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STUDIES IN MASS SPECTROMETRY IV. STERIC DIRECTION OF FRAGMENTATION IN CIS- AND TRANS- B:C RING-FUSED MORPHINE DERIVATIVES *, 1

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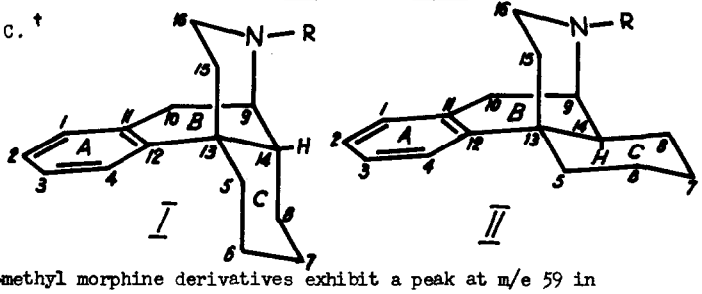
Comparison of mass spectra of various morphine derivatives epimeric at C_{14} indicated the possibility of using mass spectrometry to distinguish structurally between compounds having cis-(I) and trans-(II) fusion of rings B and C. †



All N-methyl morphine derivatives exhibit a peak at m/e 59 in rather high relative abundance provided there is a hydrogen atom at C_{14}. Thus, neopine and thebaine which have a C_8-C_{14} double bond and 14-hydroxy-codeinone show only a very low intensity peak at m/e 59.

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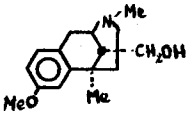
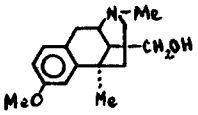
* Part III. N. Maoz, A. Mandelbaum and M. Cais, Tetrahedron Letters, in press.

† Mass spectra were measured on an Atlas CH_4 Spectrometer equipped with direct inlet system. Electron energy was maintained at 70 ev and ionization current at 20μA.

In dihydronorcodeine (NH instead of NMe), the peak at m/e 59 is of very low abundance ($\%\Sigma_{40}$=0.3), whilst the peak at m/e 45 is of much higher intensity ($\%\Sigma_{40}$= 3.2) than in either dihydrocodeine (NMe) or in other N-substituted compounds. Similarly, for 3-hydroxy-N-(γ -phenylallyl)-morphinan, the peak at m/e 59 is very low ($\%\Sigma_{40}$= 0.2) while an ion of m/e 161, containing the phenylallyl group, is much more abundant ($\%\Sigma_{40}$= 1.9). Such is the case also with 3-hydroxy-N-(cyclopropylmethyl)-morphinan (III) (m/e 59; $\%\Sigma_{40}$= 0.4) which leads to an ion, m/e 99, containing the cyclopropylmethyl group ($\%\Sigma_{40}$= 2.3). Additional support for this behaviour in morphinan derivatives has been reported recently (2).

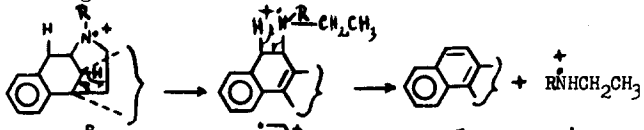
The Table summarizes results obtained for various morphine derivatives epimeric at C_{14}, the last two of which may be considered seco-ring C compounds (3).

TABLE

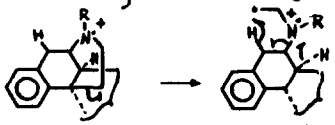
Compound	Parent Peak			Type a ion		
		$\%\Sigma_{40}$			$\%\Sigma_{40}$	
	m/e	cis-	trans-	m/e	cis-	trans-
3-Hydroxy-N-(cyclo-propylmethyl)-morphinan(III)	297	8.6	14.0	99	2.3	0.2
3-Methoxy-4-hydroxy-N-methyl-morphinan (tetrahydrodesoxy-codeine)	287	8.0	17.2	59	5.8	0.2
Thebainone	299	8.0	13.5	59	0.5	0.01
Dihydrothebainol	303	5.4	11.5	59	3.6	0.2
1-Bromodihydrocodeinone	379	6.4	6.4	59	4.5	0.9
Dihydroallopseudocodeine (IV)	301	8.7	15.4	59	4.2	1.3
 (Va)	261	10.0		59	7.3	
 (Vb)	261		11.6	59		3.2

Two mechanisms may be proposed to explain the formation of the peak at m/e 59 or its analogs for other N-substituents. Mechanism 2 is essentially that proposed by Nakata et al (2) but we prefer the alternative mechanism 1, since it enables us to explain the presence of M-15 peaks in spectra of compounds having no methyl group, e.g. in 3-hydroxy-N-(γ-phenylallyl)-morphinan. Since identical hydrogen atoms are shifted towards the leaving group in either of both mechanisms, deuteration cannot be used to distinguish between them.

Mechanism 1



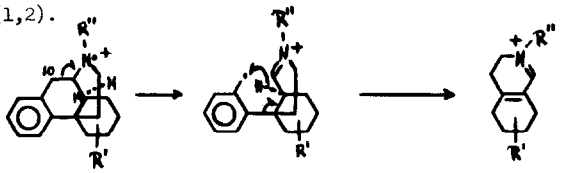
Mechanism 2



ion a

Both mechanisms require cis-fused B:C rings because in the trans-isomers the hydrogen at C_{14} is too far from either C_{15} or from the nitrogen atom to participate in a four membered ring transition state as suggested above. This is apparently the reason for the relative weak intensity of the m/e 59 peaks in the trans-isomers (see Table).

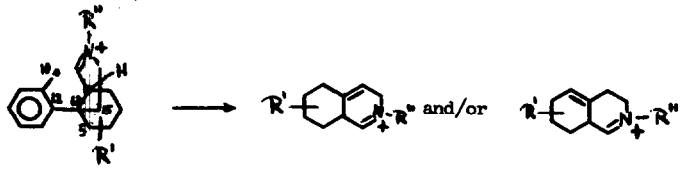
Another important difference between compounds epimeric at C_{14} was found in the fragmentation pattern leading to b ions of the hydroisoquinolinium type (1,2).



intermediate B ion b

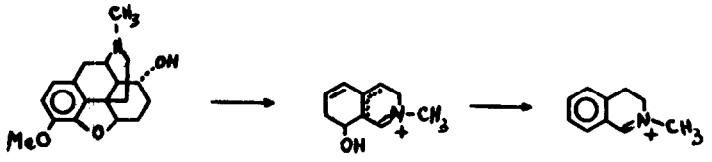
In trans-isomers, the C_{14}- hydrogen is close to C_{10}. Ion b may therefore be formed by shift of the hydrogen from C_{14} to C_{10} through a

six membered transition state. In our previous communication (1) we incorrectly proposed this shift for the cis-isomer in which such a shift is sterically impossible. It is evidently for this reason that an isomeric hydroisoquinolinium ion $\underline{b}_1$ and/or $\underline{b}_2$ is formed by migration of a hydrogen atom from either C_{15} or C_5, respectively (by corresponding rotation of the aromatic part of the intermediate B, around the C_{12}-C_{13} bond, to bring C_{10} into proximity for the formation of a six membered transition state).



intermediate B_1 ion $\underline{b}_1$ ion $\underline{b}_2$

Since the formation of ion b appears to be more favored than that of ion $\underline{b}_1$ or $\underline{b}_2$, one should be able to predict that trans-B:C compounds should give rise to more intense peaks of the ion b type, as compared to the cis-B:C isomers.



(IV) ion $\underline{b}_3$ ion $\underline{b}_4$

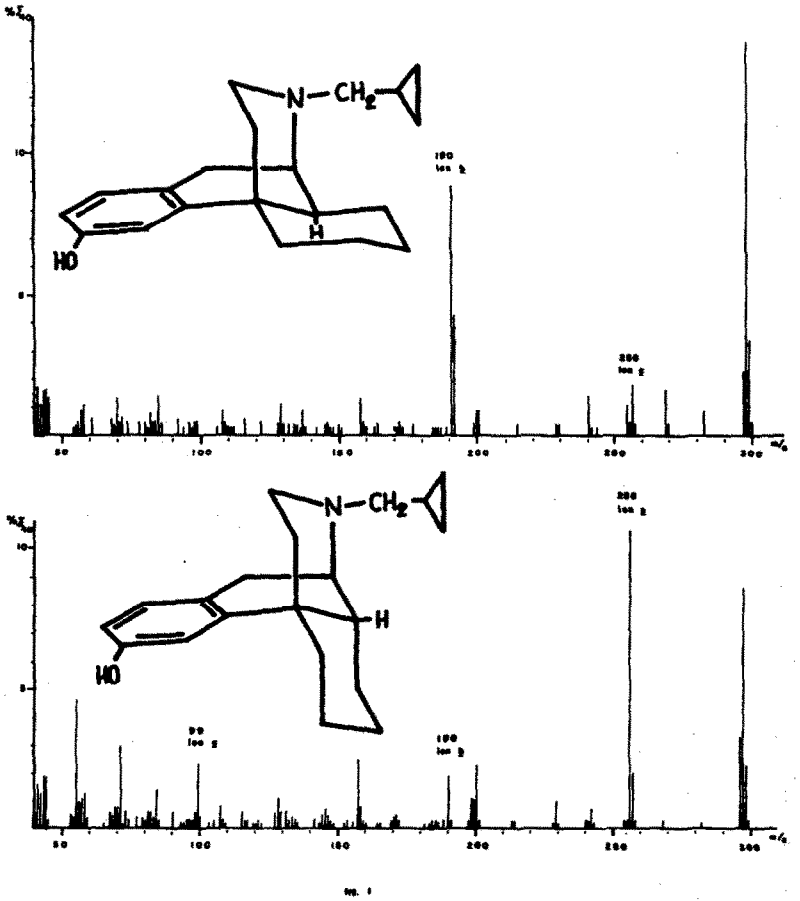
a - cis m/e 164 m/e 146

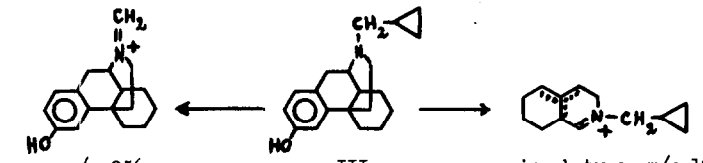
b - trans

In the mass spectrum of trans-dihydroallopseudocodeine (IVb), the corresponding ion $\underline{b}_3$ is of low abundance ($\%\Sigma_{40}$= 0.5) but ion $\underline{b}_4$, probably arising by dehydration of ion $\underline{b}_3$ is of considerable abundance ($\%\Sigma_{40}$= 4.1). In the cis-isomer (IVa), the corresponding peaks are of low intensity

(m/e 164, $\%\Sigma_{40}$= 0.7; m/e 146, $\%\Sigma_{40}$= 0.4). Similar behavior was observed for cis-dihydropseudocodeine (m/e 164, $\%\Sigma_{40}$= 0.4; m/e 146, $\%\Sigma_{40}$= 0.5).

Since in cis-isomers the hydrogen shift leading to ion b_1 or b_2 is less ready than in the trans-isomers, other fragmentations may be favored in the former. A case in point is that of cis-3-hydroxy-N-(cyclopropylmethyl)-morphinan (III) (Fig. 1):





ion c, m/e 256 III ion b type, m/e 190

$\%\Sigma_{40}$ cis = 10.6% $\%\Sigma_{40}$ cis = 1.9

$\%\Sigma_{40}$ trans = 1.8% $\%\Sigma_{40}$ trans = 8.9

The trans-isomer yields, as expected, a very abundant ion b, m/e 190. The cis-isomer yields it in much lower intensity as it can more readily form the stable ion c, m/e 256.

The isomeric benzomorphans (V) behave similarly (Fig. 2):

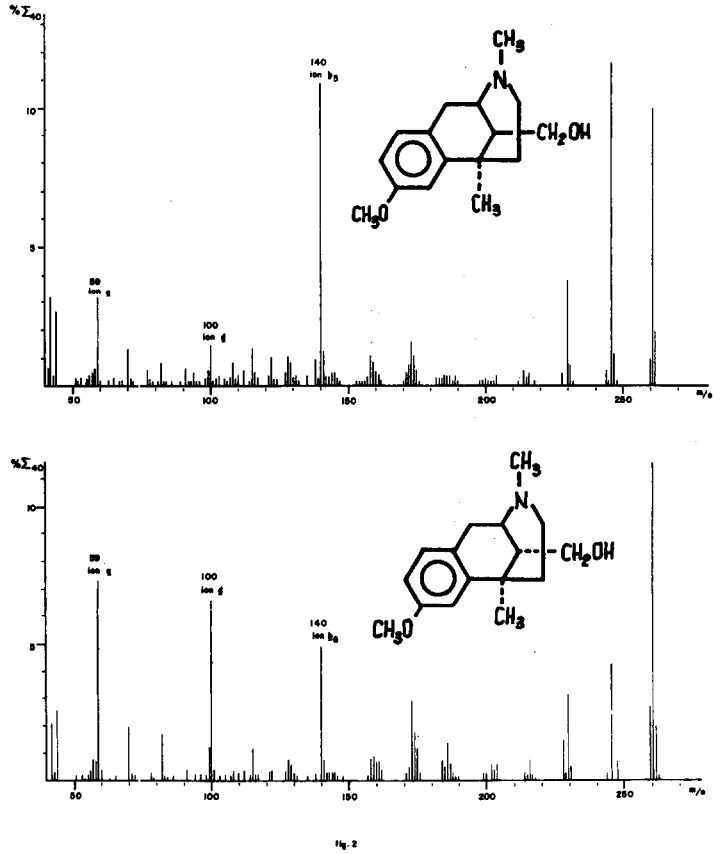
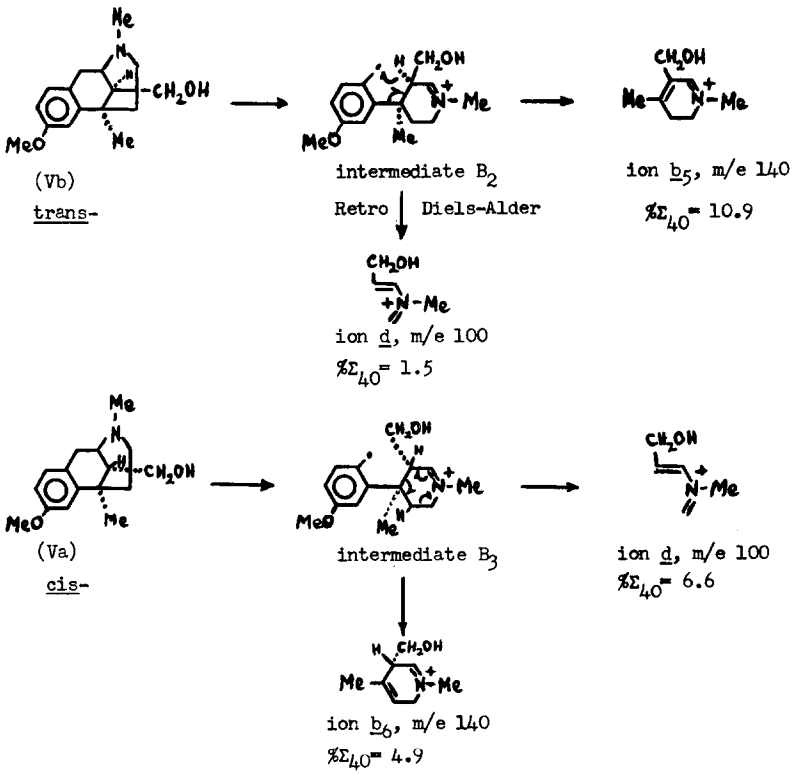
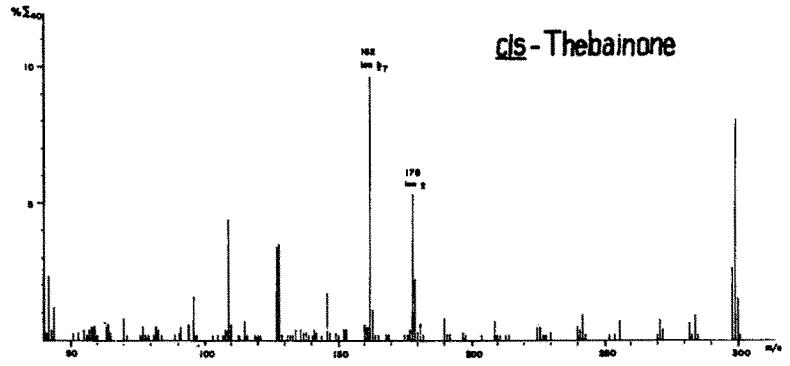


Fig. 2



In the trans-isomer, a hydrogen atom, in the position analogous to C_{14} of the morphine skeleton, may readily shift to give the conjugated ion b_5. The cis-isomer, through the intermediate B_3 cannot follow the identical route as readily, so that ion b_6 is much less abundant than ion b_5. Instead, B_3 may undergo a retro Diels-Alder type of fragmentation leading to ion d and this path is favored for the cis-isomer.

Another example is the epimeric pair of thebainones (Fig. 3):



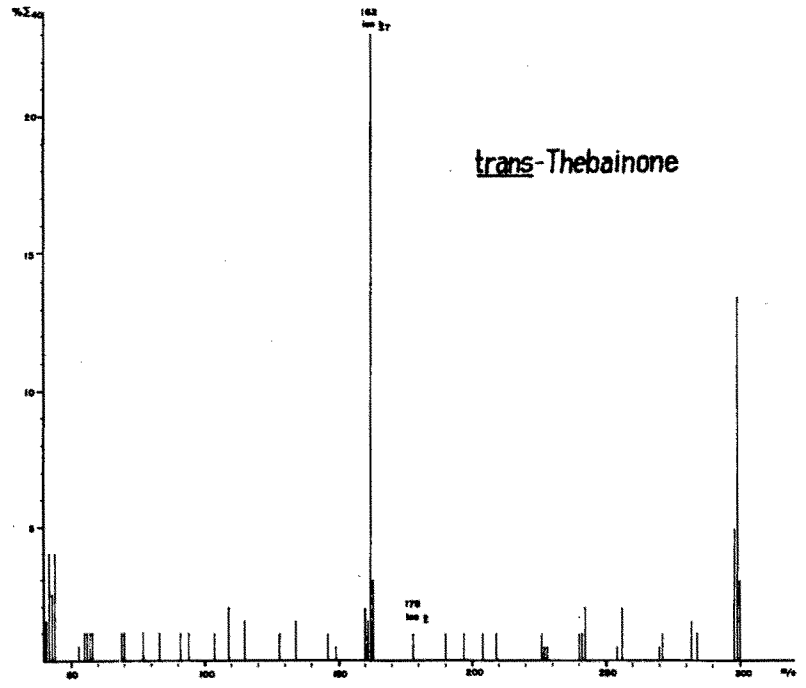
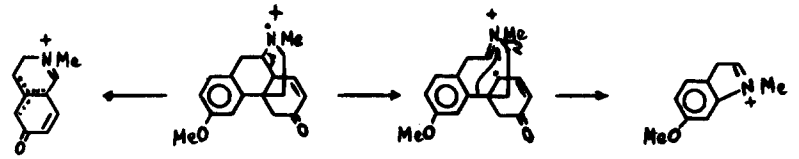


Fig. 3



ion $\underline{b}_7$
m/e 162

ion $\underline{e}$
m/e 178

Since these have an unsaturated ring C, they can undergo fragmentation leading to ion $\underline{e}$ (1). trans-Thebainone, as expected, exhibits a very intense peak at m/e 162 corresponding to ion $\underline{b}_7$ ($\%\Sigma_{40}$= 23.1; m/e 178, $\%\Sigma_{40}$= 1.0). The cis-isomer, again incapable of ready shifting of the C_{14}-hydrogen to C_{10}, exhibits the m/e 162 peak at lower intensity ($\%\Sigma_{40}$= 9.6). The alternative fragmentation to give ion $\underline{e}$ is favored (m/e 178, $\%\Sigma_{40}$= 5.3).

The Table shows that in all of the cases studied, the molecular ion of the trans-isomer is more abundant relative to that of its cis-isomer. Two criteria therefore appear to exist for distinguishing the stereochemistry of a given pair of such stereoisomers: the relative abundances of the molecular ions and those of the ion at m/e 59 (or its analog).

The possibility of prediction on the basis of relative abundances of type $\underline{b}$ ions is not, however, foolproof. Thus, in the case of the pair cis- and trans-3-methoxy-4-hydroxy-N-methylmorphinan (the tetrahydrodesoxycodeines), although the Table shows that the criteria of the molecular ion and the ion of m/e 59, permit the correct prediction to be made as to stereochemistry, yet the abundances of type $\underline{b}$ ion (m/e 150) are $\%\Sigma_{40}$= 13.7 for the cis-isomer and lower, i.e. $\%\Sigma_{40}$= 9.3 for the trans- isomer. Perhaps the reverse order of abundance for type $\underline{b}$ ions in this case arises simply from the fact that the cis-molecular ion is less stable than that of the trans-

isomer and therefore the route available for fragmentation to type b ions when ring C is completely reduced is more readily taken by the less stable cis-molecular ion.

Natalis (4) has shown that trans-decalin gives rise to a more intense parent peak than cis-decalin and makes the point that this parallels the greater thermodynamic stability of the former with respect to the latter. He has also reported (5) the same order in the hydrindanes in which the parent peak for the trans-isomer is again more intense than for the cis-isomer. This is, however, at variance with the thermodynamic stability of the two isomers (6). This is not surprising since the considerations of stability at 50 volts (4,5) are related to the fragmentation paths available to a highly energetic ionized species and not to the energy of the ground state.

We therefore note as experimental fact the relative abundance of molecular ions in our cis- and trans- B:C morphine derivatives, paralleling the behavior of the unsubstituted decalins. It does not follow that the trans-isomer in each case, is thermodynamically more stable than the cis-isomer. In fact, Nature chooses to produce the cis-isomers and the very famous case exists in the first laboratory synthesis of morphine, in which a trans- synthetic intermediate, suitably substituted in ring C, was converted by Gates into the thermodynamically more stable cis-fused derivative (7). We are unaware of thermochemical combustion data on pairs of pure cis- and trans-isomers in the morphine series which would shed light on this question.

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