It was shown that the amino acid lysine is a precursor of aphylline and aphyllidine, and the last stage of the biosynthesis of these alkaloids is connected with the oxidation of pachycarpine and the formation of a lactam group.

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SPATIAL STRUCTURE OF CYCLEANINE

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Analysis of the PMR spectra of cycleanine in $CDCl_3$ (INDOR and double-resonance spectra) measured at various temperatures has shown that the cycleanine molecule exists in a stable symmetrical boat-like conformation for the macrocycle in which the tetrahydroisoquinoline rings acquire a distorted boat form, the benzyl groups are oriented axially, and the distance between them is the greatest. A comparison of the spectra of the cycleanine and its methiodide in CF_3COOH (double-resonance spectra) has shown that in solutions of cycleanine in the salt form there are molecules with axial and equatorial methyl groups at the nitrogen atoms (1 : 1). It has been shown with the aid of paramagnetic reagents that the main associating center in the cycleanine molecule is formed by the methoxy groups in position 7 and 7', which possess an increased electron density on their oxygen atoms because of their departure from the plane of conjugation with the aromatic ring of the isoquinoline nucleus.

Cycleanine (I) belongs to the bisbenzylisoquinoline alkaloids. Its structure and absolute configuration were established by classical methods and were subsequently confirmed by physicochemical methods which have been generalized in the form of reviews and monographs [1-5]. However, until now the question of the spatial structure of cycleanine has remained open. The unusual behavior of cycleanine on dehydrogenation with mercuric acetate [6] cannot be completely explained on the basis of known features of this alkaloid. Consequently, we decided to study its conformation in solutions. At the present time information is available on the conforma-

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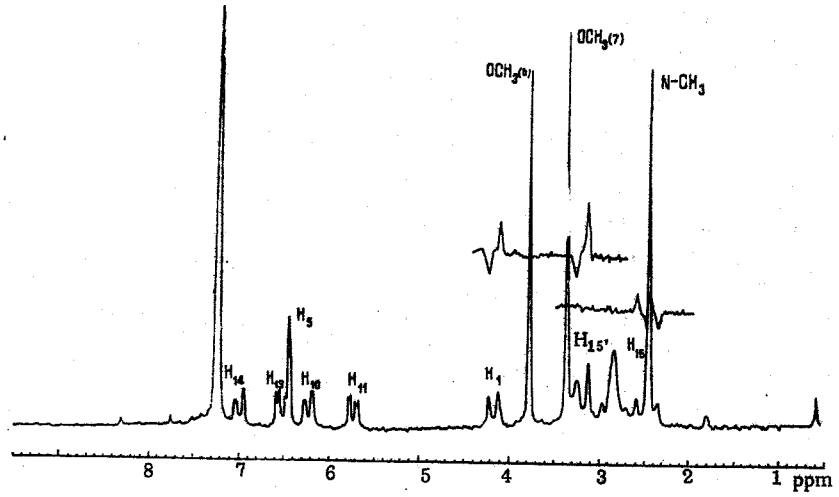

Fig. 1. PMR and INDOR spectra of cycleanine in $CDCl_3$ (0 – TMS).

tion of the alkaloid tubocurarine chloride [7, 8] and also on tetrandrine [9]. However, no systematic investigations in this direction have been performed.

It follows from the molecular models of cycleanine that its molecules, having identical configurations of the centers of asymmetry, contain an axis of symmetry running perpendicular to the plane of the macrocycle. This is shown by the presence of its PMR spectrum of only half the number of proton signals that follow from the established empirical formula. The 18-membered macrocyclic ring of this alkaloid can exist in several conformations, of which only four are symmetrical. Further information on the conformation of the macrocycle has been obtained from the PMR spectra of cycleanine in $CDCl_3$ and CF_3COOH (Table 1). The positions, structure, and assignments of the H_1 signals and of those of the protons of the methylenes of the benzyl groups were made with the aid of the INDOR method (Fig. 1) and also by a comparison of the chemical shifts of the protons in chloroform and in trifluoroacetic acid. The ortho-oriented aromatic protons of the benzyl rings form two pairs of signals. One of them is present in an unusually strong field at 5.72 and 6.22 ppm, which is undoubtedly due to the diamagnetic influence of the isoquinoline rings spatially close to the benzyl rings.

It follows from a consideration of the coupling constants of the H_1 proton with the protons of the methylene of the benzyl group ($J_{1,15} = 0$ Hz and $J_{1,15} = 10$ Hz) that one of the protons forms with it a dihedral angle close to 90° while the other has one close to 150°. Thus, the two conformations represented in the form of Newman projections in Fig. 2 are possible.

In the antiperiplanar conformation, the benzyl rings approach one another closely, while in the synclinal conformation the distance between them increases to 3.9 Å (maximum separation). In this case, the benzyl group acquires the axial orientation. The proton of the benzyl methylene group forming an angle of 90° with H_1 proton is oriented outside the macrocycle. In this case, the aromatic protons of the benzyl fragment present within the "boat" of the macrocycle fall into the region of screening by the isoquinoline aromatic rings. The approximately identical degree of screening (~ 0.7 ppm) indicates that these protons are subject to the total screening influence of the four aromatic rings of the molecule, while the remaining protons are present outside the plane of the macrocycle and do not experience this effect.

With a rise in the temperature, the form of the spectrum changes. There is a broadening of the signals of the benzyl aromatic protons (20-80 °C), an approach to one another of the weak-field and strong-field signals (80-130°C), and their final fusion (above 130°C). In these circumstances the other signals do not change. This permits the assumption that in the cycleanine molecule a benzyl benzene ring rotates about an axis passing through the $C_{(9)}-C_{(12)}$ atoms. With a rise in the temperature, the rate of inversion increases, which leads to the observed changes in the spectrum. By making use of the region of slow exchange (Fig. 3) in which only a change in the width of the signal takes place, we have determined the inversion barrier by a method described by Johnson and Bovey [10].

The width of the signal in the quartet relating to the strong-field signal of a proton adjacent to oxygen was determined at various temperatures by comparing the forms of these signals with the calculated forms (Fig. 4). The calculated spectrum consists of the superposition of four signals of Lorentzian form. The parameter varied was the relaxation time T_2 (0.5-0.05 sec, step 0.05 sec). The function was not normalized, as a result of which

TABLE 1. Chemical Shifts of the Protons (δ, ppm), Spin–Spin Coupling Constants, and Multiplicities in the PMR Spectra of Cycleanine and Cycleanine Methiodide

Compound	Solvent	H_1	C_6–OCH_3	C_7–OCH_3	H_5	H_{10}	H_{11}	H_{13}	H_{14}	H_{15}	$H_{15'}$	N–CH_3	N–CH_3
Cycleanine		4,16 d,10	3,77 s	3,39 s	6,45 s	6,22 q,8,5 2,3	5,72 q,8,5 2,3	6,56 q,8,5 2,3	7,00 q,8,5 2,3	2,48 13 10	3,18 d, 13	2,47 s	
Cycleanine	CF_3COOH	5,1 d,10	3,93 s	3,49 s	6,88 s	6 47 q,8,2 2,3	5,94 q,8,2 2,3	6,48 q,8,2 2,3	7,21 q,8,2 2,3			2,98 (a) d, 4	3,42 (e) d, 4
Cycleanine methiodide	CF_3COOH	5,1 d,10	4,1 s	3,63 s	6,94 s	6,50 q,8,5 2,3	6,05 q,8,5 2,3	6,86 q,8,5 2,3	7,32 q,8,5 2,3			3,15 s	3,73

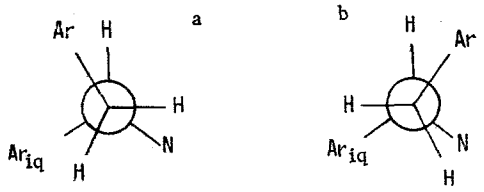

Fig. 2

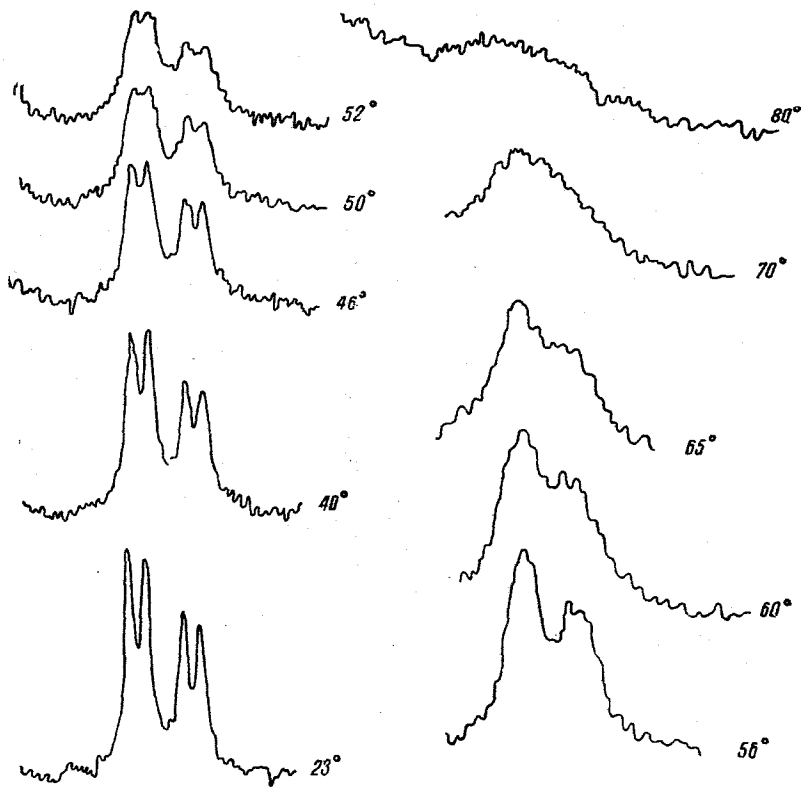

Fig. 3

Fig. 2. Synclinal (a) and antiperiplanar (b) conformations formed by the rotation of the benzyl group round the C_1-C_{15} bond.

Fig. 3. Form of the signal of the H_{11} proton at various temperatures.

the area under the curve increased with a decrease in T_2. The width of the signals due to the inhomogeneity of the magnetic field was 1 Hz. The lifetime τ was determined from the equation

$$\frac{1}{\tau} = \frac{1}{T_{2\,\text{theor}}} - \frac{1}{T_{2\,\text{inhom}}} .$$

By treating the experimental results by the method of least squares we obtained the values of the parameters in the equation

$$\ln k = \ln k_0 - \frac{\Delta E_a}{R} \cdot \frac{1}{T} ,$$

where $k = 1/\tau$.

The energy barrier proved to be 16.5 kcal/mole, and the linear correlation coefficient $r^2 = 0.98$. Such a high energy barrier indicates a strong interaction of the benzyl aromatic rings. It may be assumed that, of the possible conformations of the molecule, one is realized in which the distance between the benzyl rings is the greatest. It follows from molecular models that the greatest distance between them is observed when the tetrahydroisoquinoline ring acquires the form of a distorted boat. In this case, they are 0.5 Å further away from one another than in the case of the half-chair conformation of the tetrahydroisoquinoline rings (Fig. 5).

In the distorted boat conformation the magnetic anisotropic influence of the aromatic rings on axial and equatorial methylimino groups of a tetrahydroisoquinoline ring should differ substantially. Calculation according to a method given in the literature [11] has shown that this difference should be not less than 0.5 ppm.

The methylimino groups of cycleanine resonate at 2.45 ppm ($CDCl_3$). For comparison we measured the spectrum of cycleanine methiodide, in which the signals of N-methyl groups were observed at 3.14 ppm (a) and 3.74 ppm (e). Thus, the difference in the chemical shifts amounts to 0.6 ppm, which agrees well with the calculated magnitudes.

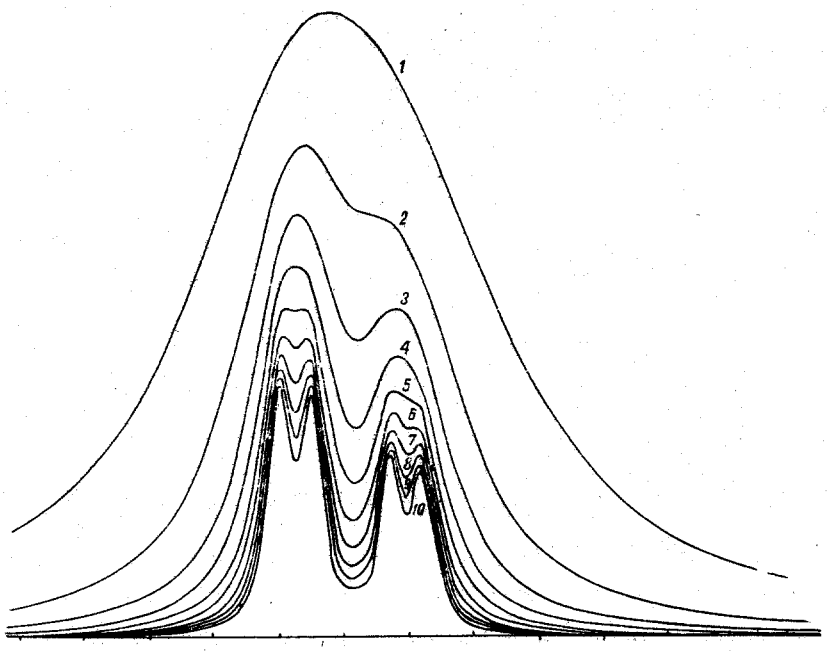

Fig. 4. Calculated form of the H_{11} quartet at various values of T_2 (0.05 → 0.5, steps of 0.05 sec).

In the PMR spectrum of a solution of cycleanine in CF_3COOH (Fig. 6) the signals of two protons of methyl ammonium groups are observed at 2.97 and 3.42 ppm (J = 3 Hz), these being oriented axially and equatorially, respectively, and the second signal being displaced by approximately 1 ppm as compared with the signal of the methylimino groups in cycleanine. Double resonance showed that the signals of the protons of the N-methyl groups interact with the geminal protons at the nitrogen atoms, which are present in the weak field region of the spectrum. The ratio of the intensities of the protons of the axial and equatorial N-methyl groups (1 : 1) did not change on dilution with chloroform. However, when CF_3COOH was added to a chloroform solution of cycleanine their intensities became different. When, in addition, a few drops of CD_3OD was added to this solution, the signal of the axial N-methyl group disappeared and the doublet of the equatorial N-methyl group was converted into the singlet because of deuterium exchange with the geminal proton on this nitrogen atom. When a solution of cycleanine in CF_3COOH was heated, the same change in the spectrum took place as in $CDCl_3$.

The information obtained has permitted us to reconsider questions of the reactivity of the cycleanine molecule. In particular, the axial configuration of the benzyl group permits an explanation of the resistance of the molecule to dehydrogenation with mercuric acetate and the cleavage of the axial carbon–carbon bond of the benzyl group during this reaction [6] (transdiaxial elimination).

In addition, we investigated the PMR spectrum of cycleanine with paramagnetic additives. It could be assumed that the main center of association in the molecule is formed by the nitrogen atoms. However, it was found that the rate of downfield displacement for the protons of the methoxy group in position 7 was 3.7 times greater than for the protons of the N-methyl groups. At the same time, the signals of the second methoxy group

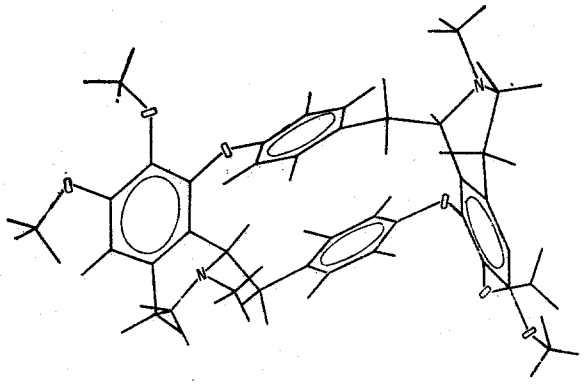

Fig. 5. Model of the cycleanine molecule.

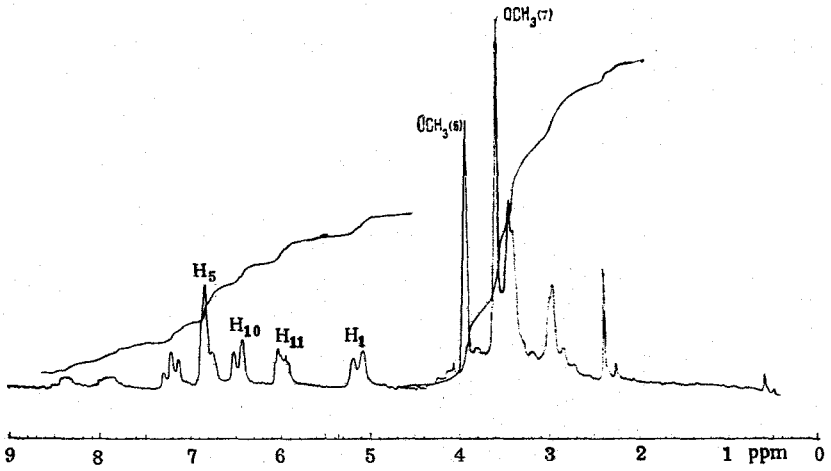

Fig. 6. PMR spectrum of cycleanine in CF_3COOH (0 – TMS).

shifted not downfield but upfield (K = −1.7).* The signal of the H_{10} aromatic proton shifted upfield (K = −1). The signals of the other aromatic protons shifted downfield. For H_{11}, K = 1.9; and for H_5, K = 0.7. This indicates a considerably greater associating capacity of the C_7-OCH_3 group than of the C_6-OCH_3 group. This difference cannot be explained by steric interaction, since the approach of the chemical shift reagent to the methoxy group in position 7 is freer. The associating capacity of the C_7-OCH_3 group is apparently higher because of the more negative charge on this group as a consequence of the departure of this methoxy group from the plane of conjugation with the aromatic ring. Because of the absence of coplanarity, the π-electrons of the oxygen atom are not expelled into the benzene ring. The increased nucleophilicity of the ethereal oxygen atom in position 7 explains the ease of C_7-O-demethylation by electrophilic reagents [12, 13].

SUMMARY

It has been established by an analysis of the PMR spectra of cycleanine (in $CDCl_3$ and CF_3COOH) and of its methiodide (INDOR and double-resonance spectra), measured at various temperatures, that the macrocyclic ring of the alkaloid exists in a stable symmetrical boat conformation while the tetrahydroquinoline rings acquire a distorted boat shape and the benzyl groups are oriented axially the distance between them being about 3.9 Å. In CF_3COOH solutions of cycleanine, signals of axial and equatorial methylammonium groups were observed. It was shown with the aid of paramagnetic reagents that the main associating centers in the molecule are the OCH_3 groups in the 7 and and 7' positions.

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* The rate of the paramagnetic shift K of protons is given relative to the displacement of the protons of the N-methyl groups according to the formula

$$K = \frac{\Delta\delta\,Hi}{\Delta\delta\,NCH_3}$$

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X-RAY STRUCTURAL INVESTIGATION OF ALKALOIDS

VI. CRYSTAL STRUCTURE OF THE ALKALOID PARFUMINE

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A complete x-ray structural investigation of the alkaloid parfumine has been performed. The lengths of the bonds and the valence angles have the usual values. Benzene rings A and D are planar, B a distorted half-chair $^{C(6)}H_N$, and rings C and E are flattened envelopes, $E_{C(14)}$ and $^{C(19)}E$, respectively.

We have previously determined the crystal structure of the alkaloid sibiricine, which crystallizes in a centrosymmetrical space group [1]. In the present paper we consider the determination of the crystal structure of the related alkaloid parfumine, isolated from Fumaria parviflora in order to confirm the structure proposed previously [2] and to determine the configuration of the spiro center. Parfumine differs from sibiricine by the absence of a hydroxy group in the five-membered ring, and also by the presence of hydroxy and methoxy groups in place of the methylenedioxy group at C(2) and C(3).

The structure of the parfumine molecule is shown in Fig. 1, which also shows the solvate ethanol molecule. The form of the thermal ellipsoids of the carbon atoms of ethanol clearly shows the unorderedness of the ethyl group of this molecule in the crystal. The lengths of the bonds and the valence angles are given in Table 1.

Figure 2 gives a sketch of the parfumine molecule with the torsion angles in the ring. The benzene ring A is somewhat deformed. Thus, the deviations of the atoms of the ring from its mean plane amount to 0.03 Å, and the departure from this plane of the closest atoms of the substituents is −0.07 Å (for C(5), see Table 2, which gives the characteristics of the planes of the fragments of the molecule). The other benzene ring, D, is planar to within 0.01 Å, including the closest atoms of the substituents. The dihedral angle between the planes of benzene rings A and D is 99.6°, i.e., somewhat greater than in the molecules of sibiricine (89.9°) and of other related alkaloids – ochrobirine [3] and ochotensine [4] (about 90°). The six-membered pyridine ring B has a distorted half-chair conformation $^{C(6)}H_N$ in Schwarz's symbols [5], but the nature of the distortion differs from that found in the sibiricine molecule. The five-membered ring C has a flattened envelope conformation $E_{C(14)}$ (the C(14) atom departs from the plane of the C(8) C(17) C(18) C(13) atoms by −0.093 Å), while in the sibiricine molecule this ring has a half-chair conformation.

The difference in the conformations of rings B and C in the parfumine and sibiricine molecules indicates a conformational flexibility of these rings, leading to the realization of different methods of reducing strain in these polycyclic condensed systems.

The other five-membered (dioxolane) ring E also has a flattened envelope conformation $^{C(19)}E$ (as in sibiricine): the C(19) atom departs from the plane of the other atoms of the ring by 0.125 Å.

The nitrogen atom has a pyramidal conformation (sum of the valence angles 334°; the departure of N from the C(6) C(14) C(21) plane amounts to −0.441 Å). All the C–N bond lengths [from 1.45(1) to 1.47(1) Å] are the same and coincide with the standard value for an ordinary C–N bond of 1.472 [6]. The C–C interatomic distances in aromatic rings A and D have a scatter of 1.33(1) to 1.44(1) Å, which exceeds 3σ and is apparently the consequence of the general strain of the skeleton of the molecule or, rather, of the failure to take libration errors into account. All the interatomic distances coincide, within the limits of accuracy, with those found for the sibiricine molecule and are the usual ones for the corresponding types of bonds.

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