IR SPECTRA AND CONFORMATION OF

2-ACETYLINDOLES

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On the basis of data from the IR spectra of 2-acetylindoles and their pyrrole-ring-substituted derivatives it is concluded that these substances exist in CCl_4 solution primarily in the s-trans conformation.

It has been reported that 2-acylpyrroles exist primarily in the s-trans conformation with respect to the relative position of the double bond of the heteroring and the carbonyl group [1], while equilibrium between the s-cis and s-trans conformers is observed for 2-acylfurans [2]. We attempted to evaluate the conformation of 2-acetylindoles, including N-substituted, pyrrole-ring-C₃-substituted, and side-chain-substituted (i.e., adjacent to the carbonyl group in various positions) compounds, considering that this sort of substitution may lead to disruption of the coplanarity, as is well known for 0,0'-disubstituted benzene rings. Disruption of the coplanarity could occur due to rotation about the bond between the carbonyl group and the pyrrole ring, and additional possibilities for the development of conformational heterogeneity of the molecule caused by rotation about the bond between the carbonyl group. A weak intramolecular hydrogen bond between the carbonyl group and the NH group has been noted in 2-acylpyrroles [1], and it therefore might have been assumed that this sort of hydrogen bonding for our models would lead to stabilization of the A conformation (the s-trans form), but it was extremely risky to draw a conclusion a priori.

We recorded and investigated the IR spectra of a series of 2-acylindoles in the form of CCl_4 solutions, directing special attention to the stretching vibrations of the NH and C=O groups, which are the most sensitive to conformational transformations. The frequencies of the vibrations of the aromatic ring were also taken into account (see Table 1).



A weak absorption band at ~ 3330 cm⁻¹, which apparently corresponds to the overtone of the frequency of the carbonyl group in the conjugated C=C-C=O system, is observed in the spectra of all of the compounds. The characteristic curves of the spectra are presented in Fig. 1. When these spectra are compared, it is seen that the frequency of the vibrations of the NH group in the 2-acylindoles is always 30 cm⁻¹ lower than in the spectrum of indole. Consequently, the intramolecular hydrogen bond between the carbonyl group and the imino group is extremely weak. The fact that the carbonyl frequency in the spectra of N-methyl-substituted compounds (R¹ = CH₃) has practically the same value as in the spectra of substances with an NH group is also evidence for this. We note that the intermolecular interaction of indole with ketones (formation of a charge-transfer complex) leads to a low-frequency shift of the frequency of the NH

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TABLE 1. IR Spectra of 2-Acylindoles

Com- pound	Ŕ1	R²	R3	cm ^{vo <u>H</u>-1}	v _{NH} , cm ⁻¹	$v_{C=0}, cm^{-1}$	$cm^{v_{C}=c}$
I III IV V VI VII IX XI XII	Ind H CH ₃ H CH ₃ H H H H H H CH ₃	lole H H H Cl Cl Cl Cl OCH ₃ OH OH	H CH₃ CH₃ Cl H H Cl H H H	 3506 3493	3493 3462 3461 3452 3462 3451 3463 3463 	$\begin{array}{c} - \\ 1665 \\ 1667 \\ 1655 \\ 1657 \\ 1662 \\ 1682 \\ 1666 \\ 1688 \\ 1667 \\ 1682 \\ 1666 \\ 1666 \\ 1666 \\ 1667 \end{array}$	$\begin{array}{c} 1620\\ 1622\\ 1619\\ 1622\\ 1617\\ 1622\\ 1622\\ 1622\\ 1618\\ 1623\\ 1625\\ 1622\\ 1619\\ \end{array}$

group of 100 cm^{-1} , and a considerably stronger hydrogen bond between the ketone molecule and the phenol molecule [4] lowers the carbonyl frequency by 8-10 cm⁻¹.

The spectra of II-V contain single bands of a C=O group, the frequencies of which are characteristic for alkyl aryl ketones [5]. When a chlorine atom is introduced into the 3-position (VI) the frequency of the C=O group remains practically unchanged as compared with 2-acetylindole (II). The steric effect of the ortho interaction is generally weakly manifested in 2,3-disubstituted indoles in view of the deformation of the five-membered ring, and the conformations of these two substances are apparently identical and correspond to the s-trans form (structures A). In the case of the cis conformation (structure B), the introduction of a chlorine atom, which has a considerable -I effect, should lead to an increase in the carbonyl frequency or to the appearance of a second highfrequency band, as is observed in the spectra of o-haloacetophenones [6]. Quantum-chemical calculations show that considerable negative charge is concentrated in the 3-position of 2-formylindole [7], and this should cause electrostatic repulsion of the unshared pair of electrons of the oxygen atom and destabilization of conformation B. In addition, the weak hydrogen bonding that was discussed above gives a certain gain in energy, although it does not have a decisive effect.

The introduction of a substituent (Cl or CH_3O) into the methyl group of the acyl group leads to splitting of the carbonyl frequency into a doublet (VII-X); this is apparently associated with internal rotation about the $OC-CH_2R^2$ bond and with the existence of a mixture of rotational isomers, in one of which the carbonyl group is disturbed by the effect of the field of the C-Cl or $C-OCH_3$ bond (Fig. 2). This sort of

disturbance leads to depolarization of the carbonyl group and an increase in the frequency of its stretching vibrations. The high-frequency component of the doublet should therefore be assigned to conformation C, while the low-frequency component should be assigned to the conformation with an undisturbed carbonyl group (D). This sort of splitting of the carbonyl frequency is observed in many spectra of α -halo- and α -alkoxycarbonyl compounds (for example, see [8, 9]). In this case, the relative intensities of the components of the doublet reflect the relative percentages of the conformers in the mixture.

The high-frequency component of the doublet of the C=O group in the spectra of VII and VIII is less intense than the low-frequency component. Consequently, these molecules exist primarily in the D conformation. The introduction of a chlorine atom into the pyrrole ring (in the 3-position) leads to redistribution of the intensities of these frequencies in IX; this is evidence in favor of the substantial shift of the $C \rightleftharpoons D$ equilibrium to the left. This can be explained by steric and electrostatic repulsion of the two chlorine atoms in the D conformation. On the other hand, only single bands of the carbonyl group are observed in the spectra of XI and XII; this is determined by the complete shift of the equilibrium to favor the conformation with a C=O...HO intramolecular hydrogen bond, which substantially hinders rotation about the $OC-CH_2R^2$ bond. This conclusion is also confirmed by the fact that the absorption bands of the OH groups for these two substances are shifted to the low-frequency region by more than 100 cm⁻¹ as compared with



Fig. 1. IR spectra of 2acetylindoles in CCl₄ (5 · 10⁻³ M): II) 2-acetylindole; VII) 2-chloroacetylindole; IX) 3chloro-2-chloroacetylindole; X) 2-methoxyacetylindole; XI) 2-hydroxyacetylindole.



Fig. 2. Newman projections of the possible stable conformations of substituted 2-acetylindoles: Ind is the indole residue and $R^2 = Cl$, OCH₃, OH.

the usual value; this is typical for α -hydroxy ketones [10]. Thus, for compounds with a substituent in the side chain we can note cases of facile conversion of the conformers (the existence of a mixture of them) or preferred stabilization of one of them if we are dealing with a conformation that depends on rotation about the OC-CH₂R² bond. The previously drawn conclusions regarding the conformation of the carbonyl group, i.e., regarding the relative orientation of the C=O group and the pyrrole ring, do not change for these systems. The introduction of substituents into the acyl group does not induce changes in the conformation in that portion which is determined by the relative orientation of the aromatic ring and the acyl group. Stability of the s-cis conformation (B) might have been expected for X because of the intramolecular bond between the NH and OCH₃ groups. However, neither a decrease in the NH frequency nor an

increase in the C=O frequency nor conversion of the band of the carbonyl group to a singlet is observed. The spectrum of X is practically the same as the spectrum of VII (Fig. 1). Consequently, even the presence of the rather strong proton-acceptor CH_3O group does not induce the formation of an appreciable amount of the s-cis form.

These conclusions are confirmed by a study of the dipole moments [11]. The experimentally found dipole moments are considerably lower in our structures than the values calculated for the s-cis conformers and are close to (although some of them do exceed) the data for the s-trans conformers. Thus, it might be assumed that the conformation of the investigated acyl indoles is close to trans form A in solutions, but the structure of the molecule is not completely planar due to small rotation (mean statistically) about the C_2 -CO bond, which leads to an increase in the dipole moment. This sort of distortion may be a consequence of solvation.

EXPERIMENTAL

The IR spectra of $5 \cdot 10^{-3}$ M solutions of the compounds in CCl₄ were recorded with a UR-20 spectrometer. The synethesis of acylindoles II, IV, VII [12], V [13], and X-XII [14] has been previously described. The individuality of the substances was monitored in all cases by chromatography on Silufol or in a thin loose layer of Al₂O₃.

<u>1-Methyl-2-acetylindole (III)</u>. A 5.6-g (0.03 mole) sample of anhydrous stannous chloride was added to a suspension of 1.99 g (0.01 mole) of 1-methyl-2-diazoacetylindole [15] in 30 ml of absolute methanol, after which 9.2 ml (0.12 mole) of concentrated HCl was added dropwise. The mixture was stirred at 45-50° for another hour, after which it was cooled and diluted with water. The resulting precipitate was removed by filtration to give 1.26 g (73%) of III with mp 70.5-71° (from benzene-hexane) (mp 71° [16]).

<u>3-Chloro-2-acetylindole (VI)</u>. An 85.5-ml (1.2 mmole) sample of thionyl chloride was added in portions to a solution of 19.5 g (0.1 mole) of 3-chloroindole-2-carboxylic acid in 150 ml of dry benzene, after which the mixture was refluxed for 1 h. The benzene was then removed by vacuum distillation, 50 ml of dry benzene was added to the residue, the mixture was stirred, and the solvent was again removed by distillation. The residue was dissolved in 250 ml of dry ether, and the solution was treated with activated charcoal and filtered. The solution of the acid chloride obtained above was added with stirring at 0-5° to 300 ml of an ether solution of diazomethane (from 45 g of nitrosomethylurea), after which the mixture was stirred at 5-10° for 3 h and allowed to stand at room temperature for 12 h. The substance that separated was removed by filtration to give 16.4 g (75%) of 3-chloro-2-diazoacetylindole with mp 171.5-172° (decomp., from benzene—hexane). IR spectrum in mineral oil: 2100 cm⁻¹ (diazo group). Found, %: C 54.4; H 2.6; N 19.0. C₁₀H₆ClN₃O. Calculated, %: C 54.7; H 2.8; N 19.1. Treatment of 2.19 g (0.01 mole) of the diazo ketone by the method used in the preparation of III gave 1.35 g (70%) of VI with mp 166-167° (from benzene hexane). Found, %: C 62.2; H 4.2; N 7.5. C₁₀H₈ClNO. Calculated, %: C 62.0; H 4.1; N 7.2.

<u>1-Methyl-2-chloroacetylindole (VIII)</u>. Concentrated HCl (3 ml) was added dropwise to a suspension of 0.98 g (5 mmole) of 1-methyl-2-diazoacetylindole in 30 ml of ether, after which the mixture was held at room temperature for 3 h. It was then evaporated to dryness in vacuo, and the residue was diluted with water. The insoluble solid was removed by filtration and washed with water to give 0.8 g (80%) of VIII with mp 124-125° (from benzene-hexane). Found, %: C 63.9; H 5.0; N 6.8. $C_{11}H_{10}CINO$. Calculated, %: C 63.6; H 4.8; N 6.7.

<u>3-Chloro-2-chloroacetylindole (IX)</u>. The method used to prepare VIII was used to obtain this compound [0.88 g (77%)] with mp 198-199° from 1.05 g (5 mmole) of 3-chloro-2-diazoacetylindole. Found, %: C 52.5; H 2.9; N 6.0. C₁₀H₇Cl₂NO. Calculated, %: C 52.6; H 3.1; N 6.1.

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