RING – CHAIN TRANSFORMATIONS WITH PARTICIPATION OF THE C=N GROUP

II.* 2-SUBSTITUTED 3-ALKYLAMINO- AND 3-ARYLAMINO-3-PHENYLISOINDOLINONES

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UDC 547.756:543.422.4

It was found that, depending on the structure of substituents R^1 and R^2, the nucleophilic agent in the reaction of 2-R^1-3-chloro-3-phenylisoindolinones II with primary amines (R^2NH_2) and diethylamine primarily attacks the primary or tertiary carbon atom of the isoindolinone (II) molecule to give 2-R^1-3-amino-3-phenylisoindolinones (III), substituted imines of 2-benzoylbenzamides (IV), and their cyclization products – 2-R^2-3-amino-3-phenylisoindolinones (V). The structures of the synthesized 2-substituted 3-alkylamino- and 3-arylamino-3-phenylisoindolinones were established by IR spectroscopy and acid hydrolysis to 2-substituted 3-hydroxy-3-phenylisoindolinones.

Monosubstituted (at the nitrogen atom) 2-acylbenzamides exist predominantly in the ring form of 2-R^1-3-hydroxy-3-aryl (or alkyl)isoindolinones (I) [1-7]. The presence of a tautomeric equilibrium that is markedly shifted to favor ring form V was recently assumed [8] in the case of 2-methyl(or phenyl)-3-amino-3-phenylisoindolinones (IV⇌V, R^1 = H, R^2 = CH_3, C_6H_5). In order to investigate such ring–chain transformations, in which the ring form arises as a result of intramolecular nucleophilic addition of the amide group N–H to the C=N bond, in the present research we studied the reaction of 2-R^1-3-chloro-3-phenylisoindolinones (IIa-e) with amines. The elucidation of the relative stability of forms IV and V and the investigation of the character of their interconversions seem of interest.

Regardless of whether the reaction of IIa-e with a nucleophilic agent occurs via an S_N1 mechanism (with the formation of intermediate cation of II [1]) or via an S_N2 mechanism, the attack may proceed in two directions – at $C_{(1)}$ or at $C_{(3)}$ to give III or IV. Primary arylamines, which are weak nucleophilic agents, attack IIa-e exclusively at $C_{(3)}$ to give 2-R^1-3-arylamino-3-phenylisoindolinones (IIId,h-k,p-r,t, Table 1). The direction of attack by more nucleophilic primary alkylamines depends on the character of the substituent (R^1) attached to the nitrogen atom in the II molecule. If R^1 = alkyl (n-propyl, isopropyl), attack proceeds primarily at $C_{(3)}$ and products IIIa-c,e-g (Table 1) are formed. Aryl groups attached to the nitrogen atom in IIc-e decrease the p-π conjugation of the electrons of the nitrogen atom and the carbonyl group, as a result of which the electrophilicity of the primary carbon atom increases. Anils of 2-benzoyl-N-alkylbenzamides (IVa-d, Table 2) are formed by the action of alkylamines on IIc. In the reactions of IIc with isopropyl- and tert-butylamines, 2-R^1-3-amino-3-phenylisoindolinones (IIIn,o) were isolated in addition to IVb, while, in the reaction with n-propylamine, in addition to IVa, a small amount of its isomerization product V (IIId) was isolated. Anils IVa-d are cyclized to 2-alkyl-3-phenylamino-3-phenylisoindolinones V (IIId, h,*l*,m) under base catalysis conditions (refluxing in ethanol in the presence of triethylamine). An increase in the polarity of the C=N bond, i.e., the presence of electron-acceptor substituents (R^1) attached to the nitrogen atom of the C=N bond, promotes the isomerization IV → V. For this reason, IV could not be isolated from the reaction of isopropylamine with IId and IIe, isomerization occurs in the reaction mixture

* See [1] for communication I.

Riga Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 762-766, June, 1973. Original article submitted March 3, 1972.

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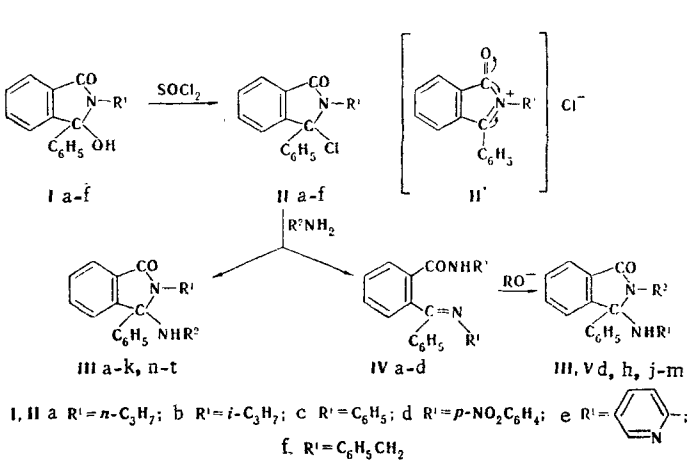
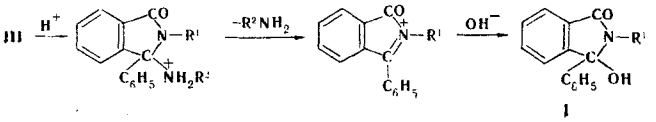


(even when the reactions are carried out in benzene solution), and V (IIIj,k) are formed. Compound IIIk is formed as a mixture with IIIs. All of the mixtures of reaction products were separated by crystallization.

In order to establish the structures of the synthesized 2-substituted 3-alkyl(or aryl)amino-3-phenylisoindolinones IIIa-t, we hydrolyzed them under mild conditions according to the following scheme:



The resulting 2-R^1-3-hydroxy-3-phenylisoindolinones (I) were identified by determination of the melting points of mixtures with known samples [1, 3]. The structures of IIId,h,j,k were also confirmed as a result of their production by two different paths (II→III and II→IV→V), when, thanks to the appropriate selection of R^1 and R^2, the final products (III and V) are identical.

The effect of the character of R^1 in II on the direction of attack of the nucleophilic agent is also manifested in the reactions of IIb,c with diethylamine, in which 2-isopropyl-3-diethylamino-3-phenylisoindolinone (IIIu, Table 1) and the anil of 2-benzoyl-N,N-diethylbenzamide (IVe, Table 2), respectively, are formed.

The intense band of the C=O vibrations of an isoindolinone at 1688-1711 cm^{-1}, which is similar in frequency and integral intensity to the C=O band in the IR spectra of 2-substituted 3-hydroxy-3-phenylisoindolinones [1, 3-7], is observed in the IR spectra of dioxane solutions of IIIa-u (Table 1). In the crystalline state, the $\nu_{C=O}$ frequency is lowered as compared with that in dioxane solution, and in some cases the band is split; this is a consequence of the formation of C=O...H−N intermolecular hydrogen bonds in the crystal lattice. In the IR spectra of anils of 2-benzoyl-N-alkylbenzamides (IVa-d), $\nu_{C=N}$ and amide I and amide II bands appear distinctly in the region of the stretching vibrations of double bonds. The $\nu_{C=N}$ and amide I bands overlap in the spectrum of diethylamide IVe.

The UV spectra of the anils of 2-benzoyl-N-alkyl(or N,N-diethyl)benzamides (IVa-e) contain an absorption band at 324-326 nm, which is characteristic for the Ar—N=C—C=C—C=O conjugated system in the spectrum of the anil of 2-carbomethoxybenzophenone [1]. When solutions of IVa,d in ethanol are stored at room temperature for days, there is a gradual decrease in intensity and disappearance of this band. This is explained by the isomerization IV→V, which is considerably accelerated after the addition of a base (triethylamine) to the ethanol solution. An increase in the steric volume of R^2 in IV hinders isomerization IV→V: N-benzylamide IVd in ethanol solution at room temperature is isomerized more slowly than N-(n-propyl)-amide IVa, while N-isopropyl- and N-tert-butyl)amides IVb,c are stable under these conditions, and their isomerization can be accomplished only by refluxing ethanol solutions containing triethylamine.

All of the synthesized III and IV are stable in dioxane solution at room temperature, and, within the limits of the sensitivity of the IR spectroscopic method, tautomeric equilibrium IV⇌V is not observed when solutions of them are stored for days.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in paraffin oil and hexachlorobutadiene and solutions in dioxane ($c = 5 \cdot 10^{-2}$ M, $l = 0.011$ cm) were recorded with an IKS-14A spectrometer. The integral inten-

TABLE 1. 2-Substituted 3-Alkylamino- and 3-Arylamino-3-phenylisoindolinones (IIIa-u)

Compound	R^1	R^2	mp, °C	Empirical formula	N, % found	N, % calc.	IR spectra, ν, cm^{-1} [a] solids $\nu_{C=O}$	solids ν_{N-H}	solutions in dioxane $\nu_{C=O}$	solutions in dioxane ε	Yield, % II→III	Yield, % II→IV→V
IIIa	n-C_3H_7	i-C_3H_7	130—131 [b]	$C_{20}H_{24}N_2O$	9,3	9,1	1679	3316	1698	915	39	
b	n-C_3H_7	t-C_4H_9	121—123 [b]	$C_{21}H_{26}N_2O$	8,6	8,7	1679	3319	1699	960	54	
c	n-C_3H_7	$C_6H_5CH_2$	137—138 [c]	$C_{24}H_{24}N_2O$	7,9	7,9	1681	3275	1702	830	30	
d	n-C_3H_7	C_6H_5	179—180 [b]	$C_{23}H_{22}N_2O$	8,1	8,2	1675	3298	1706	800	50	80 [d]
e	i-C_3H_7	n-C_3H_7	120—121 [e]	$C_{20}H_{24}N_2O$	9,1	9,1	1676	3313	1697	955	26	
f	i-C_3H_7	t-C_4H_9	146—149 [e]	$C_{21}H_{26}N_2O$	8,7	8,7	1671	3342	1688	970	43	
g	i-C_3H_7	$C_6H_5CH_2$	147—148 [b]	$C_{24}H_{24}N_2O$	7,7	7,9	1666	3275	1696	960	41	
h	i-C_3H_7	C_6H_5	193—194 [b]	$C_{23}H_{22}N_2O$	8,0	8,2	1678sh, 1671	3301	1700	830	53	53 [d]
i	i-C_3H_7	p-$CH_3OC_6H_4$	163—164 [b]	$C_{24}H_{24}N_2O_2$	7,7	7,5	1682sh, 1671	3308	1696	1025	43	
j	i-C_3H_7	p-$NO_2C_6H_4$	225—227 [b]	$C_{23}H_{21}N_3O_3$	10,8	10,8	1702sh 1680	3392	1701	845	29	20
k	i-C_3H_7	2-Pyridyl	189—190 [b]	$C_{22}H_{21}N_3O$	12,4	12,2	1683sh, 1670	3248	1699	825	59	14
l	t-C_4H_9	C_6H_5	198—199 [e]	$C_{24}H_{24}N_2O$	7,9	7,9	1673	3356	1697	960		50 [d]
m	$C_6H_5CH_2$	C_6H_5	163—164 [b]	$C_{27}H_{22}N_2O$	7,2	7,2	1684	3322	1711	770		81 [d]
n	C_6H_5	i-C_3H_7	172—173 [b]	$C_{23}H_{22}N_2O$	7,8	8,2	1678	3363	1706	690	22	
o	C_6H_5	t-C_4H_9	162—163 [b]	$C_{24}H_{24}N_2O$	7,6	7,9	1691	3351	1705	635	27	
p	C_6H_5	C_6H_5	199—200 [b]	$C_{26}H_{20}N_2O$	7,3	7,4	1684	3412 3349	1707	775	50	
q	C_6H_5	p-$CH_3OC_6H_4$	169—170 [b]	$C_{27}H_{22}N_2O_2$	6,6	6,9	1679	3337	1705	675	44	
r	C_6H_5	p-$NO_2C_6H_4$	243—245 [f]	$C_{26}H_{19}N_3O_3$	10,1	10,0	1707, 1690	3378 3338			63	
s	2-Pyridyl	i-C_3H_7	152—153 [g]	$C_{22}H_{21}N_3O$	12,3	12,2	1703	3337 3277	1704	715	44	
t	2-Pyridyl	C_6H_5	209—210 [f]	$C_{25}H_{19}N_3O$	11,3	11,1	1705	3267	1711		66	
u			122—123 [c]	$C_{21}H_{26}N_2O$	8,7	8,7	1692	—	1698	955	31	

[a] The abbreviation "sh" stands for shoulder. The integral intensities of the C=O band in dioxane solution in practical units of measurement (10^4 liter · $mole^{-1}$ · cm^{-2}, ln) were determined for some of the compounds: IIIf 4.9, IIIh 4.8, IIIi 4.8, IIIj 4.6, IIIp 4.4. [b] From ethanol. [c] From 70% ethanol. [d] This is the yield in the isomerization reaction IV → V. [e] From acetic acid; the substance was slightly soluble in dioxane. [g] From cyclohexane.

TABLE 2. Anils of 2-Benzoyl-N-alkyl(or N,N-diethyl)benzamides (IVa-e, $R^1 = C_6H_5$)

Compound	R^2	mp, °C	Empirical formula	N, % found	N, % calc.	IR spectra in dioxane, ν, cm^{-1}: C=O (amide I) ν	C=O (amide I) ε	C=N ν	C=N ε	N–H (amide II) δ	N–H (amide II) ε	UV spectra[a] λ, nm	UV spectra[a] $\varepsilon \cdot 10^{-3}$	Yield, %
IVa	n-C_3H_7	124—125[b]	$C_{23}H_{22}N_2O$	8,3	8,2	1668	530	1627	215	1533	300	324	3,2	29
b	i-C_3H_7	157—158[c]	$C_{23}H_{22}N_2O$	8,4	8,2	1666	560	1629	230	1527	290	324	2,9	36
c	t-C_4H_9	142—143[c]	$C_{24}H_{24}N_2O$	7,9	7,9	1669	560	1630	200	1528	290	326	3,3	7
d	$C_6H_5CH_2$	135—136[d]	$C_{27}H_{22}N_2O$	7,3	7,2	1671	515	1626	200	1532	280	324	3,3	27
e		115—116[c]	$C_{24}H_{24}N_2O$	7,9	7,9	1629	800	1629	800	—	—	326	2,3	35

[a] The spectra of freshly prepared solutions in ethanol were recorded starting at 220 nm. The molar extinction coefficient (ε) decreased to 690 (IVa) and 1630 (IVd) after storage of the solutions at room temperature for 48 h. The coefficient (ε) of solutions of IVb, c, e did not change on storage. In addition to the band at 324 nm, the UV spectra of IVa-d contain an inflection at ~250 nm ($\varepsilon \sim 17,000$); the spectrum of IVe has a maximum at 260 nm ($\varepsilon = 21,300$). [b] From benzene–n-hexane. [c] From cyclohexane. [d] From benzene.

sities of the CO bands were calculated by the Wilson–Wells method with corrections for the Ramsay wings [9]. The UV spectra were recorded with an SFD-2 spectrometer ($c = 10^{-4}$ M, in ethanol).

2-R^1-3-Chloro-3-phenylisoindolinones (IIa-e). A solution of 0.01 mole of Ia-d [3-(2'-pyridyl)amino-3-phenylphthalide was used in place of Ie], and 0.02 mole of thionyl chloride in 10-20 ml of dioxane was refluxed for 1 h. The solution was vacuum-evaporated, and the residue, without isolation of IIa-e, was used for the subsequent syntheses. 2,3-Diphenyl-3-chloroisoindolinone (IIc) was isolated in the crystalline form and characterized in [1].

Reactions of 2-R^1-3-Chloro-3-phenylisoindolinones with Amines. A solution of 0.005 mole of amine and 0.005 mole of triethylamine in 5 ml of dioxane was added with stirring to a solution of 0.005 mole of IIa-e in 10 ml of dioxane. After 24 h, the solution was diluted with 200 ml of water, and the precipitate was separated, dried, and recrystallized to give IIa-k,n-u and IVd,e. Mixtures IVa + IIId, IVb + IIIn, IVc + IIIo, and IIIk + IIIs were separated by crystallization. The yields in Tables 1 and 2 are those for the recrystallized substances.

Isomerization IV → V. A solution of 0.5 g of IVa-d and 1 ml of triethylamine in 10 ml of ethanol was refluxed for 2 h, after which it was vacuum-evaporated, and the residue was recrystallized to give IIId,h,l,m (Table 1).

Acid Hydrolysis III → I. A 0.2-g sample of IIIa-t was suspended in a solution prepared from 0.5 ml of concentrated sulfuric acid, 5 ml of acetic acid, and 5 ml of water, and the mixture was heated to 50-60° and allowed to stand at room temperature. After 24 h, the solution was diluted with 50-100 ml of water, and the precipitate was separated.

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