1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-o-hydroxyphenyl-benzimidazole (IIIe, $C_{27}H_{30}N_2O_2$). A mixture of iminoquinone I (0.31 g, 1 mmole) and salicylaldehyde (1 ml) were refluxed for 2-3 min, cooled, alcohol added (3 ml), and the precipitated solid filtered off and washed with alcohol. Colorless crystals (0.4 g, 95%) were obtained which changed to a bluish color with mp 196-197°C (from 1-propanol). IR Spectrum (in $CHCl_3$): 3500 (OH), 1630 (C=N), 1600 (arom.), 1250 cm^{-1} (t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-furyl) benzimidazole (IIIf, $C_{25}H_{28}N_2O_2$). Iminoquinone I (0.62 g, 2 mmole) and furfural (2 ml) were mixed. In the process, heating caused the mixture to crystallize rapidly to a dark blue mass which then became colorless. The mixture was held for 2 min at 160°C, cooled and 1-propanol (2 ml) added. The precipitate was filtered off to give colorless needles with mp 261-263°C (0.7 g, 90%) (from propanol). IR Spectrum (in vaseline mull): 1610 (C=N), 1600 (arom), 1250 cm^{-1} (t-Bu).

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-thienyl)benzimidazole (IIIg, $C_{25}H_{28}N_2O$). A mixture of iminoquinone I (0.62 g, 2 mmole) and thiophen-2-aldehyde (1 ml) were heated to 190°C, held at this temperature for 2 min, cooled, and 1-propanol (2 ml) added. The precipitate was filtered off and washed with propanol and hexane to give yellowish crystals (0.5 g, 61%) with mp 254-255°C (from toluene). PMR Spectrum ($CDCl_3$): 7.12-6.94 (9H, m, arom); 5.45 (1H, s, OH); 1.35 ppm (18H, s, two t-Bu).

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BROMINATION OF 3-ACYL-2-AMINOINDOLES

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Unlike 3-acylindoles, 3-acyl-2-aminoindoles display high selectivity on being electrophilically attacked in the benzene ring, and are substituted at the 6-position. At the same time, an unco-subsitution of the acyl group takes place (to the greatest extent – the formyl group). Direct bromination of 3-acyl- and 3-cyano-2-aminoindoles provides the 6-bromo- and 6,4-dibromo-2-aminoindoles and their derivatives.

In our preceeding publications dealing with the reactions of 2-aminoindoles with electrophilic agents, it was shown that in 2-aminoindole, present in the aminoindolenine and iminoindoline tautomeric forms, and also in its salts, having the structure of an amidinium cation, substitution proceeds preferentially at the 5-position of the indole ring, while in the 2-aminoindole tautomeric form proper – it generally takes place at the 3-position, even if there is a substituent present at this position, as for example in the case of 3-formyl-2-aminoindole I [1, 2].

In the present work we made a detailed study of the bromination of 3-acyl-2-aminoindole in order to establish the orientation of entry of the substituent into the benzene ring of these compounds. It might be assumed that by creating steric hindrances for the unco-attack at the 3-position (in the reagent or in substrate), it would be possible to effect the substitution into the benzene ring. Nevertheless, treatment of compound I with dioxane dibromide led to the same previously obtained 3-bromo derivative II, although the reaction is considerably slowed down (it does not proceed to completion at 0°C in the course of two days). At the same time, we were able by the action of pyridine dibromide, after the usual processing (alkanization, extraction with chloroform, column chromatography)

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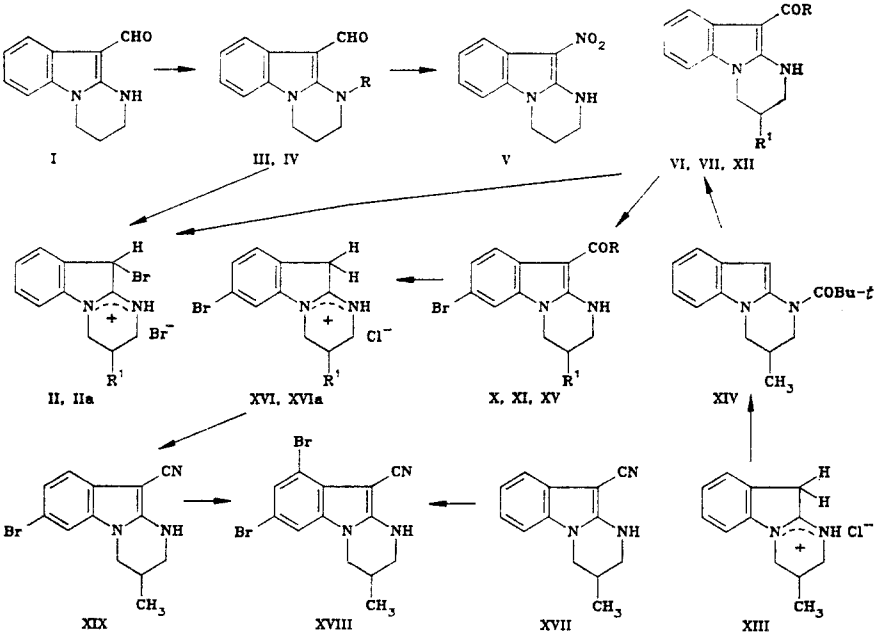
to isolate in a yield of 35-45% the previously unknown N-bromo derivative III (disappearance of the NH signal in the IR and PMR spectra), which in alkaline medium is fairly stable, but in acid medium converts into the known 3-bromo derivative II, as indicated by periodically recording a PMR spectrum of this compound in trifluoroacetic acid. A nitration product IV, analogous to derivative III, was previously obtained by us together with a 3-nitro derivative V [2], the yield of compound IV increasing with decrease in temperature and decrease in the time of nitration.

Compound IV, similarly as III, converts on standing in an inert solvent (more rapidly on heating and acidification) into 3-substituted 2-aminoindoles II, V, which permits considering the N-substituted 2-amino-3-formylindoles III, IV as intermediates in the preparation of the 3-derivatives. To increase the volume of the acyl group at the 3-position, we prepared 3-acetyl- and 3-benzyl-2-aminoindoles VI and VII by the method described in [3]. Their bromination by molecular bromine in methylene chloride, dichloroethane, or chloroform resulted in the formation of mixtures of compounds, in the PMR spectra of which in $CF_3 \cdot COOH$, together with signals of the known 3-bromo derivative II, proton signals of compounds were observed, in which the acyl group was retained. After alkanization (whereby compound II completely resinifies) and subsequent extraction, single reaction products were obtained in both cases, the PMR spectrum of which shows bromine entering the benzene ring (with retention of signals of the acyl substituent and the NH proton). The character of the splitting of the signals (two doublets with ortho- and meta-constants and a doublet of doublets with the same constants), enabled excluding the possibility of substitution in the 4 and 7 positions, but did not make it possible to state definitely, which of the possible 5- or 6-isomers was obtained. The known 5-bromo derivatives VIII, IX were synthesized by rearrangement of the corresponding p-bromophenyl-acetyl pyrazolidines [3, 4]. They differ in their spectral properties from compounds, X, XI obtained by the bromination of indoles VI, VII, thus showing that the structure of 6-bromo derivatives of 2-aminoindole should be ascribed to compounds X, XI.



III R=Br; IV R=NO_2; VI R=CH_3; VII R=Ph; **XII** R=*t*-Bu; II, VI, VII, X, XI, XVI R^1=H; IIa, XII, XV, **XVIa** R^1=CH_3

The regioselective attack at the 6-position distinguishes the 3-acyl-2-aminoindoles from most of the indole derivatives, in which the electrophilic attack is usually nonselective and leads to the formation of mixtures of 6-, 5- and 4-substituted derivatives [5]. It might be assumed that further increase in the size of the acyl radical in the 3-position, for example, the use of the 3-pivaloyl derivative of 2-aminoindole, would make it possible to exclude completely the unco-attack at this position. The corresponding starting compound XII could not be obtained by the usual rearrangement of acylpyrazolidines in the presence of the corresponding Vilsmeier complex [3] (trace amounts of this compound are detected in the reaction mixture by chromatography), but it can be obtained in satisfactory yield

TABLE 1. Conditions and Results of Synthesis of Compounds X, XI, XV, XVIII

Compound	Empirical formula	Reaction temp., °C	Reaction time, h	Column chromatography system (solvent for recrystallization)	mp, °C	PMR spectrum, δ, ppm				Yield, %
						6-H	8-H	9-H	NH (s)	
X	$C_{13}H_{13}BrN_2O$	20	18...20	Benzene-methyl ethyl ketone, 2:1	245...247	7,16 (d, J=2 Hz)	7,25 (dd)	7,33 (d, J=8 Hz)	8,45	50
XI	$C_{18}H_{15}BrN_2O$	20	18...20	Benzene-methyl ethyl ketone, 2:1	197	7,2 (d, J=1,9 Hz)	7,0 (dd)	6,67 (d, J=7 Hz)	8,65	31
XV		0—5	10...15	Benzene-chloroform, 1:1	234	7,2 (d, J=1,8 Hz)	7,15 (dd)	7,48 (d, J=8Hz)	9,1	25
XVIII*	$C_{13}H_{11}BrN_3$	—10—0	0,5...1	— (chloroform)	232	7,24 (d, J=2 Hz)	7,34 (d, J=2 Hz)	—	7,95	62

*The PMR spectrum of the compound was run in DMSO-D_6. IR spectrum: 3330 (NH), 2210 cm^{-1} (CN).

TABLE 2. Characteristics of Compounds VI-IX, XII

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm (methanol)	PMR spectrum, δ, ppm*						Yield, %
			NH	C=O		6-H	7-H	8-H	9-H	NH (s)	RC=O	
VI		197	3330	1630	261, 321	6,95...7,60 (4H, m)				8,41	2,45 (3H, s, CH_3)	54
VII		198...199	3325	1625	259, 340	6,70...7,05 (4H, m)				8,64	7,36...7,72 (5H, m, Ph)	35
VIII	$C_{13}H_{13}BrN_2O$	249...250	—	—	—	6,85 (d, J=7,8 Hz)	7,15 (dd)	—	7,60 (d J=2 Hz)	8,45	2,43 (3H, s, CH_3)	41
IX	$C_{18}H_{15}BrN_2O$	230	—	—	—	6,80 (d, J=8 Hz)	7,08 (dd)	—	6,85 (d J=2Hz)	8,60	7,45...7,65 (5H, m, Ph)	32
XII	$C_{17}H_{22}N_2O$	228...230	3295	1618	—	6,85...7,01 (4H, m)				9,10	1,4 (9H, s, CH_3)	38

*δ (ppm) of pyridine ring protons 2.0-4.3, m

(35-45%) by prolonged boiling of 2-aminoindole hydrochloride XIII with an excess of pivaloyl chloride in pyridine. Thus, first N-pivaloyl-2-aminoindole XIV is formed (at room temperature), which then slowly converts into compound XII, which can be readily detected by chromatography. The formation of the 3,N-dipivaloyl derivative is not observed, unlike the 3,N-diacetyl derivative of aminoindole XIII, which is usually obtained in a high yield.

The steric effect of the pivaloyl group in the derivative XII obtained is illustrated by the impossibility of acetylation and benzoylation of the 2-amino group of this compound by the corresponding acid chlorides, although these reactions are readily realizable for acylaminoindoles I, VI, VIII. Nevertheless, the expected unequivocal bromination of 3-pivaloyl-3-aminoindole XII at the 6-position was not observed: as in the case of acylaminoindoles VI, VII, the bromination was effected both at the 6- and the 3-position, whereby the yield of derivative XV with the retained acyl group was even lower than in the preceding two cases. We believe that this can be explained by the lability of the pivaloyl derivatives XII, XV in an acid medium, which is produced as the result of the bromination. In fact, in contrast to the formyl, acetyl and benzoyl analogs, which are deacylated only after boiling for many hours in 20% HCl, compound XII is rapidly deacylated at room temperature in the presence of CF_3COOH, which is readily detected in the UV spectra (disappearance of a long-wave maximum at 311 nm characteristic for 3-acyl derivatives of 2-aminoindoles and appearance of an intense maximum at 270 nm, characteristic for salts of 2-aminoindoles). It should be noted that the previously unobtainable 6-bromo-2-aminoindoles XVI and XVIa unsubstituted in the pyrrole ring were obtained in high yields by the deacylation of 6-bromo-3-acyl-2-aminoindoles X, XI, XV with 20% HCl.

It was previously found, in the study of electrophilic unco-substitution reactions in the indole series, that the cyano group in the 3-position is more difficultly substituted than the acyl groups [6]. By bromination of 3-cyano-2-aminoindole XVII, previously synthesized in [7], we obtained only the dibromo derivative XVIII (Table 1), in the PMR spectrum of which two doublets were observed in the region of aromatic protons at 7.24 and 7.34 ppm with a spitting constant of 2 Hz (a meta-disposition) which could correspond to the 4,6- and 5,7-dibromo derivatives. The former assignment is indicated by a converging disposition of the aromatic proton signals (the 4-H protons in 3-acyl- and 3-cyano-2-aminoindoles, in general appear separately in the weaker field); a final proof for the structure of compound XVIII was its back-synthesis from 6-bromo-2-aminoindole XVIa. The preferential activation of the $C_{(6)}$ and $C_{(4)}$ atoms of the benzene ring for the electrophilic attack when the amino group is introduced into the 2-position of indole agrees with the boundary orbital density in these compounds, calculated by the Hueckel method [8]. When less than two equivalents of bromine are used, cyanoindole XVII is not completely converted, but a monobromo derivative is not formed.

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer in mineral oil and the UV spectra on a Cary-240 spectrophotometer in alcohol. The PMR spectra were obtained in $CDCl_3$ on BS-497 (100 MHz) and WP-200-200 SY spectrometers, using TMS as internal standards. The chromatographic monitoring of the reaction mixtures was carried out on Silufol plates in a 15:1 chloroform – methanol system. A silica gel 40 × 100 was used for the column chromatography.

10-Acyl-1,2,3,4-tetrahydropyrimido[1,2-a]indoles (VI-IX) were obtained by the method described in [3] (Table 2). The data of the elemental analysis for C and H of the synthesized compounds correspond to the calculated values.

3-Methyl-1-pivaloyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (XIV, $C_{17}H_{22}N_2O$). A 0.148 ml portion (1.2 mmoles) of pivaloyl chloride was added at 0-5°C to a solution of 0.222 g (1 mmole) of 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride in 5 ml of pyridine and the mixture was stirred for 1 h at 20°C. After cooling, 5 ml of water was added, the mixture was evaporated under vacuum, the residue was neutralized with 1 N NaOH to pH 8...9 and extracted with chloroform. The extract was dried over Na_2SO_4, the solvent was evaporated, and the residue was recrystallized from a 1:1 mixture of benzene with hexane. Yield, 0.205 g (78%). IR spectrum: 1650 cm^{-1} (CO).

3-Methyl-10-pivaloyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (XII, $C_{17}H_{22}N_2O$). A solution obtained by mixing at 0-5°C 0.666 g (3 mmoles) of 3-methyl-1,2,3,4-tetrahydropyrimido-[1,2-a]-indole hydrochloride and 2.22 ml (18 mmoles) of pivaloyl chloride in 20 ml of pyridine, was gradually (30 min...1 h) heated to the boiling point, and then the mixture was

boiled for 13-15 h. Pyridine was evaporated under vacuum, the residue was neutralized, with cooling, by 2 N NaOH to pH 8-9, extracted with chloroform, the extract was concentrated and chromatographed on a column, eluting successively with benzene and its mixture with chloroform (1:1). The fractions containing the main compound were evaporated and the residue was recrystallized from acetone (see Table 2).

3-Methyl-7-bromo-10-cyano-1,2,3,4-tetrahydropyrimido[1,2-a]indole (XIX, $C_{13}H_{12}BrN_3$). A 0.182 ml portion (2 mmoles) of $POCl_3$ was added to a solution of 0.302 g (1 mmole) of 3-methyl-7-bromo-1,2,3,4-tetahydropyrimido[1,2-a]indole hydrochloride (XVIa) in 5 ml of DMFA, and the mixture was stirred at room temperature for 24 h. A 2 ml portion of water was added, and after 10 min, the mixture was evaporated to dryness under vacuum. To the solution of the immonium salt obtained in 5 ml of pyridine, 0.14 g (2 mmoles) of hydroxylamine hydrochloride was added, and the mixture was heated cautiously to boiling, and then boiled for 2-3 h. After adding 2 ml of water, the mixture was evaporated under vacuum, extracted from the alkaline medium by chloroform, and chromatographed on a column in a 15:1 chloroform-methanol system. Yield, 0.104 g (36%) of the bromo derivative XIX, mp 222-223°C. IR spectrum 2220 (CN), 3300 cm^{-1} (NH).

7-Bromo-10-acyl- and 7,9-dibromo-10-cyano-1,2,3,4-tetrahydropyrimido[1,2-a]indoles (X, XI, XV, XVIII). A 0.051 ml portion (1 mmole) of bromine (for compound XVII, 2 mmoles of bromine were used) was added to a solution of 0.93 mmole of 10-acyl(cyano)-1,2,3,4-tetrahydropyrimido[1,2-a]indole VI, VII, XII, XIX or XVII 5-10 ml of chloroform or methylene chloride. The mixture was treated with 2 N NaOH, washed with water, and the residue remaining after drying and evaporation was purified by column chromatography or by recrystallization (see Table 1).

1-Bromo-10-formyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (III, $C_{13}H_{13}BrN_2O$). A 0.056 ml portion (1.1 mmole) of bromine was added at 0°C to a solution of 0.2 g (1 mmole) of 10-formyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole in 5 ml of pyridine. After 1 h, the mixture was treated with cold water, made alkaline to pH 8-9, and extracted with chloroform; after the evaporation of the solvent, the residue was eluted from the chromatographic column with benzene. After washing with ether, 0.111 g (40%) of compound III was obtained, mp 138-140°C (dec). IR spectrum: 1668 cm^{-1} (CO). PMR spectrum ($CDCl_3$): 2.20 (2H, m, 3-H), 3.91 (2H, t, 2-H; J = 5.5 Hz), 4.08 (2H, t, 4-H); 7.00-7.25 (3H, m, 6-...8-H), 7.36-7.50 (1H, m, 9-H): 9.1 ppm (1H, s, CHO).

7-Bromo-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride (XVI, $C_{11}H_{11}BrN_2 \cdot HCl$). A solution of 0.3 g (1.02 mmole) of indole X in 5 ml of 20% HCl was heated to boiling. The precipitate that separated out on cooling was filtered off and recrystallized from a 2:1 acetone-water mixture. Yield, 0.215 g (73%), mp 240°C (dec.). PMR spectrum (CF_3COOH): 2.4 (2H, m 3-H), 3.78 (2H, s, 10-H), 4.0 (2H, t, 2-H, J = 5.5 Hz), 4.1-4.2 (2H, m, 4-H), 7.31 (1H, d, 9H, J = 7.6 Hz), 7.35 (1H, d, 6-H, J = 1.5 Hz), 7.5 (1H, d.d, 8-H), 8.68 ppm (1H, s, NH).

3-Methyl-7-bromo-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride (XVIa, $C_{12}H_{13}BrN_2 \cdot HCl$) was prepared in a similar way from 0.2 g (0.57 mmole) of indole XV. Yield, 0.131 g (76%), mp 250°C (dec.), PMR spectrum (CF_3COOH): 1.45 (3H, d, 3-CH_3), 2.60-2.75 (1H, m, 3-H), 3.75-4.70 (4H, m, 2.4-H), 3.8 (2H, s, 10-H), 7.35 (1H, d, 9-H, J = 7.8 Hz), 7.4 d (1H, d, 6-H, J = 1.5 Hz), 7.55 (1H, d.d, 8-H), 8.75 ppm (1H, s, NH).

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