Reaction of II with Magnesium Amylate. A mixture of 1 g (6.78 mmole) of nitrile II and magnesium amylate (from 0.1 g of magnesium) in 5 ml of amyl alcohol was refluxed for 3 h, after which it was poured into aqueous alcohol (1:1). The resulting precipitate was separated and washed with aqueous alcohol until the filtrate was colorless, and the residue was chromatographed on silica gel with chloroform–ethanol (100:1) to give 0.045 g (4%) of VII with R_f 0.31.

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THREE-DIMENSIONAL STRUCTURE OF 3-ACYLINDOLES

A. N. Kost,* V. I. Minkin, V. A. Budylin,
Yu. V. Kolodyazhnyi, V. V. Druzhinina,
and M. A. Yurovskaya

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On the basis of a comparison of the experimental dipole moments with the calculated values, as well as data from the UV, IR, and PMR spectra, it is shown that 3-acylindoles exist in the form of equilibrium mixtures of the planar S-cis and S-trans conformers with preponderance of the latter.

There are presently various methods for the preparation of 3-acylindoles, and these compounds are often used as starting substances for the synthesis of many indole derivatives. However, clearly insufficient study has been devoted to their three-dimensional structures, whereas they do in a number of cases determine the reactivities of these compounds and the possibility of the realization of certain transformations. With respect to the investigation of the three-dimensional structures of 3-acylindoles, one should mention only the study of some 3-formylindoles by NMR spectroscopy [1], as well as the use of shift reagents [2] for the determination of the configuration of 3-acetyl-1-methylindole.

We have investigated an extensive set of 3-acylindoles by various methods, and in the present paper we present the results of these studies.

IR Spectra

In both the solid state and in solutions [3] the carbonyl group of the investigated ketones absorbs in a region that is anomalous for aromatic ketones (Table 1). Of course, this band is made up of combination vibrations of the nitrogen atom–C_2–C_3 double bond–carbonyl group system. The magnitude of this frequency compels us to assume strong conjugation of the carbonyl group with the aromatic system of indole. This conjugation should be realized most fully in two planar variants of orientation of the carbonyl group (S-cis and S-trans).† Many of the ketones that we investigated (for example, V-VII and X-XIII) in the solid state (in mineral oil) have doublets at 1580-1640 cm^{-1}. The doublet character of the absorption vanishes on passing to solutions (in chloroform and dioxane), but the nonsymmetri-

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*Deceased

†Nomenclature that takes into account the mutual orientation of the carbonyl oxygen atom and the heteroatom is often used in the literature (for example, see [5]). It seems to us that it is more accurate to use the S-cis–S-trans nomenclature, which takes into account the mutual orientation of the double bonds, as was originally used for butadiene systems.

M. V. Lomonosov Moscow State University, Moscow 117234. Scientific-Research Institute of Physical Organic Chemistry, Rostov-on-Don 334006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1647-1652, December, 1982. Original article submitted July 14, 1982.

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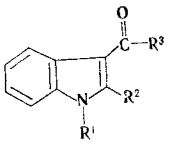
TABLE 1. Spectral Characteristics of 3-Acylindoles



Compound	R^1	R^2	R^3	ν_{CO}, cm^{-1}	Dipole moments, (μ, D)[a]			PMR spectrum, ppm (4-H)
					exptl.	calc.		
						S-cis	S-trans	
I	H	H	H	1630	5,64	2,88	4,69	8,28 7,86[b]
II	CH_3	H	H	1620	5,48[c]	2,90	4,71	8,41 8,03[b]
III	H	CH_3	H	1620	5,94	2,82	4,92	8,32
IV	CH_3	CH_3	H	1648	5,13[c]	2,82	4,92	8,26
V	H	$C(CH_3)_3$	H	1625	5,89	2,82	4,92	8,34
VI	H	H	CH_3	1625	5,22 4,95[c]	2,39	4,88	8,20 7,96[b]
VII	H	CH_3	CH_3	1620	4,40	2,25	5,17	8,09
VIII	CH_3	H	CH_3	1650	—	—	—	8,40
IX	CH_3	CH_3	CH_3	1650	—	—	—	
X	H	$C(CH_3)_3$	CH_3	1635	—	—	—	7,26
XI	H	CH_3	$CH_2C_6H_5$		4,33	2,25	5,17	8,13
XII	H	CH_3	$p\text{-}C_3H_7$	1630	4,36	2,25	5,17	8,05
XIII	H	CH_3	$i\text{-}C_3H_7$	1617	3,95[c]	2,25	5,17	8,00
XIV	CH_3	H	CH_3	1638	—	—	—	8,40 7,93[b]
XV	H	H	C_6H_5	1603	—	—	—	8,57 8,13[b]
XVI	CH_3	H	C_6H_5	1620	—	—	—	8,51 8,06[b]
XVII	H	H	$p\text{-}CH_3C_6H_4$	1600	—	—	—	8,60 8,13[b]
XVIII	H	H	C_2H_5	1610	—	—	—	8,30
XIX	H	CH_3	C_2H_5	1620	—	—	—	8,10
XX	CH_3	CH_3	C_2H_5	1645	—	—	—	8,00
XXI	H	H	$p\text{-}CH_3OC_6H_5$	1608	—	—	—	—
XXII	H	$(CH_2)_3$			5,16	—	4,88	8,30

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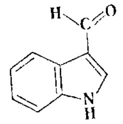
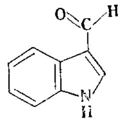
[a] The dipole moments were determined by the Debye dilute-solution method over the concentration range 0.01-0.0005 mole, the polarization at infinite dilution was calculated by the Hedestrand formula, and the atomic polarization was assumed to be 0.05 R agg. The group moments for the vector calculations were taken from [4]. The five-membered indole ring was considered to be a regular pentagon with angles of 108°. The direction of the moment of indole (2.11 D) was obtained from a comparison of it with the moment of 2-methylindole (2.47 D). [b] The PMR spectrum was recorded in trifluoroacetic acid. [c] The dipole moments were determined in benzene.



s-cis



s-trans

cal character of the band remains. Various opinions regarding the nature of the doublet character of this band exist in the literature [6], and there is apparently no basis whatsoever to ascribe it to the existence of two conformers.

Thus on the basis of the data from the IR spectra the existence of one planar structure or an equilibrium between two planar structures may be assumed.

TABLE 2. UV Spectra of 3-Formylindole[a]

Calc. λ_{max}, nm		Exptl. λ_{max}, nm
S-cis	S-trans	
226	227	212
236	243	245
249	251	260

[a] Only the first three bands of π—π* transitions were calculated.

TABLE 3. UV Spectra of 3-Acetylindoles (in methanol)

Compound	λ_{max}, nm (log ε)
VII	216 (4,05), 243 (4,14), 267 (4,03), 302 (4,05)
XII	216 (4,20), 243 (4,07), 268 (3,98), 302 (4,01)
V	212 (4,18), 247 (4,24), 267 (4,07), 318 (4,14)
IX	217 (4,54), 246 (4,22), 266 (4,01), 305 (4,15)
XXII	242 (4,15), 264 (4,08), 296 (3,97)

Quantum-Mechanical Calculations*

To evaluate the energy differences between the two possible conformers of 3-acylindoles we calculated their π-electron energies by the Pariser—Parr—Pople (PPP) method. We found that these energies differ by only 0.04 eV (0.8 kcal/mole) in favor of the S-cis form. The existence of both conformers is possible in the case of such a small difference, and small factors such as nonbonding interactions of the formyl group with the hydrogen atoms in the 2 and 4 positions of the indole ring or solvation of each of the conformers will have a substantial effect on the position of the equilibrium. The energies of overlapping of the spheres of the nonbonding atoms calculated by the method in [8] differ by 1.8 kcal in favor of the S-trans conformer. Thus in the gas phase the S-trans conformer is ∿1 kcal more favorable than the second isomer. If one takes into account the solvation energy from the electron density distribution from the formula

$$E_{solv}^{S\text{-}cis} = -1.9304(1-1/D); \qquad E_{solv}^{S\text{-}trans} = -1.8602(1-1/D),$$

it turns out that in benzene (D = 2.27), for example, the S-cis conformer is solvated to a greater extent, and the gain in energy is ∿0.04 eV (0.8 kcal).

Thus the calculations show that for 3-formylindole in benzene at room temperture the S-trans conformer is ∿0.2 kcal more favorable, and the ratio of the conformers will be ∿60:40 in its favor.

UV Spectra

It would seem that these planar conformations should have different electronic structures, which may show up in the electronic absorption spectra. However, a calculation made for 3-formylindole, for example, shows that the UV spectra of the two conformers differ little (Table 2). The experimental data (Table 3) also demonstrate a similarity in the spectra of all of the 3-acylindoles even in those cases in which steric hindrance causes changes in the PMR sepctra or the dipole moments (see below). Thus the UV spectra are of little use for the solution of the problems of the conformations of 3-acylindoles.

Dipole Moments

The situation is different in the case of the dipole moments of the conformers (Table 1). Their calculated values differ substantially, and in all cases the experimental dipole moment is close to the calculated value for the S-trans conformation. The fact that the experimental value exceeds the calculated value may be due to two reasons. The first reason is the effect of the solvent (dioxane), which on the basis of the dipole moments of 3-acetylindole (VI) can be estimated as being ∿0.3 D. The effect of the solvent is evidently smaller for N-substituted compounds because of the impossibility of the formation of hydrogen bonds. The second reason for the difference between the calculated and experimental dipole moments is associated with the "moment of interaction" that arises in the case of conjugation of the acyl group with the π-electron system of indole. Since the group moments of the substituents from the benzene ring were used in the calculations, the existence of a "moment of interaction" indicates that the indole system is more sensitive to the effect of the acyl group than the benzene ring; this is characteristic for systems with less pronounced aromatic properties.

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*The calculations were made by the Pariser—Parr—Pople (PPP) method. The two-electron coulombic integrals were calculated by the Mataga—Nishimoto method. The principal parameters (ionization potentials and one-electron coulombic integrals) were taken from the literature [7].

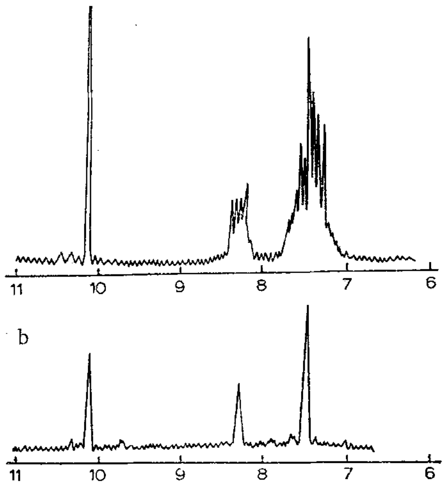
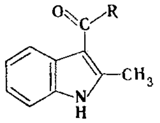


Fig. 1. PMR spectrum: a) 2-methyl-3-formylindole; b) 2-methyl-5-bromo-3-formylindole.

The introduction of a substituent in the position adjacent to the acyl group leads to a change in the dipole moments. The magnitude of this change depends on the mutual steric requirements of the substituent introduced and the acyl group. None of the formyl derivatives experiences a substantial effect on the adjacent group, even of such a bulky group as the tert-butyl group. For acetylindoles, however, the introduction of an adjacent methyl group leads to a substantial decrease in the dipole moment. An increase in the steric hindrance leads to a regular change in the dipole moments:



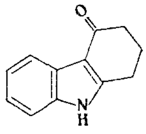
III R=H, $\mu=5{,}94$; VII R=CH_3, $\mu=4{,}40$; XII R=p-C_3H_7, $\mu=4{,}36$; XI R=CH_2Ph, $\mu=4{,}33$; XIII R=*i*-C_3H_7, $\mu=3{,}95$

PMR Spectra

The same tendency can be noted upon examining the PMR spectra of 3-acylindoles. When an acyl group is introduced in the 3 position of the indole ring, the multiplet signal with an intensity of one proton unit, which in the case of 5-bromo-2-methyl-3-formylindole is converted to a broad singlet (Fig. 1), is separated from the overall mass of aromatic protons to weak field. On the basis of this fact one can with confidence assert that this is the signal of the proton in the 4 position of the indole ring. In addition, this multiplet is shifted to strong field in the spectra recorded in trifluoroacetic acid. It has been shown [9] that 3-acylindoles are protonated at the carbonyl oxygen atom. The anisotropy of the carbonyl bond changes upon protonation, and the solvent therefore has such a pronounced effect on the position of the signal of the 4-H proton. The position of the signal of this proton is presented in Table 1. In addition, signals of the aldehyde protons of 3-formylindoles and signals of the protons of the α-carbon atom of 2-unsubstituted indoles are found at weak field (Table 4). The chemical shifts of the signals of the protons in the 2 and 4 positions should depend markedly on the state of the conformational equilibrium, since this value depends not only on the electronic effect but also on the anisotropic effect of the carbonyl bond. Quantum-mechanical calculations of indole itself and 3-acetylindole [10] show that the introduction of an acetyl group in the 3 position of indole increases the positive charge on the α-carbon atom by a factor of almost eight, whereas the electron density in the benzene ring of the molecule (including the electron density in the 4 position) remains virtually unchanged. Thus the shift of the signal of the proton in the 4 position of 3-acylindoles to weak field is due exclusively to the anisotropic effect of the carbonyl function. In fact, in the case of the spectrum of 4-oxo-1,2,3,4-tetrahydrocarbazole (XXII) – a 3-acylindole with a fixed conformation – a characteristic multiplet with an intensity of one proton unit is observed at 8.30 ppm.

TABLE 4. Data from the PMR Spectra of 3-Acylindoles That Are Necessary for the Accurate Assignment of the Signals

Compound	CHO	Chemical shifts, ppm	
		2-H	4-H
I	10,07	8,30	8,28
II	9,93	8,23	8,41
III	10,20	—	8,32
VI	—	8,37	8,20
VIII	—	8,37	8,40



XXII

Conclusion

Thus the data presented above do not contradict the fact that 3-acylindoles exist in the form of equilibrium mixtures of the S-cis and S-trans conformers with preponderance of the latter. The S-trans conformation is preferred for 3-acylindoles with a substituted or unsubstituted nitrogen atom, and the stability of this conformation is explained by the large energy gain in the case of conjugation along the S-trans chain.

The assumption of the existence of a nonplanar structure, as has been postulated for 2-formylthiophene [5], could, of course, be an alternative explanation. If this sort of structure is imagined for the most sterically hindered 3-acylindoles, on the basis of the dipole moments the dihedral angle for ketones VII, XI, and XII (Table 1) should be 70°, whereas in the case of XIII the carbonyl group should be perpendicular to the plane of the aromatic ring. Such structures would probably have anomalous UV and IR spectra, whereas all of these compounds have indicated spectra that differ little from the spectra of compounds in which the dihedral angle is close to zero for one or another reason.

EXPERIMENTAL

The UV spectra of solutions of the compounds in methanol were recorded with a Cary-15 spectrophotometer. The IR spectra of mineral oil suspensions or solutions in chloroform and dioxane were recorded with a UR-20 spectrometer. The PMR spectra of solutions in dimethyl sulfoxide with tetramethylsilane as the internal standard and in trifluoroacetic acid with hexamethyldisiloxane as the external standard were recorded with RS-60 and T-60 spectrometers.

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BISINDOLES.

11.* ELECTROPHILIC SUBSTITUTION REACTIONS IN THE BIS(5-INDOLYL) SULFONE SERIES AND DATA ON THE REACTIVITY INDEXES OF SOME BISINDOLES

Sh. A. Samsoniya, I. Sh. Chikvaidze,
Dzh. A. Kereselidze, and N. N. Suvorov

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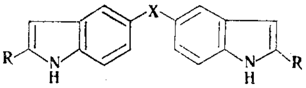
The principles of the electron density distribution in 5,5'-bis-1H-indole, bis(5-indolyl)methane, and bis(5-indolyl) sulfone were determined on the basis of quantum-chemical calculations. Several electrophilic substitution reactions in the bis(5-indolyl) sulfone series were realized.

We have previously reported [2-4] the synthesis of a number of new bisindole systems that each have two pyrrole rings with unsubstituted β positions, viz., 5,5'-bis-1H-indole (I), bis(5-indolyl)methane (II), bis(5-indolyl) sulfones (III), and their 2,2'-bis(ethoxycarbonyl) derivatives (IV-VI):



I–VI

I X=—, R=H; II X=CH_2, R=H; III X=SO_2, R=H; IV X=—, R=$COOC_2H_5$; V X=CH_2, R=$COOC_2H_5$; VI X=SO_2, R=$COOC_2H_5$

In order to theoretically examine the potential reaction centers in the electrophilic substitution reactions of bisindoles I-III we subjected their molecules and, for comparison, the indole molecule to quantum-chemical calculations by the CNDO (complete neglect of differential overlap) MO method [5].† As in the case of 3,5'-bis-1H-indole, a planar structure was selected for 5,5'-bis-1H-indole (I) [7]. A tetrahedral structure of the central bonding atoms was taken into account for bisindoles II and III. To simplify the calculations the indole fragments were situated in the same plane. The angles and bond lengths of the indole ring [8] were used in all cases.

The results of the quantum-chemical calculations are presented in the form of molecular diagrams in Fig. 1 (the overall electron charges are given; the π-electron densities are indicated in parentheses).

It is apparent from the diagrams presented below that the character of the electron density distribution of the indole ring is retained in bisindoles I-III. The highest electron density, both the overall and the π-electron density, is concentrated in the 3 and 3' positions of the bisindoles; consequently, initial attack should be directed to these positions in electrophilic substitution reactions.

We have previously reported [9] some electrophilic substitution reactions of bis(5-indolyl)methane (II). It was shown that in the Vilsmeier, Mannich, and diazo coupling reactions bis(5-indolyl)methane (II) undergoes reaction in the 3 and 3' positions to give disubstitution products, which is in good agreement with the data for its molecular diagram.

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*See [1] for Communication 10.

†The calculations were performed by means of the program of V. G. Maslov [6] with a BÉSM-6 computer in the Institute of Applied Mathematics of Tbilisi State University.

Tbilisi State University, Tbilisi 380028. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1653-1656, December, 1982. Original article submitted February 22, 1982.

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