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INFRARED SPECTROSCOPIC INVESTIGATION OF MORPHINE DERIVATIVES, I

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The infrared spectra of codeine (**IA**), dihydrocodeine (**IIA**) and their derivatives were studied in order to examine the applicability of this method for the elucidation of structural and steric structural problems in ring C.

It was found that

— the saturated or unsaturated character of ring C can be established unambiguously on the basis of the infrared spectra;

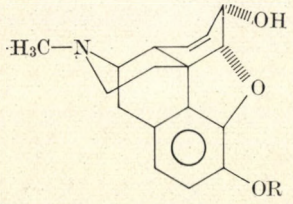
— in C_6—X and C_8—X substituted unsaturated compounds characteristic differences appear in the 800—1000 cm^{-1} region. Here bands of high intensity — denoted by "E" — appear in the case of a closed ring E; substituents C_6—X and C_8—X give rise to bands in the 940 ± 10 cm^{-1} and 900 ± 13 cm^{-1} regions, respectively;

— the characteristic bands of the C_6—X substituents appear in the compounds examined in accordance with the supposed configurations, and in agreement with the general statements of the literature;

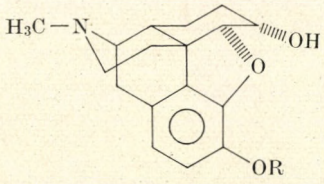
— on the basis of the results obtained with compounds containing saturated ring C and axial C_6—X substituents, in these derivatives a conformational equilibrium is supposed between molecules containing ring C in chair and flexible boat conformations.

The aim of the present work was to examine the utility of infrared spectroscopy, the elucidation of the structural and steric structural problems of codeine, dihydrocodeine and their derivatives. The present investigations have been focussed primarily on ring C.

These problems have been studied by several researchers by means of chemical [1a,b,c,d,e,f,g,h,i], as well as modern physical X-ray [2a,b,c] and NMR [3a,b] methods. The most probable steric structures of codeine (**IA**), morphine (**IB**), dihydrocodeine (**IIA**) and dihydromorphine (**IIB**), which are in the best agreement with the results of the above investigations can be given as follows:



IA: R=CH_3
IB: R=H



IIA: R=CH_3
IIB: R=H

Infrared spectroscopic studies on the steric structural problems of ring C of morphine derivatives have not been published yet; only the investigations of RÜLL [4] on three codeine derivatives approached this field.

The following questions of detail have been investigated by us: the use of infrared spectroscopy in

(a) deciding the saturated or unsaturated character of ring C,

(b) the differentiation between the position of the substituent X located at C_6 ($\Delta^{7,8}$) or C_8 ($\Delta^{6,7}$).

(c) the determination of the steric arrangement of the C_6—X substituents in saturated and unsaturated compounds.

The compounds listed in Table I were used for these investigations; a new nomenclature was suggested for the substance [5]. The infrared spectra

Table I

Name	Configuration of substituent X		Ref.
Dihydrocodeinone	**III**	C_6=O	6
Isocodeine	**IV**	C_6—OH (*ax'*)	7
Dihydroisocodeine	**V**	C_6—OH (*eq*)	7
8-Deoxy-8-thiol-pseudocodeine	**VI**	C_8—SH (*eq'*)	8
6-Deoxy-6-thiol-dihydroisocodeine	**VII**	C_6—SH (*eq*)	8
Codeine-6-0-methylether	**VIII**	C_6—OCH_3 (*eq'*)	9
Tetrahydrothebaine	**IX**	C_6—OCH_3 (*ax*)	9
6-Deoxy-6-chloroisocodeine	**X**	C_6—Cl (*ax'*)	6
6-Deoxy-6-fluoroisocodeine	**XI**	C_6—F (*ax'*)	10
6-Deoxy-6-chlorodihydroisocodeine	**XII**	C_6—Cl (*eq*)	6
Deoxycodeine-E	**XIII**	—	11
Dihydrodeoxycodeine D	**XVI**	—	12
Dihydrothebainone	**XV**	C_6=O	9
6-0-Acetyldihydroisocodeine	**XVI**	C_6—$OCOCH_3$ (*eq*)	7
6-0-Acetyldihydrocodeine	**XVII**	C_6—$OCOCH_3$ (*ax*)	6
3-0-Benzylmorphine	**XVIII**	C_6—OH (*eq'*)	6
Norcodeine	**XIX**	C_6—OH (*eq'*)	6
Isomorphine	**XX**	C_6—OH (*ax'*)	13
8-Desoxy-8-azidopseudocodeine	**XXI**	C_8—N_3 (*eq'*)	14
3-0-Acetyl-8-deoxy-8-azidopseudomorphine	**XXII**	C_8—N_3 (*eq'*)	14
8-Deoxy-8-aminopseudocodeine	**XXIII**	C_8—NH_2 (*eq'*)	14
8-Deoxy-8-chloropseudocodeine	**XXIV**	C_8—Cl (*eq'*)	6
8-Deoxy-8-bromopseudocodeine	**XXV**	C_8—Br (*eq'*)	12
8-Deoxy-8-iodopseudocodeine	**XXVI**	C_8—I (*eq'*)	6
8-Deoxy-8-isothiocyanopseudocodeine	**XXVII**	C_8—NCS (*eq'*)	15

of the compounds containing phenolic hydroxyl groups — except dihydrothebainone (**XV**) — were studied only in the 800—1000 cm^{-1} wavenumber range, since the presence of a phenolic hydroxyl group makes the spectra very complicated.

(a) Investigation of the saturated or unsaturated character of ring C

In the case of the compounds examined, the band of the C = C stretching vibration (ν C =C) cannot be utilized for the determination of the saturated or unsaturated character of ring C, since this is usually overlapped by a strong band appearing in the same region; this is due to the slightly deformed aromatic ring.

However, bands of medium intensity characteristic of the ν(= CH) and γ(= CH) vibrations of *cis* ethylene double bonds could be found in the regions given in the literature [16] (Table II); these bands are missing in the spectra of the corresponding saturated analogues.

It should be noted, however, that on the basis of these bands (Table II) no unambiguous differentiation was possible between compounds containing $\Delta^{6,7}$ or $\Delta^{7,8}$ unsaturated bonds.

Table II

Compound	ν(=CH) cm^{-1}	γ(=CH) cm^{-1}	
IA	3020	687	709
IV	3028	680	718
VIII	3028	?	707
X	3029	687	710
XI	3023	690	720
XIII	3028	687	709
VI	3012	697	710
XIX	3010	693	722 ?
XX	3030	683	722
XXI	3024	682	705
XXII	3025	685	702
XXIII	3020	685	702
XXIV	3032	687	703
XXV	3031	690	?
XXVI	3029	683	701
XXVII	3031	?	704

The saturated or unsaturated character of ring C is also indicated by the bands assigned to ring *E* (dihydrofuran ring). The great strain of the C_4——O—C_5 bond in the ring will deform ring A, and this effect is even more pronounced in ring C [3a].

On the basis of the literature [17], it can be stated that if the furan skeleton is attached to a rigid ring system, a band of ν C — O character can be found in the 930—980 cm^{-1} region. In addition to this, the spectrum has further characteristic absorption maxima between 1210—1260 cm^{-1} and 985—1000 cm^{-1}.

In the spectra of morphine derivatives, several characteristic bands can be found in the 880—1210 cm^{-1} region; further on, these will be denoted as "E"-bands (Table III) which are missing in the absence of the C_4—O—C_5 bond.

Table III

Character of ring C	"E"-bands, cm^{-1}				
Unsaturated	910±10 m	940±10 vs	965±10 s	1035±10 vs	1200 m—w
Saturated	910±10 m—w	945±10 m	965±5 m	1010? 1040?	1080±1 s
					1190±5 m—w

The intensities of the bands are indicated as usual in the literature: vs: very strong; s: strong; m: medium; w: weak.

If ring C has unsaturated character, these absorption have usually high intensities. They are due to complex group vibrations and can, in general, be considered characteristic of the strained dihydrobenzofuran ring system.

(b) Determination of the position of substituent X at C_6 $\Delta^{7,8}$ or C_8 $\Delta^{6,7}$

Table IV lists the wavenumber values of the most intense maxima of the band groups usually appearing as triplets in the infrared spectra of the compounds (recorded in KBr pellets).

It can be seen that the substitution pattern (C_6 or C_8) of ring C can be determined unambiguously on the basis of the appearance of the "E"-bands in the 880—1000 cm^{-1} region.

This observation can be well utilized in the structural investigations of the products formed in the nucleophilic substitution reactions of the 6-0-tosyl and 6-0-mesyl derivatives studied by us, thus indirectly facilitating the evaluation of the reaction mechanism [5].

Table IV

Compound	Substituent	Band maximum, cm^{-1}	Average cm^{-1}
IA	6—OH (*eq'*)	936 s	
IV	6—OH (*ax*)'	942 s	
VIII	6—OCH_3 (*eq*)'	941 s	
X	6—Cl (*ax*)'	938 s	940±10
XI	6—F (*ax*)'	945 vs	
XIX	6—OH (*eq*)'	950 s	
XX	6—OH (*ax*)'	930 s	
VI	8—SH	903 vs	
XXI	8—N_3	913 vs	
XXII	8—N_3	913 vs	
XXIII	8—NH_2 (*eq'*)	887 s	
XXIV	8—Cl	901 s	900±13
XXV	8—Br	900 vs	
XXVI	8—I	895 vs	
XXVII	8—NCS	892 vs	

The values measured can be found within ±5 cm^{-1} in the spectra recorded in chloroform solution.

(c) Steric position of the C_6—X substituents

Table V shows the wavenumber values of the C_6—X and X—H stretching vibrations of the C_6—X ($\Delta^{7,8}$) unsaturated derivatives.

It can be seen that the characteristic vibrational frequency values of the C_6—X substituents correspond to the supposed steric positions, in accordance with the general statements given in the literature [18,a,b,c] (Table I). The dissimilar positions of the C_6—OH groups in codeine (**IA**) and isocodeine (**IV**) clearly appear in the 3000—3700 cm^{-1} regions of the spectra (Fig. 1).

It can be seen that in the spectra recorded in KBr pellets a sharp intense band (3520 cm^{-1}) and a broad absorption maximum (3150 cm^{-1}) appear in the case of codeine and isocodeine, respectively (Fig. 1A). In the spectra recorded in chloroform solution (Fig. 1B) the characteristic bands are found at 3580 cm^{-1} (**IA**) and 3610 cm^{-1} (**IV**). On dilution, the band of codeine (**IA**) found at 3580 cm^{-1} shows only small changes within the limit of error, while in the case of isocodeine (**IV**) an intensity variation can be observed: the intensity of the maximum at 3150 cm^{-1} decreases, while that appearing at 3610 cm^{-1} shows increased intensity. In order to explain these phenomena — starting with the known configuration of the C_6—OH groups — the formation of a weak intramolecular hydrogen bridge can be assumed in the solid state

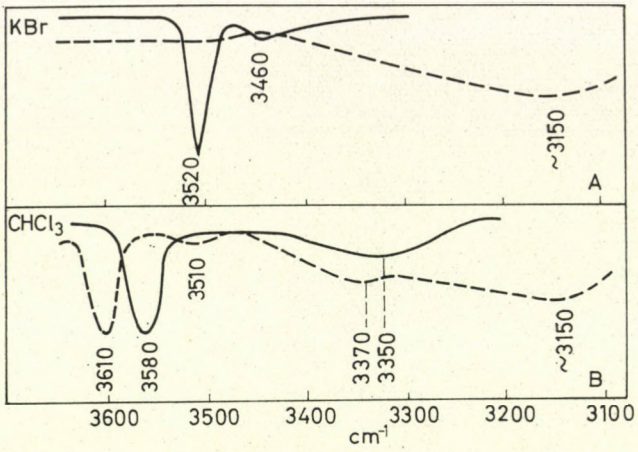


Fig. 1. OH stretching vibration bands of codeine (———) and isocodeine (— — —) in spectra recorded in KBr pellets (A) and $CHCl_3$ solutions (B)

Table V

Compound	Substituent	Steric position	$\nu(C_6-X)$ cm^{-1}		$\nu(X-H)$ cm^{-1}	
			$CHCl_3$	KBr	$CHCl_3$	KBr
Codeine (**IA**)	OH	(*eq'*)	1060	1060	3560	3520
			(1050)+		(3549)+	3460
					3350	
					(3665)+	
Isocodeine (**IV**)	OH	(*ax'*)	1024	1022	3610	3150
					3370	
					3150	
Codeine-6-0-methyl-ether (**VIII**)	OCH_3	(*eq'*)	1125	1120		
α-Chloro-codide (**X**)	Cl	(*ax'*)		761		
				808?		
α-Fluorocodide (**XI**)	F	(*ax'*)	1155	1152		

* The data of RÜLL [4] are given in brackets.

between the *quasi-equatorial* OH *(eq')* group and the ethereal oxygen atom of ring E in the case of codeine (**IA**), while the *quasi-axial (ax')* OH group of isocodeine (**IV**) can participate in a stronger intermolecular hydrogen bond.

In the chloroform solution spectra, however, the presence of solvent-solute associates of various stability should be assumed. This is probably also responsible for the different positions of the 3610 cm^{-1} and 3580 cm^{-1} bands, in addition to the appearance of bands of low intensity between 3200 cm^{-1}

and 3500 cm^{-1}. Namely, the two OH groups cannot be considered chemically equivalent, thus bond strength of the associates formed with the solvent may also be different. (Carbon tetrachloride is not a suitable solvent because of the poor solubility of a considerable number of these compounds.) It should be noted that in isocodeine (**IV**) the existence of a probably very weak intramolecular hydrogen bond between the C_6—OH *(ax')* group and the $\Delta^{7,8}$ double bond cannot be excluded, but this could not be confirmed unambiguously.

Ring C in the $\Delta^{7,8}$-unsaturated compounds has a flat boat conformation, while in the saturated derivatives it has a chair conformation which is slightly distorted because of the C_4—O—C_5 bond [3a, 4]. Thus, in the dihydro derivatives the configuration of the C_6—X substituent is changed as compared with the corresponding unsaturated derivatives. This configurational change is also revealed by the wavenumber values of the characteristic vibrations of the bonds in question. The wavenumbers characteristic of the C_6—X bonds in the saturated derivatives are listed in Table VI.

Table VI

Compound	Substituent	Steric position	$\nu(C_6-X)$ cm^{-1}		$\nu(X-H)$ cm^{-1}	
			$CHCl_3$	KBr	$CHCl_3$	KBr
Dihydrocodeine (**IIA**)	OH	*ax*	1044 (1035)* 1079	1050	3590 (3645)* (3580)* 3565 3380 3160	3127
Dihydroisocodeine (**V**)	OH	*eq*	1042 (1038)*	1048 3648	3605 (3648)* (3586)* 3415 3150	3130
6-Deoxy-6-thiol-dihydroisocodeine (**VII**)	SH	*eq*	640	642	2500 broad	2549
Tetrahydrothebaine (**IX**)	OCH_3	*ax*	1120 1109 broad 1098	1097		
Dihydro-α-chlorocodide (**XII**)	Cl	*eq*		751		

Table VI (continued)

Compound	Substituent	Steric position	ν C=O cm^{-1}		ν_{as}C–O–C cm^{-1}		δ_sCH$_2$ cm^{-1}	
			CCl_4	KBr	CCl_4	KBr	CCl_4	KBr
6-0-Acetyl-dihydrocodeine (**XVII**)	CH_3COO	*ax*	1748 broad	1738	1245	1248	1379 br	1380
					1225	1225	1365	1374
					1205	1195		1363
					1190			
6-0-Acetyl-dihydroisocodeine (**XVI**)	CH_3COO	*eq*	1743	1740	1240 broad	1240	1380	1875
					1200		1362	1365

* Data by RÜLL [4]

The wavenumber values observed, in accordance with the literature data [18a, b, c], are in agreement with the supposed steric positions. Similarly to the case of the unsaturated compounds, it can be stated that the configuration of the C_6—X group usually alters the wavenumber values of the νC_6—X band only slightly.

The νO—H regions of the epimeric pair containing C_6—OH group, dihydrocodeine (**IIA**) and dihydroisocodeine (**V**), are shown in Fig. 2.

It is surprising that the spectra recorded in KBr pellets (Fig. 2A) show almost no difference. This indicates that in both compounds the C_6—OH groups participate in stable hydrogen bands. Significant differences appear, however, in the 3500—3650 cm^{-1} regions of the solution spectra. Dihydroisocodeine (**V**) gives one band at 3603 cm^{-1}, while dihydrocodeine (**IIA**)

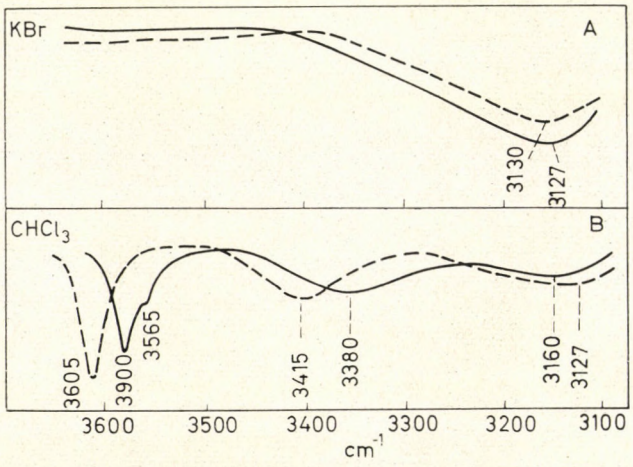


Fig. 2. OH stretching vibration bands of dihydrocodeine (———) and dihydroisocodeine (— — —) in spectra recorded in KBr pellets (A) and $CHCl_3$ solutions (B)

absorbs at 3590 cm^{-1} and 3565 cm^{-1}. The different positions of the bands found at 3590 cm^{-1} and 3603 cm^{-1} can be explained by the existence of a hydrogen bond between the C_6—OH group and the ethereal oxygen atom of ring E. In dihydrocodeine (**IIA**) the C_6—OH group is in axial position, and this configuration may give rise to a stronger hydrogen bridge with the ethereal oxygen atom of ring E, since the two pillar atoms of the hydrogen bridge are nearer to each other than in dihydroisocodeine (where C_6—OH is in *equatorial position*).

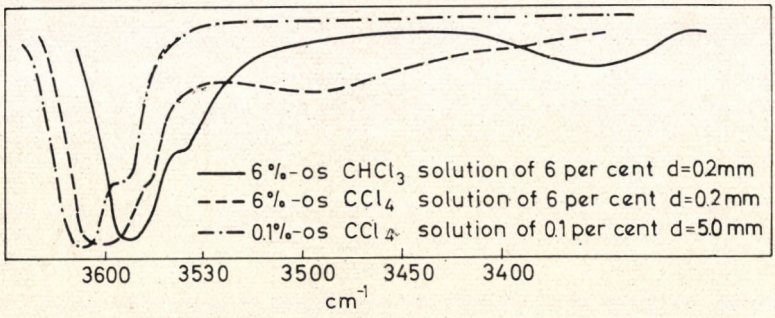


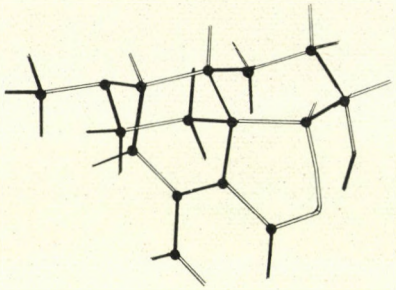
Fig. 3. OH stretching vibration bands of dihydrocodeine

In order to elucidate whether the band positions observed in chloroform solutions, as well as the shoulder appearing at 3565 cm^{-1} in the case of dihydrocodeine are due to associates formed with the solvent molecules which have different strengths because of the different steric positions, dihydrocodeine (**IIA**) was also examined in an apolar solvent (CCl_4); the corresponding part of the spectrum is shown in Fig. 3.

It can be seen that in carbon tetrachloride solution — as compared with the chloroform solution of identical concentration — a frequency increase of 10 cm^{-1} occurs, which confirms the existence of associates with chloroform. On the effect of dilution (Fig. 3), however, a further — although small, about 5—6 cm^{-1} — wavenumber shift occours, which is probably due to the rupture of the weak intramolecular hydrogen bridge formed with the ethereal oxygen atom of ring E. Still, the shoulder characteristic of dihydrocodeine (**IIA**) which is shifted to higher wavenumber values as a result of the decreased polarity of the solvent and dilution, appears in each case. In general it can also be observed in other regions of the spectra (Table VI) that in the presence of *axial* C_6—X groups, characteristic band splittings of "shoulder" appear as compared with the corresponding equatorial compounds.

In order to explain these phenomena, on the basis of the literature dealing primarily with steroids [18b, 19a, b, c, d] it can be supposed that the dihydro compounds containing axial C_6—X groups are present in a shifted conformer equilibrium in solutions. This conformer equilibrium may exist

between form *a* characterized by the chair conformation of ring C and form *c* of 'flexible boat' conformation (which is strongly shifted toward *a*); the so-called "classical boat" conformation *b* of ring C cannot develop because of energetical reasons (Fig. 4). This assumption is confirmed by an inspection of the Dreiding model. Detailed theoretical and temperature-dependent infrared and NMR studies of this problem are in progress.



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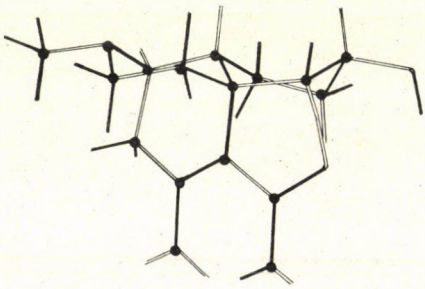

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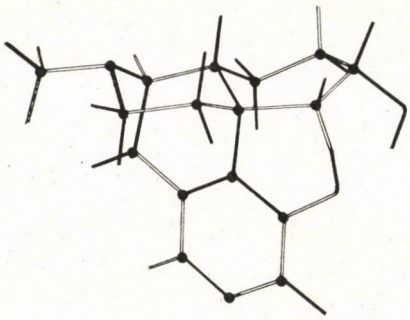

c)

Fig. 4. Supposed conformational limiting cases of ring C in dihydro- (C_6—X *ax*) derivatives: *(a)* chair; *(b)* classical boat; *(c)* flexible boat

Experimental

The infrared spectra were recorded with a Zeiss UR-10 spectrophotometer. The wavenumber calibration of the instrument was checked by recording the spectrum of a polystyrene foil ($d = 0.25\,\mu$). The accuracy of the wavenumber values given is $\pm 2\ cm^{-1}$. The spectra were recorded in solid state (KBr pellets) and in chloroform (in some cases, in carbon tetrachloride solutions). Unfortunately, the general use of carbon tetrachloride as a solvent, which would have been more advantageous from several points of view, was not possible because of the poor solubility of a significant number of the compounds examined.

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