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Synthesis of B/C *trans*-Fused Morphine Structures. VI.[1a] Mass Spectrum, Optical Rotatory Dispersion and Circular Dichroism of B/C *trans*-Morphine Derivatives

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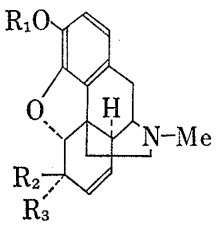
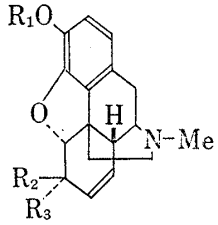
Mass, optical rotatory dispersion (ORD) and circular dichroism (CD) spectra of the B/C *trans*-morphine derivatives have been studied in comparison with the natural (B/C *cis*) isomers. A characteristic difference between isomers epimeric at C_{14} was found in mass spectrum in accord with the reported observation for the *cis*- and *trans*-morphinan derivatives. The stereochemistry of C_5 of *trans*-dihydrocodeinone (V) was established by ORD study and its conversion to *trans*-dihydrocodeine (VI) by $NaBH_4$ reduction.

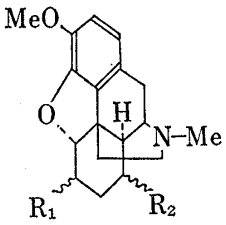
Previous papers of this series[1] described the synthesis of B/C *trans*-morphine (Ia) and related compounds. The present report concerns studies on the mass spectrum, optical rotatory dispersion (ORD) and circular dichroism (CD) of the B/C *trans*-morphine derivatives in comparison with the natural (B/C *cis*) isomers.



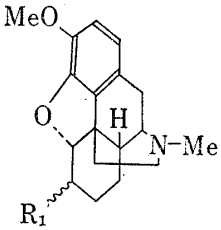
I a: $R_1=R_2=H$, $R_3=OH$ (*trans*-morphine)
I b: $R_1=R_3=H$, $R_2=OH$ (*trans*-isomorphine)
I c: $R_1=Me$, $R_2=H$, $R_3=OH$ (*trans*-codeine)
I d: $R_1=Me$, $R_2=OH$, $R_3=H$ (*trans*-isocodeine)



II a: $R_1=R_2=H$, $R_3=OH$ (morphine)
II b: $R_1=Me$, $R_2=H$, $R_3=OH$ (codeine)
II c: $R_1=Me$, $R_2=OH$, $R_3=H$ (isocodeine)



III a: $R_1=\alpha$-OH, $R_2=H$
III b: $R_1=\beta$-OH, $R_2=H$
III c: $R_1=R_2=\alpha$-OH
III d: $R_1=\beta$-OH, $R_2=\alpha$-OH
III e: $R_1=R_2=H$



IV a: $R_1=\beta$-OH (dihydroisocodeine)
IV b: $R_1=H$ (dihydrodeoxycodeine)

Chart 1

1) *a*) Part V: H. Kugita, M. Takeda, and H. Inoue, *J. Med. Chem.*, **13**, 973 (1970); *b*) M. Takeda, H. Inoue, and H. Kugita, *Tetrahedron*, **25**, 1839 (1969); *c*) H. Kugita, M. Takeda, and H. Inoue, *Tetrahedron*, **25**, 1851 (1969); *d*) H. Inoue, M. Takeda, and H. Kugita, *Chem. Pharm. Bull.* (Tokyo), **18**, 1569 (1970).

2) Location: *2-2-50, Kawagishi, Toda, Saitama.*

Mass Spectrum

Studies on the mass spectrum of the natural morphine derivatives have been reported by several workers.[3-5] Comparison of the mass spectra of B/C *trans*-morphine (Ia) and natural (B/C *cis*) morphine (IIa) revealed a significant difference in their fragmentation patterns (Fig. 1a and c). The peak for an ion *m/e* 162 of *trans*-morphine (Ia) and related compounds (Ib, Ic, Id) bearing C_7-C_8 double bond is more intense than that of the corresponding B/C *cis* isomers (IIa, b, c) (Table I).

This is apparently accounted for by a fragmentation *via* an ion b to the hydroisoquinolinium ion e[5] (Chart 2). The high intense metastable peak for ion b→ ion e is thus observed

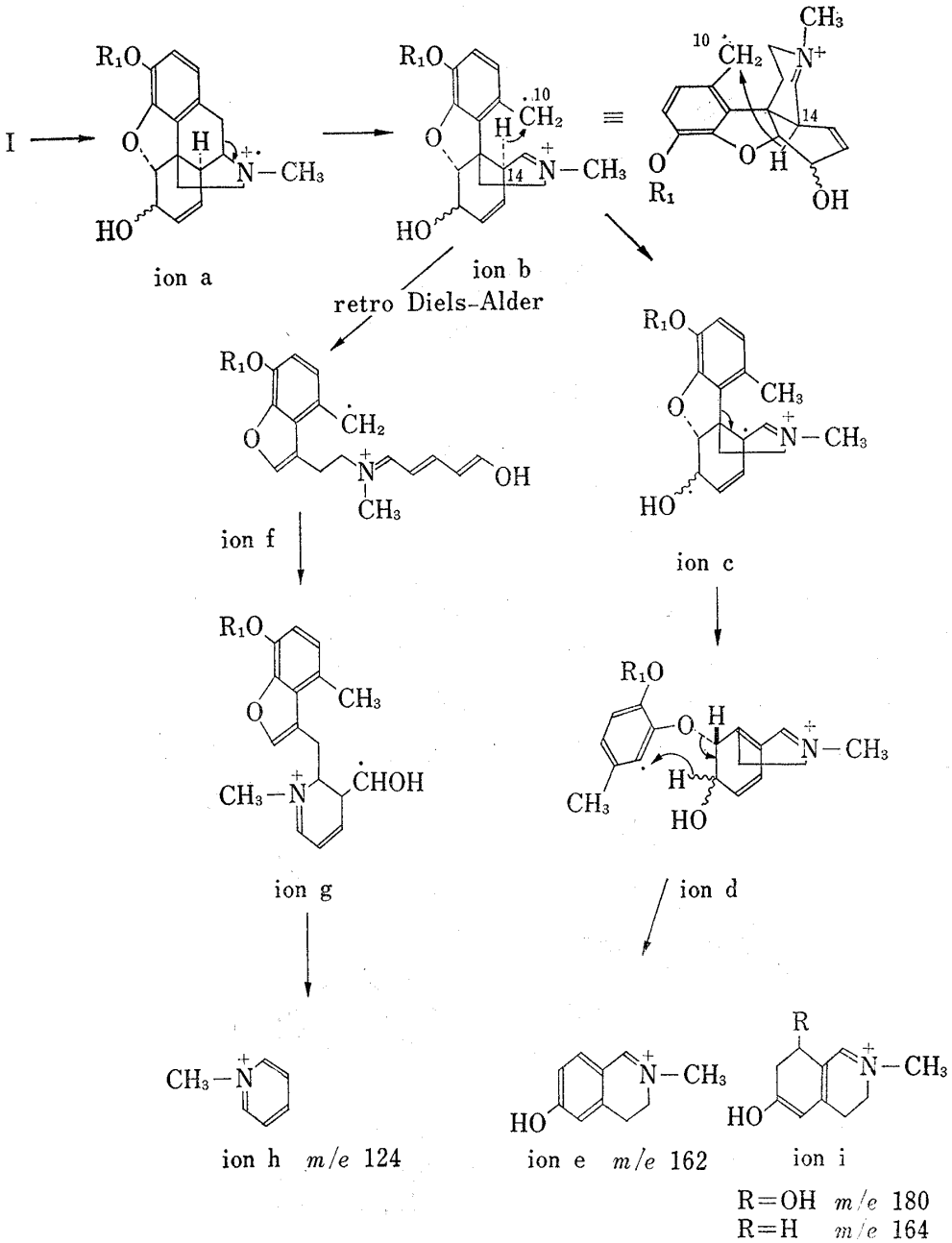


Chart 2

3) D.M.S. Wheeler, T.H. Kinstle, and K.L. Rinehart, Jr., *J. Am. Chem. Soc.*, **89**, 4494 (1967).
4) H. Nakata, Y. Hirata, A. Tatematsu, H. Tada, and Y.K. Sawa, *Tetrahedron Letters*, **1965**, 829; H. Audier, H. Fetison, D. Ginsburg, A. Mandelbaum, and Th. Rüll, *Tetrahedron Letters*, **1965**, 13.
5) A. Mandelbaum and D. Ginsburg, *Tetrahedron Letters*, **1965**, 2479.

at 92.4 (calculated M* 92.1) for Ia and Ib. With B/C *trans* derivatives, transfer of C_{14} hydrogen can occur as in ion b→ion c, since the C_{14} hydrogen is close to C_{10} as shown in Chart 2. However, with the related *cis* isomers, such a process is sterically impossible.[6] Thus, in the B/C *trans*-isomers, the formation of ion e seems to be a more favourable process and the *m/e* 162 peak

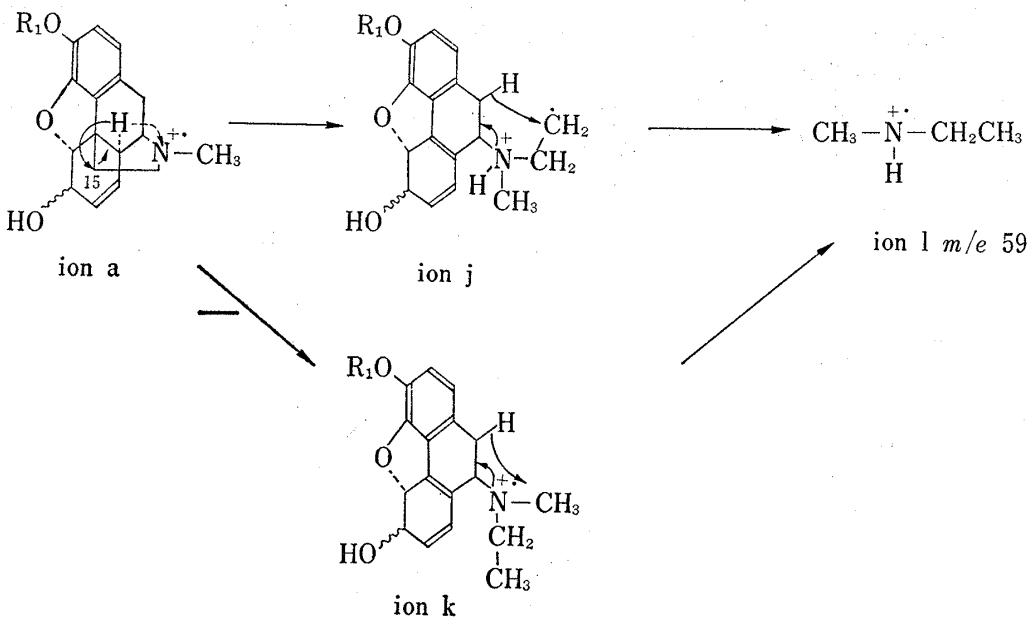


Chart 3

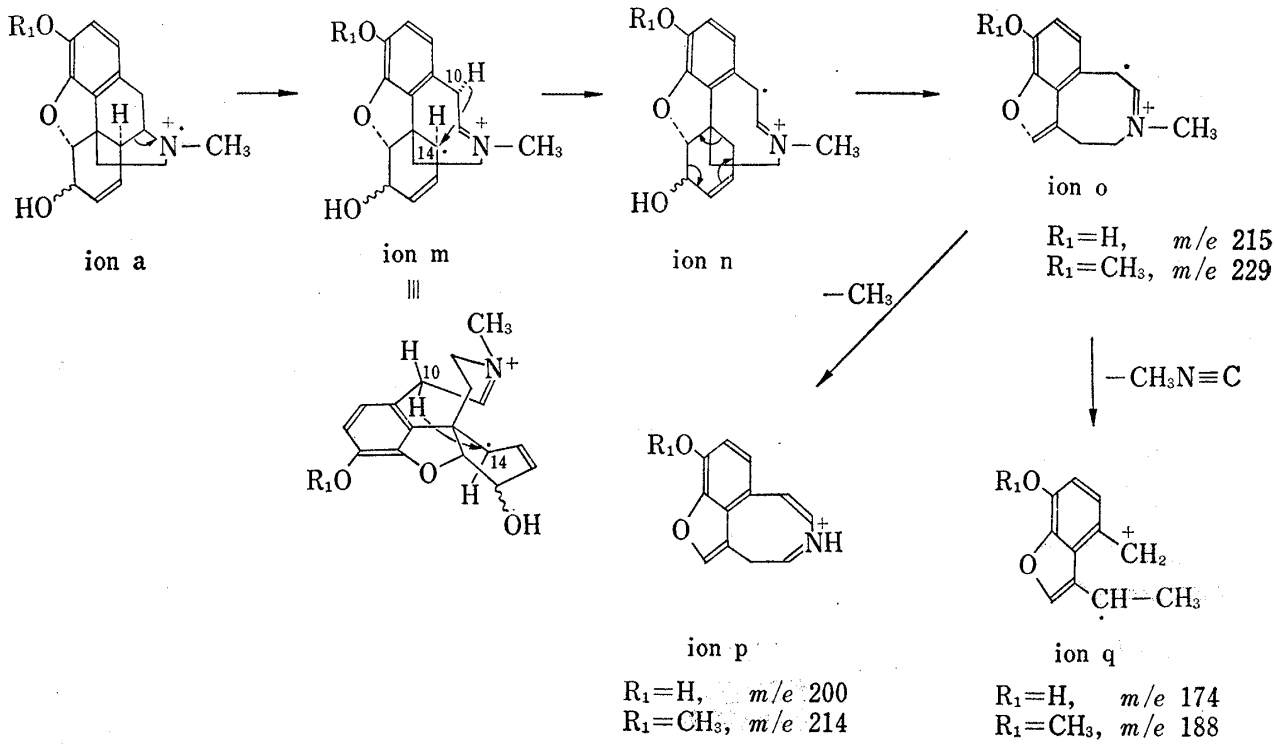
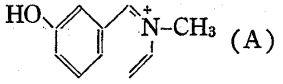


Chart 4

6) The peak for an ion *m/e* 162 in *cis*-morphine (IIa) has been ascribed to an isomeric ion A. See ref. 3



is more intense than that of the corresponding *cis* isomers. This parallels the reported observation for B/C *cis* and *trans* morphinan derivatives.[5]

The presence of an ion i derived from a similar type of fragmentation is also observed in the spectrum of dihydromorphine derivatives (III) and (IV). Again, this peak is more intense in the *trans* isomers[5] (Table II).

Concomitantly, ion b has been also suggested as the precursor of the pyridinium ion h (found in the morphine spectrum at *m/e* 124) through retro Diels–Alder fragmentation[3] (Chart 2). The relatively weak intensity of this ion in the *trans* derivatives, when compared with the *cis* counterparts (Table I), may be attributable to the pronounced tendency of an ion b to undergo fragmentation leading to ion e as mentioned above.

An another difference between compounds epimeric at C_{14} appears in patterns leading to the peak *m/e* 59. The fragmentations *via* ion j and/or ion k to ion l has been proposed for the B/C *cis* morphine and morphinan derivatives[3,5] (Chart 3). Both processes require a *cis* arrangement of the ethanamine chain and C_{14} hydrogen. The weak intensity of the peak *m/e* 59 in the *trans* isomers (Table I and II) is presumably due to the fact that $C_{14\alpha}$ hydrogen is unable to participate either with C_{15} or the nitrogen atom. A similar observation has been reported in the *trans* morphinan series.[5]

In the *cis* morphine derivatives, Wheeler, *et al.*[3] proposed that the transfer of the sterically available hydrogen at $C_{10\alpha}$ to the radical at $C_{14\alpha}$ in ion m gave the stable benzylic radical n, which underwent a reverse Diels–Alder reaction to afford the aromatic benzofuran o. The latter further underwent fragmentations leading to ion p and ion q, respectively (Chart 4). Since the formation of ion n (shift of hydrogen at $C_{10\alpha}$ to the radical at $C_{14\beta}$) may be difficult in the *trans* isomers, the peaks of ion o, p and q are of lower abundance than that of the *cis* isomers (Table I).

Compositions of the all ions (e, h, l, o, p and q) were confirmed by high resolution mass spectra (Table III).

Thus, mass spectrometry allows identifying distinction to be drawn between B/C *cis* and *trans*-derivatives in the morphine series.

Optical Rotatory Dispersion and Circular Dichroism

ORD and CD spectra of the natural morphine derivatives have

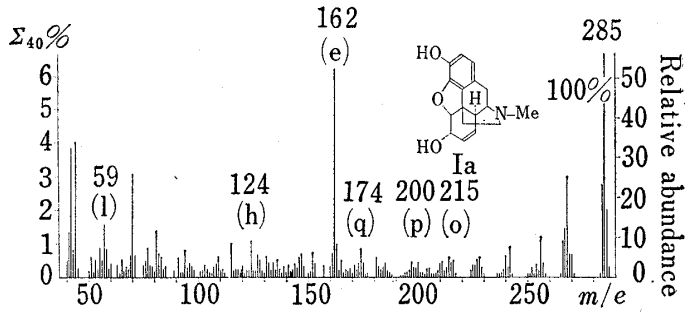


Fig. 1a. Mass Spectrum of *trans*-Morphine (Ia)

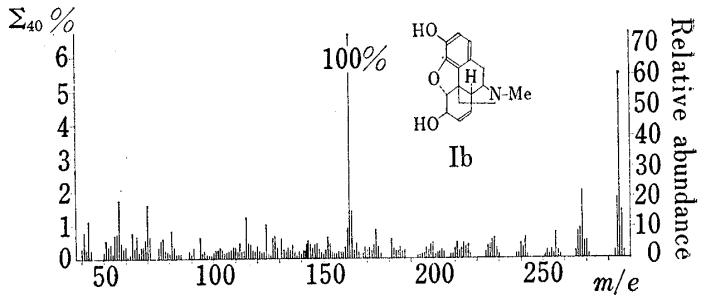


Fig. 1b. Mass Spectrum of *trans*-Isomorphine (Ib)

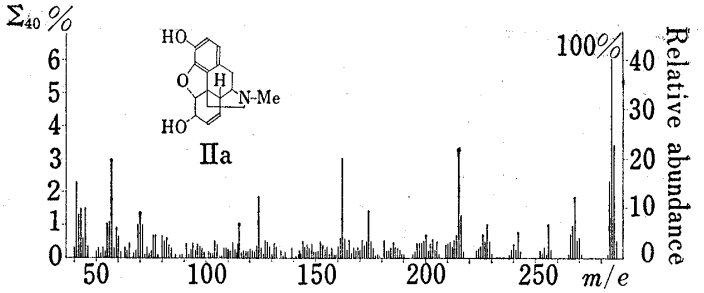


Fig. 1c. Mass Spectrum of *cis*-Morphine (IIa)

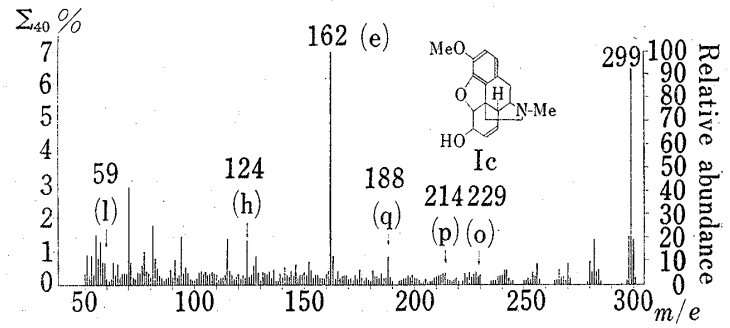


Fig. 1d. Mass Spectrum of *trans*-Codeine (Ic)

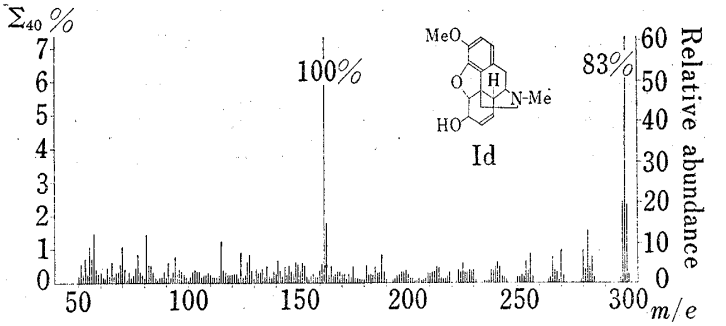


Fig. 1e. Mass Spectrum of *trans*-Isocodeine (Id)

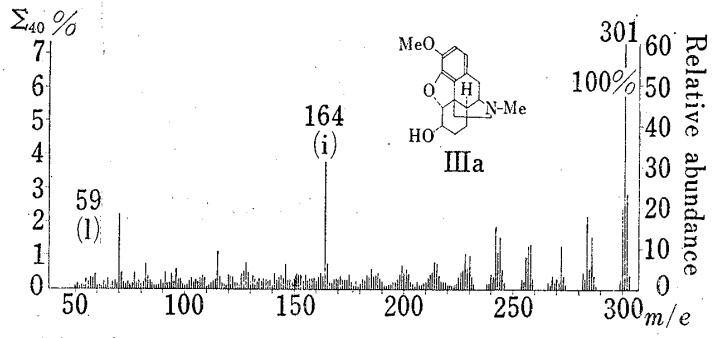


Fig. 1f. Mass Spectrum of *trans*-Dihydrocodeine (IIIa)

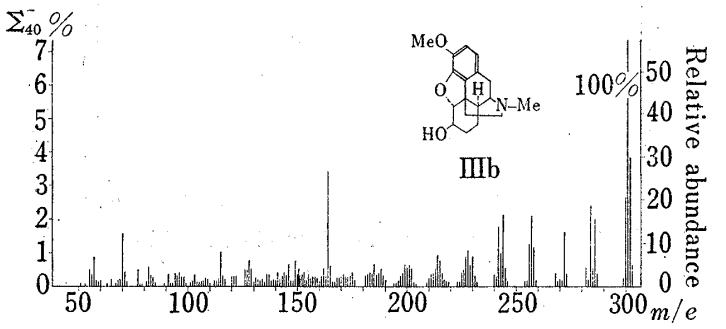


Fig. 1g. Mass Spectrum of *trans*-Dihydroisocodeine (IIIb)

been studied by several workers.[7-9] The B/C *cis* derivatives which contain no carbonyl function exhibit the negative Cotton effect in the 280 mμ region and the positive one in the 245 mμ region respectively, associated with an aromatic chromophore.[7]

ORD and CD spectra for the *trans*-morphine derivatives (Ic, Id and IIIe) are similar to that of the corresponding *cis* isomers (IIb, IIc, and IVb) (Fig. 2 and 3, Table IV).

B/C *cis* and *trans* morphinan derivatives are known to exhibit similar ORD curves and the sign of the Cotton effect depends on the absolute configuration of C_{13} rather than that of C_{14}.[10] A close similarity of the ORD and CD curves of the *cis* and *trans* morphine isomers is thus attributable to a similar stereochemical environment of C_{13} in the both isomers (Chart 5).

The ORD and CD spectra of the two carbonyl compounds (V and IX) were also examined. In our previous paper,[1a] *trans*-dihydrocodeinone (V) has been prepared by Oppenauer oxidation of *trans*-dihydrocodeine (VI) and identified with an authentic sample synthesized from *trans*-1,7-dibromo-dihydrothebainone (VII) by Gates, *et al.*[11] (Chart 6).

However, no definite proof has been given for the stereochemistry of C_5 in this compound. Recently, Bentley[12] and Lewis[13] suggested

7) U. Weiss and T. Rüll, *Bull. Soc. Chim. France*, **1965**, 3707.
8) A.F. Casy and M.M.A. Hassan, *J. Pharm. Pharmac.*, **19**, 132 (1967); J.M. Bobbitt, U. Weiss, and D.D. Hanessian, *J. Org. Chem.*, **24**, 1582 (1959).
9) T. Rüll, *Bull. Soc. Chim. France*, **1965**, 3715.
10) Y. Sawa, K. Kawasaki, S. Maeda, R. Maeda, K. Okabe, N. Tsuzi, K. Kuriyama, and T. Nakagawa, "Abstract of the 6th Symposium on the Chemistry of Natural Products (Sapporo)," 1962, p. 23.
11) Private communication from Professor M. Gates, University of Rochester. See footnote 7 of reference 1a.
12) K.W. Bentley, "The morphine alkaloids" in "The Alkaloids," XIII, R.M.F. Manske, Ed., Academic Press, New York, 1971, p. 17.
13) J.W. Lewis, K.W. Bentley, and A. Cowan, *Annual Review of Pharmacology*, **11**, 241 (1971).

Table I. Relative Intensity ($\sum_{40}$ %)

Compounds	Isomerism at C_{14}	Ion e	Ion h	Ion l	Ion o	Ion p	Ion q	M+
		m/e 162	*m/e* 124	*m/e* 59	*m/e* 215	*m/e* 200	*m/e* 174	*m/e* 285
Ia	*trans*	6.2	1.1	0.25	0.45	0.43	0.85	11.7
Ib	*trans*	9.0	1.0	0.25	0.33	0.45	0.85	5.5
IIa	*cis*	3.0	1.8	0.90	3.3	0.70	1.4	15.0
					m/e 229	*m/e* 214	*m/e* 188	*m/e* 299
Ic	*trans*	7.0	1.3	0.65	0.25	0.33	0.83	6.5
Id	*trans*	12.0	0.93	0.25	0.33	0.46	0.87	10.0
IIb	*cis*	3.1	4.3	3.8	2.2	1.0	1.4	7.1
IIc	*cis*	4.7	1.5	1.9	3.1	1.4	1.3	16.0

Table II. Relative Intensity ($\sum_{40}$ %)

Compounds No.		Ion l	Ion i	M+
		m/e 59	*m/e* 164	*m/e* 301
IIIa[a)]	*trans*	0.67	3.3	10.3
IIIb[a)]	*trans*	0.13	3.4	12.8
IVa[a)]	*cis*	1.2	1.3	23.8
			m/e 180	*m/e* 317
IIIc	*trans*	1.5	1.7	6.3
IIId	*trans*	1.1	0.83	6.3

a) Ionization chamber was maintained at 110°.

Table III. High Resolution Mass Spectra of *trans*-Morphine (Ia) and Isomorphine (Ib)

Measured mass		Formula	Calculated mass	Ion
trans-Morphine (Ia)	*trans*-Isomorphine (Ib)			
285.1388	285.1351	$C_{17}H_{19}O_3N$	285.1365	M+
268.1333	268.1335	$C_{17}H_{18}O_2N$	268.1337	
256.1334	256.1303	$C_{16}H_{18}O_2N$	256.1337	
215.0921	215.0928	$C_{13}H_{13}O_2N$	215.0946	ion o
200.0721	200.0782	$C_{12}H_{10}O_2N$	200.0711	ion p
174.0692	174.0683	$C_{11}H_{10}O_2$	174.0681	ion q
162.0916	162.0918	$C_{10}H_{12}ON$	162.0919	ion e
124.0769	124.0765	$C_7H_{10}ON$	124.0762	ion h
59.0738	59.0715	C_3H_9N	59.0735	ion l

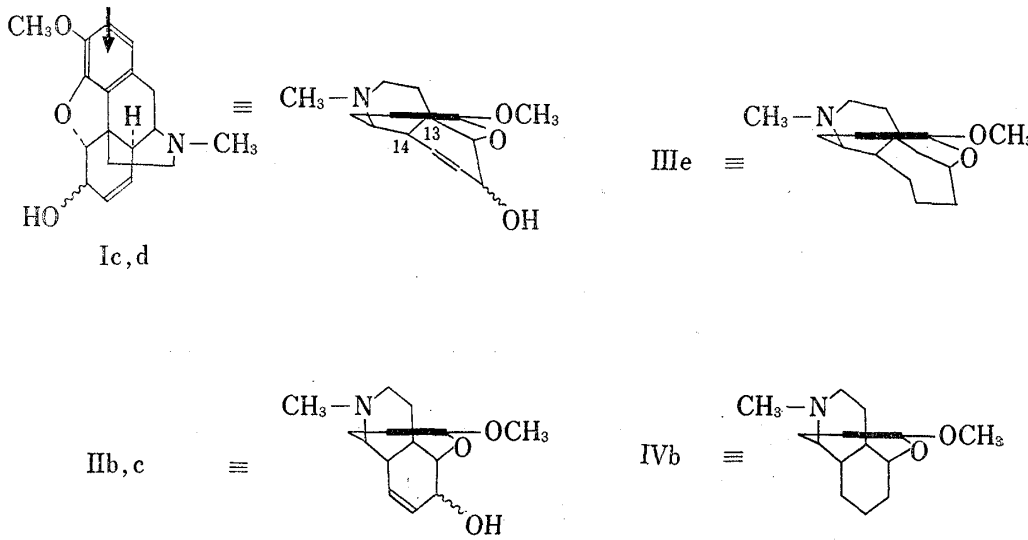


Chart 5. Projection of B/C *cis*- and *trans*-Morphine Derivatives

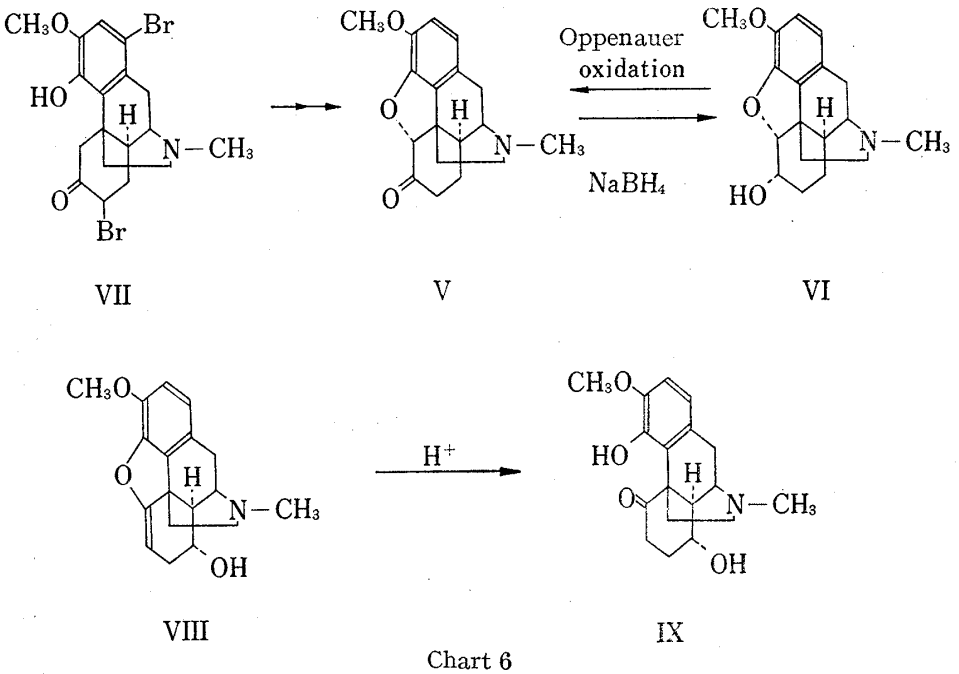


Chart 6

that V would have the structure (B) with a *trans*-fusion of the oxygen-containing ring and ring C on the basis of a mechanistic consideration for the cyclization of VII. They also presumed that the inversion at C_5 could occur in the initial oxidation product (V) under the condition of Oppenauer oxidation.

Now, *trans*-dihydrocodeinone (V) exhibits the negative Cotton effect at 302 mμ attributable to the carbonyl chromophore[14] (Fig. 4). Accordingly, by an application of octant rule,

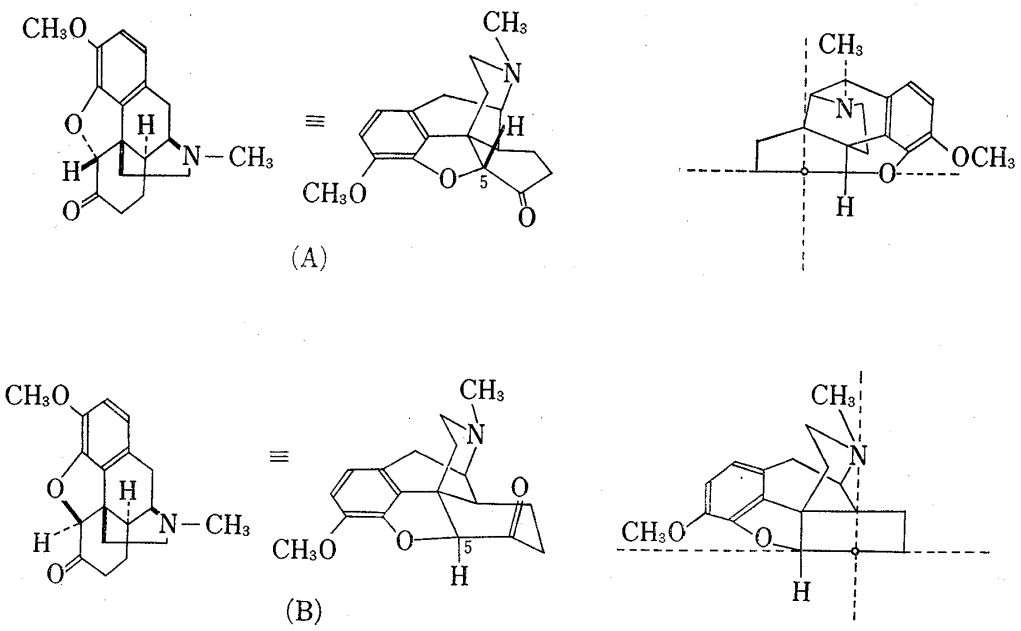
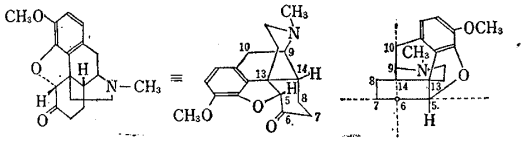


Chart 7. Stereoformulas and Octant Projection of *trans*-Dihydrocodeinone (V)

14) A similar Cotton effect has been reported for the *cis*-dihydrocodeinone. See ref. 9.



the absolute configuration of C_5 was assigned for R-configuration as shown in structure (A) (Chart 7). Furthermore, $NaBH_4$ reduction of V regenerated *trans*-dihydrocodeine (VI) in good yield.[15] These results unequivocally confirm that *trans*-dihydrocodeinone (V) has the structure (A), with a *cis*-fusion of oxygen-containing ring and ring C.

trans-5-Oxo-tetrahydroallo-ϕ-codeine (IX), prepared by acid hydrolysis of trans-Δ^5-dihydroallo-ϕ-codeine (VIII),[1c] exhibits the positive Cotton effect at 290 mμ attributable to C_5 carbonyl chromophore (Fig. 5).

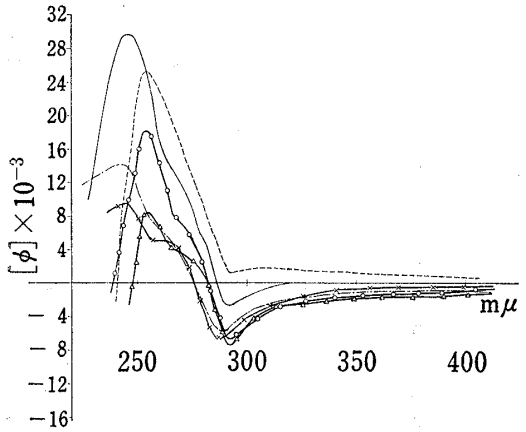


Fig. 2. Optical Rotatory Dispersion Curves of I, II, III, and IV

- – – – – :*trans*-codeine (Ic)
- ——— :*trans*-isocodeine (Id)
- —·—·—·— :*trans*-dihydrodeoxycodeine (IIIe)
- —○—○— :*cis*-codeine (IIb)
- —△—△— :*cis*-isocodeine (IIc)
- —×—×— :*cis*-dihydrodeoxycodeine (IVb)

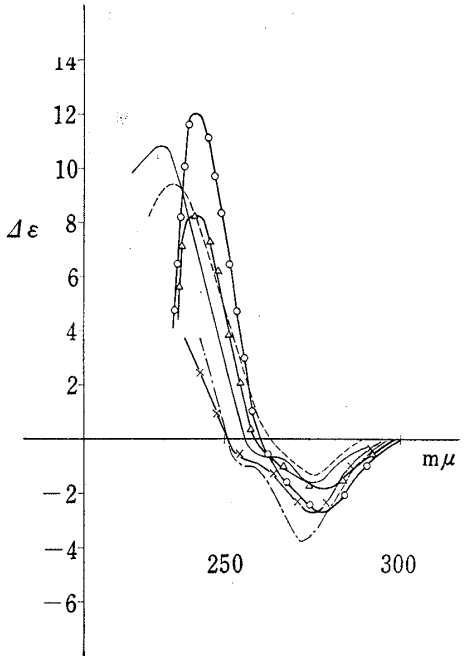


Fig. 3. Circular Dichroism Curves of I, II, III, and IV

- – – – – :*trans*-codeine (Ic)
- ——— :*trans*-isocodeine (Id)
- —·—·—·— :*trans*-dihydrodexoycodeine (IIIe)
- —○—○— :*cis*-codeine (IIb)
- —△—△— :*cis*-isocodeine (IIc)
- —×—×— :*cis*-dihydrodeoxycodeine (IVb)

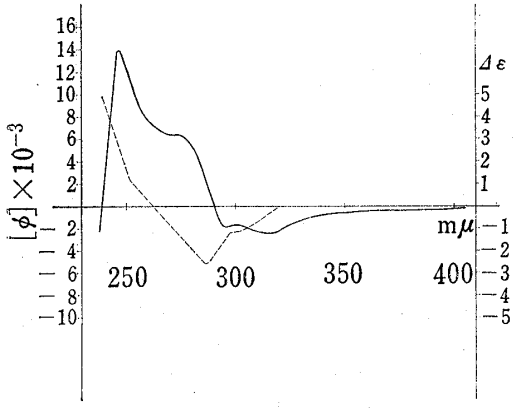


Fig. 4. Optical Rotatory Dispersion and Circular Dichroism Curves of V

—— :ORD
---- :CD

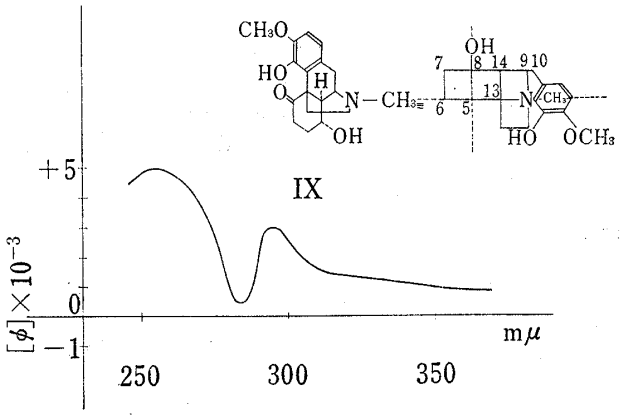


Fig. 5. Optical Rotatory Dispersion Curve of IX

15) Stereoselective formation of the 6α-carbinol (VI) is apparently due to the steric crowding of the α-side of the molecule.

Table IV

Compounds	ORD		CD	
	mμ	[φ]	mμ	Δε
trans-Codeine (Ic)	292	+800	288	0
	254	+25600	275	−1.20
			263	0
			236	+9.6
trans-Isocodeine (Id)	291	−2400	294	0
	246	+29400	275	−1.51
			258	0
			232	+10.8
trans-Dihydrodeoxycodeine (IIIe)	288	−5900	296	0
	264	+5100	272	−3.61
	242	+14200	252	0
Codeine (IIb)	292	−6800	300	0
	270	+6450	278	−2.34
	254	+18000	260	0
			242	+12.4
Isocodeine (IIc)	292	−7300	298	0
	271	+3630	278	−1.72
	254	+8400	259	0
			242	+8.2
Dihydrodeoxycodeine (IVb)	287	−6350	294	0
	260	+5050	276	−2.47
	245	+9500	251	0
trans-Dihydrocodeinone (V)	316	−2590	320	0
	296	−1820	302	−1.04
	274	+6460	286	−2.67
	247	+14000	262	0
trans-5-Oxo-tetrahydro-allo-ψ-codeine (IX)	294	+3000		
	284	+400		
	256	+5000		

Experimental

Mass Spectral Measurements——The mass spectra were recorded on a Hitachi RMS-4 single-focusing mass spectrometer. The ionizing potential was 70 eV and ionizing current was 50 μA. The accelerating potential was 1500 V. Samples were introduced into the mass spectrometer through the use of a direct insertion probe. The ionization chamber temperature was usually maintained at 150° unless otherwise stated.

The high resolution spectra was determined by an A.E.I.MS-9 double-focusing mass spectrometer.

ORD and CD Curves Measurements——ORD and CD spectra were measured by JASCO-Model ORD/UV-5 instrument of Japan Spectroscopic Co., Ltd., in 150—200 γ/ml MeOH solution using a cell of 5—10 mm width at ambient temperature (24°).

Compounds——Morphine (IIa) and codeine (IIb) were commercial samples. Isocodeine (IIc),[16] dihydroisocodeine (IVa)[17] and dihydrodeoxycodeine (IVb)[18] were prepared by standard procedures.

***trans*-5-Oxo-tetrahydro-allo-ψ-codeine (3-Methoxy-4,8α-dihydroxy-5-oxo-N-methyl Isomorphinan, IX) Hydrochloride**——A solution of VIII (150 mg) in 13% HCl–EtOH (6 ml) was refluxed for 1.5 hr. After cooling, precipitated crystals were collected, washed with cold EtOH and recrystallized from EtOH to give 120 mg of IX·HCl, mp 280—283° (68%). IR ν_{max}^{Nujol} cm^{-1}: 3290, 1710. *Anal.* Calcd. for $C_{18}H_{24}O_4NCl$: C, 61.10; H, 6.84; N, 3.96. Found: C, 61.11; H, 6.87; N, 3.61.

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$NaBH_4$ Reduction of *trans*-Dihydrocodeinone (V)——To a cold solution of V (regenerated from the picrate 208 mg) in EtOH (8 ml), was added $NaBH_4$ (50 mg). The mixture was stirred for 2 hr at room temperature, diluted with H_2O and extracted with $CHCl_3$. Evaporation of the dried (Na_2SO_4) solvent gave an oil, which was converted to the hydrochloride. Recrystallization from EtOH–ether gave needles, 107 mg (80.8 %), mp 246—248° (decomp.). This proved to be identical with an authentic sample of VI·HCl in every respects (TLC, mp and IR).

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