SYNTHESES AND ABSORPTION SPECTRA OF SOME COMPOUNDS WITH THE BERBINE STRUCTURE

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The paper describes the syntheses and absorption spectra of some 13-alkyl-, 13-alkoxy-, 9-alkoxy- and 8-oxo derivatives of berberine and the related dehydropseudoberberinium compounds, viz. corylane (XIX) and norcorylane (XX).
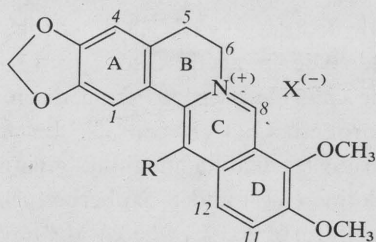
Berberine (I) and certain related protoberberine alkaloids have recently been found[1] to be inhibitors of alcohol dehydrogenase from horse liver. The set of alkaloids and related compounds, chosen for a systematic study of interactions of horse-liver alcohol dehydrogenase with protoberberine alkaloids[2], includes a number of berberine derivatives, synthetized in an attempt to find a compound whose bonds would give more information on the active site of the enzyme. Syntheses of some berbine compounds and determination of their absorption spectra are the subject of this paper. Preparation and properties of many of the compounds mentioned here were described as early as the beginning of the century, but the reported data are often incomplete or inaccurate.

The starting compound for all the berberine derivatives we synthetized was berberinium chloride (9,10-dimethoxy-2,3-methylenedioxy-5,6-dihydrodibenzo[a,g]quinolizinium chloride, I). Berberine reacts in strongly alkaline media[3] (above pH 13) in a pseudobasic carbinol form with acetone, forming the so-called "berberine-acetone"[4] (8-(2'-oxopropyl)-7,8-dihydroberberine; VII) in an almost quantitative yield. Like 8-alkyldihydroberberines, the ketone VII can be alkylated to $C_{(13)}$ by alkyl halides. Reaction of the ketone VII with methyl iodide in a sealed ampoule gave 13-methylberberinium iodide (II), reaction with ethyl iodide afforded a mixture of berberinium iodide (Ia) and 13-ethylberberinium iodide (III).
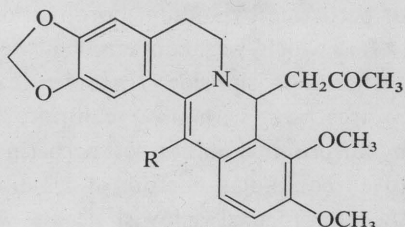
Pyman[5] described oxidation of the ketone VII by potassium permanganate to the so-called "neooxyberberineacetone", whose enol structure is described by formula
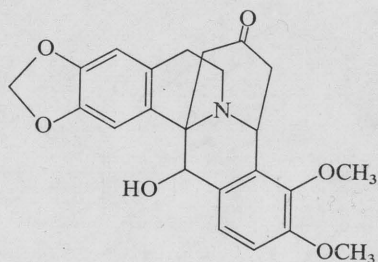
VIII (13-hydroxy-8-(2'-oxopropyl)-7,8-dihydroberberine). (On the basis of its in-solubility in aqueous sodium hydroxide the keto formula was given preference[5]). Iwasa and Naruto[6] proposed structure *IX* for this compound (13-hydroxy-9,10-di-methoxy-2,3-methylenedioxy-8,14-(2'-oxo-propano)dibenzo[*a,g*]quinolizidine). How-ever, both Pyman[5] and Iwasa and Naruto[6] obtained the same product by acid hydro-lysis of "neooxyberberineacetone" followed by alkalization, *viz.* 13-hydroxyberberine (*VIa*), but different melting points were reported. By a modification of Pyman's procedure[5] we obtained "neooxyberberineacetone" whose melting point and other properties agreed with the reported data[5,6]. The ^{1}H-NMR and the ultraviolet spectra of our preparation safely confirm the structure *IX*. The ^{1}H-NMR spectrum lacks the proton signal of the CH_3CO group of the acetonyl residue, which, if structure *VIII* were the correct one, should appear as a three-proton singlet at $\delta \approx 1\cdot9 - 2\cdot1$ p.p.m.
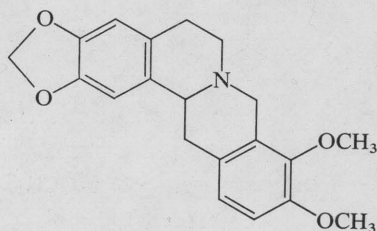

I, R = H,   X = Cl
Ia, R = H,   X = I
II, R = CH_3, X = I
IIa, R = CH_3, X = Cl
III, R = C_2H_5, X = I

IV, R = OCH_3, X = I
IVa, R = OCH_3, X = Cl
V, R = OC_2H_5, X = I
VI, R = OH,   X = Cl
VIa, R = $O^{(-)}$

VII, R = H
VIII, R = OH

IX

X
XI, CH_3 on N

Instead, the spectrum contains two two-proton signals at $\delta \approx 2\cdot8 - 3\cdot1$ p.p.m., as-sociated with the two methylene groups adjacent to carbonyl in the 2'-oxopropane bridge. The long-wave absorption band in the UV spectrum of "neooxyberberine-acetone" exhibits a peak at 287 nm, identical with that of non-substituted tetrahydro-berberine (*X*). This indicates a common tetrahydroisoquinoline chromophoric system,

unconjugated with π-electrons of the next aromatic ring. In structure *VIII* the peak of the long-wave absorption band would occur in the region 350−370 nm, like with 7,8-dihydroberberine (*XII*), owing to their common *trans*-stilbenoid chromophoric system. Refluxing "neooxyberberineacetone" with dilute hydrochloric acid released acetone and the separated 13-hydroxyberberinium chloride (*VI*) was converted by an excess of sodium hydroxide into the base *VIa*; its m.p. 239°C was identical with the reported one[7]. Alkylation of *VIa* with methyl iodide or ethyl iodide gave an almost quantitative yield of 13-methoxyberberinium iodide (*IV*) or 13-ethoxyberberinium iodide (*V*).

Berberine is easy to reduce[8] to racemic tetrahydroberberine ((±)-canadine, *X*). Alkylation of *X* (obtained by reduction of berberine with sodium borohydride in methanol) by methyl iodide and reaction of the product with silver chloride gave N-methylcanadinium chloride, *XI* (a mixture of the α and β forms). Partial reduction of berberine by sodium borohydride in tetrahydrofuran[9] gave 7,8-dihydroberberine (*XII*), which was condensated with formaldehyde in acetic acid[10] to 13-methylberberinium chloride (*IIa*), identical with the chloride prepared from the iodide *II* by treatment with silver chloride. The dihydroberberine *XII* can also be prepared by disproportionation of berberine in a strongly alkaline medium, giving rise[11] to an equimolar mixture of 7,8-dihydroberberine (*XII*) and 8-oxoberberine (*XIII*); the latter formed yellowish needles with a sharp m.p. of 203°C, whereas the reported[11] m.p. is 198−200°C. By the action of gaseous hydrogen chloride[12] or concentrated hydrochloric acid on a solution of the oxoberberine *XIII* in glacial acetic acid the methyl group splits off and 9-demethoxy-9-hydroxy-8-oxoberberine (*XIV*) is formed; this was also prepared[13] by treating the oxoberberine with phosphorus oxychloride.

XII

XIII, R = CH$_3$
XIV, R = H
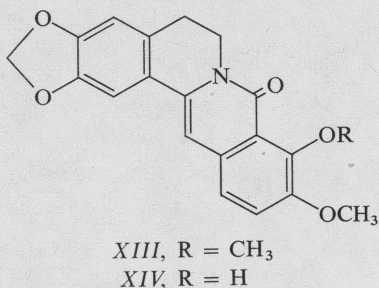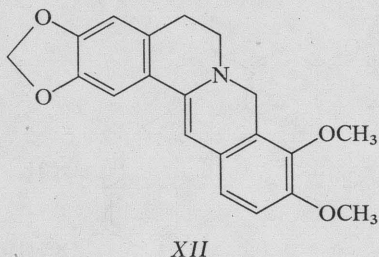
The splitting-off of methyl from the methoxy group on C$_{(9)}$ also occurs in fusion of berberine with urea[14]. From the alkalified melt the violet 9-demethoxy-9-hydroxyberberine (berberrubine, *XV*) can be isolated. Berberrubine can be prepared in a larger yield by pyrolysis of berberinium chloride in an atmosphere of carbon dioxide; alkylation of this preparation with ethyl iodide[15] gave 9-demethoxy-9-ethoxyberberinium iodide (*XVI*).
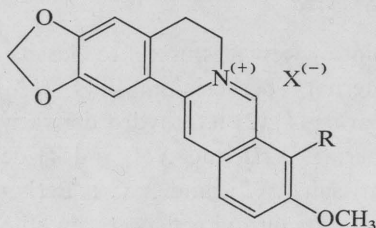
XV, R = O$^{(-)}$
XVa, R = OH,   X = Cl
XVI, R = OC$_2$H$_5$, X = I

To prepare compounds with the berbine structure of coralyne (*XIX*) and nor-coralyne (*XX*) the benzylisoquinoline alkaloid papaverine (*XVII*) was used. Acetylation of papaverine with sulphoacetic acid[16], accompanied by ring closure, afforded an almost quantitative yield of coralynium sulphoacetate. This salt was converted in an excess of concentrated hydrochloric acid into coralynium chloride (8-methyl-2,3,10,11-tetramethoxydibenzo[*a, g*]quinolizinium chloride, *XIX*). Norcoralynium chloride (2,3,10,11-tetramethoxydibenzo[*a,g*]quinolizinium chloride, *XX*) was obtained in a 70% yield by oxidation of 6'-hydroxymethylpapaverine (*XVIII*) with potassium dichromate in 50% acetic acid[17]. Whereas Wiegrebe and coworkers[17] prepared 6'-hydroxymethylpapaverine (*XVIII*) by a multistep synthesis from papaverine *via* 6'-acetylpapaverine and 6'-carboxypapaverine in a overall yield of about 18%, we have succeeded in preparing the intermediate *XVIII* in one step in a yield over 90% by reaction of papaverine with paraformaldehyde in concentrated hydrochloric acid. Thin-layer chromatography on silica gel showed that in addition to the main product, *XVIII*, only traces of a quaternary fluorescent compound were formed.
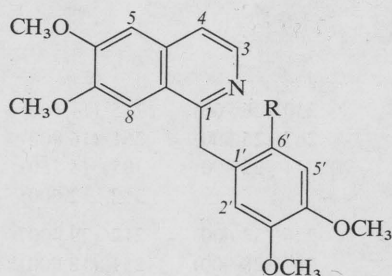
XVII, R = H
XVIII, R = CH$_2$OH
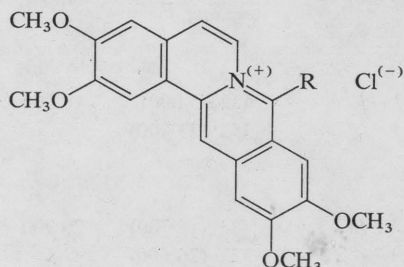
XIX, R = CH$_3$
XX, R = H

Ultraviolet Absorption Spectra

From the spectroscopic point of view it is useful to classify the compounds prepared into four groups: *1*) quaternary berberinium salts, *II — VI*, *XV*, *XVa* and *XVI*, including the starting berberine (*I*); *2*) tetrahydro derivatives of berberine, *IX — XI*; *3*) oxo derivatives of berberine, *XIII* and *XIV* and *4*) dehydropseudoberberinium (dibenzo[*a,g*]quinolizinium) salts, *XIX* and *XX*. ("Berberineacetone", *VII*, liberates acetone in polar media and its ultraviolet spectra in ethanol or water are identical with the spectra of the quaternary salts of berberine).

1) Quaternary salts of protoberberinium alkaloids and their derivatives in polar media exhibit four well-defined absorption bands, designated in the order of decreasing wave lengths as *A*, *B*, *C* and *D*. Bands *B* and *D* probably each consist of at least two absorption bands (Table I, Fig. 1, *cf*.[18−20]). In salts of these quaternary bases in the excited state even electrons of the anions participate in the conjugated π-electron system. The magnitude of shift of an absorption maximum associated with exchange of anions depends on the polarity difference of the linkage base--anion[21]. The decrease in electronegativity of the anion with the exchange of iodide for chloride (and the consequent decrease in polarity of the linkage quaternary nitrogen-halogen) produces a significant hypsochromic ($\Delta\lambda \approx 5$ nm) and a hyperchromic ($\Delta\varepsilon \approx 12\,000$) shift of the band *D* and a small bathochromic shift of the band *A*, with a simultaneous increase in intensity of all absorption bands; *cf*. salts of berberine (*I*, *Ia*), 13-methylberberinium (*II*, *IIa*) and 13-methoxyberberinium (*IV*, *IVa*) in Table I. The patterns of ultraviolet absorption spectra of quaternary protoberberinium and pseudoprotoberberinium salts are determined by auxochromic groups

TABLE I

Absorption Maxima and Minima (nm) and Molar Absorptivities (ε) of Quaternary Salts of Berberine and Some of Its Derivatives in Ethanol

Compound	$\lambda_{max}A$ $\lambda_{max}B$	$\Delta\varepsilon_{B-A}{}^{a}$	$\Delta\lambda_{max}A^{b}$	λ_{max}	λ_{min}
I	432 (5 000)	18 200	—	230 (26 700)	215 (17 500)
	352 (23 200)			267 (25 500)	251 (16 800)
				344 (22 800) s	305 (5 750)
					382 (2 600)
Ia	433 (5 700)	20 900	—	226 (38 600)	212 (29 400)
	352 (26 600)			267 (28 900)	251 (18 800)
				344 (26 200) s	305 (6 250)
					383 (2 600)

Тавle I
(Continued)

Compound	$\lambda_{max}A$ $\lambda_{max}B$	$\Delta\varepsilon_{B-A}{}^a$	$\Delta\lambda_{max}A^b$	λ_{max}	λ_{min}
II	430 (5 600) 344 (23 000)	17 400	−3	228 (38 200) 266 (30 000)	213 (29 300) 250 (18 600) 305 (7 300) 380 (2 650)
IIa	427 (5 300) 344 (20 800)	15 500	−5	233 (27 000) 266 (27 600)	216 (17 300) 250 (16 500) 306 (7 000) 376 (2 400)
III	425 (5 700) 344 (22 500)	16 800	−8	227 (34 800) 267 (29 600)	212 (27 800) 250 (17 500) 306 (6 900) 379 (2 500)
IV	433 (7 200) 351 (24 800)	17 600	0	227 (35 000) 268 (28 400) 340 (23 500) s	208 (26 500) 251 (19 200) 309 (7 100) 383 (3 000)
IVa	433 (7 500) 352 (25 600)	18 100	1	235 (31 600) 267 (29 400) 342 (24 600) s	217 (21 200) 251 (20 800) 307 (7 400) 383 (3 000)
V	432 (6 500) 353 (21 500)	15 000	−1	227 (33 100) 269 (25 100) 342 (20 500) s	212 (27 000) 252 (17 500) 309 (6 500) 381 (2 500)
XVI	435 (5 350) 352 (24 300)	18 950	2	226 (35 100) 269 (25 900) 345 (23 600) s	214 (27 900) 252 (16 600) 306 (5 600) 384 (2 400)
XVa	455 (5 400) 353 (20 200) −358	14 800	23	234 (26 200) 275 (23 700)	213 (15 200) 255 (14 000) 306 (5 000) 394 (2 250)
XV	521 (6 400)	—	89	240 (35 600) 278 (27 400) 328 (11 400) 396 (13 700)	220 (23 400) 260 (18 200) 308 (9 350) 352 (6 000)

^{a} Difference of molar absorptivities between bands B and A; ^{b} shift (nm) of band A from the corresponding band of berberinium chloride or iodide.

on carbons $C_{(9,10)}$ or $C_{(10,11)}$ of the benzene ring D of an isoquinoline system[19-21]. Further substituents on the protoberberine skeleton produce small shifts of absorption bands and small changes of their intensities, but the number of absorption bands and the fundamental features of the spectral pattern remain unchanged.

Substitution of an alkyl for hydrogen on $C_{(13)}$ in berberine results in a marked hypsochromic shift of the longest-wave absorption bands A and B, with a simultaneous decrease in intensity of band B. This can be explained by the steric effect outweighing the hyperconjugation effect, which is known to affect absorption spectra in the very opposite sense. Attachment of a bulky substituent to position 13 produces a greater tilt of the aromatic ring A from the plane of the rings C and D, thereby diminishing the extent of conjugation of π-electrons of these aromatic rings, which manifests itself in the absorption spectra by a hypsochromic shift of the longest--wave absorption bands. The angle of the tilt can roughly be calculated from spectroscopic data:

Planar structures (*e.g.* corylane, *XIX*, and norcoralyne, *XX*) obey equation (*1*) (analogous to the Hammett equation)

$$\tilde{v} - \tilde{v}_0 = k(\sigma_p - \sigma_m), \qquad (1)$$

where $\tilde{v}$ designates the wave number of the peak of the last absorption band of a substituted planar compound (coralyne, *XIX*), $\tilde{v}_0$ the peak wave number of the longest-wave absorption band of the non-substituted (reference) planar compound (norcoralyne, *XX*), k a constant of proportionality and $(\sigma_p - \sigma_m)$ the difference of Hammett's constants for the given substituent. On substitution of the measured wave numbers for coralyne, $\tilde{v} = 23 \cdot 3 \cdot 10^3 \text{ cm}^{-1}$, and norcoralyne, $\tilde{v}_0 = 23 \cdot 6 \cdot 10^3 \text{ cm}^{-1}$, and the difference of Hammett's constants for the methyl group, $(\sigma_p - \sigma_m)_{CH_3} = -0 \cdot 10$, into equation (*1*) the constant of proportionality can be calculated as $k \approx 3 \cdot 0$. From equation (*2*)

$$\tilde{v}_{p1} = \tilde{v}_{nonp1} \cos \alpha \qquad (2)$$

we can calculate the angle α formed by the two conjugated parts of the non-planar molecule. Here $\tilde{v}_{p1}$ denotes the peak wave number of the planar (reference) compound long-wave absorption band and $\tilde{v}_{nonp1}$ the peak wave number of the long-wave absorption band of an equally substituted non-planar compound. On substitution of the measured values for norcoralyne, $\tilde{v}_{p1} = 23 \cdot 6 \cdot 10^3$. cm^{-1}, and for pseudopalmatine[18] (differing from norcoralyne only in saturation of ring B), $\tilde{v}_{nonp1} = 26 \cdot 35 \cdot 10^3 \text{ cm}^{-1}$, the value of α is calculated from equation (*2*) as $\alpha \approx 26 \cdot 5°$. With the measured wave numbers of another pair of similar compounds, also differing in saturation of ring B only, *viz.* coralyne ($\tilde{v}_{p1} = 23 \cdot 3 \cdot 10^3 \text{ cm}^{-1}$) and tetradehydrocoralydine[21] ($\tilde{v}_{nonp1} = 26 \cdot 15$. 10^3 cm^{-1}), practically the same result is arrived at ($\alpha \approx 27°$). Combination of relations (*1*) and (*2*) gives equation (*3*), from which we can calculate the angle between the planes of the aromatic ring A and the rings C and D in molecules of berberine derivatives with substituents on $C_{(13)}$:

$$\tilde{v}_X \cdot \cos \alpha_X - \tilde{v}_0 \cdot \cos \alpha_0 = k \cdot (\sigma_p - \sigma_m)_X, \qquad (3)$$

whence

$$\cos \alpha_X = [\tilde{v}_0 \cdot \cos \alpha_0 + k \cdot (\sigma_p - \sigma_m)_X]/\tilde{v}_X. \qquad (4)$$

TABLE II

Calculated Values of Angle α between the Plane of Ring A and the Plane of Rings C and D in Molecules of $C_{(13)}$-Derivatives of Berberine

$\tilde{v}_X$ is the wavenumber of the longest-wave absorption band of a derivative, $(\sigma_p - \sigma_m)$ is difference of Hammett's constants for a substituent.

| Substituent on $C_{(13)}$	$(\sigma_p - \sigma_m)$	$\dfrac{\tilde{v}_X}{10^3\,cm^{-1}}$	α^0
H	0	23·12	26·5
CH_3	−0·10	23·35	29
C_2H_5	−0·09	23·54	30
OCH_3	−0·38	23·10	32
OC_2H_5	−0·34	23·16	32

In equations (3) and (4) α_X denotes the angle formed by the plane of ring A and the plane of rings C and D in a berberine derivative with a substituent X on the carbon $C_{(13)}$, α_0 the angle between these two parts of the conjugated system in a molecule of non-substituted berberine ($\alpha_0 \approx 26\cdot5°$), $\tilde{v}$ the peak wave number of the long wave absorption band of the berberine derivative, $\tilde{v}_0$ the peak wave number of the long-wave absorption band of berberine, k a constant of proportionality ($k \approx 3\cdot0$) and $(\sigma_p - \sigma_m)$ the difference of Hammett's constants for the substituent X. The values of α_X for the investigated $C_{(13)}$-derivatives of berberine, calculated from equation (4), are given in Table II.

Alkoxy-substitution on $C_{(13)}$ produces negligible shifts of the absorption bands. Evidently the steric effect of an alkoxy group is compensated for by its conjugation effect, which is stronger than that of the corresponding alkyl.

Whereas the berberine homologue 9-demethoxy-9-ethoxyberberinium iodide (*XVI*), compared to berberinium iodide (*Ia*), exhibits only a small bathochromic shift of the bands *A*, *B* and *C* in the UV spectrum, replacement of methoxyl on $C_{(9)}$ by hydroxyl (9-demethoxy-9-hydroxyberberinium chloride, *XVa*) results in a marked bathochromic shift of all the absorption bands. The absorption spectrum of ber-

FIG. 1

UV Spectra of Protoberberine Alkaloids in Ethanol

1 Berberinium chloride (*I*), *2* 9-demethoxy-9-hydroxyberberinium (berberrubinium) chloride (*XVa*), *3* berberrubine (free base *XV*).
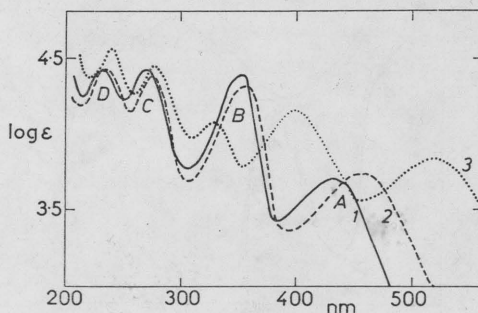
berrubine (XV) is different at first sight from that of its quaternary salts (Table I, Fig. 1). The dissociated dipolar form (XV) exhibits additional significant batho-chromic shifts of absorption bands, especially of the A band. These changes of absorption properties of berberrubine solutions are probably due to ready changes of the chromophoric system of berberrubine, which is very sensitive to polarity and particularly to pH of the medium. The possible formation of a conjugated quinoid structure of berberrubine was discussed in a previous paper[18].

2) In the case of tetrahydroprotoberberine alkaloids the positions of the absorption bands depend on the nature of the auxochromic groups bound to carbons $C_{(2,3)}$, whereas substituents on $C_{(9,10)}$ or $C_{(1,110)}$ little affect the wave lengths of the absorption maxima[19,22]. Further substituents on the berbine skeleton of these compounds affect the absorption spectra even less than in the case of quaternary berberinium salts: the UV spectrum of "neooxyberberineacetone" (IX) is virtually identical with the spectrum of canadine (X). This is quite comprehensible considering that tetrahydroberberines are, in fact, 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives with hindered rotation of the benzyl group, and that the chromophoric system of these compounds is formed by the tetrahydroisoquinoline ring[18]. Quaternarization of the heterocyclic nitrogen by the attachment of a methyl group, with the formation of N-methylcanadinium chloride (XI), results in only a small batho-chromic shift of the absorption spectrum and in separation of the shorter-wave band B (Table III, Fig. 2). Consequently, the changes of spectra are small, like in quaternarization of 3,4-dihydroisoquinoline salts[20].

3) The ultraviolet spectra of 8-oxoberberines are represented by two bands: a characteristic band A in the region $300-400$ nm with a peak at $340-350$ nm, and a narrow intense band B in the region $210-250$ nm with a peak at 226 nm. Whereas replacement of methoxyl on $C_{(9)}$ of berberine by hydroxyl occasions a marked bathochromic shift of all the absorption bands, the same substitution in a mole-
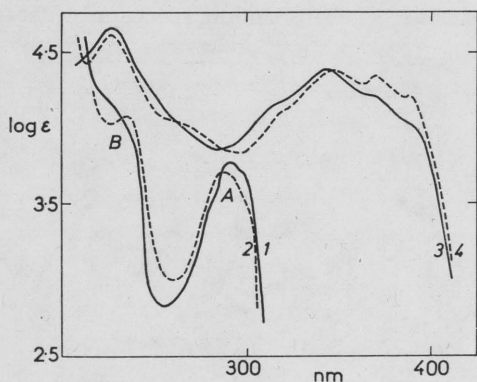
FIG. 2

UV Spectra of Tetrahydro and 8-Oxo Derivatives of Berberine in Ethanol

1 Canadine (X), 2 N-methylcanadinium chloride (XI), 3 8-oxoberberine $(XIII)$, 4 9-demethoxy-9-hydroxy-8-oxoberberine (XIV).

cule of oxoberberine $(XIII)$ alters the absorption spectrum very little (Table III, Fig. 2). This may be due to berberine (I) and berberrubine (XV) having a chromophoric system different from that of oxoberberine $(XIII)$ and 9-demethoxy-9-hydroxy--8-oxoberberine (XIV). The free electron pairs of the hydroxyl oxygen on $C_{(9)}$ of berberrubine can be involved directly in the conjugated π-electron chromophoric system of the isoquinoline nucleus (rings C and D), whereas in structure XIV their possible part in the conjugation is much limited.

4) The chromophoric system of the planar dehydropseudoberberinium salts XIX and XX is constituted by the heteroaromatic quinolizinium nucleus (rings B and C of their berbine structure). Extension of this conjugated chromophoric system by the attachment of two substituted aromatic rings A and D results in marked bathochromic and hyperchromic shifts of the quinolizinium absorption bands — $cf.$ the sequence of the spectra of quinolizinium iodide, 7-methylbenzo[a]quinolizinium iodide and norcoralynium (2,3,10,11-tetramethoxydibenzo [a,g]quinolizinium) chloride, and the sequence of the spectra of quinolizinium iodide, benzo[b]quinolizinium bromide and norcoralynium (2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium) chloride in Fig. 3 and Table IV. In contrast to the UV spectra of quaternary berberinium salts, the absorption bands of coralyne (XIX) and norcoralyne (XX) retain much of their fine vibration structure even in strongly polar media (water, ethanol). This fact is due to the rigid planar structures of these compounds. In the non-planar berberinium salts, with a looser structure, one part of a molecule (substituted ring A)

TABLE III

Absorption Maxima and Minima (nm) and Molar Absorptivities (ε) of Tetrahydro Derivatives and 8-Oxo Derivatives of Berberine

Compound	$\lambda_{max}A$	$\lambda_{max}B$	λ_{max}	λ_{min}
IX	287 (5 600)	230 (14 000) s	—	262 (1 600)
X	287 (5 600)	229 (13 500) s	—	253 (700)
XI	287 (5 800)	234 (11 700)	—	226 (10 800)
				260 (1 000)
$XIII$	344 (24 000)	226 (44 600)	316 (14 000) s	281 (7 000)
			368 (15 700) s	
			386 (11 000) s	
XIV	348 (23 100)	226 (40 100)	370 (21 300)	213 (26 000)
			388 (15 800)	297 (7 000)
				363 (19 000)
				386 (16 000)

TABLE IV

Absorption Maxima and Minima (nm) and Molar Absorptivities (ε) of Quinolizinium and Dibenzoquinolizinium Salts

| Compound				Compound			
λ_{max}		λ_{min}		λ_{max}		λ_{min}	
	XIX^a				XX^a		
221	(23 200)	215	(19 800)	219	(22 300)	226	(18 800)
235	(22 000)	228	(21 400)	237	(21 200)	255	(12 800)
243	(20 000) s	254	(10 500)	244	(20 100) s	291	(33 700)
287	(34 600) s	323	(34 600)	282	(37 600)	308	(44 300)
304	(46 200) s	355	(6 300)	303	(46 500)	324	(33 000)
314	(51 500)	379	(5 800)	314	(49 300)	350	(6 300)
329	(40 400)	419	(11 800)	327	(35 300)	374	(5 800)
362	(7 100)			365	(7 100)		
406	(12 100) s			410	(11 900)		
424	(15 200)			429	(15 800)		
	Quinolizinium iodide^b						
226	(17 800)						
272	(2 630)						
283	(2 950)						
310	(10 700)						
316·5	(9 550)						
323·5	(17 000)						

^{a} Measured in ethanol; ^{b} taken from ref.[23].
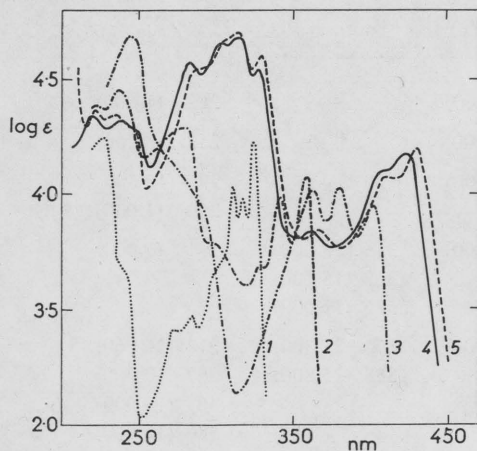
FIG. 3

UV Spectra of Quinolizinium Salts
   1 Quinolizinium iodide (water), from[23], *2* 7-methylbenzo[a]quinolizinium iodide (ethanol), from[24], *3* benzo[b]quinolizinium bromide (water), from[25], *4* norcoralynium chloride (*XX*) (ethanol), *5* coralynium chloride (*XIX*) (ethanol).

can move in respect to the other (rings C and D); this slow motion gives rise to a number of vibration bands, which overlap and fuse into wide non-structural absorption bands.

Infrared Spectra

With most of the derivatives prepared the IR absorption spectra were measured in the wave number regions $400-1800$ and $2800-3800$ cm^{-1}. The positions of the fundamental absorption bands in the IR spectra of berberine, eight of its derivatives and coralyne are given in Table V. The data reveal close relationships between the spectra of 8-oxoberberine $(XIII)$ and 9-demethoxy-9-hydroxy-8-oxoberberine (XIV) and between the spectra of "berberineacetone" (VII) and berberine pseudocyanide (a pseudo salt of berberine with a covalently bound CN group in position 8 and a single $N-C_{(8)}$ linkage). Some absorption bands, common to most of the compounds measured, can be assigned as follows. The intense diffuse band with a peak at $3450-3420$ cm^{-1} probably corresponds to the stretching vibration of OH groups in the molecules of crystal water, or possibly of ethanol, associated by hydrogen bridges. The triad of absorption bands with peaks around $3005, 2945$ and 2905 cm^{-1} is conditioned by the presence of methoxy groups; however, the diagnostic absorption band for a methoxy group occurs at 2840 cm^{-1} (ref.[26]). The intense absorption bands in the wave-number regions $1610-1580$ and $1500-1480$ cm^{-1} are associated with the stretching vibrations of C=C bonds in the aromatic rings and with the stretching vibration of the C=N bond. The intense band at $1390-1365$ cm^{-1} belongs to the plane deformation vibrations of C—H bonds in the CH$_3$ and CH$_2$ groups. The very intense absorption bands in the regions $1275-1230$ and 1045 to 1035 cm^{-1} correspond to the stretching vibrations of aromatic or aliphatic C—O bonds, and are common to methylenedioxy and methoxy groups. The truly characteristic absorption band of a methylenedioxy group is that at $940-928$ cm^{-1} (ref.[26]). This band is common to all the compounds measured excepting coralyne (XIX), whose molecule contains only methoxy groups, so that in its IR spectrum this band is absent. The feeble to medium-intensity absorption bands in the regions 880 to 860 cm^{-1} and $838-820$ cm^{-1} belong to the out-of-plane deformation vibrations of C—H bonds in a 1,2,4,5-tetrasubstituted aromatic ring (ring A of the berbine structure) or in a 1,2,3,4-tetrasubstituted aromatic ring (ring D). This last absorption band is also absent in the IR spectrum of coralyne (XIX) — both the ring A and the ring D are tetrasubstituted, in positions 1,2,4 and 5.

TABLE V

Positions of Absorption Bands (cm^{-1}) in IR Spectra (KBr) of Some Berbine Compounds

I	IIa	IVa	VIa	X
3 420 s[a]	3 420 s[a]	3 420 s[a]		3 450 m[a]
3 060 m			3 088 m[a]	
3 025 m[a]	3 022 m	3 010 m[a]	3 005 m	3 002 m
	2 982 m	2 975 m	2 978 m	
2 950 w	2 943 m	2 941 m	2 945 m	2 945 m
2 910 w	2 906 w	2 908 m	2 900 m	2 905 m
2 845 w	2 842 w	2 842 w	2 839 m	2 830 m
		1 705 w		2 810 m
1 630—1 600 s	1 600 s	1 603 s	1 605 s	1 605 w[a]
	1 581 s	1 578 s		
1 505 s	1 491 s	1 491 s	1 500 s[a]	1 495 s[a]
	1 470 s	1 469 s	1 476 s	
	1 448 s	1 450 s		
1 390 s	1 402 m			
1 365 s	1 370 s	1 375 s	1 361 s	1 390 m
1 338 s	1 333 s	1 321 s	1 315 s	1 343 m
1 275 s	1 265 s	1 264 s	1 265 s	1 280 s
1 235 s			1 230 s	1 242 s
			1 200 s	
1 145 m	1 168 m	1 186 m	1 166 m	1 162 w
1 112 s	1 105 s	1 102 s	1 098 s	1 085 s
1 044 s	1 032 s	1 040 s	1 045 s	1 045 s
980 m	960 w	988 m	1 000 m	
928 m	935 m	929 m	938 m	942 m
		880 w	875 w	862 s
837 w	831 m	838 m	830 m	810 w
			635 w	760 w

EXPERIMENTAL

Spectroscopic Measurements

For measuring the ultraviolet spectra the compounds were dried for 2 h at 90°C and 0·1Torr (except for 13-methoxyberberinium chloride, *IVa*, which undergoes partial decomposition at this temperature). The substances were weighed with a precision of ±0·005 mg and dissolved in 96% ethanol. The ultraviolet absorption spectra were measured with a recording spectrophotometer Specord UV-VIS (Zeiss) and the infrared spectra with a recording spectrometer UR 10 (Zeiss) in KBr pellets. The ^{1}H-NMR spectra were measured with an 80 MHz spectrometer Tesla BS 478 A in deuteriochloroform or trifluoroacetic acid.

Tᴀʙʟᴇ V
(Continued)

XIII	XIV	Berberine ψ-cyanide	VII	XIX
	3 450 m^a	3 430 m^a		3 440 s^a
		3 072 w	3 072 w	3 065 m^a
2 990 m	3 010 m	2 992 w	3 000 m	3 020 m^a
2 942 w		2 938 m	2 932 m	
2 907 m	2 905 m	2 905 m	2 905 m^a	2 900 m^a
2 835 m	2 840 m	2 830 m	2 833 s	2 838 m
1 635 s	1 640 s			
1615—1590s	1610—1592s	1605—1590m	1600—1580s	1 610 s
1 490 s	1 490 s	1 485 s^a	1 480 s^a	1 510 s^a
		1 400 m	1 405 m	1 430 s
1 378 s	1 392 s	1 375 m	1 372 m	1 382 m
1 323 m	1 323 s	1 332 m	1 341 s	
1 275 s	1 272 s	1 285 s	1 275 s	1 295 s^a
1 224 s	1 230 s	1 232 s	1 226 s	1 240 s
1 175 s	1 180 s	1 165 s	1 167 s	1 138 m
1102—1088s	1100—1090s	1 088 s	1 090 s	1 053 s
1 042 s	1 040 s	1 042 s	1 035 s	1 030 s
		992 m	990 w	991 m
		972 m	975 w	
938 m	938 m	940 m	931 s	916 m
870 m	862 m	864 m	860 s	860 m
835 m	832 s	820 s	818 s	
780 m	780 w			745 w
725 w	730 m			632 w
660 w	668 m			550 m

^{a} Diffuse band.

Syntheses of the Compounds

The starting compounds were commercial berberinium chloride (Merck) and papaverine hydrochloride (Farmakon, Nat. Corp., Olomouc). All melting points were determined on a Kofler block and were not corrected.

13-Methylberberinium Iodide (II) and Chloride (IIa)

A) A mixture of VII (prepared according to[4], 200 mg) and methyl iodide (1 ml) in a sealed ampoule was heated for 2 h in a boiling water bath. The excess of methyl iodide was distilled off and the residue was taken into dichloromethane. Concentration of the extract in vacuo gave 220 mg

(90%) of the crude 13-methylberberinium iodide; repeated crystallization from water afforded yellow crystals melting at $218-220°C$ (decomposition). For $C_{21}H_{20}INO_4.H_2O$ (495·3) calculated: 50·88% C, 4·44% H, 2·83% N; found: 50·88% C, 4·80% H, 2·64% N.

B) To a solution of *XII* (prepared according to [9], 250 mg) in 20% acetic acid (15 ml) 40% formaldehyde (5 ml) was added and the mixture was heated in a boiling water bath for 2 h. The solution was then concentrated to about a half of its volume. An addition of concentrated hydrochloric acid separated yellow needles of the chloride *IIa* (255 mg, 90%), melting with decomposition above 195°C. For $C_{21}H_{20}ClNO_4.2\ H_2O$ (421·9) calculated: 59·37% C, 5·96% H, 3·32% N; found: 59·15% C, 5·02% H, 3·18% N.

13-Ethylberberinium Iodide (*III*)

A mixture of *VII* (prepared according to[4], 200 mg), and ethyl iodide (1 ml) in a sealed ampoule was heated for 5 h in a boiling water bath. The excess of ethyl iodide was distilled off and the residue was crystallized from water; yellow needles of berberinium iodide (*Ia*), m.p. $262-265°C$ (decomposition), and yellow needles of 13-ethylberberinium iodide, decomposing above 210°C were obtained. For $C_{22}H_{22}INO_4$ (491·3) calculated: 53·73% C, 4·50% H, 2·85% N; found: 53·96% C, 4·41% H, 2·65% N.

13-Methoxyberberinium Iodide (*IV*)

This was obtained by methylation of *VIa* (prepared according to [5,7]) with methyl iodide as in the synthesis of 13-methylberberinium iodide (*II*); tawny crystals, yield 95%, m.p. $238-240°C$ (decomp.). For $C_{21}H_{20}INO_5$ (493·3) calculated: 51·08% C, 4·08% H, 2·84% N; found: 50·82% C, 4·39% H, 2·63% N. The chloride *IVa*, prepared from the iodide *IV* by conversion with silver chloride in water, formed ochre crystals (dichloromethane–ether) decomposing above 110°C.

13-Ethoxyberberinium Iodide (*V*)

This was obtained from *VIa* (prepared according to [5,7]) and ethyl iodide, by the procedure for 13-ethylberberinium iodide (*III*); brown needles, m.p. $154-155°C$ (dedomp.), yield 95%. For $C_{22}H_{22}INO_5.2\ H_2O$ (543·3) calculated: 48·59% C, 4·78% H, 2·57% N; found: 48·84% C, 4·88% H, 2·47% N.

9-Demethoxy-9-hydroxyberberine (Berberrubine, *XV*)

Dried berberinium chloride (1 g) was heated to 190°C for 30 min in a jet of carbon dioxide. From an aqueous solution of the product berberrubine was separated from the unreacted berberine by repeated extraction into chloroform. The chloroform extract was dried with sodium sulphate and distilled *in vacuo*. An addition of concd. hydrochloric acid to an aqueous solution of the residue separated brown crystals of 9-demethoxy-9-hydroxyberberinium chloride (*XVa*, 0·7 g, 75%), carbonizing above 230°C. For $C_{19}H_{16}ClNO_4.H_2O$ (375·8) calculated: 60·67% C, 4·79% H, 3·72% N; found: 60·77% C, 4·37% H, 3·54% N. The free base *XV* was prepared by alkalinization of the aqueous chloride *XVa* with an excess of sodium hydroxide; it formed violet leaflets, partially thawing above 280°C (ethanol) (ref.[14] gives an approximate m.p. of 285°C). For $C_{19}H_{15}NO_4$ (321·3) calculated: 71·03% C, 4·67% H, 4·36% N; found: 71·05% C, 4·80% H, 4·12% N.

6'-Hydroxymethylpapaverine (*XVIII*)

A solution of papaverine hydrochloride (3 g) and paraformaldehyde (0·35 g) in concd. hydrochloric acid (15 ml) was heated 2 h at 60°C, then left standing at room temperature for 24 h. The needles of the separated product (3·25 g, 100%) were collected on a filter, m.p. 125—145°C. The free base *XVIII* was released by alkalinization of an aqueous solution of this salt with concentrated sodium carbonate and taken into chloroform. The extract was dried with sodium sulphate and distilled *in vacuo*. The residue was recrystallized from ethanol; m.p. 172—173°C (reported[17] m.p. 172°C). For $C_{21}H_{23}NO_5$ (369·4) calculated: 68·28% C, 6·28% H, 3·79% N; found: 68·12% C, 6·51% H, 3.64% N.

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