RING–CHAIN TRANSFORMATIONS WITH THE PARTICIPATION OF THE C=N GROUP. V.* REACTIONS OF 2-(tert-BUTYL)-3-CHLORO-3-(p-CHLOROPHENYL)ISOINDOLINONE WITH AMINES

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UDC 547.756:543.422.4

It was established that attack by the nucleophilic agent in the reactions of 2-(tert-butyl)-3-chloro-3-(p-chlorophenyl)isoindolinone with methylamine and ethylamine proceeds at $C_{(1)}$ with subsequent ring opening and a new cyclization leading to 2-alkyl-3-(tert-butylamino)-3-(p-chlorophenyl)isoindolinones. A decrease in the nucleophilicity of the amine or an increase in the size of the substituent attached to the nitrogen atom leads to nucleophilic substitution at $C_{(3)}$. Thermal isomerization of an aminolactam to an imino carboxylic acid amide was realized for the first time in the case of 2-(tert-butyl)-3-phenylamino-3-(p-chlorophenyl)isoindolinone. The structure of the 2-alkyl-3-amino-3-(p-chlorophenylisoindolinones was established by IR spectroscopy and acid hydrolysis to the corresponding 2-alkyl-3-hydroxy-3-(p-chlorophenyl)isoindolinones.

We recently showed [2] that N-(tert-butyl)-2-aroylbenzamides with electron-acceptor substituents in the aroyl ring (4-NO_2, 3-NO_2, and 4-Cl) can be obtained both in the open amide form and in the ring form of 2-(tert-butyl)-3-aryl-3-hydroxyisoindolinones. The amides react with thionyl chloride to give o-cyanobenzophenones [3], and their ring isomers are converted to 2- and alkyl-3-chloro-3-arylisoindolinones [4, 5].

In the present research we synthesized 2-(tert-butyl)-3-chloro-3-(p-chlorophenyl)isoindolinone (IIa) and studied its reactions with amines in order to ascertain the effect of the tert-butyl substituent attached to the nitrogen atom of the isoindolinone on the primary direction of attack by a nucleophilic agent (see [5]), and we also investigated the ring–chain isomeric transformation of the products of these reactions.

Chloroisoindolinone IIa was obtained by the action of thionyl chloride on 2-(tert-butyl)-3-hydroxy-3-(p-chlorophenyl)isoindolinone (Ia) and was characterized in the form of the 1-oxo-2-(tert-butyl)-3-(p-chlorophenyl)-1H-isoindolium hexachloroantimonate (III). In the reactions of IIa with methylamine and ethylamine the attack by the strong nucleophilic agent proceeds at $C_{(1)}$ with subsequent ring opening, whereas the intermediately formed amides IV in the reaction medium are cyclized to 2-alkyl-3-(tert-butylamino)-3-(p-chlorophenyl)isoindolinones (Va, b). The $\nu_{C=O}$ band of the isoindolinone and a ν_{N-H} band are observed in their IR spectra (Table 1). Acid hydrolysis under mild conditions [5, 6] gives, respectively, 2-methyl- and 2-ethyl-3-hydroxy-3-(p-chlorophenyl)isoindolinones (Ic, d), which were also obtained by alternative synthesis [7] from 3-chloro-3-(p-chlorophenyl)-phthalide and the appropriate amines.

Primarily the $C_{(3)}$ atom undergoes attack in the reaction of IIa with aniline to give 2-(tert-butyl)-3-phenylamino-3-(p-chlorophenyl)isoindolinone (VIa). Its structure was confirmed by IR spectra (Table 1) and acid hydrolysis to 2-(tert-butyl)-3-hydroxy-3-(p-chlorophenyl)isoindolinone (Ia). Compound VIa is isomerized to N(tert-butyl)-2-(p-chlorobenzoyl)-benzamide anil (VII) when it is heated to 220°C. Reverse isomerization (VII → VIa) is ac-

*See [1] for communication IV.

Riga Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1207-1210, September, 1976. Original article submitted September 25, 1975.

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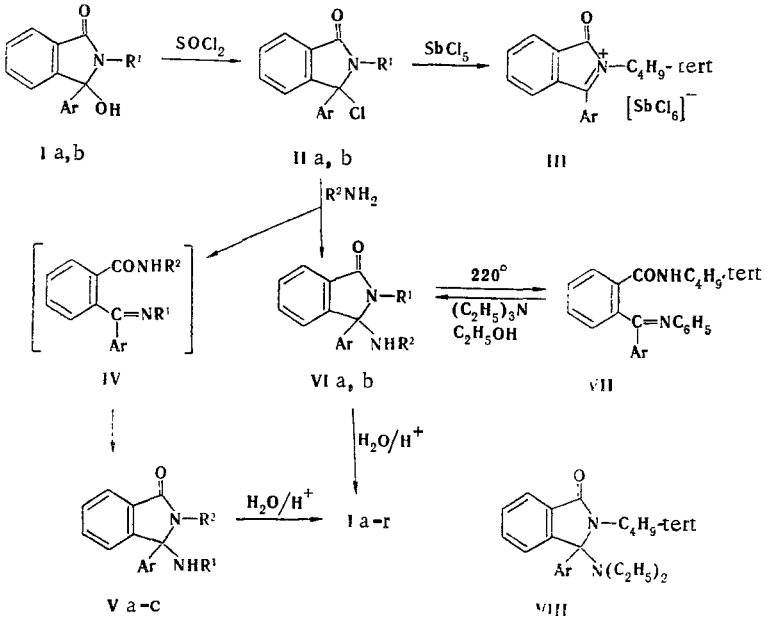
TABLE 1. 2-Alkyl-3-hydroxy(amino)-3-(p-chlorophenyl)isoindolinones

Compound	mp, °C	Crystallization solvent	Empirical formula	Found, %				Calc., %				IR spectra, cm^{-1}			Yield, %
												in Nujol		in dioxane	
				C	H	Cl	N	C	H	Cl	N	C=O	O–H, N–H	C=O	
Ib	161—163	Benzene	$C_{17}H_{16}ClNO_2$	67,9	5,5	11,6	4,4	67,7	5,3	11,8	4,6	1677	3265*	1701	77
Ic	194—195†	Ethanol	$C_{15}H_{12}ClNO_2$	65,9	4,4	13,0	5,2	65,8	4,4	13,0	5,1	1678	3270*	1710	66
Id	202—203	Ethanol	$C_{16}H_{14}ClNO_2$	66,4	4,8	12,6	4,8	66,8	4,9	12,3	4,9	1691 1657	3310*	1705	90
Va	191—196	Benzene	$C_{19}H_{21}ClN_2O$	69,5	6,5	10,7	8,5	69,4	6,4	10,8	8,5	1677	3320	1698	32
Vb	141—143	Hexane	$C_{20}H_{23}ClN_2O$	70,7	6,6	10,5	8,3	70,1	6,8	10,3	8,2	1675	3327	1696	41
Vc	179—182	Ethanol	$C_{18}H_{19}ClN_2O$	69,2	6,1	11,5	8.8	68,7	6,1	11,3	8,9	1678	3305	1702	40
VIa	204—210	Benzene	$C_{24}H_{23}ClN_2O$	73,6	5,9	9,4	7,0	73,7	5,9	9,1	7,2	1674	3352	1694	32
VIb	125—127	Hexane	$C_{20}H_{23}ClN_2O$	70,2	6,8	10,4	8,3	70,1	6,8	10,3	8,2	1673	3302	1693	46
VIII	160—168	Hexane	$C_{22}H_{27}ClN_2O$	71,0	7,3	9,3	7,3	71,2	7,3	9,6	7,6	1683	—	1693	49

*Broad.

†According to [7], this compound has mp 196-199.5°.

complished in a refluxing ethanol solution of triethylamine, which is a catalyst of intramolecular nucleophilic addition of the N–H amide group to the C=N bond [5, 6]. Bands of amide C=N, and NH groups are observed in the IR spectrum of VII. Both isomers are stable in solutions in dioxane at room temperature, and the VIa ⇄ VII tautomeric equilibrium is not observed. Thus, thermal isomerization of an aminolactam to an imino carboxylic acid amide was accomplished for the first time in the case of VIa. We were unable to realize this sort of isomerization in the case of the previously synthesized [5], 2-(n- or sec-alkyl)-3-phenylamino-3-phenylisoindolinones. The VIa → VII thermal isomerization is evidently facilitated by the effect of the bulky tert-butyl substituent in the 2 position, which destabilizes ring structure VIa.



I—VIII Ar=*p*-ClC$_6$H$_4$; I—II a R^1=tert-C$_4$H$_9$; b R^1=*i*-C$_3$H$_7$; c R^1=CH$_3$; d R^1=C$_2$H$_5$; IV, V a R^1=tert-C$_4$H$_9$, R^2=CH$_3$; b R^1=tert-C$_4$H$_9$, R^2=C$_2$H$_5$; c R^1=iso-C$_3$H$_7$, R^2=CH$_3$; VI a R^1=tert-C$_4$H$_9$, R^2=C$_6$H$_5$; b R^1=iso-C$_3$H$_7$, R^2=C$_3$H$_7$.

In the reaction of IIa with diethylamine attack by the nucleophilic agent also takes place at C$_{(3)}$ to give 2-(tert-butyl)-3-diethylamino-3-(p-chlorophenyl)isoindolinone (VIII).

We synthesized 2-isopropyl derivative IIb in order to make a comparative study of the effect of the three-dimensional structure of the substituent attached to N$_{(2)}$ in isoindolinone II on the primary direction of attack by the nucleophilic agents. Reaction of this compound with methylamine gave 2-methyl-3-isopropylamino-3-(p-chlorophenyl)isoindolinone (Vc), whereas reaction with propylamine gave 2-isopropyl-3-propylamino-3-(p-chlorophenyl)-isoindolinone (VIb). The structures of both compounds were proved by acid hydrolysis to the corresponding hydroxyisoindolinones (Ib, c). It follows from this that the probability of nucleophilic attack of the isoindolinone at C$_{(3)}$ increases as the volume of the substiuent attached to the nitrogen atom in the nucleophilic agent increases.

EXPERIMENTAL

The IR spectra of mineral oil and hexachlorobutadiene suspensions and dioxane solutions (c $2.5 \cdot 10^{-2}$ M, $l = 1.2 \cdot 10^{-2}$ cm) of the compounds were recorded with an IKS-14A spectrometer. The UV spectra of ethanol solutions of the compounds (c $4 \cdot 10^{-1}$ M) were recorded with a Specord UV-vis spectrophotometer (Zeiss, Jena).

2-Alkyl-3-hydroxy-3-(p-chlorophenyl)isoindolinones (Ib-d, Table 1). A solution of 0.01 mole of 2-(p-chlorobenzoyl)benzoic acid and 0.02 mole of thionyl chloride in 10 ml of benzene was refluxed for 1 h, after which it was vacuum evaporated, and the residue was dissolved in 10 ml of dioxane. A solution of 0.02 mole of the amine and 0.02 mole of triethylamine in 5 ml of dioxane was then added to dioxane solution with stirring. After 24 h, the mixture was diluted with 200 ml of water, and the precipitate was separated, dried, and recrystallized.

2-(tert-Butyl)-3-chloro-3-(p-chlorophenyl)isoindolinone (IIa). A solution of 0.01 mole of 2-(tert-butyl)-3-hydroxyl-3-(p-chlorophenyl)isoindolinone (Ia) [2] and 0.02 mole of thionyl chloride in 10 ml of methylene chloride was refluxed for 1 h, after which it was vacuum evaporated, and the residue was dissolved in dioxane or benzene and used for the subsequent syntheses. Compound IIa was obtained in crsytalline form only by crystallization from carbon tetrachloride, from which it crystallized with a molecule of solvent to give a product with mp 97-99° (dec.) in 98% yield. IR spectrum in Junjol, cm^{-1}: 1690 (C=O). Found: Cl 43.5; N 2.9%. $C_{18}H_{17}Cl_2NO \cdot CCl_4$. Calculated: Cl 43.6; N 2.9%.

2-Isopropyl-3-chloro-3-(p-chlorophenyl)isoindolinone (IIb). This compound was similarly obtained from 2-isopropyl-3-hydroxy-3-(p-chlorophenyl)isoindolinone (Ib) but was not isolated in crystalline form.

1-Oxo-2-(tert-butyl)-3-(p-chlorophenyl)-1H-isoindolium Hexachloroantimonate (III). A 2-mmole sample of antimony pentachloride was added to a solution of 2 mmole of IIa in 10 ml of benzene, and the resulting precipitate was separated and washed with hot benzene to give yellow crystals, with mp 215-220° (dec.), in 36% yield. IR spectrum in Jujol, cm^{-1}: 1770, 1580, and 1528. Found: Cl 38.2; N 2.5%. $C_{18}H_{17}Cl_7NOSb$. Calculated: Cl 39.2; N 2.2%.

2-Alkyl-3-amino-3-(p-chlorophenyl)isoindolinones (Va-c, VIa,b, and VIII, Table 1). A solution of 0.01 mole of IIa,b in 10 ml of dioxane was added with stirring to a solution of 0.02 mole of the amine and 0.02 mole of triethylamine in 5 ml of dioxane. After 24 h, the mixture was diluted with 200 ml of water, and the precipitate was separated.

N-(tert-butyl)-2-(p-chlorobenzoyl)benzamide Anil (VII). A 0.8-g sample of VIa was heated at 220° for 10 min, after which it was cooled and triturated with 10 ml of petroleum ether. The light-yellow solid was separated to give a product with mp 125-126° (from hexane) in 51% yield. IR spectrum in dioxane, cm^{-1}: 1666 (amide I), 1623 (C=N), 1523 (amide II), and 3388 and 3363 (N–H, in Nujol). UV spectrum in ethanol, λ_{max}, nm(ε): 263 (16,800) and 335 (3000). Found: C 73.0; H 5.8; Cl 9.5; N 7.3%. $C_{24}H_{23}ClN_2O$. Found: C 73.7; H 5.9; Cl 9.1; N 7.2%.

Isomerization of Anil VII. A solution of 0.5 g of anil VII 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 VIa (Table 1).

Acid Hydrolysis of 3-Aminoisoindolinones. A 0.15-g sample of Va-c, VIa,b, or VIII 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 suspension was heated to 50-60°, and the resulting solution was allowed to stand at room temperature. After 24 h, it was diluted with 50-100 ml of water, and the resulting precipitate was separated. The identity with Ia-d was proved by mixed-melting-point determinations and the IR spectra.

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