RING-CHAIN TRANSFORMATIONS WITH THE PARTICIPATION OF A C=N GROUP

I. 3-ARYLAMINO-3-PHENYLPHTHALIDES AND 2-ARYL-3-HYDROXY-3-PHENYLISOINDOLINONES

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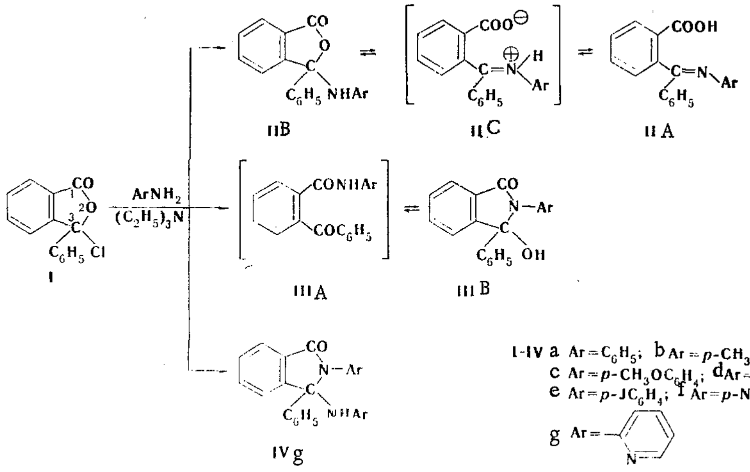
In reactions with 3-chloro-3-phenylphthalides, aromatic amines attack the primary and tertiary carbon atoms to give a mixture of 2-aryl-3-hydroxy-3-phenylisoindolinones and 3-arylamino-3-phenylphthalides. The effect of the nucleophilicity of the amine on the primary direction of attack was studied. The ring-chain tautomerism of 3-arylamino-3-phenylphthalides and 2-benzoylbenzoic acid arylimines was studied by IR and UV spectroscopy.

It has been demonstrated [1,2] that 3-chloro-3-phenylphthalide (I) in reactions with primary aliphatic amines forms 2-alkyl-3-hydroxy-3-phenylisoindolinones or N-(tert-alkyl)amides of 2-benzoylbenzoic acid, depending on the structure of the group attached to the nitrogen atom. The reaction of I with aromatic amines was first studied by Meyer [3,4], but the absence of spectroscopic methods of investigation made it impossible for him to correctly establish the structure of the compounds obtained. The structure and problems of the tautomerism of 3-phenylamino-3-phenylphthalide (IIa) and 2,3-diphenyl-3-hydroxyisoindolinone (IIIa) have been investigated by polarography [5]. We [6] and Flitsch [7] independently showed that the results of these investigations [5] were not in complete agreement with the data obtained by means of IR spectroscopy. It is known [8] that polarographically derived judgments regarding the structure of substances capable of tautomeric transformations is not always reliable.



In the present research, we have investigated the structures of the products of the reaction of I with aromatic amines. There are two electrophilic centers – C_1 and C_3 – in the I molecule. Strong nucleophilic reagents – primary and secondary aliphatic amines – polarize the carbonyl group, as a result of which they attack the primary carbon atom exclusively [1,2]. Aromatic amines, which are weaker nucleophilic re-

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TABLE 1. 3-Arylamino-3-phenylphthalides (IIa-g), 2-Aryl-3-hydroxy-3-phenylisoindolinones (IIIa-g), and 2-(2'-Pyridyl)-3-(2"-pyridyl)amino-3-phenylisoindolinone (IVg)

Comp.	Ar	mp, °C	IR spectra,[a] cm^{-1}						Empirical formula	N, %		Yield, %
			$\nu_{C=O}$	ν_{O-H}, $_{N-H}$	ν	ε	ν	ε		found	calc.	
IIa	C_6H_5 [3]	221—222[b] 221	1733, 1698 Sh	3335	1759	845	1719	125	$C_{20}H_{15}NO_2$	4,76	4,65	8
IIb	p-$CH_3C_6H_4$	217—218[c]	1740, 1702 Sh	3355	1766	630	1723	130	$C_{21}H_{17}NO_2$	4,27	4,44	6
IIc	p-$CH_3OC_6H_4$ [4]	192—193[b] 198	1744, 1709 Sh	3365	1764	620	1723	165	$C_{21}H_{17}NO_3$	4,45	4,23	8
IId	p-BrC_6H_4	202—203[b]	1737, 1701 Sh	3343	1772	725	1724	135	$C_{20}H_{14}BrNO_2$[f]	3,48	3,68	3
IIe	p-IC_6H_4	216—217[b]	1740, 1702 Sh	3343	1771	640	1728	210	$C_{20}H_{14}INO_2$[g]	3,29	3,28	5
IIf	p-$NO_2C_6H_4$	196—198[c]	1748, 1710 Sh	3315	1772	785	1719	110	$C_{20}H_{14}N_2O_4$	8,04	8,09	15
IIg	2-Pyridyl	174—175[d]	1733	3330	1770	890	—	—	$C_{19}H_{14}N_2O_2$	9,36	9,27	48
IIIa	C_6H_5 [3]	195—196[b] 195	1675, 1660 Sh	3181b	1707	815	—	—	$C_{20}H_{15}NO_2$	4,77	4,65	58
IIIb	p-$CH_3C_6H_4$	187—189[b]	1680	3251b	1712	760	—	—	$C_{21}H_{17}NO_2$	4,41	4,44	42
IIIc	p-$CH_3OC_6H_4$ [4]	200—201[b] 204	1674	3214b	1711	745	—	—	$C_{21}H_{17}NO_3$	4,04	4,23	59
IIId	p-BrC_6H_4	228—229[b]	1679	3285b	1717	685	—	—	$C_{20}H_{14}BrNO_2$[h]	3,82	3,68	38
IIIe	p-IC_6H_4	227—228[b]	1681	3322b	1718	730	—	—	$C_{20}H_{14}INO_2$[i]	3,32	3,28	34
IIIf	p-$NO_2C_6H_4$	215—216[b]	1688	3271b	1720	635	—	—	$C_{28}H_{14}N_2O_4$	8,03	8,09	23
IIIg	2-Pyridyl	170—171[e]	1715	3234b	1718	660	—	—	$C_{19}H_{14}N_2O_2$	9,16	9,27	73[j]
IVg	p-IC_6H_4	210—211[d]	1693	3339	1711	820	—	—	$C_{24}H_{18}N_4O$	14,62	14,81	3

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[a] The abbreviations sh for shoulder and b for broad band are used.

[b] From acetic acid.

[c] From dioxane.

[d] From ethanol.

[e] From cyclohexane.

[f] Found: Br 20.85%. Calculated: Br 21.02%.

[g] Found: I 29.83%. Calculated: I 29.71%.

[h] Found: Br 21.28%. Calculated: Br 21.02%.

[i] Found: I 29.92%. Calculated: I 29.71%.

[j] This is the yield of isomerization reaction IIg → IIIg.

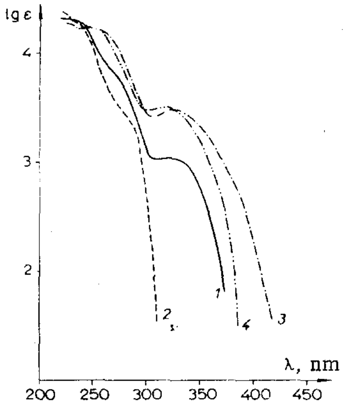


Fig. 1. UV spectra in ethanol: 1) IIa; 2) V; 3) VI; 4) IIa in the presence of 0.1 N KOH in ethanol.

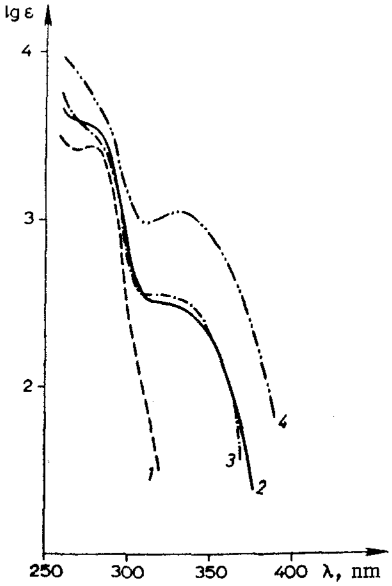
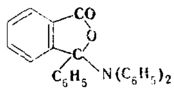
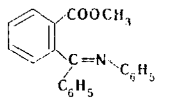


Fig. 2. UV spectra of 3-phenylamino-3-phenylphthalide (IIa): 1) in dichloroethane; 2) in dioxane; 3) in tetrahydrofuran; 4) in dimethyl sulfoxide.

agents, attack both C_1 and C_3 to give readily separable mixtures of 3-arylamino-3-phenylphthalides (II) and 2-aryl-3-hydroxy-3-phenylisoindolinones (III, Table 1), since II, in contrast to III, dissolve readily in 5% sodium carbonate solution. The carboxylate anion of tautomeric form IIA is apparently formed in this case. From the reactions of I with seven aromatic amines, it appears that a decrease in the nucleophilicity of the amine by introduction of electron-acceptor groups into the aromatic ring increases the probability of attack at C_3, as a result of which one observes an increase in the yields of II and a decrease in the yields of III. With diphenylamine, the single reaction product formed is 3-(N,N-diphenylamino)-3-phenylphthalide (V); i.e., the attack of a very weak nucleophilic reagent proceeds exclusively at C_3.



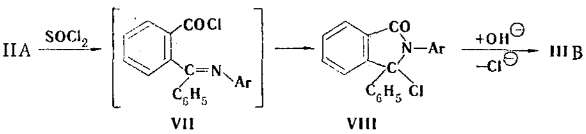
V



VI

In the reaction of I with 2-aminopyridine, 2-(2'-pyridyl)-3-(2''-pyridyl)amino-3-phenylisoindolinone (IVg) was isolated from the reaction mixture instead of IIIg. The anil of o-carbomethoxybenzophenone (VI) was obtained by the reaction of diazomethane with IIa. Compounds V and VI were used as fixed models in the spectroscopic investigation of the tautomeric equilibrium IIA ⇌ IIB.

Meyer [3,4] and Flitsch [7] have demonstrated the possibility of the isomerization II → III. The isomerization is most conveniently realized by successive treatment of IIa-g with thionyl chloride and aqueous sodium carbonate solution. The mechanism of the isomerization can be represented as follows:



Compound II reacts with thionyl chloride in the A form; the resulting acid chloride (VII) cyclizes rapidly to VIII. It is known [1,2] that o-acylbenzoyl chlorides, with a few exceptions [9], exist in the chain form of 3-R-3-chlorophthalides. The greater polarity of the C=N bond as compared with the C=O bond facilitates the cyclization. 2,3-Diphenyl-3-chloroisoindolinone (VIIIa) is formed in the reactions of both IIa and IIIa with thionyl chloride.

The IR spectra of dioxane solutions of 2-aryl-3-hydroxy-3-phenylisoindolinones (IIIa-g, Table 1) contain an intense C=O band of isoindolinone at 1707-1720 cm^{-1}. The considerably lower $\nu_{C=O}$ and broader bands of an associated hydroxyl group (ν_{O-H}) in the IR spectra of crystalline IIIa-f attest to a strong O–H . . . O=C intermolecular hydrogen bond. We also observed this [2] in the case of 2-alkyl-3-hydroxy-3-phenylisoindolinones. The position of the $\nu_{C=O}$ band in the spectrum of IIIg changes only slightly on passing from the crystalline state to a dioxane solution. The presence of the broad band of an associated hydroxyl group in the spectrum of crystalline IIIg can be explained by intramolecular or intermolecular $\mathrm{O{-}H} \ldots \mathrm{N}{<}$ (2-pyridyl) hydrogen bonds. The IR spectra of Nujol mulls and dioxane solutions of IIIa-e, g do not contain a δ_{N-H} (II amide) band. There is a band from the antisymmetrical stretching vibrations of a nitro group in the spectrum of IIIf in Nujol at 1518 cm^{-1} and in dioxane at 1523 cm^{-1}. It follows from the IR

TABLE 2. Tautomeric Equilibrium Constants K = [A]/[B] in Solutions of 3-Phenylamino-3-phenylphthalide (IIa)

Solvent	K
Ethanol	0.61
Dimethyl sulfoxide	0.87
Tetrahydrofuran	0.19
Dioxane	0.15
Dichloroethane	0

spectra that IIIa-g exist only in the chain form (IIIB) in the crystalline state and in dioxane solution. The IIIA form is absent within the limits of the sensitivity of the IR spectroscopic method.

The IR spectra of Nujol mulls and dioxane solutions of IIa-g confirm the presence of the tautomeric equilibrium IIA $\rightleftharpoons$ IIB. The spectrum of fixed model V contains the intense C=O band of the lactone at 1773 cm^{-1} (in dioxane). The same band is observed in the spectra of IIa-g at 1733-1748 cm^{-1} (in Nujol) and 1759-1772 cm^{-1} (in dioxane). In addition, a low-intensity absorption, affiliated with a carboxyl $\nu_{C=O}$ band (IIA), appears at 1700-1710 (in Nujol) and ~1720 cm^{-1} (in dioxane). Judging from the IR spectra of IIa-g, the IIA $\rightleftharpoons$ IIB tautomeric equilibrium in dioxane is shifted markedly to the right. The intensity of the C=O band of the carboxyl group (IIA) in the spectra of dioxane solutions of IIa-g is reduced as the electron-acceptor properties of the substituents attached to nitrogen increase. Electron-acceptor groups ($p\text{-}NO_2C_6H_4$, 2-pyridyl) increase the polarity of the C=N bond (IIA), and the probability of intramolecular nucleophilic addition consequently increases, and the IIA $\rightleftharpoons$ IIB equilibrium is shifted even more to the right. Crystalline substances IIa-f are also mixtures of both forms with considerable predominance of IIB. Judging from the IR spectrum, an unrecrystallized sample of IIa, obtained by precipitation from alkaline solution, contains considerably larger amounts of IIA.

It follows from the UV spectra (Fig. 1) of model substances V and VI that the UV spectroscopic method can be successfully used for quantitative investigation of the IIA $\rightleftharpoons$ IIB equilibrium in different solvents. An absorption band at 324 nm (ε 2930) is observed in the UV spectrum of fixed model VI. This band (320 nm, ε 3120) is also present in the spectrum of the carboxylate anion of form IIaA, i.e., in a solution of IIa in ethanol in the presence of 0.1 N KOH, and is due to the presence of a conjugated $\mathrm{Ar{-}N{=}\overset{|}{C}{-}\overset{|}{C}{=}\overset{|}{C}{-}\overset{|}{C}{=}O}$ system in form IIa. Fixed model V does not absorb at ~320 nm (Fig. 1). It is apparent in Fig. 2 that the intensity of the band at ~324 nm in the UV spectra of solutions of IIa depends markedly on the solvent. Having assumed that the intensities of the bands at 324 nm in the spectra of tautomeric form IIaA and model substance VI are equal, the tautomeric equilibrium constant K = [A]/[B] in different solvents can be calculated from the molar extinction coefficients. It is apparent from Table 2 that the solvent polarity has a pronounced effect on the tautomeric equilibrium constant.

EXPERIMENTAL

The IR spectra of suspensions in paraffin oil and in hexachlorobutadiene and dioxane solutions were recorded with an IKS-14A spectrometer (c $2.5 \cdot 10^{-2}$ M, L 0.011 cm). The UV spectra were recorded with an SFD-2 spectrometer (c 10^{-4} M).

Reactions of 3-Chloro-2-phenylphthalide (I) with Aromatic Amines (Table 1). A solution of 0.03 mole of I in 30 ml of dioxane was added with stirring to a solution of 0.03 mole of aromatic amine and 0.04 mole of triethylamine in 20 ml of dioxane, and the mixture was heated on a water bath at 100° for 3 h. The mixture was then poured with vigorous stirring into 300 ml of 5% aqueous sodium carbonate solution. Compounds IIIa-f and IVg separated after 24 h and were recrystallized. The filtrate was neutralized with dilute hydrochloric acid to pH 7, and IIa-g were separated and recrystallized.

2-(2'-Pyridyl)-3-hydroxy-3-phenylisoindolinone (IIIg) (Table 1). A solution of 0.003 mole of IIg and 0.01 mole of thionyl chloride in 10 ml of dioxane was refluxed for 1 h and diluted with 50 ml of 5% aqueous sodium carbonate solution. Compound IIIg separated after 24 h and was recrystallized.

3-(N,N-Diphenylamino)-3-phenylphthalide (V). A solution of 0.01 mole of I, 0.01 mole of diphenylamine, and 0.01 mole of triethylamine in 10 ml of dioxane was heated at 100° for 2 h. The mixture was cooled and diluted with 100 ml of water, and the precipitate was separated and recrystallized twice from ethanol to give 2.0 g (53%) of colorless crystals of V with mp 193-194°. Found: C 83.08; H 5.32; N 3.92%. $C_{26}H_{19}NO_2$. Calculated: C 82.74; H 5.07; N 3.71%. IR spectrum, cm^{-1} (in Nujol): 1758 (C=O), 1597 and 1500 (aromatic ring C=C); in dioxane: 1773 (CO), the integral band intensity, calculated via the Wilson–Wells method with Ramsay's corrections for "wings" [10] was 6.21 practical units.*

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*A practical unit is 10^4 liter $\cdot$ $\text{mole}^{-1} \cdot \text{cm}^{-2}$.

Anil of o-Carbomethoxybenzophenone (VI). Excess diazomethane in ether solution was added to a solution of 1 g of IIa in 20 ml of dioxane. After 24 h, the solution was vacuum-evaporated, and the residue was recrystallized twice from cyclohexane to give 0.45 g (43%) of yellow crystals with mp 127-128°. Found: C 79.86; H 5.35; N 4.28%. $C_{21}H_{17}NO_2$. Calculated: C 79.98; H 5.43; N 4.44%. IR spectrum, cm^{-1} (in Nujol): 1726 (CO), 1623 (C=N), 1591 (C=C); in dioxane (ε): 1727 (625) (CO), 1625 (215) (C=N), 1596, 1587 (C=C).

2,3-Diphenyl-3-chloroisoindolinone (VIIIa). A solution of 0.004 mole of IIIa (or IIa) and 0.01 mole of thionyl chloride in 10 ml of dioxane was refluxed for 1 h. The mixture was vacuum-evaporated, and the residue was recrystallized from benzene–n-hexane (1 : 1) to give 0.9 g (71%) of colorless crystals of VIIIa with mp 154-156°. Found: Cl 11.13; N 4.58%. $C_{20}H_{14}ClNO$. Calculated: Cl 11.09; N 4.38%. IR spectrum (in dioxane): 1730 cm^{-1} (ε 750) (CO).

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