CYCLIZATION OF 3-ARYL-2-ACYLAMINOINDOLES TO BENZO[c]-α-CARBOLINES

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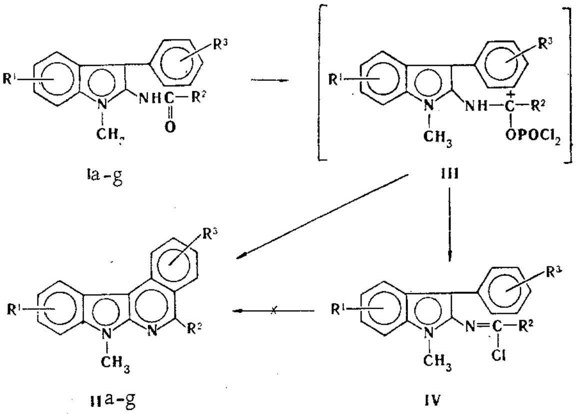
3-Aryl-2-acylaminoindoles form a new heterocyclic system – benzo[c]-α-carbolines – under the conditions of the Bischler–Napieralski reaction.

Cyclization of acylamides under the conditions of the Bischler–Napieralski reaction has been previously used for the preparation of β-, γ-, and o-benzocarbolines [1, 2]. The development of a convenient method for the synthesis of 3-aryl-2-aminoindoles [3] with their subsequent acylation makes it possible to obtain 3-aryl-2-acylaminoindoles (I) (see Table 1) in good yields; the latter are cyclized to benzo[c]-α-carbolines (II) (see Table 2) under the conditions of the Bischler–Napieralski reaction.



Acylation of the 2-aminoindole molecule, which has high nucleophilicity, gives rise to several difficulties. Thus acetylation of 1-methyl-3-phenyl-2-aminoindole hydrochloride with acetic anhydride in triethylamine at room temperature gave, in 68% yield, 1-methyl-3-phenyl-2-acetamidoindole (If) containing a small amount of the diacetyl derivative, which was detected chromatographically and is easily separated. The UV spectrum of Ia has indole character: λ_{max}, nm (log ε): 229 (4.48) and 288 (4.14). Characteristic absorption bands are observed in the IR spectrum at 3200 (NH) and 1660 cm^{-1} (amide C=O). The PMR spectrum (in CF_3COOH) contains singlets of methyl groups at 2.23 (3H, CH_3CO) and 3.68 (3H, NCH_3) and a singlet of a β proton at 6.05 ppm (1H). The spectrum of the compound in CCl_4 retains the singlets of two methyl groups but does not contain the signal of a β proton. Thus even the 2-acetamidoindole of this structure is protonated under the influence of the solvent (CF_3COOH), in the 3 position of the indole ring.

In an attempt to acetylate other 3-aryl-2-aminoindoles under the same conditions we were unable to isolate the individual monoacetyl derivatives. The mixtures of mono- and diacetyl derivatives that we obtained were difficult to separate.

Better results were obtained in the case of Schotten–Baumann benzoylation, which made it possible to obtain the monobenzoyl derivative (see Table 1) containing a small amount of the dibenzoyl derivative, which was easily separated by chromatography with a column filled with Al_2O_3. Thus a mixture of two substances with R_f 0.5 and 0.15 [thin-layer chromatography (TLC), Al_2O_3, benzene–petroleum ether (1 : 1)] was obtained from 1-methyl-3-phenyl-5-bromo-2-aminoindole. A small amount of an oily substance with R_f 0.5, which apparently

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TABLE 1. 1-Methyl-3-aryl-2-acylaminoindoles (Ia-g)

Compound	R¹	R²	R³	mp, °C*	Empirical formula	Found, %		Calc., %		IR spectrum, cm⁻¹		Yield, %
						C	H	C	H	NH	C=O	
Ia	H	C_6H_5	2,4-$(CH_3)_2$	218—219	$C_{24}H_{22}N_2O$	80,8	6,4	81,0	6,2	3250	1660	74
Ib	H	C_6H_5	4-OCH_3	249—251	$C_{23}H_{20}N_2O_2$	77,2	5,4	77,4	5,6	3220	1650	51
Ic	H	C_6H_5	4-Br	254—255	$C_{22}H_{17}BrN_2O$	64,9	4,3	65,1	4,2	3205	1650	75
Id	H	C_6H_5	4-NO_2	244—245	$C_{22}H_{17}N_3O_3$	71,2	5,2	71,1	5,0	3200	1645	60
Ie	H	C_6H_5	H	233—234	$C_{22}H_{18}N_2O$	80,8	5,7	80,9	5,7	3250	1650	70
If	H	CH_3	H	175—176	$C_{17}H_{16}N_2O$	77,2	6,3	77,2	6,1	3210	1660	68
Ig	5-Br	C_6H_5	H	231—232	$C_{22}H_{17}BrN_2O$	65,6	4,5	65,1	4,2	3250	1657	55

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*Compound Ia was purified by crystallization from hexane—CCl_4 (1 : 2), Ib,e,g were purified by crystallization from ethyl acetate, Ic was purified by crystallization from chloroform, Id was purified by crystallization from ethyl acetate—hexane (1 : 1), and If was purified by crystallization from aqueous ethanol.

TABLE 2. Benzo[c]-α-carbolines (IIa-g)

Compound	R¹	R²	R³	mp, °C*	Empirical formula	Found, %		Calc., %		UV spectrum, λ_{max}, nm (log ε)	Yield, %
						C	H	C	H		
IIa	H	C_6H_5	1,3-$(CH_3)_2$	186—187	$C_{24}H_{20}N_2$	86,1	6,2	85,7	5,9	268 (4,64); 345 (4,15); 407 (3,93)	91
IIb	H	C_6H_5	3-OCH_3	168—169	$C_{23}H_{18}N_2O$	81,3	5,8	81,5	5,3	250 (4,60); 278 (4,61); 345 (4,18); 417 (3,98)	50
IIc	H	C_6H_5	3-Br	213—214	$C_{22}H_{15}BrN_2$	68,1	4,3	68,2	4,0	248 (4,46); 282 (4,55); 351 (4,10); 390 (3,63); 408 (3,62)	14
IId	H	C_6H_5	3-NO_2	300—301	$C_{22}H_{15}N_3O_2$	(mass spectrally) 353		353		250 (4,53); 278 (4,14); 344 (4,56); 400 (4,12)	16
IIe	H	C_6H_5	H	190—191	$C_{22}H_{16}N_2$	85,9	5,3	85,7	5,2	251 (4,62); 271 (4,63); 380 (4,00); 397 (3,98)	32
IIf	H	CH_3	H	137—138	$C_{17}H_{14}N_2$	(mass spectrally) 246		246		227 (4,40); 247 (4,38); 270 (4,48); 335 (3,89); 337 (3,63); 390 (3,62)	34
IIg	10-Br	C_6H_5	H	206—207	$C_{22}H_{15}{}^{79}BrN_2$ $C_{22}H_{15}{}^{81}BrN_2$	(mass spectrally) 386 388		386 388		277 (4,55); 3,50 (4,21); 402 (3,68)	31

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*The compounds were purified by crystallization: IIa from heptane, IIb from petroleum ether, IIc, d, g from ethanol—benzene (1 : 10), and IIe from ethanol. Compounds IIf, g were purified by vacuum sublimation. The UV spectra were obtained from solutions: IIa, b, e in ethanol, IIc, d, g in chloroform, and IIf in methanol.

has the structure of an N-N-dibenzoyl derivative (absorption of an NH group is absent in its IR spectrum, but the spectrum contains intense bands at 1778 and 1712 cm^{-1}, which are characteristic for diacylamines), was obtained by column chromatography. The principal reaction product was 1-methyl-2-benzamido-3-phenyl-5-bromoindole (Ig). The ease of formation of diacyl derivatives of 2-aminoindoles has been previously noted [3]. The ability of some mono- and diacylamines to give difficult-to-separate mixtures is also known [4].

The cyclization of 3-aryl-2-acylaminoindoles I to benzo[c]-α-carbolines II proceeds well in an inert solvent (optimally in toluene) by heating with the acidic reagents that are usually employed in the Bischler-Napieralski reaction [$POCl_3$, P_2O_5, PCl_3, PBr_3, polyphosphoric acid (PPA)]; we most often used phosphorus oxychloride (in a fivefold to tenfold excess).

The disappearance of the spot of the starting substance (R_f 0.15) and the appearance of a spot with R_f 0.9 (fluorescence in UV light) were observed chromatographically [Al_2O_3, in a benzene–petroleum ether system (1 : 1)] when 1-methyl-3-phenyl-2-benzamidoindole (Ie) was heated in toluene with a tenfold excess of phosphorus oxychloride for 6 h. The following bands [λ_{max}, nm (log ε)] were observed in the UV spectrum: 251 (4.62), 271 (4.63), 345 (4.26), 380 (4.00), 397 (3.98); this spectrum is analogous to the spectra of similar condensed structures [5]. A singlet of protons of an NCH_3 group (3H, 4.01 ppm) and a multiplet of aromatic protons (13H, 7.43-8.19 ppm) are observed in the PMR spectrum (in CF_3COOH). The molecular ion peak, $M^{+\cdot}$ 308 (which coincides with the value calculated for $C_{22}H_{16}N_2$), is the maximum peak in the mass spectrum of this compound. The second most intense peak, $M^+ - 1$ (307)*, is characteristic for fragmentation of an isoquinoline structure. The presence in the mass spectrum of doubly charged ions at 154 and 153.5 and the absence of other fragment ions also confirm the 7-methyl-5-phenylbenzo[c]-α-carboline structure (IIe).

1-Methyl-3-aryl-2-acylaminoindoles with donor substituents in the 3 position of the aryl ring (see Table 2) are cyclized in 1-2 h to give products in good yields (50-91%). The use of excess condensing agent as the solvent considerably shortens the reaction time, but more pronounced resinification is observed in this case. Compounds Ic, d, which have strong electron-acceptor groups (Br, NO_2) in the same ring, are cyclized only on prolonged refluxing (~24 h) and give the products in very low yields (14-16%). This substituent effect is in good agreement with the assumption of electrophilic attack on the aromatic ring by the carbonium ion of the acylamide fragment, as is well known for the Bischler–Napieralski reaction [5]. In the case of passivation of the 3-phenyl ring to electrophilic attack by electron-acceptor substituents, cation III may undergo other transformations; in particular, it may form imidoyl chloride IV, which is less capable of electrophilic attack of the aromatic ring. When the reaction mixture is treated with aqueous potassium carbonate solution, both chloride IV and intermediate III should be converted to the starting compound. This is evidently the reason for the fact that the starting compound is partially recovered along with the product even on prolonged heating of Ic-g with phosphorus oxychloride without a solvent.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with Cary and Unicam SP 800 spectrophotometers. The IR spectra of mineral oil suspensions of the compounds were recorded with IKS-22 and UR-20 spectrometers. The PMR spectra were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were obtained with an MKh-1303 spectrometer at an ionizing-electron energy of 50 eV.

1-Methyl-3-(2,4-dimethylphenyl)-2-benzamidoindole (Ia). A 0.3-g (1.5 mmole) sample of 1-methyl-3-(2,4-dimethylphenyl)-2-aminoindole hydrochloride was added to 50 ml of a 10% aqueous solution of sodium hydroxide, after which 7 ml of benzoyl chloride was added, and the mixture was shaken vigorously with periodic cooling with cold water until the odor of benzoyl chloride vanished. The reaction products were extracted with chloroform, the solvent was evaporated, and the residue was separated with a chromatographic column filled with Al_2O_3 with successive elution with petroleum ether, benzene, and benzene–chloroform to give a small amount of the dibenzoyl derivative (R_f 0.5) and 0.28 g (74%) of 1-methyl-3-(2,4-dimethylphenyl)-2-benzamidoindole (R_f 0.15). PMR spectrum (CCl_4) δ, ppm: 3.97 (s, 3H, NCH_3); 2.50, 2.73 (2s, 6H, 2,4-di-$CH_3C_6H_3$); 7.20-8.4 (m, 12H). Compounds Ib-g were similarly obtained (see Table 1).

1,3,7-Trimethyl-5-phenylbenzo[c]-α-carboline (IIa). A 0.11-g (0.32 mmole) sample of Ia was refluxed for 2 h in 15 ml of absolute toluene containing 2 ml of phosphorus oxychloride, after which the solvent and the excess phosphorus oxychloride were vacuum evaporated, and the residue was treated with an aqueous solution

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*Here and subsequently, the m/e values are presented.

of potassium carbonate and extracted with ether. The ether was removed by evaporation, and the residue was chromatographed with a column filled with Al_2O_3.

Compounds IIb-g were similarly obtained (see Table 2).

5,7-Dimethylbenzo[c]-α-carboline (IIf). A 0.09-g (3 mmole) sample of If was refluxed for 4 h with 2 ml of phosphorus oxychloride, after which the excess phosphorus oxychloride was removed by distillation, and the residue was treated with 10% aqueous potassium carbonate solution and extracted with ether. The ether was evaporated, and 0.025 g (34%) of IIf was isolated preparatively in a thick layer of Al_2O_3 [benzene–methanol (35 : 1)]. PMR spectrum, δ, ppm: 3.15 (s, 3H, 5-CH_3), 3.93 (s, 3H, 7-CH_3), and 7.48 (m, 8H, aromatic). The mass spectrum contained an $M^{+\cdot}$ peak at 246 (calculated value 246).

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3-(INDOLYLAMINO)VINYL KETONES

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The reaction of 5- and 6-aminoindoles with 1,3-diketones leads to 3-(indolylamino)vinyl ketones, which have an enamino ketone structure. A study of the mass-spectral fragmentation of the enamino ketones makes it possible to unambiguously determine the direction of the reaction and also to distinguish and identify isomeric pairs.

Aromatic amines react with 1,3-dicarbonyl compounds to give 3-(arylamino)vinyl ketones (arylamino crotonates in the case of acetoacetic ester) [1], which, for a series of models, are converted to the corresponding ketimines. The ketimine form was even found to be the preferred form in the case of the products of condensation of p-phenylenediamines having an electron-acceptor group in the ring with acetoacetic ester [2]. The solution of the problem of the structure of substances of this sort in solution frequently requires a precise study of the PMR spectra (for example, see [1]), and in the case of the solid state this can be accomplished by means of the mass spectra [3]. In a number of heteroaromatic amines the problem is complicated by the fact that for electron-surplus compounds (for example, for 2-aminoindoles [4]) condensation with 1,3-dicarbonyl compounds generally may occur with primary attack on the adjacent carbon atom rather than on the amino group, and, consequently, the necessary compounds generally are not formed in this reaction. Moreover, the overall reactivities of heteroaromatic amines depend substantially on the position of the amino group in the aromatic ring. They cannot always be predicted, since, for example, for indoles, transmission of the effect of substituents through the aromatic systems is not subject to simple principles [5].

In connection with the above, we made a study of the reaction of 5- and 6-aminoindoles (Ia and Ib) with 1,3-diketones.

As in the condensation with aniline [6], the reaction with acetylacetone proceeds considerably more readily than in the case of dibenzoylmethane, the electrophilicity of the carbonyl atoms of which is considerably lower. The PMR spectra of IIa-f [in dimethyl sulfoxide (DMSO)–acetone] contain signals of protons of vinyl and imino

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