CONFORMATIONAL STATES OF QUATERNARY SALTS OF PACHYCARPINE AND APHYLLINE

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The interactions of pachycarpine and aphylline with some alkyl halides have been studied. On the basis of chemical reactions and of PMR, IR, and mass spectrometry it has been established that the main products of the reaction of pachycarpine with methylene iodide and chloride have the A/B-trans and C/D-cis configuration with methano bridges between N_1 and N_{16}. It has been found with the aid of PMR and IR spectra that pachycarpine and aphylline methiodides have the ring configuration A/B-trans and C/D-cis.

Sparteine has been found in nature in two optically active forms and as the racemate [1]. Pachycarpine (D-sparteine), which is found in plants of Central Asia [2], is the main fragment of many oxygen-containing quinolizidine alkaloids, which are constructed of two quinolizidine systems condensed in the 1,3-positions [3, 4].

It has been shown previously that sparteine (pachycarpine) has the C/D-trans conformation in the boat-chair form [5, 6].

The present paper gives the results of a study of the conformational states of pachycarpine, some of its oxygen-containing derivatives, and their quaternary salts.

We have studied the interaction of pachycarpine with methylene iodide and chloride. The reaction with methylene iodide was carried out under the conditions of a modified Galinowsky method [7] in a sealed tube in an atmosphere of nitrogen at 150-180°C. The reaction with methylene chloride was carried out at various temperatures (from 80 to 160°C). The reaction of methylene iodide with pachycarpine formed two substances. One of them, with R_f 0.29, was the main reaction product. It was isolated by treating the mixture with 80% ethanol. We were unable to isolate the second substance, with R_f 0.38, in the individual state, since during purification it was readily converted into the compound with R_f 0.29. The main product with R_f 0.29 formed yellowish crystals with mp 348-350°C, $[\alpha]_D^{25}$ +24.8°. It had the composition $C_{16}H_{28}N_2I_2$. A similar phenomenon was observed in the action of methylene chloride on pachycarpine under the same conditions (160°C). The yield of the main product $C_{16}H_{28}N_2Cl_2$ with R_f 0.27 and mp 286-288°C was 78.2%. When the reaction was performed at low temperatures (80°C), the yield of desired product was 40-50% and it did not increase appreciably on prolonged heating.

On the basis of the results of the experiment, we propose for the compounds obtained with R_f 0.29 and 0.27 formulas (II) and (IIa), the N_1,N_{16}-methanodiiodide (II) and the N_1,N_{16}-methanodichloride (IIa) of pachycarpine (bridge compounds).

The results of the mass-spectrometric analysis of compounds (II) and (IIa) and of the titration of the halides (Volhard method) comfirm their monomolecularity. The mass spectra showed the presence of a molecular ion with m/e 246, $C_{16}H_{26}N_2$, formed by the splitting out of two molecules of halogen derivatives from (II) and (IIa). On this basis it may be concluded that the inner nucleus of the molecules of (II) and (IIa) is a system of the adamantane type [8] where mass-spectrometric fragmentation takes place mainly round the nitrogen in the outer rings (rings A and D), forming the corresponding fragment with m/e 246 (IV).

To elucidate the structure of (II) we recorded PMR spectra (Fig. 1) in which there were two doublets at 5.05 and 5.65 ppm with J_{gem} = 12 Hz. They correspond to the α-axial and

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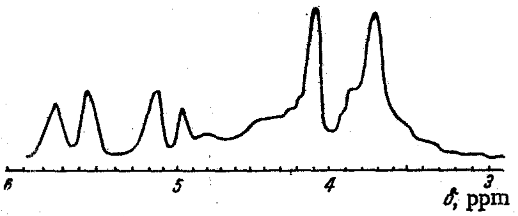
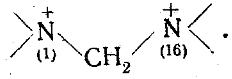
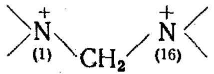
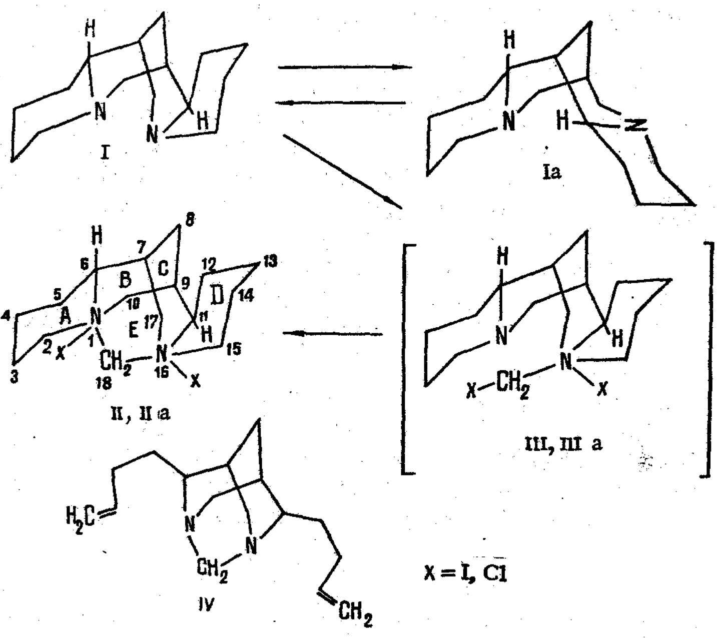


Fig. 1. PMR spectrum of pachycarpine methanodiiodide.

equatorial protons at C_{18} which are fixed between two nitrogen atoms in the following way: . At 3.80 and 4.15 ppm there are signals relating to α-axial and equatorial portions located near a nitrogen atom. The formation of the  type of linkages from the boat-shaped configuration of (Ia) and its N-oxide and methiodide, which have the chair configuration, can apparently be explained by an inversion of the quinolizidine system of sparteine. If configuration (II) is considered with a Dreiding model, it is clear that such compounds can be formed only if both nitrogen atoms N_1 and N_{16} are in the immediate propinquity of one another, i.e., when rings B and C have the chair form. The course of this process can be explained in the following way: the addition of methylene iodide to the cis-quinolizidine moiety of pachycarpine (I) with the formation of the N_{16}-iodomethiodide (III) and its subsequent conversion by ring closure into (II).



Thus, it may be concluded that a dynamic equilibrium exists between these two interconverting conformations of sparteine (I and Ia).

On the basis of the facts given above, we have come to the conclusion that the formula put forward for the methanodiiodide and methanodichloride of pachycarpine does actually correspond to the chair formations (II and IIa).

The configuration of the methiodides of lupinine and epilupinine has been shown previously with the aid of IR and PMR spectra [9, 10].

We have directed attention to the interaction of pachycarpine and aphylline with methyl iodide and also to the conformational states of the corresponding methiodide.

We have isolated the methiodides of (I) and of aphylline (10-oxopachycarpine) by direct methylation in methanol, and also in benzene. The reaction of pachycarpine with methyl iodide forms a mixture of crystalline substances. The main product with Rf 0.29, mp 243-244°C,

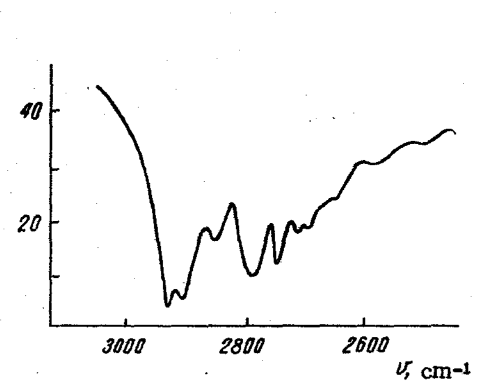


Fig. 2

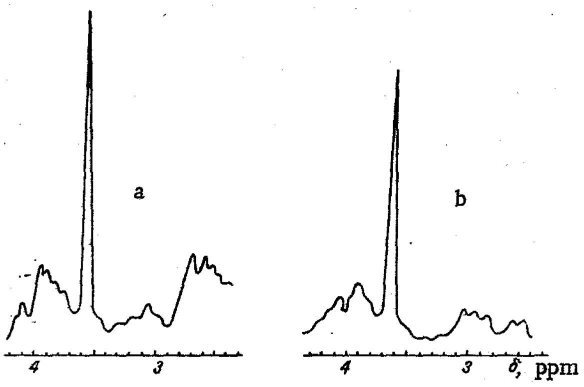


Fig. 3

Fig. 2. IR spectra of pachycarpine methiodide.

Fig. 3. PMR spectra of the methiodides of pachycarpine (a) and of aphylline (b).

$[\alpha]_D^{25}$ +23.8° corresponds to the N_{16}-monomethiodide, which coincides (apart from the specific rotation) with sparteine monomethiodide (α-monomethiodide) with mp 243-244°C, $[\alpha]_D^{25}$ −24.4° isolated previously by Schopf [11].

The second substance, with R_f 0.52, mp 234-235°C, proved to be the pachycarpine monohydriodide that in the literature is called sparteine α'-methiodide [11].

The IR spectrum of pachycarpine monomethiodide (Fig. 2) has bands in the 2800-2650 cm^{-1} region that are characteristic for a trans-quinolizidine, which permits the assumption that the methiodide is formed through the potential N_{16} valence. PMR spectroscopy shows that for pachycarpine monomethiodide the chemical shift of the $N-CH_3$ group is 3.53 ppm, and for aphylline methiodide it is 3.52 ppm (Fig. 3a, b). A comparison of these magnitudes shows that both compounds have the cis configuration of the C/D rings. According to the literature [12, 13], the chemical shift of $>\overset{+}{N}-CH_3$ in a trans-quinolizidine is usually represented by a signal in a higher field than that of the corresponding cis form. It is obvious that the formation of pachycarpine methiodide takes place in two ways: either by direct addition to (I) or as the result of N-inversion taking place after a collision between the $>N-CH_3$ and the $C_{12}-H$ of rings C/D.

Thus, although sparteine has the configuration (Ia) which, in solution, is present in equilibrium with (I), the existence of a mono-N-oxide [14], a monomethiodide, a methanodiiodide, and a methanodichloride shows that these reaction products have form (I). But since rapid configurational changes may take place in the sparteine molecule during the reaction, form (I) may also be present in equilibrium with other labile forms.

EXPERIMENTAL

The IR spectra of the substances were taken on a UR-10 spectrophotometer (KBr tablets) the PMR spectra on an H-60 (Hitachi) spectrometer in heavy water, and the mass spectra on an MKh-1303 instrument at 130°C with an ionizing voltage of 40 V. For chromatography we used type "M" ["slow"] chromatographic paper (Leningrad) and the solvent system butan-1-ol—hydrochloric acid—water (100:13.5:27). The results of the elementary analysis of the compounds corresponded to the calculated figures.

Pachycarpine Methanodiiodide. To 4.68 g (0.012 mole) of pachycarpine was added 16.08 g (0.06 mole) of methylene iodide. The mixture was heated in a sealed tube filled with nitrogen in an autoclave at 170°C (in a special thermostat) for 36 h. After cooling, the mixture was treated with water, the excess of methylene iodide was eliminated, and the aqueous solution was evaporated to dryness. On paper chromatography, three spots were detected with R_f 0.52 (pachycarpine), 0.38 (pachycarpine iodomethiodide, uncyclized), and 0.29 (pachycarpine methanodiiodide, cyclized).

The amorphous precipitate was purified by recrystallization from ethanol—water (4:1). The yield of pachycarpine methanodiiodide was 81.3%, mp 346-348°C, $[\alpha]_D^{27}$ +18.2° (c 1.52; water).

The mass spectrum showed the presence of a fragment of the molecular ion with m/e 246 ($C_{16}H_{26}N_2$) (−2HI).

Pachycarpine Methanodichloride. The reaction between pachycarpine and methylene chloride was carried out at various temperatures (80, 100, 130, and 160°C). Below we give an example of a typical experiment.

To 0.02 g (0.03 mole) of pachycarpine was added 7.65 g (0.09 mole) of methylene chloride. The mixture was heated in a sealed tube filled with nitrogen in an autoclave at 160°C for 30 h. After cooling, the solution was treated with water, the excess of methylene chloride was separated off, and the aqueous layer was evaporated to dryness. Paper chromatography showed three spots with R_f 0.36 (pachycarpine chloromethochloride, uncyclized), 0.27 (pachycarpine methanodichloride, cyclized), and 0.52 (pachycarpine).

Compound (IIa), a white crystalline substance with a yellowish tinge, was purified by recrystallization from absolute ethanol. Yield 17.4 g (78.2%), mp 286-288°C, $[\alpha]_D^{20}$ +21.6° (c 1.7; water).

The mass spectrum contained a fragment of the molecular ion with m/e 246 ($C_{16}H_{26}N_2$) (—2CH1).

Pachycarpine Methiodide. To 2.34 g (0.01 mole) of pachycarpine was added 5.68 g (0.04 mole) of methyl iodide in 20 ml of methanol. The reaction mixture was boiled for 5-6 h. After cooling, the crystals that had deposited were filtered off and recrystallized from ethanol. Pachycarpine methiodide had mp 243-244°C, R_f 0.29, $[\alpha]_D^{25}$ +23.8° (c 1.5; ethanol). Yield 6.5 g (81.10%).

Pachycarpine monohydriodide with R_f 0.44, mp 234-235°C (from water) was isolated from the mother liquor by adsorption chromatography on alumina (acetone—methanol (4:1) system).

Aphylline methiodide was obtained under similar conditions; mp 212-213°C, $[\alpha]_D^{20}$ +15.6° (c 1; ethanol). Yield 78.2%.

SUMMARY

1. The interaction of pachycarpine and aphylline with a number of alkyl halides has been studied.

2. On the basis of chemical reactions and PMR, IR, and mass spectrometry it has been established that pachycarpine methanodiiodide and methanodichloride have the A/B-trans, C/D-cis configuration with bridge links between N_1 and N_{16}.

3. It has been shown by PMR and IR spectroscopy that pachycarpine and aphylline methiodides have the A/B-trans, C/D-cis configuration of the rings.

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