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 C₁₄ was found in mass spectrum in accord with the reported observation for the *cis*- and *trans*-morphinan derivatives. The stereochemistry of C₅ of *trans*-dihydrocodeinone (V) was established by ORD study and its conversion to *trans*-dihydrocodeine (VI) by NaBH₄ reduction.

Previous papers of this series¹⁾ 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: R₁=R₂=H, R₃=OH (*trans*-morphine)
 I b: R₁=R₃=H, R₂=OH (*trans*-isomorphine)
 I c: R₁=Me, R₂=H, R₃=OH (*trans*-codeine)
 I d: R₁=Me, R₂=OH, R₃=H (*trans*-isocodeine)

- II a: R₁=R₂=H, R₃=OH (morphine)
 II b: R₁=Me, R₂=H, R₃=OH (codeine)
 II c: R₁=Me, R₂=OH, R₃=H (isocodeine)

- III a: R₁=α-OH, R₂=H
 III b: R₁=β-OH, R₂=H
 III c: R₁=R₂=α-OH
 III d: R₁=β-OH, R₂=α-OH
 III e: R₁=R₂=H

- IV a: R₁=β-OH (dihydroisocodeine)
 IV b: R₁=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 C₇-C₈ 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 e⁵⁾ (Chart 2). The high intense metastable peak for ion b $\rightarrow$ ion e is thus observed

- 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 $\rightarrow$ 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* isomers⁵⁾ (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 fragmentation³⁾ (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.

Another difference between compounds epimeric at C₁₄ 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 C₁₄ 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 α} hydrogen is unable to participate either with C₁₅ 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 α} to the radical at C_{14 α} 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 α} to the radical at C_{14 β}) 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 m μ region and the positive one in the 245 m μ 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 C₁₃ rather than that of C₁₄.¹⁰⁾ 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 C₁₃ 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 C₅ in this compound. Recently, Bentley¹²⁾ and Lewis¹³⁾ suggested

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- 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 (Σ_{40} %)

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

TABLE II. Relative Intensity (Σ_{40} %)

Compounds No.		Ion l	Ion i	M ⁺
		<i>m/e</i> 59	<i>m/e</i> 164	<i>m/e</i> 301
IIIa ^{a)}	<i>trans</i>	0.67	3.3	10.3
IIIb ^{a)}	<i>trans</i>	0.13	3.4	12.8
IVa ^{a)}	<i>cis</i>	1.2	1.3	23.8
			<i>m/e</i> 180	<i>m/e</i> 317
IIIc	<i>trans</i>	1.5	1.7	6.3
IIId	<i>trans</i>	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
<i>trans</i> -Morphine (Ia)	<i>trans</i> -Isomorphine (Ib)			
285.1388	285.1351	C ₁₇ H ₁₉ O ₃ N	285.1365	M ⁺
268.1333	268.1335	C ₁₇ H ₁₈ O ₂ N	268.1337	
256.1334	256.1303	C ₁₆ H ₁₈ O ₂ N	256.1337	
215.0921	215.0928	C ₁₃ H ₁₃ O ₂ N	215.0946	ion o
200.0721	200.0782	C ₁₂ H ₁₀ O ₂ N	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 ₇ H ₁₀ ON	124.0762	ion h
59.0738	59.0715	C ₃ H ₉ N	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 C₅ 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 m μ attributable to the carbonyl chromophore¹⁴⁾ (Fig. 4). Accordingly, by an application of octant rule,

Chart 7. Stereofomulas 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 m μ 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*-dihydrodeoxycodeine (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 6 α -carbinol (VI) is apparently due to the steric crowding of the α -side of the molecule.

TABLE IV

Compounds	ORD		CD	
	m μ	[ϕ]	m μ	$\Delta\epsilon$
<i>trans</i> -Codeine (Ic)	292	+800	288	0
	254	+25600	275	-1.20
			263	0
			236	+9.6
<i>trans</i> -Isocodeine (Id)	291	-2400	294	0
	246	+29400	275	-1.51
			258	0
			232	+10.8
<i>trans</i> -Dihydrodeoxycodine (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
Dihydrodeoxycodine (IVb)	287	-6350	294	0
	260	+5050	276	-2.47
	245	+9500	251	0
<i>trans</i> -Dihydrocodeinone (V)	316	-2590	320	0
	296	-1820	302	-1.04
	274	+6460	286	-2.67
	247	+14000	262	0
<i>trans</i> -5-Oxo-tetrahydro-allo- ϕ -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 μ A. 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 dihydrodeoxycodine (IVb)¹⁸ were prepared by standard procedures.

***trans*-5-Oxo-tetrahydro-allo- ϕ -codeine (3-Methoxy-4,8 α -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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3290, 1710. Anal. Calcd. for C₁₈H₂₄O₄NCl: C, 61.10; H, 6.84; N, 3.96. Found: C, 61.11; H, 6.87; N, 3.61.

16) L. Knorr and H. Hörlein, *Chem. Ber.*, **41**, 972 (1908).

17) M.M. Baizer, A. Loter, K.S. Ellner, and D.R. Satriana, *J. Org. Chem.*, **16**, 543 (1951).

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NaBH₄ Reduction of *trans*-Dihydrocodeinone (V)—To a cold solution of V (regenerated from the picrate 208 mg) in EtOH (8 ml), was added NaBH₄ (50 mg). The mixture was stirred for 2 hr at room temperature, diluted with H₂O and extracted with CHCl₃. Evaporation of the dried (Na₂SO₄) 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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