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THE EFFECT OF HYDROXY, METHOXY AND METHYLENEDIOXY GROUPS ON THE ULTRAVIOLET SPECTRA OF AROMATIC AND HETEROCYCLIC COMPOUNDS - ALKALOIDS

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Abstract - This review describes the work done in the field of electron spectroscopy (ultraviolet spectra) of aromatic and heterocyclic compounds with or without electron accepting groups substituted by hydroxy, methoxy or methylenedioxy groups in different positions of the aromatic nucleus.

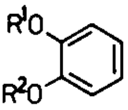
An analysis of the ultraviolet spectra of many structurally related benzyltetrahydroisoquinoline alkaloids revealed a difference in the position and absorption of their bands at ca. 280 nm (*A*-band - *Secondary band*) and 240 nm (*B*-band - *First primary band*). A similar phenomenon was observed in the spectra of other groups of alkaloids with one or two aromatic nuclei. Some authors[1,2] have made use of this difference between the molar absorptions of the above mentioned bands for the differentiation of related alkaloids, and this phenomenon they called the "*Mantissen-Difference*". In view of this finding we undertook to study the effect of substituents on the UV spectra of simple aromatic compounds, particularly on the effect of the methoxy group or the pairs of *ortho*-methoxyls versus methylenedioxy groups. Studies carried out on a larger group of alkaloids with the same type of skeleton showed that the different position and the molar absorptivity of the above-mentioned *A* and *B* bands were conditioned by the presence of hydroxy, methoxy or methylenedioxy groups and their positions versus the other parts of the molecule, particularly versus the electron accepting groups.

Having completed our work in 1965,[3-7] we found that the effect of the methoxy versus methylenedioxy groups on the UV spectra of alkaloids and of some other aromatic compounds had already been studied by Kitasato[8] (Japan) in 1927, by Feist, Awe and Etzrodt[9] (Germany) in 1934, by Láng and Bározai[10] (Hungary) in 1964, and by Sebe et al.[11] (Japan) in 1967.

Shamma et al.[12] studied the UV spectra of tetrahydroprotoberberine, protoberberine, dihydroprotoberberine, dehydroprotoberberine, and pseudoprotoberberine salts, however, without paying attention to the effect of the methoxy/methylenedioxy groups on the position and extinction of the individual bands. These authors also studied the effect of the formation of phenolic salts on the UV spectra of protoberberine alkaloids.

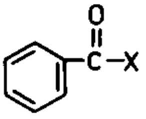
The first three groups of authors[8-10] examined only the bands at higher wavelengths than 300 nm. Sebe[11] has drawn attention to Kitasato's paper[8] which due to insufficient citation in the "*Chemical Abstracts*" and "*Chemisches Zentralblatt*" has fallen into oblivion. Sebe[11] studied the effect of the methoxy versus the methylenedioxy group on the UV spectra of tetrahydroprotoberberine and protoberberine alkaloids of the normal and the **pseudo**-series. Awe, a coworker in the joint paper by Feist and Etzrodt,[9] did not make use of this effect in his further work and the term "**Mantissen-Difference**" he utilized[1] only for the differentiation of compounds.

Studies of model compounds have shown that this phenomenon is attributable not only to the effect of hydroxy or methoxy versus methylenedioxy groups but also to the size of the alicyclic component attached to the aromatic ring; a similar effect was observed in connection with the pair of 1,2-methylenedioxybenzene versus 1,2-ethylenedioxybenzene, indane versus tetralin or 4,5-trimethylenepyridazine versus 4,5-tetramethylenepyridazine (Summarizingly[3,20]). An analysis of the **A** and **B** bands of simple aromatic compounds with oxygen substituents showed that in unpolar and polar solvents the shorter wavelength band **B** is attributable to the π-π^* transition, whereas the longer wavelength band **A** to the n-π^* transition. The papers by Huisgen et al.[13] and Moore et al.[14] and the findings reported in the monograph by Dewar[15] indicate that the different location and absorption of the **A** and **B** bands of compounds with methylenedioxy groups (contrary to those of similar compounds with two **ortho**-methoxy groups) are conditioned by an increased torsion and distorsion of the adjacent aromatic ring and coplanarity of the whole system. Some authors[14] interpret such an effect as caused by hyperconjugation.



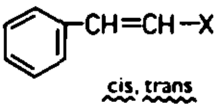
R^1, R^2 = H, Me
$R^1 + R^2 = CH_2$

Ia



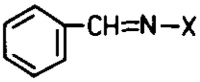
Xa=H; Xb=OH; Xc=OMe
Xd=Alkyl

II



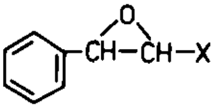
Xa=H; Xb=CHO
Xc=COOH
Xd=COOMe; Xe=Alkyl

III



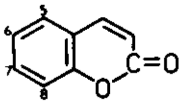
X=OH, Alkyl

IV

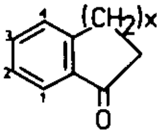


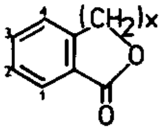
X=Alkyl

V

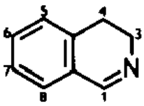


VI

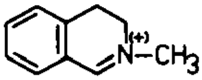




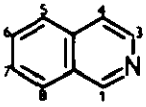
VIIa X = 1 VIIIa
VIIb X = 2 VIIIb



IX



X



XI

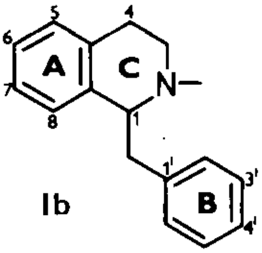
A. Simple Aromatic Compounds and Heterocyclic Compounds With a Hydrogenated Heterocyclic Ring

The results obtained from the analysis of simple aromatic compounds and alkaloids can be summarized in the following way:

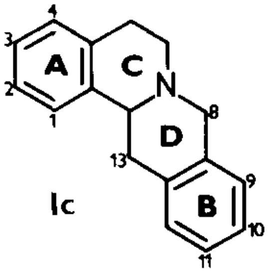
(1) The *A* and *B* bands of all the studied compounds with one (Ia) or two (Ib and Ic) aromatic rings undergo a red shift when the pairs of *ortho*-methoxy groups are substituted by a methylenedioxy group. At the same time, an increase in the molar absorption of the *A* band and a decrease in that of the *B* band are observed (Fig. 1). E.g. see also the alkaloids 1 and 2 (hydrochloride) from *Pheline comosa* Labil.[16]

(2) Substitution of one methoxy group with a hydroxy group in the corresponding pair of methoxy groups has no effect upon the location of the *A* band it may, however, moderate the difference between the molar absorption of the *A* and *B* bands.

(3) The compounds Ib and Ic with two aromatic rings show[3,11] only a small difference in molar absorption when the methylenedioxy group is on the ring *A* and the *ortho*-methoxy pair on the ring *B* or vice versa:



Ib



Ic

(4) In compounds of the type Ic, the shift of the oxygen substituents of the aromatic ring *B* from the positions 9,10 to the positions 10,11 causes a very small difference between the molar absorptions.[3,11]

The fact mentioned sub (3) indicates that the difference in the behaviour of the compounds in UV light depends on that whether the oxygen substituents of both aromatic rings versus the other non-chromophorous substituents (or versus the saturated moiety of the molecule) are in the *ortho* or in the *para* position. The *A* band of the pseudotetrahydroprotoberberine alkaloids undergoes a red shift by ca. 3 nm and a hyperchromic shift by ca. λ_{max} 1500 compared to the normal series.

(5) The effect of the position of electron donating oxygen substituents on

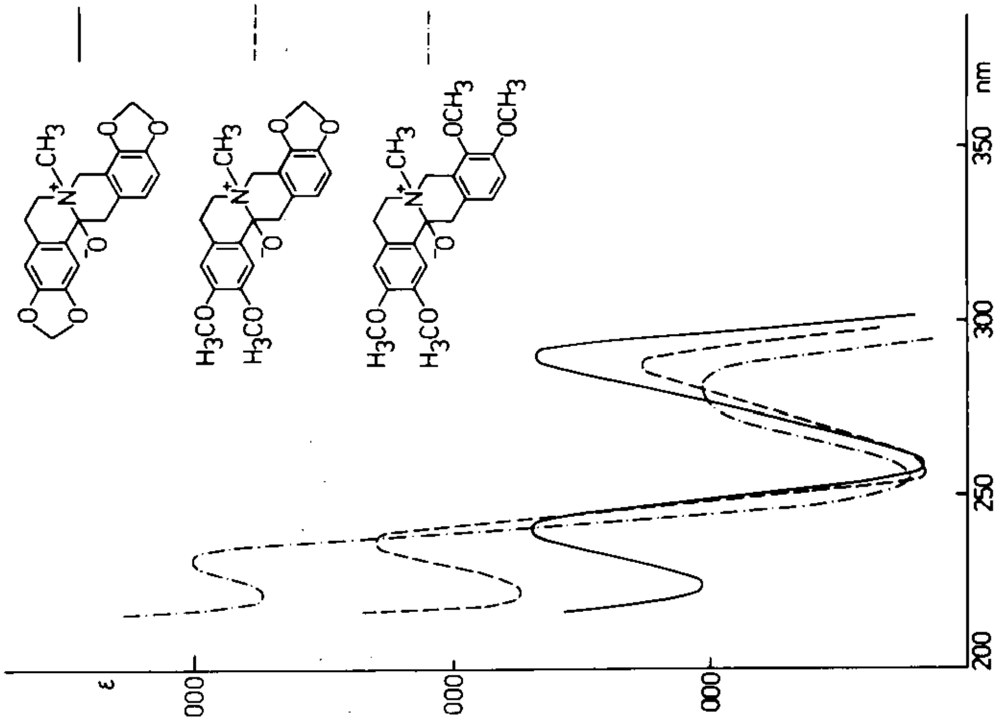

ε
15 000
10000
5 000
200
250
300
350
nm
CH_3
H_3CO
OCH_3

Fig.1

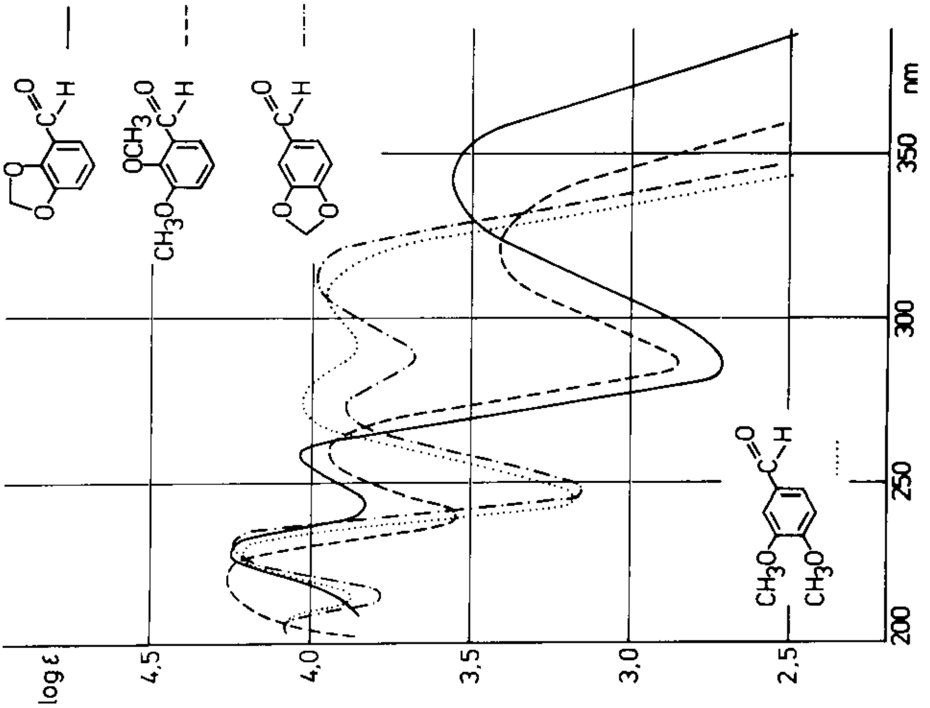

log ε
4,5
4,0
3,5
3,0
2,5
200
250
300
350
nm
CH_3O
OCH_3

Fig.2

the intensity of the *A* band can also be observed in the promorphinan alkaloids O-methylsalutaridine (*ortho-para* condensation of the aromatic rings *A* and *C*) and O-methylflavinantine (*para-para* condensation of the rings *A* and *C*).[17]

B. Aromatic Compounds with Conjugated Electron Accepting Chromophores or with Conjugated Double Bond

After the confirmation[3] of the effect of the methylenedioxy groups on the UV spectra of simple aromatic compounds and different natural products, this phenomenon has been studied[4,6] on more complex aromatic compounds and on compounds whose aromatic nucleus is in conjugation with an α,β-double bond, an α-carbonyl group or an epoxy group (Compounds II - VIII). The results show that the shape and the position of the *A* and *B* bands are not affected only by the methylenedioxy group versus the *ortho*-methoxy groups but also by their positions on the aromatic ring versus the electron accepting group (Fig. 2). This effect is also observed in aromatic oxo-compounds with only one hydroxy or methoxy group. The UV spectra of *ortho* and *meta*-methoxybenzoic acids (or other oxo-compounds) (II) greatly resemble contrary to those of *para*-compounds where the *A* band is markedly shifted to the blue and the *B* band to the red. The effect of the *ortho*, *meta* and *para* substituents of aromatic compounds on their UV spectra has been studied by many authors,[18-21] however, no satisfactory explanation, particularly for the *A* band, has been given (Summarizingly[19]). We assume that in the case of the *A* band it is not so much a steric interaction, for example of the carboxy group with the methoxy group in the *ortho* position, but a symmetry of the compounds.

The absorption of 3,4-methylenedioxypropenylbenzene (III Xe) is similar to that of 3,4-methylenedioxypropiophenone (II Xd) (the behaviour of 3,4-dimethoxypropenylbenzene resembles that of 3,4-dimethoxypropiophenone or acetophenone).[6,20,22] These two types of compounds exhibit an additional band at ca. 300 nm but due to the presence of the methylenedioxy group the molar absorption of the band at 300 nm is increased and displaced bathochromically and that one at ca. 270 nm shows to be decreased. The UV spectrum of 3,4-methylenedioxypropiophenone is practically identical with that of piperonal (3,4-methylenedioxybenzaldehyde) and the UV spectrum of 3,4-dimethoxypropiophenone (II Xd) with that of 3,4-dimethoxybenzaldehyde (II Xa). A similar

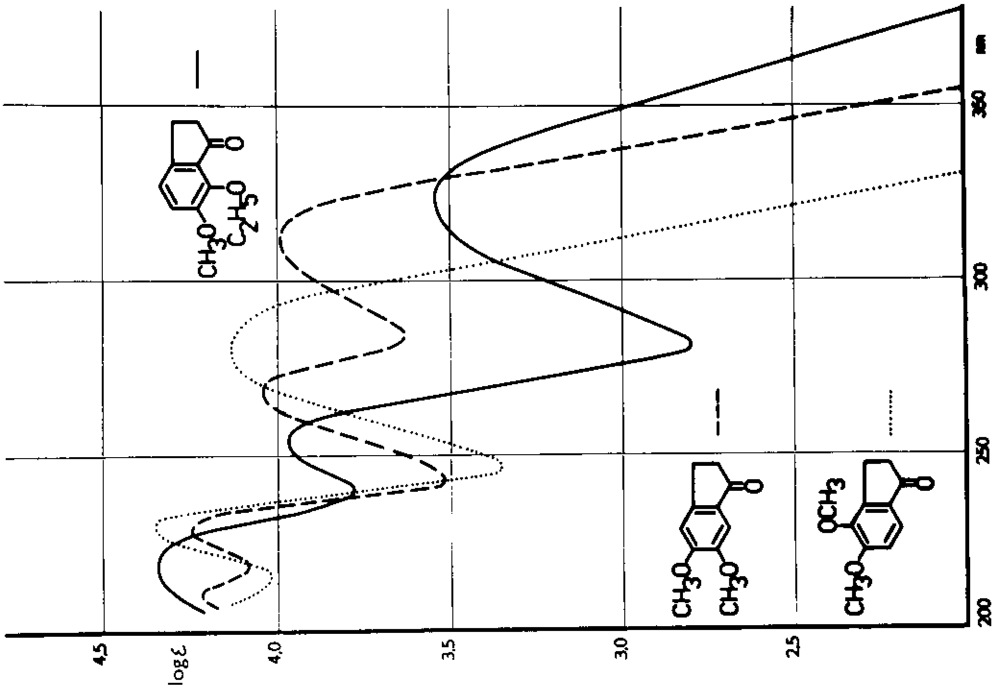

4.5
log ε
4.0
3.5
3.0
2.5
200
250
300
350
nm
CH3O
C2H5O
CH3O
CH3O
OCH3
CH3O

Fig.3

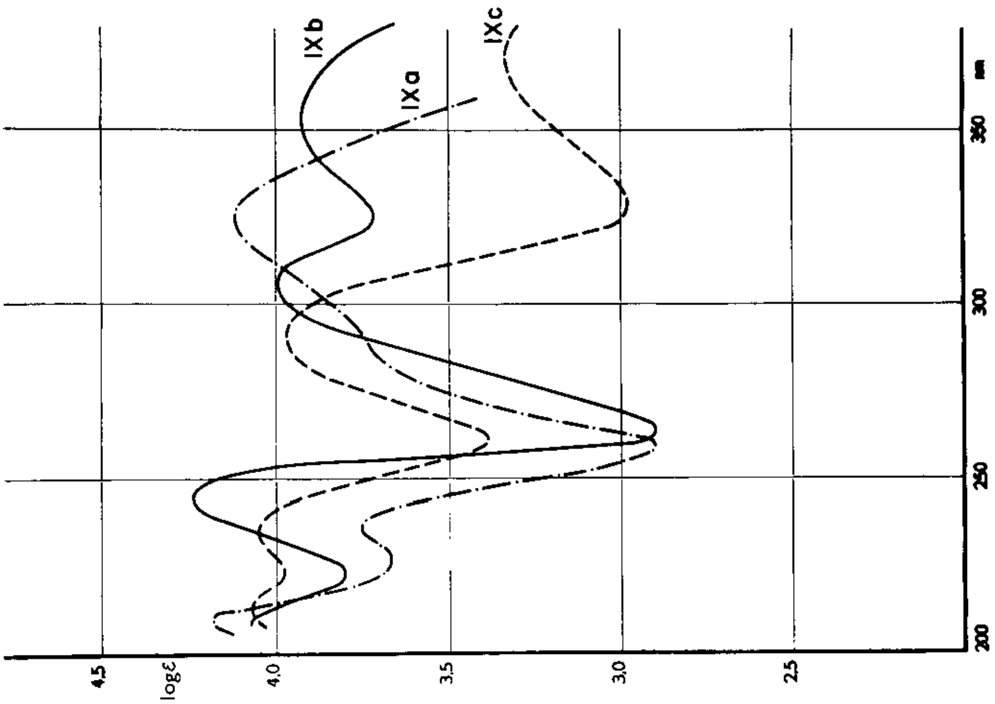

4.5
log ε
4.0
3.5
3.0
2.5
200
250
300
350
nm
IX b
IX a
IX c

Fig.4

phenomenon is also to be seen in the spectrum of 3,4-methylenedioxybenzoic acid compared to that of 3,4-dimethoxybenzoic acid (II Xb) or in the spectra of their esters (II Xc).[4,20,22] These spectra also resemble those of the electron donating derivatives of *trans*-cinnamic acids (III Xc), its methyl esters (III Xd) and of analogous derivatives of the oximes (IV), resp.[6,20] From that follows that it is decisive whether a hydrogen, hydroxyl, alkoxyl or an aliphatic remainder is present at the carbon atom carrying a carbonyl. The resulting spectra arise by superposition of the spectra of compounds monosubstituted by hydroxy or methoxy groups[6,20,22] (Figs 2 and 3).

The same effect as that produced by the double bond of 3,4-methylenedioxypropenylbenzene and 3,4-dimethoxypropenylbenzene (III Xe) is brought about by the epoxy group (V) located in the same position.[7,23,24] Such spectra are also exhibited by tetrahydroprotoberberine alkaloids which have undergone Hofmann degradation.[7] In analogous compounds with electron donating oxygen substituents in the positions 2,3 (compared to compounds whose positions 3,4 are occupied), the *A* and the *B* band are shifted to the red. This effect can be accounted for by the restricted rotation of the electron accepting group and by the greater symmetry of the molecule of compounds whose auxochromic substituents are in the positions 3 and 4. The aromatic compounds with a carbonyl group or a double bond in the side chain are of importance for the elucidation of the constitution for example of lignine.[23,24] When the carbonyl group is in conjugation with the benzene ring by the double bond, as in the case of methylenedioxy or *ortho*-dimethoxycinnamic acid,[6] then all the bands are shifted to the red by ca. 20 nm. The relative position and extinction of the bands are, however, similar to those exhibited by the above-mentioned substituted benzoic acid. The UV spectra of coumarine derivatives (VI)[25] resemble those of *cis*-cinnamic acids (III Xc and Xd) in that respect that the substituents in the *ortho* and *para* positions versus the double bond of the ring *B* have a decisive effect on the form of the spectrum; 5-methoxycoumarine corresponds to 2,6-dimethoxy-*cis*-cinnamic acid.[25,26]

In the spectra of 1-indanones (VIIa),[4] 1-tetralones (VIIb) and phthalides (VIIIa) or homophthalides (VIIIb), the position of the spectroscopic bands is also affected by 1,2; 2,3 or 3,4 dimethoxy/methylenedioxy substituents.[4,27,28] The closer the location of the carbonyl group to the electron donating

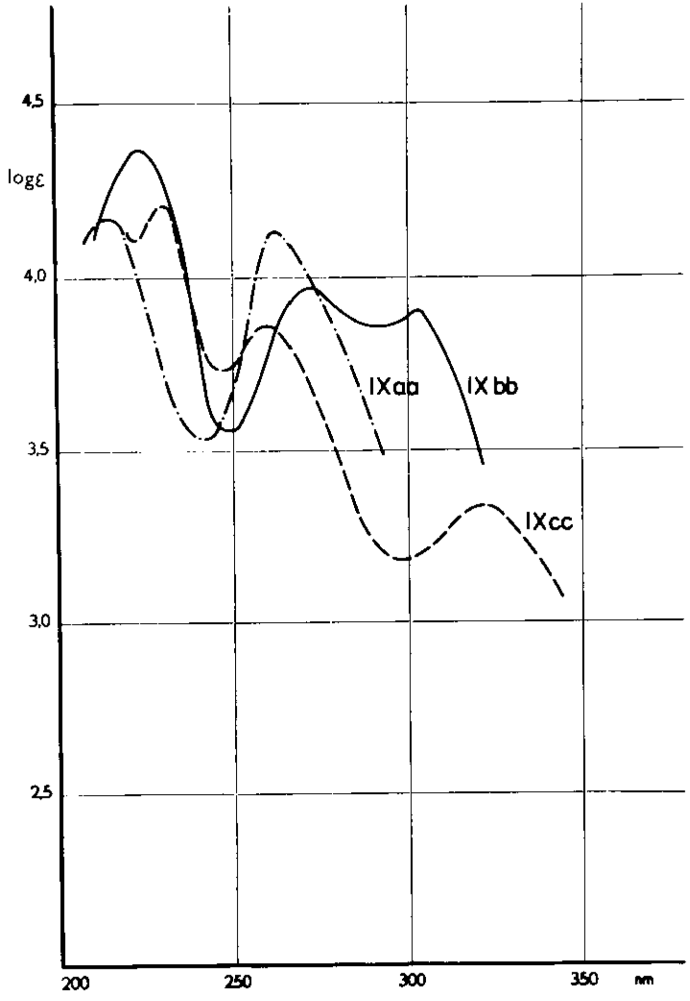

4,5
logε
4,0
3,5
3,0
2,5
200
250
300
350
nm
IXaa
IXbb
IXcc

Fig.5

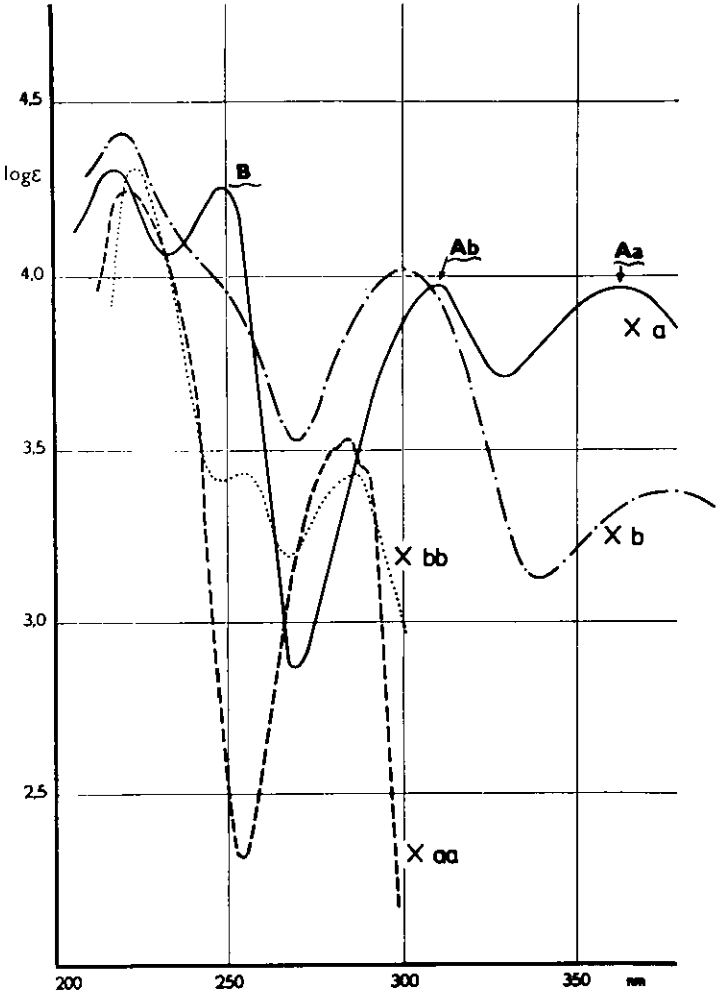

4,5
logε
4,0
3,5
3,0
2,5
200
250
300
350
nm
B
Ab
Aa
X a
X b
X bb
X aa

Fig.6

substituents, the smaller the symmetry of the molecule and the greater the red shift of the A and the B band. These findings are of value for the interpretation of the UV spectra of phthalidetetrahydroisoquinoline or ochotensimine alkaloids or of similar compounds.[4,27]

Regarding the compounds with two aromatic rings with different auxochromic substituents, whose distance from the keto group or double bond of the side chain varies, it is assumed that their UV spectrum is the result of two chromophorous systems similar to those observed for example in 13-oxoprotopine, phthalidetetrahydroisoquinoline, rhoeadine or oxoprotoochotensimine alkaloids.[4] The UV spectra of 13-oxoprotopine alkaloids show[4] that the interaction takes place only between the nitrogen and C-14.

ORD and CD analyses show that the effect of the shift of the A and B bands, in dependence on the presence of the methylenedioxy/methoxy groups, acts upon the position of the Cotton bands.[29,30]

C. Compounds with a Heterocyclic Chromophore

While studying these compounds, we also paid attention[5,28,31] to the UV spectra of 3,4-dihydroisoquinoline (IX), 3,4-dihydroisoquinolinium (X) and isoquinoline (XI) compounds and to those of berbine (XII) and benzophenanthridine (XIII) alkaloids with oxygen substituents in different positions. In the first three types of compounds, the bands B and A are affected by the presence and the position of the methoxy/methylenedioxy groups. The electron spectra of di- and trisubstituted isoquinoline, 3,4-dihydroisoquinoline, and 3,4-dihydroisoquinolinium compounds are also superimposed to those of monosubstituted compounds. There is great resemblance between the spectra of the salts of 3,4-dihydroisoquinoline and 3,4-dihydroisoquinolinium compounds substituted by oxygen electron donating substituents in the same positions (5,6; 6,7 and 7,8). In alkaline medium (NaOH + ethanol), the spectra of 3,4-dihydroisoquinoline compounds are, however, similar to those of their salts except that the A and B bands are shifted to the blue. The 3,4-dihydroisoquinolinium compounds in alkaline medium exhibit electron spectra similar to those of the analogously substituted benzene due to the formation of a carbinol form.[28,31] (Figs 4-6).

In alkaloids of the berberine (XIIa) and sanguinarine (chelirubine, resp.) (XIIIa) types whose aromatic nuclei form the major part of the π-electron

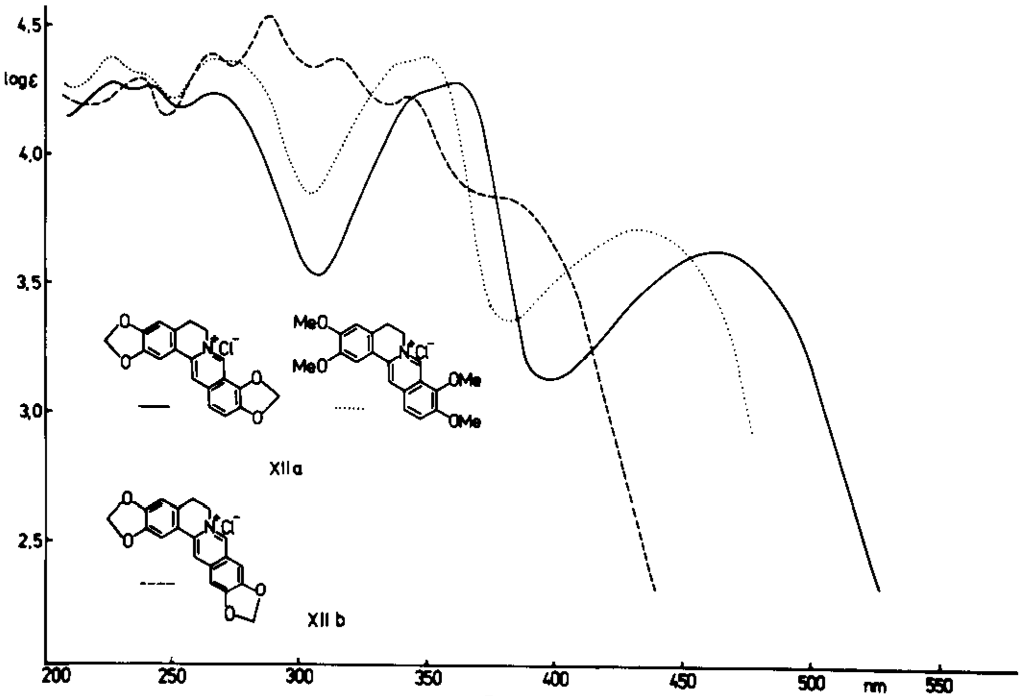

4,5
logε
4,0
3,5
3,0
2,5
200
250
300
350
400
450
500
nm
550
Cl⁻
MeO
MeO
Cl⁻
OMe
OMe
XIIa
Cl⁻
XII b

Fig.7

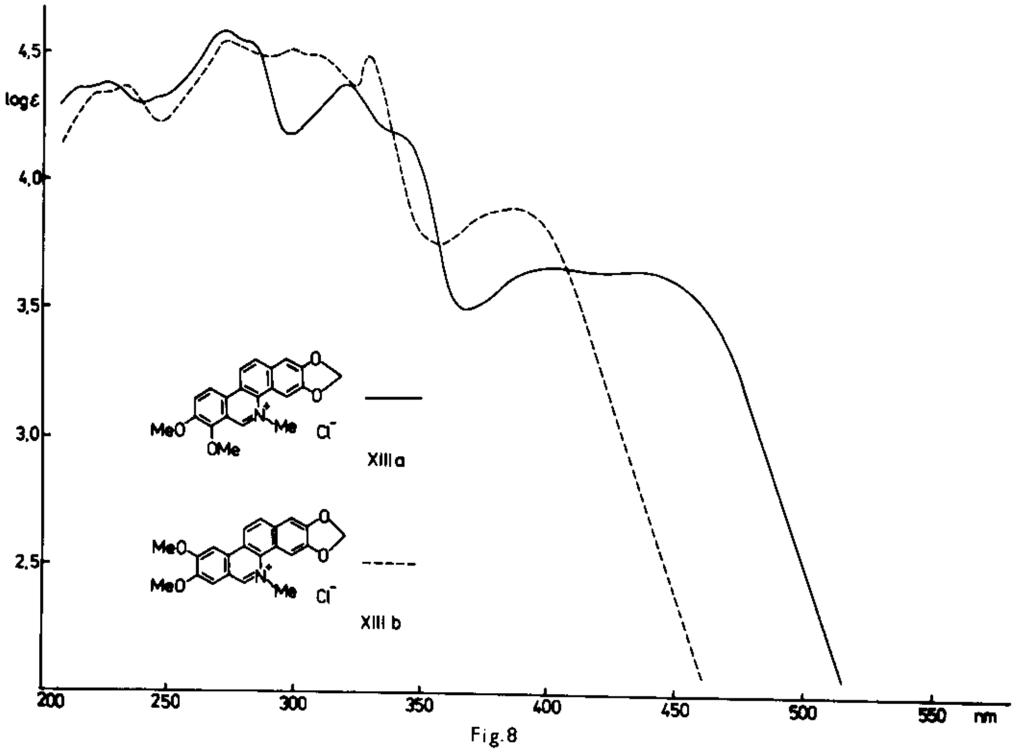

4,5
logε
4,0
3,5
3,0
2,5
200
250
300
350
400
450
500
550
nm
MeO
OMe
Me
Cl⁻
XIII a
MeO
MeO
Me
Cl⁻
XIII b

Fig.8

donating system, only the bands at 340 and 280 nm and those at ca. 440, 330 and 280 nm, resp., are affected by the oxygen substituents of the aromatic ring which is attached to the heterocyclic ring *D*. The spectra of compounds of protoberberine (XIIa) and benzophenanthridine (sanguinarine) (XIIIa) types differ from those of compounds of pseudoberberine (XIIb) and nitidine (XIIIb) types. Thus even here evidence is provided for the considerable effect of the position of electron donating oxygen substituents[5] on the electron spectra (Figs 7 and 8). The colour of protoberberine (XIIa) and benzophenanthridine (XIIIa) alkaloids shows whether an ortho-dimethoxy or methylenedioxy group is present on ring *B*. The salts of these compounds carrying methoxy groups are yellow, whereas those with a methylenedioxy group are orange and red, respectively.

LEGENDS TO FIGURES

Fig. 1: Ultraviolet spectra of some protopine alkaloids (in ethanol after acidification with 0.1 M sulphuric acid)

Fig. 2: Ultraviolet spectra (in ethanol) of some *ortho*-dimethoxy or methylenedioxy benzaldehydes

Fig. 3: Ultraviolet spectra (in ethanol) of some *ortho*-dimethoxyindanones

Fig. 4: Ultraviolet spectra (salts in ethanol) of 5,6- (IXa), 6,7- (IXb) and 7,8- (IXc) dimethoxy-3,4-dihydroisoquinoline compounds

Fig. 5: Ultraviolet spectra (ethanol with 0.1 M NaOH) of 5,6- (IXaa), 6,7- (IXbb) and 7,8- (IXcc) dimethoxy-3,4-dihydroisoquinoline compounds

Fig. 6: Ultraviolet spectra (in ethanol) of 6,7- (Xa) and 7,8- (Xb) dimethoxy-3,4-dihydroisoquinolinium salts. Spectra of the same substances (Xaa and Xbb) in ethanolic alcaline medium

Fig. 7: Ultraviolet spectra (salts in ethanol) of some protoberberine (XIIa) and pseudoberberine (XIIb) alkaloids

Fig. 8: Ultraviolet spectra (salts in ethanol) of some benzophenanthridine (chelerythrine (XIIIa) and nitidine (XIIIb)) alkaloids

REFERENCES

1. W. Awe and W. Winkler, Arch. Pharm., 1957, 290, 367.
2. S. Pfeifer and J. Teige, Pharmazie, 1962, 17, 692.
3. L. Hruban and F. Šantavý, Symposium Biochem. u. Physiol. d. Alkaloide, Halle (Saale) 1965. Tagungsbericht: Abhandl. Deut. Akad. Wiss., Kl. Chem., Geol., Biol. No. 3, pp. 625-628, Akademie Verlag, Berlin 1966; Collection Czechoslov. Chem. Commun., 1967, 32, 3414.
4. F. Šantavý, L. Hruban, V. Šimánek, and D. Walterová, Collection Czechoslov. Chem. Commun., 1970, 35, 2418.
5. L. Hruban, F. Šantavý, and S. Hegerová, Collection Czechoslov. Chem. Commun., 1970, 35, 3420.
6. F. Šantavý, D. Walterová, and L. Hruban, Collection Czechoslov. Chem. Commun., 1972, 37, 1825.
7. V. Šimánek, V. Preininger, V. Sedmera, and F. Šantavý, Collection Czechoslov. Chem. Commun., 1970, 35, 1440.
8. Z. Kitasato, Acta Phytochem. (Japan), 1927, 3, 243; Chem. Abstr., 1928, 22, 1779; Chem. Zbl., 1927, 98 (II), 1965.
9. K. Feist, W. Awe, and H. Etzrodt, Arch. Pharm., 1934, 272, 817.
10. L. Láng and B.M. Bárczai, Periodica Polytechnica, 1964, 8, 261.
11. E. Sebe, S. Abe, N. Murase, and Y. Shibata, J. Chinese Chem. Soc. Taiwan, 1967, 14, 135; Chem. Abstr., 1968, 69, 6319.
12. M. Shamma, M.J. Hillman, and C.D. Jones, Chem. Rew., 1969, 69, 779.
13. R. Huisgen, W. Rapp, I. Ugi, H. Walz, and E. Morgenthaler, Liebigs Ann. Chem., 1954, 586, 1.
14. W.R. Moore, E. Marcus, S.E. Fenton, and R.T. Arnold, Tetrahedron, 1959, 5, 179.
15. M.J.S. Dewar, Hyperconjugation. The Ronald Press Company, New York 1962.
16. J. Holubek, Spectral Data and Physical Constants of Alkaloids, Plans 903 and 905, Czechoslov. Acad. Sci., Prague 1973.
17. S. Dvořáčková, L. Hruban, V. Preininger, and F. Šantavý, Heterocycles, 1975, 3, 575.
18. L. Doub and J.M. Vandenbelt, J. Am. Chem. Soc., 1955, 77, 4535.

19. A.I. Scott, Interpretation of the Ultraviolet Spectra of Natural Products, pp. 123 and 187, Pergamon Press, Oxford 1964.

20. F. Šantavý, S. Hegerová, L. Hruban, A. Klásek, A. Němečková, V. Šimánek, and D. Walterová, *Acta Univ. Olomuc.*, *Fac. Med.*, Suppl. XIII, 1973.

21. J.C. Dearden and W.F. Forbes, *Can. J. Chem.*, 1959, **37**, 1305.

22. D. Walterová, L. Hruban, and F. Šantavý, *Collection Czechoslov. Chem. Commun.*, 1974, **39**, 2449.

23. A. Hillmer and P. Schorning, *Z. Physik. Chemie*, 1934, **168-A**, 81.

24. O.R. Herzog and A. Hillmer, *Ber.*, 1931, **64**, 1288.

25. L. Hruban, S. Dvořáčková-Hegerová, V. Šimánek, and F. Šantavý, *Acta Univ. Olomuc.*, *Fac. Med.*, 1978, **86**, 25.

26. H. Böhme and T. Severin, *Arch. Pharm.*, 1957, **290**, 285, 405, 448, 486.

27. F. Šantavý, Papaveraceae Alkaloids. II., p. 508. In the book H.R.F. Manske, *The Alkaloids*, Vol. XVII., New York 1978.

28. F. Šantavý and I. Vácha, *Collection Czechoslov. Chem. Commun.* - in the Press.

29. R.J. Swan, W. Klyne, and H. MacLean, *Can. J. Chem.*, 1967, **45**, 319.

30. G. Snatzke, G. Wollenberg, J., Jr., Hrbek, F. Šantavý, K. Bláha, W. Klyne, and R.J. Swan, *Tetrahedron*, 1969, **20**, 5059.

31. V. Šimánek, V. Preininger, S. Hegerová, and F. Šantavý, *Collection Czechoslov. Chem. Commun.*, 1972, **37**, 2746.

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