced with $LiAlH_4$ and the resulted hydroxymethyl compounds (XVIb and c) were submitted to tosylation followed by reduction with $LiAlH_4$ to yield a mixture of the methyl compounds (XVIIIb and c).

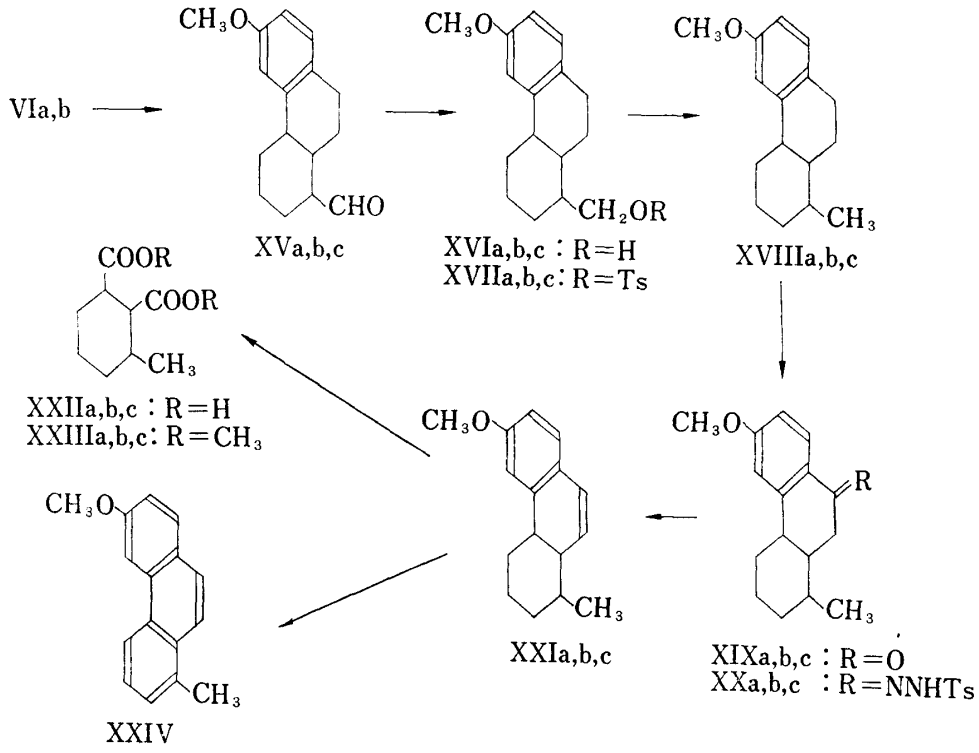


Chart 7

Oxidation of this mixture with chromium trioxide in acetic acid gave a mixture of the oxo compounds, XIXb, mp 92°, $[\alpha]_D^{23}$ −24.1° (MeOH) and XIXc, mp 122°, $[\alpha]_D^{25}$ +125° (MeOH), which were isolated as the respective tosylhydrazones, XXb, mp 210°, XXc, mp 205°.

The over all yields of the tosylhydrazones (XXb and c) from the aldehyde (XVb) were estimated to be 35 and 33% yield, respectively. When the epimerization procedure was excluded, these tosylhydrazones, XXb and XXc, were obtained in 61.6% and 5.8% yields from the aldehyde (XVb), respectively.

Both of these two tosyl hydrazones, XXb and XXc, were converted to 1-methyl-6-methoxyphenanthrene (XXIV) by Bamford reaction followed by dehydrogenation of the resulted hexahydrophenanthrenes (XXIb and c) with Pd/C.

These results suggested that the minor tosylhydrazone (XXc) was derived from the epimerized aldehyde (XVc) and hence the substituents at C_1 of these compounds would orient to the α side.

To establish this assumption the tosylhydrazones (XXb and c) were transformed into the 3-methylcyclohexane-1,2-dicarboxylic acids according to the method used in the degradation of the tosylhydrazones (IXa and b) to the corresponding 3-ethylcyclohexane-1,2-dicarboxylic acids (XIa and b).

The carboxylic acid (XXIIc) obtained from XXc was purified by distillation of its dimethyl ester (XXIIIc), $[\alpha]_D^{26.5}$ $-1.4°$ (EtOH), the IR spectrum of which was identical with that of the synthetic (±)*cis*-3-methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid dimethyl ester (XXXIXc).

On the other hand the IR spectrum of the carboxylic acid (XXIIb), mp 112—114°, $[\alpha]_D^{22}$ $+38.6°$ (MeOH), obtained from XXb was identical with that of (±)*trans*-3-methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid (XXXVIIb) and also the IR spectra of dimethyl esters (XXIIIb and XXXIXb) of these carboxylic acids were superimposable.

These results established that the tosylhydrazones (XXb and c) were derived from the original and the epimerized aldehyde, XVb and XXc, respectively and that the substituents at C_1 of the hydrophenanthrenes (XVc—XXIc) oriented to the α side.

The B/C ring conformation of the aldehydes (XVb and c) were also proved by comparison of the chemical shifts of the aromatic C_5-protons of the methyl compounds (XVIIIb and c) and the oxo compounds (XIXb and c) with those of the corresponding B/C *trans* compounds XVIIIa and XIXa as follow.

The methyl compounds (XVIIIb and c) were prepared from XXIb and XXIc by catalytic hydrogenation, respectively and the compounds XVIIIa and XIXa were derived from the vinyl compound (VIa) in the same way as used in the conversion of VIb to XIXb (Chart 7).

It can be seen from Table II that the signals of the aromatic C_5-protons of the B/C *cis* methyl compounds (XVIIIb and c) and oxo compounds (XIXb and c) appear at higher fields compared with those of the corresponding B/C *trans* compounds XVIIIa and XIXa, respectively so that the B/C ring conformation of these compounds and also the aldehydes (XVb and c) was proved to be the nonsteroidal form.

In this conformation, the hydrophenanthrenes (XVc—XXIc) were considered to be more stable than the corresponding dihydrophenanthrenes (XVb—XXIb) since the α-substituents at C_1 of the former must be in the equatorial orientation and the β-substituents at C_1 of the latter must be in the axial orientation.

The former would therefore be expected to exist more predominantly in the nonsteroidal form compared with the latter at the equilibrium between the steroidal and nonsteroidal forms.

Table II. The Chemical Shifts of the C_5 and C_8 Protons (at 60 Mc, in $CDCl_3$)

Compounds	B/C	C_8–H (τ)	C_5–H (τ)	$\Delta\tau_{5,8}$ (ppm)
XVIIIa	*trans*	3.03	3.17	0.14
XIXa	*trans*	1.98[a]	3.11	1.13
XVIIIb	*cis*	3.06	3.30	0.24
XIXb	*cis*	2.02[a]	3.23	1.21
XVIIIc	*cis*	3.04	3.36	0.32
XIXc	*cis*	2.01[a]	3.32	1.31

a) The deshielding of this proton was due to the effect of the anisotropy of the carbonyl group at C_9.

This consideration was supported by the following NMR and CD spectral evidences.

As shown in Table II, the signals of the C_5-protons of the compounds XVIIIc and XIXc resonated at higher fields than those of the compounds XVIIIb and XIXb, respectively.

In these mobile B/C *cis* hydrophenanthrene systems, the chemical shift of any given proton will be the weighted time average of its chemical shift in the pure steroidal conformation and in the pure nonsteroidal conformation, provided conformational interchange is rapid.

As described before, it is known that the aromatic C_5-protons of the B/C *cis* hydrophenanthrenes appear at lower fields in the case of the steroidal form compared with the nonsteroidal form.[9]

Therefore, the $\Delta\tau_{5,8}$ values were considered to become smaller in proportion as the contribution of the steroidal form to the equilibria increased.

The CD curve of the oxo compound (XIXc) exhibited negative Cotton effects at 300—400 mμ as well as that of XIXb. However, the amplitude of the former was larger than that of the latter as shown in Table III.

Table III. Circular Dichroism of 6-Methoxy-1-methyl-9-oxo-octahydrophenanthrenes

Compounds	Concentrations (mg/ml)	Cotton effects mμ ($\Delta\varepsilon$)
XIXb	0.171	353(−0.29), 340(−0.66), 326(−0.77), 314(−0.64)
XIXc	0.394	354(−0.75), 340(−1.66), 327(−1.85), 314(−1.46)

CD measurements were made at 24° with a JASCO ORD/UV-5 in dioxane.

This difference would also be explained by the above mentioned consideration since these compounds were expected to show positive Cotton effects in the case of the steroidal conformation judging from the Snatzke's rule.[12]

The absolute configuration assigned to IVb was further supported by the same signed Cotton effects of XIXb and XIXc as those of XIV.[11]

Preparation of 3-Alkylcyclohexane-1,2-dicarboxylic Acids

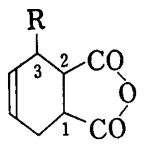
The four possible geometrical isomers of 3-methylcyclohexane-1,2-dicarboxylic acid and 3-ethylcyclohexane-1,2-dicarboxylic acids so far described in this paper were prepared by the methods of Bussert,[6] Craig,[13] and Alder.[5]

Among the four isomers of 3-methylcyclohexane-1,2-dicarboxylic acid, the three isomers, *i.e.* *cis*-3-methylcyclohexane-*cis,trans*-1,2-dicarboxylic acid (XXXVIIa), *trans*-3-methylcyclohexane-*cis,cis*-1,2-dicarboxylic acid (XXXVIIb) and *cis*-3-methylcyclohexane-*cis,cis*-1,2-dicarboxylic acid (XXXVIIc) were already prepared from *trans*-piperylene and maleic anhydride by Bussert[6] and Craig.[13] The remaining isomer, *i.e.* *cis*-3-methylcyclohexane-*trans,cis*-1,2-dicarboxylic acid (XXXVIId), has not been prepared, while its precursor, *cis*-3-methylcyclohexene-(4)-*trans,cis*-1,2-dicarboxylic acid (XXXVd) was reported by Craig.[13]

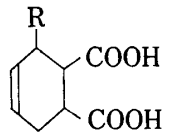
On the other hand, two isomers of 3-ethylcyclohexane-1,2-dicarboxylic acid, *i.e.* *cis*-3-ethylcyclohexane-*cis,trans*-1,2-dicarboxylic acid (XXXVIIIa) and *cis*-3-ethylcyclohexane-*cis,cis*-1,2-dicarboxylic acid (XXXVIIIc) were already prepared from 1,3-hexadiene and maleic anhydride by Alder, *et al.*[5] but the other two isomers, *i.e.* XXXVIIIb and XXXVIIIc have not been reported yet.

Thus, the three isomers of 3-methylcyclohexane-1,2-dicarboxylic acid, *i.e.* XXXVIIa, mp 167—169°, XXXVIIb, mp 130° and, XXXVIIIc, mp 169—170°, were prepared by the methods of Craig[13] and Bussert.[6]

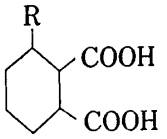
12) G. Snatzke, *Tetrahedron*, **21**, 413, 421, 439 (1965).
13) D. Craig, *J. Am. Chem. Soc.*, **72**, 1678 (1950).



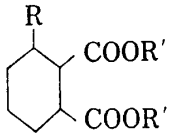
XXXIIIa,b,c,d : R=CH_3
XXXIVa,b,c,d : R=C_2H_5



XXXVa,b,c,d : R=CH_3
XXXVIa,b,c,d: R=C_2H_5



XXXVIIa,b,c,d : R=CH_3
XXXVIIIa,b,c,d: R=C_2H_5



XXXIXa,b,c,d : R=CH_3, R′=CH_3
XLa,b,c,d : R=C_2H_5, R′=CH_3
XLIa : R=CH_3, R′=H,CH_3
XLIIa,c : R=C_2H_5, R′=H,CH_3

Chart 8

The relationship of the substituents at C_1, C_2, and C_3 is denoted by *cis* or *trans*.

	substituents at		
	C_1	C_2	C_3
a:	*cis*	*trans*	*cis*
b:	*cis*	*cis*	*trans*
c:	*cis*	*cis*	*cis*
d:	*trans*	*cis*	*cis*

Catalytic hydrogenation of *cis*-3-methylcyclohexene-(4)-*trans*,*cis*-1,2-dicarboxylic acid (XXXVd), mp 162—163°, gave the remaining isomer (XXXVIId), mp 176—178°, which was obviously different from the other three isomers in every respect and was subsequently converted to XXXVIIa by acid catalyzed isomerization.

And the above mentioned two isomers of 3-ethylcyclohexane-1,2-dicarboxylic acid, *i.e.* XXXVIIIa, mp 175—176°, and XXXVIIIc, mp 117—119°, were also prepared by the Alder's method.[5]

The third isomer, *trans*-3-ethylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid (XXXVIIIb) was prepared by catalytic hydrogenation of the dicarboxylic acid (XXXVIb), mp 156—158°, which was obtained by treatment of the Diels–Alder adduct (XXXIVc), mp 52—53°, with a catalytic amount of diethylaniline and the successive hydrolysis with boiling water according to the Bussert's method used in the synthesis of *trans*-3-methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid (XXXVIIb).

This compound (XXXVIIIb) was isomerized to the first isomer (XXXVIIIa) by the action of concentrated hydrochloric acid in a sealed tube.

In order to obtain the fourth isomer, *cis*-3-ethylcyclohexane-*trans*,*cis*-1,2-dicarboxylic acid (XXXVIIId), 1,3-hexadiene and fumaric acid were submitted to the Diels–Alder reaction to yield a mixture of the adducts, XXXIVa and XXXIVd.

Since it was not feasible to isolate these isomers, the mixture was hydrolyzed with boiling water.

The isolated compound (XXXVId), mp 155°, was hydrogenated to the fourth isomer (XXXVIIId), mp 173—174°, which was different from the other three isomers in every respect and was isomerized to XXXVIIIa by the action of concentrated hydrochloric acid.

Therefore, this compound must be *cis*-3-ethylcyclohexane-*trans*,*cis*-1,2-dicarboxylic acid (XXXVIIId).

Experimental

All melting points are uncorrected, UV spectra were determined in 95% EtOH solutions, NMR spectra were measured on a varian A-60 spectrometer in $CDCl_3$ solutions with tetramethylsilane as an internal stand-

ard, ORD curves were obtained with a Rudolph recording spectrometer. Alumina (Merck, standard) was used for column chromatography. Organic extracts had been washed with water and dried over $MgSO_4$ before evaporation.

(+)-6-Methoxy-1-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (Va) and Its Methiodide——The conversion of (+)-10-hydroxy-1,2,3,3a,11b,11c-hexahydroaporphine A (IVa) into Va was reported in the previous paper.[1]

The methiodide was recrystallized from EtOH as colourless cubes, mp 240—242°. $[\alpha]_D^{23.5}$ +39.3° (c=1.074, EtOH). *Anal.* Calcd. for $C_{20}H_{32}ONI$: C, 55.94; H, 7.51; N, 3.26; I, 29.56. Found: C, 55.98; H, 7.53; N, 3.09; I, 29.74.

(+)-6-Methoxy-1-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (Vb) and Its Methiodide——The degradation (+)-10-hydroxy-1,2,3,4a,11b,11c-hexahydroaporphine B (IVb) into Vb and its methiodide was reported in the previous paper.[1]

(+)-6-Methoxy-1-vinyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (VIa)——A solution of Va methiodide (23.75 g) in EtOH (45 ml) and water (230 ml) was stirred with fresh Ag_2O (prepared from 14 g of $AgNO_3$) for 30 min at 70—80°. The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was heated at 180° for 1 hr and the separated oily material was extracted with ether. The extract was washed with 10% HCl and then evaporated to give a crystalline residue (8.26 g), mp 65—67°.

Recrystallization from EtOH gave VIa as colourless prisms, mp 67—68°. $[\alpha]_D^{25}$ +134.4° (c=2.084, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 1644 (vinyl). NMR τ: 3.03—3.37 (3H, ABX, aromatic H), 3.9—5.2 (3H, multiplet, $-CH=CH_2$), 6.24 (3H, singlet, OCH_3). *Anal.* Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.18; H, 9.21.

The acidic solution was made basic with conc. NH_4OH and extracted with ether. The ethereal solution was evaporated to dryness. The residue was dissolved in acetone and treated with CH_3I to give the starting material (5.22 g), mp 240°.

(+)-6-Methoxy-1-vinyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (VIb)——Hofmann degradation of Vb methiodide (126.9 g) was carried out as above. Recrystallization of the crystalline product (45.0 g, 63%) from EtOH gave VIb as colourless prisms, mp 43—44°. $[\alpha]_D^{24}$ +60.7° (c=2.075, MeOH). NMR τ: 3.0—3.4 (3H, ABX, aromatic H), 3.7—5.2 (3H, multiplet, $-CH=CH_2$), 6.24 (3H, singlet, OCH_3). *Anal.* Calcd. for $C_{17}H_{22}O$: C,84.25; H, 9.15. Found: C, 84.46; H, 9.15.

The basic material was recovered as crystals (3.04 g), mp 58—60°. The identity of this compound with the starting material (Vb) was confirmed by comparison of the IR spectra and the mixed melting point determination.

(+)-6-Methoxy-1-ethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (VIIa)——A solution of VIa (6.20 g) in EtOAc (40 ml) was hydrogenated over PtO_2 (100 mg). After the uptake of hydrogen had ceased, the catalyst and the solvent were removed. The crystalline residue (5.75 g), mp 52—53°, was recrystallized from EtOH to give VIIa as colourless needles, mp 52—53°. $[\alpha]_D^{24.5}$ +66.1° (c=2.049, dioxane). NMR τ: 3.04—3.45 (3H, ABX, aromatic H), 6.24 (3H, singlet, OCH_3), 9.10 (3H, triplet, J=7 cps, CH_2–CH_3). *Anal.* Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.30; H, 9.89.

(+)-6-Methoxy-1-ethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (VIIb)——Catalytic hydrogenation of VIb (10.0 g) over PtO_2 (90 mg) as above gave an oily residue (10.2 g). Chromatography of the residue in benzene gave VIIb as colourless oil (10.0 g). $[\alpha]_D^{22}$ +1.8° (c=1.922, MeOH). NMR τ: 3.06—3.40 (3H, ABX, aromatic H), 6.26 (3H, singlet, OCH_3), 9.10 (3H, triplet like, $-CH-_2CH_3$). *Anal.* Calcd. for $C_{17}H_{21}O$: C,83.55; H, 9.90. Found: C, 83.30; H, 9.70.

(−)-6-Methoxy-1-ethyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (VIIIa) and Its Tosylhydrazone (IXa)——A solution of CrO_3 (4.40 g) in 80% AcOH (16 ml) was added dropwise to a stirred solution of VIIa (5.23 g) in AcOH (90 ml) over a period of 30 min at below 10°. The mixture was stirred for an additional 3.5 hr at room temperature, diluted with water (300 ml) and extracted with ether. The ethereal solution was evaporated to dryness. Chromatography of the residue (5.25 g) in benzene gave VIIIa (4.42 g, 79.9%), mp 110—112°, which was recrystallized from EtOH as colourless needles, mp 111—112°. $[\alpha]_D^{24.5}$ −37.9° (c=2.013, dioxane). NMR τ: 1.98—3.23 (3H, aromatic H), 6.32 (3H, singlet, OCH_3), 9.15 (3H, triplet like, $-CH_2$–CH_3). UV λ_{max} mμ (log ε): 278 (4.21). ORD (c=0.503, dioxane) $[\alpha]^{23}$ +1060° (361), +540° (354), +980° (346), −700° (336), −650° (333), −1440° (325). *Anal.* Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.20; H, 8.64.

A solution of VIIIa (4.0 g) in EtOH (40 ml) was refluxed with tosylhydrazine (3.20 g) for 10 min. After cooling, the separated crystals (6.31 g), mp 231° (decomp.) were collected and recrystallized from EtOH to give IXa as colourless needles, mp 231° (decomp.). *Anal.* Calcd. for $C_{24}H_{30}O_2N_2S$: C, 67.57; H, 7.09; N, 6.57; S, 7.50. Found: C, 67.41; H, 7.18; N, 6.64; S, 7.50.

(−)-6-Methoxy-1-ethyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (VIIIb) and Its Tosylhydrazone (IXb)——Oxidation of VIIb (10.0 g) with CrO_3 (7.63 g) was carried out in the same way as described above. The oily product (10.38 g) was treated with tosylhydrazine as above and the resulted crystals (13.30 g), mp 207° (decomp.) were recrystallized from EtOH to give IXb as colourless plates, mp 209° (decomp.). $[\alpha]_D^{27}$ −79.0° (c=1.916, MeOH). *Anal.* Calcd. for $C_{24}H_{30}O_2N_2S$: C, 67.57; H, 7.09; N, 6.57. Found: C, 67.88; H, 7.37; N, 6.56.

The suspension of IXb (300 mg) in 50% aq. acetone (20 ml) was refluxed with pyruvic acid (400 mg) for 7 hr, until IXb had completely dissolved. The solution was evaporated under reduced pressure and the residue was extracted with ether. The extract was washed with aq. $NaHCO_3$ and then evaporated. Chromatography of the residue in benzene gave VIIIb as colourless oil (180 mg). $[\alpha]_D^{23}$ −27.9° (c=1.948, MeOH). UV λ_{max} mμ (log ε): 227 (4.14), 276.5 (4.22). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678 (C=O). NMR τ: 2.0—3.3 (3H ABX, aromatic H), 6.33 (3H, singlet, OCH_3), 9.1 (3H, triplet like, $-CH_2\underline{CH_3}$). ORD (c=0.0405, dioxane)$[\alpha]^{24}$ (mμ): −840° (360) (trough), −600° (352) (peak), −920° (346) (trough), −220° (337°) (peak), −500° (333) (trough), +70° (323) (peak), −150° (317) (trough), −50° (313) (peak). *Anal.* Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.05; H, 8.62.

(−)-6-Methoxy-1-ethyl-1,2,3,4,4a,10a-hexahydrophenanthrene A (Xa)——To a solution of Na (1.50 g) in ethylene glycol (65 ml) was added IXa (6.30 g) and the mixture was refluxed for 2 hr. After cooling, the reaction mixture was diluted with water and extracted with benzene. After removal of the solvent, the residue (4.0 g) was dissolved in benzene (80 ml) and refluxed with $KHSO_4$ (1.0 g) for 4 hr. The benzene solution was evaporated to dryness. Chromatography of the residue (3.50 g) in petr. ether and recrystallization from EtOH gave Xa as colourless needles (2.34 g, 65.1%), mp 65—66°. $[\alpha]_D^{23.5}$ −27.1° (c=1.995, acetone). UV λ_{max} (log ε): 273 (4.17). NMR τ: 3.04—3.37 (3H, ABX, aromatic H), 3.5—4.1 (2H, vinyl H), 6.22 (3H, singlet, OCH_3), 9.12 (3H, triplet, J=6 cps, $-CH_2-\underline{CH_3}$). *Anal.* Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.30; H, 9.29.

(+)-6-Methoxy-1-ethyl-1,2,3,4,4a,10a-hexahydrophenanthrene B (Xb)——Treatment of IXb (6.42 g) with Na (1.44 g) in ethylene glycol (62 ml) and then with $KHSO_4$ (1.0 g) in benzene (90 ml) as described above gave an oily material (3.60 g). Chromatography of the residue in petr. ether gave Xb as colourless oil (3.15 g, 86%). $[\alpha]_D^{22}$ +157.5° (c=2.141, MeOH). UV λ_{max} mμ(log ε): 273 (4.16). NMR τ: 3.0—3.4 (3H, ABX, aromatic H), 3.5—4.4 (2H, vinyl H), 6.23 (3H, singlet, OCH_3), 9.13 (3H, triplet like, $-CH_2-\underline{CH_3}$).

(+)-*cis*-3-Ethylcyclohexane-*cis,trans*-1,2-dicarboxylic Acid (XIa) and Its Dimethyl Ester (XIIa)——The oxygen stream (containing 4% O_3, 110 ml/min) was passed through a solution of Xa (2.03 g) in AcOEt (40 ml) and 80% formic acid (25 ml) for 50.5 hr under ice-cooling. The mixture was allowed to stand overnight with a solution of 30% H_2O_2 (10 ml) and 80% formic acid (10 ml) at room temperature. After decomposition of the excess reagent with SO_2 and concentration, the remaining solution was salted out with NaCl and extracted with ether. The ethereal solution was shaken with aq. $NaHCO_3$ to extract the acidic material.

The aqueous layer was acidified with conc. HCl and extracted with ether. Evaporation and recrystallization from ether–petr. ether gave XIa as cubes (610 mg), mp 175—177°. $[\alpha]_D^{25.5}$ +2.9° (c=2.088, MeOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.75; H, 8.05.

The IR spectrum of this compound in CCl_4 was in good agreement with that of (±)-*cis*-3-ethylcyclohexane-*cis,trans*-1,2-dicarboxylic acid (XXXVIIIa) except a slight difference in 1300—1250 cm^{-1} region.

A solution of XIa (200 mg) in ether (40 ml) was allowed to stand overnight with excess diazomethane prepared from nitrosomethylurea (500 mg) at room temperature. After removal of the solvent, the residue (200 mg) in petr. ether was chromatographed to give XIIa as an oil. $[\alpha]_D^{24.5}$ +8.8° (c=1.945, MeOH). *Anal.* Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.28; H, 8.72.

The IR spectrum of XIIa in CCl_4 was identical with that of (±)-*cis*-3-ethylcyclohexane-*cis,trans*-1,2-dicarboxylic acid dimethyl ester (XLa).

(+)-*cis*-3-Ethylcyclohexane-*cis,trans*-1,2-dicarboxylic Acid Monomethyl Ester (XIIIa)——The suspension of XIIa (150 mg) in 15% KOH (15 ml) was stirred for 8 hr at room temperature. The clear solution was acidified with conc. HCl and exrtacted with ether. The ethereal solution was evaporated to give XIIIa as an oil (118 mg). $[\alpha]_D^{23}$ +3.5° (c=0.886, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710 (COOH), 1738 ($COOCH_3$). The IR spectrum of XIIIa in CCl_4 was identical with that of (±)-*cis*-3-ethylcyclohexane-*cis,trans*-1,2-dicarboxylic acid monomethyl ester (XLIIa).

Esterification of XIIIa with diazomethane gave the dimethyl ester (XIIa).

(+)-*trans*-3-Ethylcyclohexane-*cis,cis*-1,2-dicarboxylic Acid (XIb) and Its Dimethyl Ester (XIIb)——Ozonolysis of Xb (2.0 g) followed by performic acid oxidation as above gave an oily product (1.2 g). Treatment of the residue with diazomethane as above and repeated distillation gave XIIb as colourless oil (280 mg), bp 115—130° (0.1 mmHg) (bath temperature). $[\alpha]_D^{23}$ +32.2° (c=2.092, MeOH). *Anal.* Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.28; H, 8.72.

The IR spectrum of XIIb in CCl_4 was identical with that of (±)-*trans*-3-ethylcyclohexane-*cis,cis*-1,2-dicarboxylic acid dimethyl ester (XLb).

The dimethyl ester (XIIb) (220 mg) was treated with 15% KOH (22 ml) as described for XIIIa to give a crystalline residue (190 mg).

Recrystallization from ether–petr. ether gave XIb as colourless granules (150 mg), mp 127—129°. $[\alpha]_D^{25}$ +34.6° (c=1.021, MeOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.98; H, 8.08.

The IR spectrum of this compound in CCl_4 was identical with (±)-*trans*-3-ethylcyclohexane-*cis,cis*-1,2-dicarboxylic acid (XXXVIIIb).

(+)-6-Methoxy-1-formyl-1,2,3,4,4a,9,10,10a-octahydrolphenanthrene A (XVa)——The oxygen stream (containing 4% O_3, 110 ml/min) was passed through a solution of VIa (4.84 g) in EtOAc (200 ml) at −60—70° for 2.5 hr. The solution was bubbled with N_2 and then hydrogenated over 30% Pd/C (prepared from

$PdCl_2$ (0.2 g) and carbon (0.4 g)). After the uptake of hydrogen had ceased, the catalyst was removed. The solution was washed with aq. $NaHCO_3$ and then with water and the solvent was removed under reduced pressure. The residue was crystallized from EtOH to give XVa as colourless plates (2.52 g, 51.8%), mp 132—134°. $[\alpha]_D^{23.5}$ +93.1° (c=1.973, acetone). IR ν_{max}^{Nujol} cm^{-1}: 1725, 2690 (CHO). *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.58; H, 8.24.

(+)-6-Methoxy-1-formyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (XVb)——Ozonolysis of VIb (9.70 g) in EtOAc (280 ml) as described above gave XVb as an oil (9.30 g), which was converted to the semicarbazone (8.57 g), mp 210° in usual way. Recrystallization from EtOH gave colourless cubes, mp 213—214°. *Anal.* Calcd. for $C_{17}H_{23}O_2N_3$: C, 67.52; H, 8.00; N, 13.90. Found: C, 67.39; H, 7.75; N, 13.74.

A suspension of the semicarbazone (9.80 g) in acetone (100 ml) and water (50 ml) was refluxed with pyruvic acid (8.0 g) for 4 hr. After removal of the solvent, the residue was extracted with ether. The ethereal solution was washed with aq. $NaHCO_3$, and the solvent was removed. The residue in benzene was chromatographed to give XVb as an oil (7.27 g). $[\alpha]_D^{20}$ +11.1° (c=1.50, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729, 2700 (CHO). *Anal.* Calcd. for $C_{16}H_{20}O_2$: C,78.65; H, 8.25. Found: C, 78.29; H. 8.27.

(+)-6-Methoxy-1-hydroxymethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (XVIa)——A solution of XVa (2.07 g) in ether (180 ml) was added dropwise to a well stirred suspension of $LiAlH_4$ (0.50 g) in ether (50 ml) and the mixture was refluxed for 2 hr. After decomposition of the excess reagent with EtOAc, the ethereal solution was evaporated to give a crystalline residue (2.07 g, 95.8%), mp 57—61°. Recrystallization from petr. ether afforded XVIa as colourless plates, mp 62—63°. $[\alpha]_D^{23}$ +89.6° (c=2.030, acetone). IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH). *Anal.* Calcd. for $C_{16}H_{22}O_3 \cdot 1/3H_2O$: C, 76.15; H, 9.05; H_2O, 2.38. Found: C, 76.29; H, 9.19; H_2O, 2.35.

(+)-6-Methoxy-1-tosyloxymethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (XVIIa)——To a solution of XVIa (2.02 g) in pyridine (6 ml) was added a solution of tosylchloride (1.87 g) in pyridine (5 ml). The mixture was allowed to stand overnight in a refrigerator, poured into conc. HCl (13 ml) and ice (20 g), and extracted with benzene. Evaporation and recrystallization from ether gave XVIIa as colourless pillars (2.47 g, 77%), mp 115—118°, increasing to 121—122° upon recrystallization from EtOH. $[\alpha]_D^{24}$ +62.9° (c=2116, acetone). IR ν_{max}^{Nujol} cm^{-1}: 1172, 1355 (OTs). *Anal.* Calcd for $C_{23}H_{28}O_4S$: C, 68.97; H, 7.05; S, 8.01. Found: C, 69.17; H, 7,21; S, 8.23.

(+)-6-Methoxy-1-tosyloxymethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (XVIIb) ——Reduction of XVb (3.07 g) in ether (60 ml) with $LiAlH_4$ (0.70 g) as in the case of XVIa gave XVIb as an oil (2.82 g). Without further purification, a solution of XVIb (2.82 g) in pyridine (5 ml) was treated with tosylchloride (2.61 g) as above to give a crystalline material (4.38 g). Recrystallization from ether gave XVIIb as colourless plates (3.28 g, 72%), mp 88—89°. $[\alpha]_D^{23}$ +5.2° (c=0.837, acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1180, 1365 (OTs). *Anal.* Calcd. for $C_{23}H_{28}O_4S$: C, 68.97; H, 7.05; S, 8.01. Found: C,68.80; H, 7.14; S, 8.10.

(+)-6-Methoxy-1-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (XVIIIa)——A solution of XVIIa (1.91 g) in tetrahydrofuran (30 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.5 g) in tetrahydrofuran (30 ml) for 10 min and the mixture was refluxed for 3 hr. After decomposition of the excess reagent with EtOAc, the organic layer was evaporated under reduced pressure and the residual crystalline material was recrystallized from EtOH to give XVIIIa as colourless plates (1.06 g, 96.5%), mp 75—76°. $[\alpha]_D^{24}$ +91.9° (c=2.083, acetone). NMR τ: 3.0—3.4 (3H, ABX, aromatic H), 6.23 (3H, singlet, OCH_3), 9.02 (3H, $-CH_2-CH_3$). *Anal.* Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.75; H, 9.72.

(+)-6-Methoxy-1-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (XVIIIb)——A solution of XVIIb (3.13 g) in ether (90 ml) was reduced with $LiAlH_4$ (0.70 g) as described above to give an oily material (1.64 g). Chromatography of the residue in petr. ether gave XVIIIb as an oil (1.59 g, 88%). $[\alpha]_D^{22}$ +40.6° (c=1.810, MeOH). *Anal.* Calcd. for $C_{16}H_{22}O$: C 83.43; H, 9.63. Found: C, 83.30; H, 9.63.

(−)-6-Methoxy-1-methyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene A (XIXa) and Its Tosylhydrazone (XXa)——Oxidation of XVIIIa (2.45 g) with CrO_3 (1.95 g) was carried out in the same way as described for VIIIa. The resulted material was recrystallized from EtOH to give XIXa as colourless prisms (1.95 g, 70%), mp 134—135°. $[\alpha]_D^{24}$ −16.6° (c=2.120, acetone). UV λ_{max} mμ (log ε): 278 (4.20). IR ν_{max}^{Nujol} cm^{-1}; 1670 (C=O). NMR τ: 1.9—3.3 (3H, ABX, aromatic H), 6.16 (3H, singlet, OCH_3), 9.02 (3H, $-CH_2-CH_3$). *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 79.01; H, 8.27.

Treatment of XIXa (1.95 g) with tosylhydrazine (1.28 g) as described for IXa gave XXa (3.20 g), mp 224° (decomp.). Recrystallization from EtOH gave colourless needles, mp 226.5° (decomp.). $[\alpha]_D^{23}$ −1.8° (c=0.991, acetone). *Anal.* Calcd. for $C_{23}H_{28}O_3N_2S$: C, 66.96; H, 6.84; N, 6,79. Found: C, 67.44; H, 6.82; N, 6.92.

(−)-6-Methoxy-1-methyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (XIXb) and Its Tosylhydrazone (XXb)——A solution of XVIIIb (1.57 g) in AcOH (25 ml) was oxidized with CrO_3 (1.29 g) as in the case of VIIIa to give XIXb (1.49 g), mp 90°. Recrystallization from EtOH gave colourless cubes (1.04 g, 63%), mp 92°. $[\alpha]_D^{23}$ −24.1° (c=2.10, MeOH). UV λ_{max} mμ (log ε): 277 (4.21). IR ν_{max}^{Nujol} cm^{-1}: 1673 (C=O). NMR τ: 2.02—3.25 (3H, ABX, aromatic H), 6.16 (3H, singlet, OCH_3), 8.97 (3H, doublet, J=5.5 cps, $-CH-CH_3$). *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.66; H, 8.36.

The tosylhydrazone (XXb) was prepared as above and recrystallized from EtOH as colourless granules, mp 210°. $[\alpha]_D^{28}$ −21.6° (c=2.012, acetone). *Anal.* Calcd. for $C_{23}H_{28}O_3N_2S$: C, 66.96; H, 6.84; N, 6.79; S, 7.77. Found: C, 66.95; H, 6.93; N, 6.94; S, 7.83.

(+)-6-Methoxy-1-methyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene C (XIXc) and Its Tosylhydrazone (XXc)——An oily material (805 mg) obtained from the mother liquor of XVIIb was also reduced with $LiAlH_4$ (200 mg) as described for XVIIIa to give an oily material (530 mg). Chromatography of the residue in petr. ether afforded a colourless oil (450 mg). A solution of this material (440 mg) in AcOH (7.5 ml) was oxidized with CrO_3 (0.35 g) as above. Fractional recrystallization of the crude product from EtOH gave XIXb (31 mg), mp 92°, and XIXc (47 mg) as colourless prisms, mp 122°. $[\alpha]_D^{25}$ +12.5° (c=2.075, MeOH). UV λ_{max} mμ (log ε): 277 (4.20). IR ν_{max}^{Nujol} cm^{-1}: 1665 (C=O). NMR τ: 2.05—3.32 (3H, ABX, aromatic H), 6.15 (3H, singlet, OCH_3), 9.10 (3H, doublet, J=6 cps, –CH–C<u>H</u>$_3$). *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.62; H, 8.32.

The mother liquor was evaporated and treated with tosylhydrazine as in the case of XXa. The resulted crystalline material was subjected to fractional recrystallization from EtOH to give XXb (147 mg), mp 210°, and XXc as colourless plates (123 mg) mp 205°. $[\alpha]_D^{22}$ −77.1° (c=1.913, acetone). *Anal.* Calcd. for $C_{23}H_{28}O_3N_2S$: C, 66.96; H, 6.84; N, 6.79; S, 7.77. Found: C, 67.12; H, 7.03; S, 7.96.

The tosylhydrazone (XXc, 300 mg) was liberated in the same way as described for VIIIb. The resulting material (200 mg) in benzene was chromatographed and a crystalline material (185 mg) eluted with the same solvent was recrystallized from EtOH to give XIXc as colourless prisms, mp 122°.

Epimerization of (+)-6-Methoxy-1-formyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene B (XVb)——A solution of XVb (15.0 g) liberated from the semicarbazone by the action of pyruvic acid was refluxed with 10% HCl (85 ml) in acetone (250 ml) for 1 hr. After removal of the solvent, the residue was extracted with ether. The ethereal solution was evaporated to give a mixture of XVb and XVc as an oil (15.0 g).

The mixture was subjected to reduction with $LiAlH_4$ (3.50 g) followed by tosylation as described above to yield XVIIb (5.93 g), mp 85—87°. The mother liquor of XVIIb was evaporated to dryness.

The residue (16 g) was subjected to the reduction with $LiAlH_4$ followed by the oxidation with CrO_3 (7.10 g) as described above.

The product (8.0 g) in benzene was chromatographed. After removal of the solvent, the residue (7.83 g) was fractionally recrystallized from EtOH to give XIXb (1.10 g), mp 92°, and XIXc (4.16 g), mp 122°.

The mother liquor was evaporated to dryness and treated with tosylhydrazine to give a crystalline material. Fractional recrystallization from EtOH gave XXb (1.32 g), mp 210°, and XXc (1.31 g), mp 205°.

(−)-6-Methoxy-1-methyl-1,2,3,4,4a,10a-hexahydrophenanthrene A (XXIa)——Bamford reaction of XXa (3.20 g) was carried out as described in the case of Xa to yield a crystalline product (1.67 g), mp 58—60°. Chromatography of the production in petr. ether and recrystallization from EtOH to give XXIa as colourless plates (1.40 g, 79.5%), mp 66—67°. $[\alpha]_D^{23}$ −256.6° (c=2.022, MeOH). UV λ_{max} mμ (log ε): 272.5 (4.17). NMR τ: 3.06—3.40 (3H, ABX, aromatic H), 3.5—4.2 (2H, vinyl H), 6.22 (3H, singlet, OCH_3), 8.98 (3H, $-CH_2-C\underline{H}_3$). *Anal.* Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.02; H, 8.84.

(+)-6-Methoxy-1-methyl-1,2,3,4,4a,10a-hexahydrophenanthrene B (XXIb)——Bamford reaction of XXb (2.40 g) as described for Xa gave XXIb as an oil (1.44 g). Chromatography developing with petr. ether gave an oil (1.10 g, 83%). $[\alpha]_D^{22}$ +156.1° (c=1.986, MeOH). UV λ_{max} mμ (log ε) 272 (4.14). NMR τ: 3.07—3.40 (3H, ABX, aromatic H), 6.23 (3H, singlet, OCH_3), 9.05 (3H, doublet, J=6 cps, –CH–C<u>H</u>$_3$), 3.5—4.4 (2H, multiplet, vinyl H). *Anal.* Calcd, for $C_{16}H_{20}O$; C, 84.16; H, 8.83. Found: C, 83.93; H, 8.84.

(+)-6-Methoxy-1-methyl-1,2,3,4,4a,10a-hexahydrophenanthrene C (XXIc)——Bamford reaction of XXc (6.50 g) as described for Xa gave an oily material (3.80 g) which was purified by chromatography with petr. ether to give XXIc as an oil (3.11 g, 86.3%). $[\alpha]_D^{23.5}$ +171.9° (c=2.096, MeOH). UV λ_{max} mμ (log ε): 273.5 (4.14). *Anal.* Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.77; H, 8.86.

Catalytic Hydrogenation of (+)-6-Methoxy-1-methyl-1,2,3,4,4a,10a-hexahydrophenathrene B (XXIb)——A solution of XXIb (320 mg) in EtOAc (7 ml) was hydrogenated over PtO_2 (40 mg). After the uptake of hydrogen had ceased, the catalyst and the solvent were removed to give an oily material (310 mg), which was identified as XVIIIb by comparison of the IR spectra.

(+)-6-Methoxy-1-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene C (XVIIIc)——1. Catalytic hydrogenation of XXIc (500 mg) over PtO_2 (80 mg) as described above gave a yellow oil (480 mg). Chromatography of the product in petr. ether gave XVIIIc as an oil (470 mg). $[\alpha]_D^{24}$ +136° (c=2.309, MeOH). *Anal.* Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.53; H, 9.95.

2. A solution of XIXc (450 mg) in AcOH (5 ml) was hydrogenated over PtO_2 (100 mg). After the uptake of hydrogen, the catalyst and the solvent were removed. The residue was dissolved in ether, washed with aq. $NaHCO_3$ and the solvent was removed to give an oily material, which was purified by chromatography developing with petr. ether. Removal of the solvent gave a colourless oil (410 mg) which was identified as XVIIIc by comparison of the IR spectra.

Dehydrogenation of (+)-6-Methoxy-1-methyl-1,2,3,4,4a,10a-hexahydrophenanthrene B (XXIb)——A mixture of XXIb (153 mg) and 10% Pd/C (100 mg) was heated for 2.5 hr at 300—310° and then extracted with ether.

The ethereal solution was evaporated to give an oil (136 mg). Chromatography of the residue in petr. ether gave XXIV (21 mg), which was recrystallized from EtOH to give colourless needles, mp 87—88° (lit[14] 84—85°). UV λ_{max} mμ (log ε): 258 (4.70), 295 (4.05), 307 (4.12). *Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.77; H, 6.34.

The picrate recrystallized from EtOH as reddish needles, mp 137—138° (lit[14] 136—137°).

Dehydrogenation of (+)-3-Methoxy-1-methyl-1,2,3,4,4a,10a-hexahydrophenanthrene C (XXIc)——Treatment of XXIc (114 mg) with 10% Pd/C (80 mg) as described above gave colourless needles (43 mg), mp 87—88°.

The comparison of the IR spectra and the mixed melting point determination showed that this compound was identical with XXIV obtained above.

(+)-*cis*-3-Methylcyclohexane-*cis,trans*-1,2-dicarboxylic Acid (XXIIa) and Its Dimethyl Ester (XXIIIa)——Ozonolysis of XXIa (1.40 g) followed by performic acid oxidation as described for XIa gave a crystalline material, which was recrystallized from ether–petr. ether to give XXIIa as colourless needles (150 mg), mp 150°, $[\alpha]_D^{23.5}$ +18.2° (c=1.080, MeOH). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.17; H, 7.60.

The IR spectrum of this compound in CCl_4 was in good agreement with that of (±)-*cis*-3-methylcyclohexane-*cis,trans*-1,2-dicarboxylic acid (XXXVIIa) except a slight difference in 1300—1250 cm^{-1} region.

A solution of XXIIa (100 mg) in ether (20 ml) was treated with excess diazomethane in usual way to give an oily material (100 mg). Chromatography of the residue in petr. ether gave XXIIIa as colourless oil. $[\alpha]_D^{26.5}$ +22.2° (c=1.119, MeOH). *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.59; H, 8.54.

The IR spectrum of this compound in CCl_4 was identical with that of (±)-*cis*-3-methylcyclohexane-*cis, trans*-1,2-dicarboxylic acid dimethyl ester (XXXIXa).

(+)-*trans*-3-Methylcyclohexane-*cis,cis*-1,2-dicarboxylic Acid (XXIIb) and Its Dimethyl Ester (XXIIIb)——Ozonolysis of XXIb (2.93 g) followed by performic acid oxidation as described in the case of XIa gave an amorphous powder (1.86 g), which was treated with excess diazomethane and purified by distillation to give XXIIIb as colourless oil, bp 115—125° (0.1 mmHg) (bath temperature). $[\alpha]_D^{23.5}$ +45.9° (c=2.057, MeOH). *Anal.* Calcd. for $C_{11}H_{18}O$: C, 61.66; H, 8.47. Found: C, 61.58; H, 8.64.

The IR spectrum of this compound in CCl_4 was identical with that of (±)-*trans*-3-methylcyclohexane-*cis,cis*-1,2-dicarboxylic acid dimethyl ester (XXXIXb). Treat ment of XXIIIb (370 mg) with 15% KOH (37 ml) as described for XIIIa gave an acidic material (325 mg), mp 107—109°. Recrystallization from benzene–*n*-hexane afforded XXIIb as colourless plates, mp 112—114°. $[\alpha]_D^{22}$ +38.6° (c=2.069, MeOH). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.22; H, 7.65.

The IR spectrum of this compound in CCl_4 was identical with that of (±)-*trans*-3-methylcyclohexane-*cis,cis*-1,2-dicarboxylic acid (XXXVIIb).

(—)-*cis*-3-Methylcyclohexane-*cis,cis*-1,2-dicarboxylic Acid Dimethyl Ester (XXIIIc)——Ozonolysis of XXIc (2.41 g) followed by performic acid oxidation was carried out in the same way as described for XIa. The resulted acidic material (1.37 g) was treated with excess diazomethane to give an oily material (1.11 g). Distillation gave XXIIIc as colourless oil (270 mg), bp 110—123° (0.1 mmHg) (bath temperature). $[\alpha]_D^{26.5}$ −1.4° (c=0.495, MeOH). The IR spectrum of this compound in CCl_4 was identical with that of (±)-*cis*-3-methylcyclohexane-*cis,cis*-1,2-dicarboxylic acid dimethyl ester (XXXIXc).

Conversion of (+)-3-Hydroxy-N-methylisomorphinan (III) into (—)-6-Methoxy-9-oxo-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXXI) and (—)-*trans*-2-Methyl-2-carboxycyclohexylacetic Acid (XXXII)

(—)-6-Methoxy-4a-(2-dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXV) and Its Methiodide——The degradation of (+)-3-hydroxy-N-methylisomorphinan (III) to XXV was reported in the previous paper.[1]

The Methiodide was recrystallized from EtOH as colourless needles, mp 222—223°. $[\alpha]_D^{21}$ −25.2° (c= 1.951, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{29}ON \cdot CH_3I$: C, 55.94; H, 7.51; N, 3.26; I, 29.55. Found: C, 55.90; H, 7.67; N, 3.44; I, 29.51.

(—)-6-Methoxy-4a-vinyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXVI)——Hofmann degradation of the above mentioned methiodide (9.0 g) was carried out in the same way as described for VIa to yield a yellow oily material (3.40 g). Chromatography of the residue in petr. ether gave XXVI as a colourless oil (3.15 g, 62%). $[\alpha]_D^{23}$ −74.1° (c=2.364, dioxane). IR ν_{max}^{film} cm^{-1}: 1611 (vinyl). *Anal.* Calcd. for $C_{17}H_{22}O$: C, 84.25; N, 9.15. Found: C, 83.88; H, 9.20.

The basic material (2.1 g) was recovered as in the case of VIa.

The methiodide of this material was recrystallized from EtOH as colourless needles (2.5 g, 28%), mp 222—223°, and identified with the starting material by comparison of the IR spactra and the mixed melting point determination.

(—)-6-Methoxy-4a-formyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXVIII)——1. A mixture of XXVI (890 mg), pyridine (1 ml) and OsO_4 (1.0 g) in dehydrated ether (10 ml) was allowed to stand overnight

14) F.E. King, T.J. King, and J.G. Topliss, *Chem. Ind.* (London), **1954**, 108.

at room temperature. The resulting complex was separated and dissolved in CH_2Cl_2 (45 ml). A solution of mannite (9.0 g) in 20% NaOH (90 ml) was added to the CH_2Cl_2 solution and the mixture was stirred for 3.5 hr at room temperature under nitrogen. The CH_2Cl_2 layer was washed with water, dried over K_2CO_3 and the solvent was removed to give a crystalline residue (840 mg, 84%), mp 117—118°. Recrystallization from ether–petr. ether gave XXVII as colourless needles, mp 117—118°. $[\alpha]_D^{22}$ −85.0° (c=1.962, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3448 (OH). *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.98; H, 8.89.

A solution of HIO_4 (700 mg) in water (3 ml) was added to a solution of XXVII (630 mg) in MeOH (30 ml) at 5—7° under stirring. The mixture was stirred for an additional 2 hr at room temperature and the solvent was removed under reduced pressure. The oily residue was dissolved in ether, washed with water, dried over $MgSO_4$ and the solvent was removed to give XXVIII as an oil (520 mg), which gave a crystalline semicarbazone (500 mg), mp 228—230°. Recrystallization from MeOH gave colourless needles, mp 229—230°. *Anal.* Calcd. for $C_{17}H_{23}O_2N_3$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.96; H, 7.93; N, 13.60.

2. The oxygen stream (containing 4.3% O_3, 110 ml/min) was passed through a solution of XXVI (1.56 g) in EtOAc (50 ml) for 40 min at −60°. The solution was bubbled with nitrogen and then hydrogenated over Pd/C (prepared from $PdCl_2$ (0.4 g) and carbon (0.8 g)). After the uptake of hydrogen had ceased, the catalyst and the solvent were removed to give a pale brown oil which was converted to a crystalline semicarbazone (600 mg), mp 229—230°.

Identity of this compound with the semicarbazone of XXVIII was confirmed by comparison of the IR spectra and the mixed melting point determination.

(−)-6-Methoxy-4a-formyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene Thioacetal (XXIX)——A mixture of XXVIII (5.0 g), ethanedithiol (11.2 ml) and BF_3-etherate (1.2 ml) was allowed to stand overnight at room temperature and the excess reagent was removed under reduced pressure. The last traces of ethanedithiol were removed by distillation of added water (30 ml). The residue was dissolved in ether, washed with 5% NaOH and then the solvent was evaporated to give pale brown crystals (4.80 g). Trituration of the solid with ether and filtration afforded XXIX (1.24 g), mp 123—125°. Recrystallization from ether gave colourless prisms, mp 127—128°. $[\alpha]_D^{24.5}$ −86.3° (c=2.031, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{24}OS_2$: C, 67.45; H, 7.55; S, 20.01. Found: C, 67.46; H, 7.62; S, 20.20.

(−)-6-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXX)——To a solution of XXIX (620 mg) in EtOH (140 ml) was added Raney Ni (7 g) and the mixture was refluxed for 3.5 hr. After removal of the catalyst and the solvent, the residue was taken up in ether and the solvent was removed to dryness. Chromatography of the residue (360 mg) in petr. ether gave XXX as colourless oil (350 mg). $[\alpha]_D^{23.5}$ −95.6° (c=2.137, dioxane). *Anal.* Calcd, for $C_{16}H_{22}O$: C, 83.54; H, 9.63. Found: C, 83.52; H, 9.79.

(−)-6-Methoxy-9-oxo-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXXI)——Oxidation of XXX (720 mg) with CrO_3 (400 mg) was carried out in the same way as described for VIIIa to yield an oily product (700 mg) which was dissolved in petr. ether and chromatographed. Elution with petr. ether gave the starting material XXX as an oil (90 mg). Elution with benzene gave XXXI as an oil (600 mg, 79%). $[\alpha]_D^{24}$ −54.1° (c=0.802, dioxane). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1680 (C=O). UV λ_{max} mμ (log ε): 280 (4.18). ORD (c=0.335, dioxane) $[\alpha]^{24}$ mμ: −1880° (364) (trough), −1300° (355) (peak), −1940° (350) (trough), 0° (340) (peak), −360° (335) (trough), +1150° (325) (peak). *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.48; H, 8.29.

(−)-*trans*-2-Methyl-2-carboxycyclohexylacetic Acid (XXXII)——The oxygen stream (containing 4.3% O_3 110 ml/min) was passed through a solution of XXXI (720 mg) in 80% formic acid (35 ml) for 3 hr under ice cooling and for an additional 18.5 hr at room temperature. To this solution were added 80% formic acid (10 ml) and 30% H_2O_2 (10 ml). The mixture was allowed to stand overnight at room temperature and then concentrated to about 5 ml under reduced pressure. The residue was taken up in ether, and extracted with 5% $NaHCO_3$. The aqueous layer was acidified with conc. HCl, salted out with NaCl and extracted with ether. The ethereal solution was evaporated to dryness. The residue (170 mg), mp 142—144°, was recrystallized from acetone–petr. ether to give XXXII as colourless cubes, mp 144—146° (lit[8] 146—147°). $[\alpha]_D^{23}$ −12.2° (c=0.981, acetone) (lit[8] $[\alpha]_D$ −11° (acetone)). IR ν_{max}^{Nujol} cm^{-1}: 1695 (COOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.59; H, 8.03.

Preparation of the Isomers of (±)-3-Alkylcyclohexane-1,2-dicarboxylic Acids

(±)-*cis*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic Acid (XXXVIIc) and Its Dimethyl Ester (XXXIXc)——According to Bussert's method[6], the solution of *trans*-piperylene (2.72 g) and maleic anhydride (1.96 g) in benzene (10 ml) was gently refluxed for 20 hr in the presence of picric acid (0.01 g). The product (3.22 g) was recrystallized from benzene–petr. ether to give XXXIIIc as colourless needles (2.60 g, 81.5%). mp 64° (lit[6] 63°). *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.07; H, 6.15.

Treatment of XXXIIIc (800 mg) with boiling water (30 ml) for 15 min gave XXXVc as crystals (810 mg, 92%), mp 152—154°. Recrystallization from benze ne gave colourless prisms, mp 153—154° (lit[6] 153—154°). *Anal.* Calcd. for $C_{19}H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.83; H, 6.66.

Catalytic hydrogenation of XXXVc (650 mg) in AcOH (10 ml) over PtO_2 (100 mg) gave XXXVIIc (600 mg), mp 168—170°, wihch was recrystallized from benzene-*n*-hexane as colourless prisms, mp 169—170° (lit[6] 169—170°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710 (COOH). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.93; H, 7.47.

To a solution of XXXVIIc (20 mg) in ether (10 ml) was added an excess of ethereal diazomethane under ice cooling. The mixture was allowed to stand overnight in a refrigerator, washed with 5% $NaHCO_3$, dried over $MgSO_4$ and the solvent was removed to give XXXIXc as an oil (20 mg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1732 (ester).

(±)-*trans*-3-Methylcyclohexane-*cis*,*cis*-1,2,-dicarboxylic Acid (XXXVIIb) and Its Dimethyl Ester (XXXIXb) ——According to Craig's method,[13] XXXIIIc (300 mg) was heated with diethylaniline (10 mg) for 3 hr at 195—200°. The oily product (XXXIIIb) (290 mg) was treated with boiling water (12 ml) for 20 min to give XXXVb as crystals (290 mg), mp 148—154°. Recrystallization from benzene gave colourless prisms, mp 159—160° (lit[13] 161—162°). *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.74; H, 6.63.

Catalytic hydrogenation of XXXVb (500 mg) in AcOH (10 ml) over PtO_2 (55 mg) afforded XXXVIIb (490 mg), mp 130°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715 (COOH). Recrystallization from benzene–petr. ether gave colourless prisms, mp 130° (lit[13] 129°). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.26; H, 7.59.

Treatment of XXXVIIb with diazomethane as above gave XXXIXb as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (ester).

(±)-*cis*-3-Methylcyclohexane-*trans*,*cis*-1,2-dicarboxylic Acid (XXXVIId) and Its Dimethyl Ester (XXXIXd) ——According to Craig's method,[13] a stirred suspension of fumalic acid (5.80 g) in Ac_2O (25 ml) was heated with *trans*-piperylene (5.50 g) for 6 hr to give a mixture of XXXIIIa and XXXIIId as crystals (8.5 g), mp 98—104°.

Treatment of the product (2.5 g) with boiling water (65 ml) for 30 min and then recrystallization from benzene gave XXXVd as colourless cubes (420 mg), mp 162—163° (lit[13] 156—158°). *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.75; H, 6.68.

Catalytic hydrogenation of XXXVd (150 mg) in AcOH (5 ml) over PtO_2 (15 mg) gave XXXVIId (150 mg), mp 174—176°. Recrystallization from benzene gave colourless cubes, mp 176—178°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1713 (COOH). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.41; H, 7.60.

Treatment of XXXVIId with diazomethane as above gave XXXIXd as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1738 (ester).

(±)-*cis*-3-Methylcyclohexane-*cis*,*trans*-1,2-dicarboxylic Acid (XXXVIIa) and Its Dimethyl Ester (XXXIXa) ——1. According to Bussert's method,[6] XXXVIIc (300 mg) was heated with conc. HCl (3 ml) for 7 hr in a sealed tube at 170—180° to give XXXVIIa as pale brown needles (230 mg) mp 154°, which was recrystallized from benzene–petr. ether as colourless needles, mp 167—169° (lit[6] 162—163°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1713 (COOH). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.29; H, 7.79.

2. Treatment of XXXVIIb (150 mg) with conc. HCl (1.5 ml) as above gave XXXVIIa as colourless needles (130 mg), mp 167—169°.

3. Treatment of XXXVIId (150 mg) with conc. HCl (1.5 ml) as above gave XXXVIIa as colourless needles (130 mg), mp 167—169°. Treatment of XXXVIIa with diazomethane as above gave XXXIXa as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740.

(±)-*cis*-3-Ethylcyclohexane-*cis*,*cis*-1,2-dicarboxylic Acid (XXXVIIIc) and Its Dimethyl Ester (XLc)—— According to Alder's method,[5] the mixture of 1,3-hexadiene (2.40 g) and maleic anhydride (3.0 g) in benzene was refluxed for 2 hr in the presence of a small amount of hydroquinone. The crystalline product (4.10 g), mp 43—47°, was recrystallized from ether–petr. ether to give XXXIVc as colourless needles, mp 52—53°. *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.41; H, 6.65.

Treatment of XXXIVc (4.0 g) with boiling water (20 ml) for 30 min afforded XXXVIc (2.70 g), mp 165—169°. Recrystallization from EtOAc gave colourless prisms, mp 176—177° (lit[5] 176°). *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.24; H, 7.02.

Catalytic hydrogenation of XXXVIc (580 mg) in MeOH (20 mg) over PtO_2 (80 mg) afforded XXXVIIIc (570 mg), mp 113—115°, which was recrystallized from AcOEt—MeOH as colourless needles, mp 117—119° (lit[5] 119°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710 (COOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.23; H, 8.18.

Treatment of XXXVIIIc with diazomethane as above gave XLc as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (ester).

(±)-*trans*-3-Ethylcyclohexane-*cis*,*cis*-1,2-dicarboxylic Acid (XXXVIIIb) and Its Dimethyl Ester (XLb)—— Treatment of XXXIVc (1.80 g) with diethylaniline (60 mg) followed by the hydrolysis of the resulted oil (1.70 g) with boiling water (40 ml) as described for XXXVIIb gave a crystalline product (1.58 g), which was recrystallized from ether–petr. ether to give XXXVIb as colourless cubes (1.0 g), mp 156—158°. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.53; H, 7.15.

A solution of XXXVIb (570 mg) in MeOH (30 ml) was hydrogenated over PtO_2 (50 mg). After the uptake of hydrogen had ceased, the catalyst and the solvent were removed and the residue (530 mg) was recrystallized from ether–petr. ether to give XXXVIIIb as colourless cubes (320 mg), mp 140°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720 (COOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.27; H, 8.12.

Treatment of XXXVIIIb with diazomethane as above gave XLb as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1742 (ester).

(±)-*cis*-3-Ethylcyclohexane-*trans*,*cis*-1,2-dicarboxylic Acid (XXXVIIId) and Its Dimethyl Ester (XLd)—— According to the similar method as in the case of XXXVIId, a mixture of fumaric acid (5.6 g) and 1,3-hexadiene (4.0 g) in Ac_2O (24 ml) was refluxed for 5 hr in the presence of a small amount of hydroquinone to yield a yellow oil (4.60 g), which was treated with boiling water (70 ml) for 30 min and extracted with ether.

The ethereal solution was dried over $MgSO_4$ and the solvent was removed to give a mixture of XXXVIa and XXXVId as crystals (3.0 g), mp 120—125°.

Repeated recrystallization from ether–petr. ether gave XXXVId as colourless cubes, mp 155°. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.60; H, 7.23.

Catalytic hydrogenation of XXXVId (100 mg) as above gave XXXVIIId as crystals (97 mg), mp 170—172°. Recrystallization from ether–petr, ether gave colourless prisms, mp 173—174°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715 (COOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.21; H, 8.25.

Treatment of XXXVIIId with diazomethane as above gave XLd as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (ester).

(±)-*cis*-3-Ethylcyclohexane-*cis,trans*-1,2-dicarboxylic Acid (XXXIIIa) and Its Dimethyl Ester (XLa)——

1. According to the same method as that described for XXXVIIa, XXXVIIIb (300 mg) was converted to XXXVIIIa (300 mg), mp 147—153°. Recrystallization from ether–petr. ether gave colourless prisms, mp 175—176°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1713 (COOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.36; H, 8.13.

2. Treatment of XXXVIIId (200 mg) with conc. HCl (2 ml) in the same manner as described above gave XXXVIIIa as colourless prisms (180 mg), mp 175—176°.

3. The same reaction of XXXVIIIc (200 mg) as above gave XXXVIIIa as colourless prisms (185 mg), mp 175—176°.

Treatment of XXXVIIIa with diazomethane as above gave XLa as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1741 (ester).

(±)-*cis*-3-Ethylcyclohexane-*cis,cis*-1,2-dicarboxylic Acid Monomethyl Ester (XLIIc)——Treatment of XLc (410 mg) with 15% KOH (40 ml) as described for XIIIa gave a solid material. Recrystallization from *n*-hexane gave XLIIc as colourless needles (360 mg), mp 42—44°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710 (COOH), 1738 ($COOCH_3$). *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.92; H, 8.62.

Esterification of XLIIc with diazomethane gave the original dimethyl ester (XLc).

Saponification of (±)-*trans*-3-ethylcyclohexane-*cis,cis*-1,2-dicarboxylic Acid Dimethyl Ester (XLb)——Treatment of XLb (390 mg) with 15% KOH (40 ml) as described for XIIIa gave XXXVIIIb as crystals (340 mg), mp 124—128°. Recrystallization from ether–petr. ether gave colourless cubes, mp 140°.

Saponification of (±)-*cis*-3-ethylcyclohexane-*trans,cis*-1,2-dicarboxylic Acid Dimethyl Ester (XLd)——Treatment of XLd (410 mg) with 15% KOH (40 ml) as described for XIIIa gave a crystalline residue (350 mg), mp 153—157°, which was recrystallized from ether–petr. ether as colourless prisms, mp 173—174°. This compound was identified as XXXVIIId by comparison of the IR spectra and the mixed melting point determination.

(±)-*cis*-3-Ethylcyclohexane-*cis,trans*-1,2-dicarboxylic Acid Monomethyl Ester (XLIIa)——Treatment of XLa (430 mg) with 15% KOH (43 ml) as described for XIIIa gave XLIIa (370 mg), mp 80—82°, which was recrystallized from *n*-hexane as colourless prisms, mp 80—82°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710 (COOH), 1738 ($COOCH_3$). *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.69; H, 8.52.

Esterification of this compound with diazomethane gave the starting material (XLa).

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