AN INVESTIGATION OF QUINOLIZIDINE ALKALOIDS BY THE OPTICAL ROTATORY DISPERSION (ORD) METHOD

I. ORD OF ALKALOIDS OF THE LUPININE, CYTISINE, SPARTEINE, AND APHYLLINIC ACID GROUP

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The ORD method has been used by many workers in the conformational analysis of proteins, amino acids, steroid compounds and alkaloids. Information on the study of the quinolizidine alkaloids by the ORD method has been given only in a few brief communications [1, 2].

The present paper gives the results of an investigation of the quinolizidine alkaloids sparteine, lupinine, cytisine, and some derivatives of aphyllinic acid.

Analysis of the ORD curve shows that a quinolizidine system having no chromophoric group, as in pachycarpine (I) is characterized by a flat curve and may serve as a standard in the study of anomalous curves of related compounds.

Figure 1 gives the ORD curves characteristic for sparteine alkaloids differing from one another in the position of the lactam group and of the double bonds, and in configuration.

The ORD of (+)-aphylline (II) which contains a trans-cis-quinolizidine system with the lactam group in ring B in its molecule has an anomalous curve with a positive Cotton effect (CE). The effect of the background has no appreciable influence on the sign and shape of the curve (see Fig. 1). In (+)-lupanine (III) with the lactam carbonyl in ring A, the CE is also positive.

A stereoisomer of aphylline – (+)-α-isoaphylline (IV) with a trans-trans-quinolizidine system – has a positive CE at 235 nm.

The ORD curve of (+)-17-oxopachycarpine (V) with a cis-quinolizidine linkage of the nuclei around the $>N-\overset{|}{C}=O$ group differs in shape and sign from the curves of (III) and (IV); as in the case of (II) the effect of the background plays no fundamental part (see Fig. 1).

It follows from what has been said that the arrangement of the lactam carbonyl in a cis- or a trans-quinolizidine nucleus adjacent to the asymmetric center affects the sign, shape, and molecular amplitude of the ORD curve (Table 1). A similar relationship has been observed for the steroid ketones [3-6] and for some alkaloids of the sparteine series [1]. A more complex pattern is observed where the molecule contains two lactam groups. For example, the curve of oxoaphylline (VI) possesses a distinct negative CE. This difference is obviously connected with the vicinal arrangement of the two carbonyl chromophores, which is analogous to that found in the cyclic diketones [3].

TABLE 1

Compound	Position $-\overset{|}{C}-O$	$a\times10^{-2}$	$\Delta a\times10^{-2}$	Peak, λ, nm	$\Delta\lambda$, nm
(+)-Lupanine	2	+1052	–	240	–
(+)-Aphylline	10	+365,6	+686,4	234	6
(+)-17-Oxo-pachycarpine	17	+228,0	+824,0	216	24

The arrangement of the double bond in ring A or D of the dehydro derivatives of (II) (see Fig. 1), of

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TABLE 2

Compound	Position of double bond	$a \times 10^{-2}$	$\Delta a \times 10^{-2}$	Peak, λ, nm	$\Delta\lambda$, nm
(+)-Aphylline	—	+365,6	—	234	—
(+)-Aphyllidine	5—6	+177,8	+187,8	240	6
(+)-Dehydro-aphylline	11—12	+56,8	+308,8	235	1

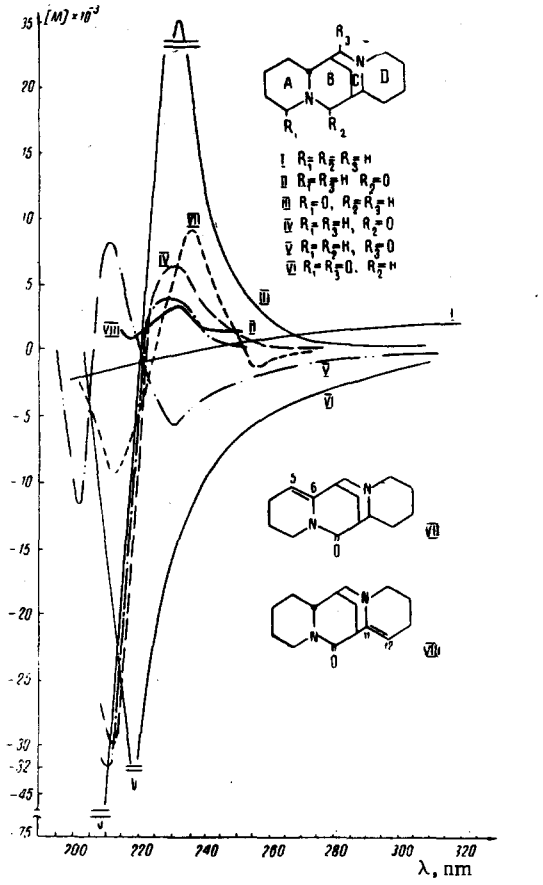

Fig. 1. ORD curves of (+)-pachycarpin (I), (+)-aphylline (II), (+)-lupanine (III), (+)-α-isoaphylline (IV), (+)-17-oxopachycarpine (V), (+)-oxoaphylline (VI), (+)-aphyllidine (VII), and (+)-dehydroaphylline (VIII).

(+)-aphyllidine (VII), and of (+)-dehydroaphyllidine (VIII) affects the magnitude of the molecular rotation while the sign of the curve does not change (Table 2).

The dehydro derivatives of aphylline have a slight bathochromic shift as compared with aphylline.

Figure 2 gives the ORD curves of (-)-tetrahydrocytisine (IX) and (-)-isolupanine (X) with the trans linkage of rings A/B. The ORD curves differ only by the amplitude of the rotation, in spite of the absence of ring D in (IX).

In an analysis of the spectra of (-)-thermopsine (XI) and (-)-anagyrine (XII), which are epimers at C_{11}, it can be seen that because of the presence of an α-pyridone ring the curves are extremely similar (Fig. 3).

Curves with a broad unresolved peak and with two maxima, which may be considered as the superposition of two partial molecular rotations are characteristic for (XI) and (XII).

The first positive extremum in the curves of (XI) and (XII) at 280 nm is due to the $n-\pi^*$ transition in the lactam group and corresponds approximately to the absorption maximum in the UV region [9, 10] (Table 3). The second peak, at 240 nm, is due to a $\pi-\pi^*$ transition in the α-pyridone ring.

Cytisine (XIII) and argentine (XIV) belong to another group of alkaloids with the α-pyridone ring. Characteristic for them are unresolved curves with two maxima due to a lactam carbonyl conjugated with double bonds, the curve for (XIV), consisting of two cytisine fragments having a peak with an intensity approximately twice that for compound (XIII) (see Fig. 3).

The ORD curve of N-methylcytisine (XV) is similar in sign and shape to that of (XIII), but is displaced in the long-wave direction. The difference in the molecular amplitude is large, which is due to the influence on the rotation of a methyl group in the equatorial position (Table 4) [3, 7].

The intensity of the first positive extremum at 272 is slightly greater in (XVI) than in cytisine and its derivatives which is apparently the result of the $\pi-\pi^*$ transition of the $-\overset{|}{C}=\overset{|}{C}-$ bond in the α-pyridone ring and of the $n-\pi^*$ transition of the $-N=O$ bond.

Figure 4 gives some ORD curves of lupinine (XVII) and its derivatives with CEs almost approximating to smooth curves. The shift of the curve of epilupinine (XVIII) as compared with that of (XVII) is due to the different orientations of the substituent about the asymmetric center [axial in (XVII) and equatorial in (XVIII)]. The curve of epilupininic acid (XIX) is similar in shape to the curves of other carboxylic acids [11], especially to that of aphyllic (XX). The curve of epilupininoylpiperidine (XXI) has a trough at 238 nm.

In aphyllinic acid (XX) there is a weak carbonyl-group chromophone: (XX) appears in the form of a curve with a trough at 220 nm as the result of a $n-\pi^*$ transition in the carbonyl of the carboxy group.

Smooth positive curves with a gentle inflection in the 235 nm region are characteristic for methyl and ethyl aphyllinates (XXII and XXIII); a negative curve with a gentle inflection in the 235 nm region is characteristic for aphyllinamide (XXIV).

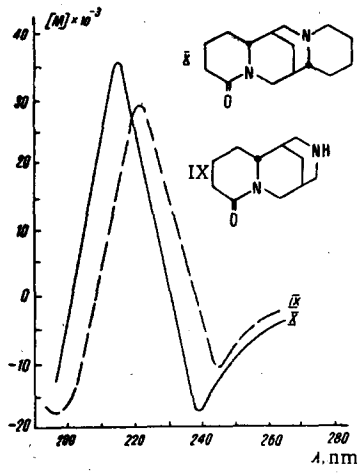

Fig. 2

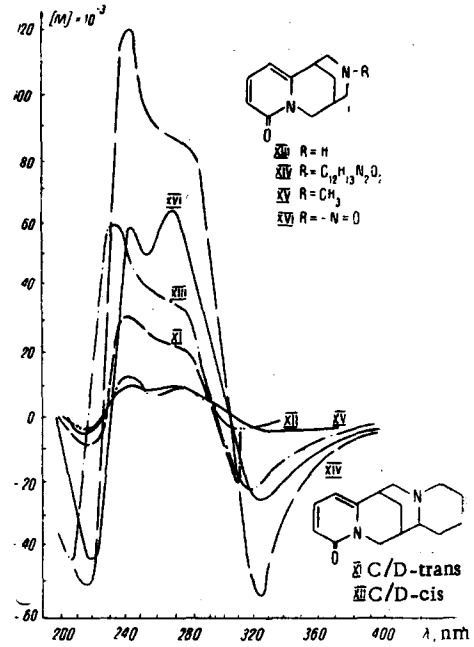

Fig. 3

Fig. 2. ORD curves of (-)-tetrahydrocytisine (IX) and (-)-α-isolupanine (X).

Fig. 3. ORD curves of (-)-thermopsine (XI), (-)-anagyrine (XII), (-)-cytisine (XIII), (-)-argentine (XIV), (-)-N-methylcytisine (XV), and N-nitrosocytisine (XVI).

The behavior of the $-CO-NH_2$ and $-CO-OH$ groups is extremely similar, which is in harmony with literature information [7]. Ethyl N-benzoylaphyllinate is characterized by a negative curve with troughs and a peak close to the axis of zero rotation. Aphylline alcohol (XXVI) is characterized by a smooth curve.

The hydroxy group absorbs in the far UV region, and at the present time it is practically impossible to measure ORDs in the region of absorption of the hydroxy chromophore [7, 12].

On the basis of an analysis of the curves of model compounds, it has been found that of the tetracyclic systems with an α-pyridone ring the greatest molecular amplitude is characteristic of the epimers with the trans-quinolizidine linkage of the nuclei, as in the case of (XI) as compared with the corresponding cis epimer (XII), while the opposite pattern is found for the hydrogenated compounds (III) and (X).

Curves of approximately smooth form are characteristic for derivatives of lupinine and aphyllinic acid. In the case of aphyllinic acid, the introduction of various substituents shifts the curves in the long-wave direction.

TABLE 3. UV Spectra of Some Quinolizidine Alkaloids

Compound	λ_{max}, nm	log ε	Solvent	Reference
Lupanine	215	3,7	C_2H_5OH	[13]
Aphyllidine	240	3,94		[14]
Anagyrine	233	3,82		[15]
	309	3,89		
Cytisine	234	3,7	CH_3OH	[16]
	310	3,8		
N-Methylcytisine	234	3,7		[15]
	309	3,9		
Argentine	235	4,19	C_2H_5OH	[17]
	306	4,16		
	232	4,19		[18]
	309	4,16		

The above facts indicate that the standard curves of the quinolizidine alkaloids can be used for their identification and for the determination of the spatial structure of this group of alkaloids.

EXPERIMENTAL

The ORD curves were taken on a Cary-60 spectrophotometer (Institute of the Chemistry of Natural Compounds, Academy of Sciences of the USSR).

The range of measurements of the UV spectra was 190-400 nm. Ethanol was used as solvent.

TABLE 4

Compound	Substituent R	$a \times 10^{-2}$	$\Delta a \times 10^{-2}$	Peak, λ, nm	Δλ, nm
Cytisine	—H	+1056,3	—	233	—
N-Methylcytisine	$-CH_3$	+180,3	+876,2	242	9
Nitrosocytisine	—N=O	+1052,0	+4,3	245	12
Argentine	$-C_{12}H_{13}N_2O_2$	+1731,4	+674,9	244	
		−1741,0	+2797,5	205	27

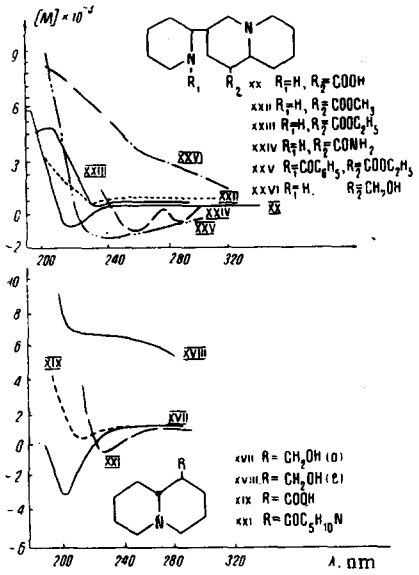

Fig. 4. ORD curves of (-)-lupinine (XVII), (+)-epilupinine (XVIII), (+)-epilupininic acid (XIX), (+)-aphyllinic acid (XX), (+)-epilupininoylpiperidine (XXI), methyl (+)-aphyllinate (XXII), ethyl (+)-aphyllinate (XXIII), (+)-aphyllinamide (XXIV), ethyl (-)-N-benzoylaphyllinate (XXV), and (+)-aphylline alcohol (XXVI).

The dependence of the molecular rotation [M] on the wavelength (λ) of the compounds investigated was illustrated graphically.

SUMMARY

1. The ORD curves of alkaloids of the sparteine, lupinine, and cytisine groups and of some derivatives of aphyllinic acid have been investigated. In the compounds investigated with an α-pyridone ring the epimers with the trans-quinolizidine linkage of the nuclei have a greater molecular amplitude than the corresponding cis isomers.

2. It has been shown that the alkaloids with a lactam group in an outer ring have higher molecular amplitudes than the corresponding compounds with the $>N-\overset{|}{C}=O$ group in an inner ring. A dependence of the shape, sign, and molecular amplitude of the curves on the type of linkage of the quinolizidine nuclei and also a dependence of the molecular rotation of the position of a double bond in ring A or D have been given.

3. Derivatives of lupinine and of aphyllinic acid are characterized by curves approximating to a smooth shape with low-intensity anomalies, and in the case of the derivatives of aphyllinic acid studied they are shifted in the long-wave direction.

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