1-Oxo-1,2,3,4-tetrahydro-β-carbolines (VIa-i). A solution of 0.03 mole of enamine IV [3] (method A) or dimer III [3] (method B) in 10 ml of a 50% solution of isopropyl alcohol in water was added to a solution of 0.03 mole of the hydrochloride or sulfate of the arylhydrazine in a mixture of 35 ml of isopropyl alcohol, 15 ml of water, and 5 ml of concentrated hydrochloric acid, and the mixture was refluxed for 3 h. It was then cooled to room temperature, and the precipitated crystals of VIa,c-h were removed by filtration. In the case of VIb and VIi the reaction mixture was evaporated to dryness with a rotary evaporator, 100 ml of benzene and 100 ml of water were added to the residue, and the mixture was shaken. The benzene layer was separated and filtered through a layer of Al_2O_3, the benzene was removed by evaporation, and the residue was crystallized from hexane.

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RING–CHAIN ISOMERISM OF 3-HYDROXY-3-(2-IMIDAZOLYL)ISOINDOLINONES

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It was established by IR, UV, and PMR spectroscopy that N-unsubstituted and N-(n-alkyl, sec-alkyl, or aryl)-2-(2-imidazolylcarbonyl)benzamides obtained from imidazo[1,2-b]isoquinoline-5,10-dione and ammonia or amines have the 3-hydroxy-3-(2-imidazolyl)isoindolinone chain structure in the crystalline state and in solutions in dimethyl sulfoxide. The N-(tert-alkyl)amides exist in the open form under these conditions. Protonation of the imidazole nitrogen atom in the N-(tert-butyl)amide molecule leads to its cyclization to 3-hydroxyisoindolinone.

It is known [1] that N-unsubstituted and N-monosubstituted 2-acylbenzamides exist in the stable 3-hydroxyisoindolinone chain form. Those cases in which the formation of a hydroxyisoindolinone ring is impossible because of the large volume of the substituent attached to the nitrogen atom or the keto group, as well as because of the strong–I effect of the substituent attached to the nitrogen atom, constitute exceptions.

TABLE 1. 3-Hydroxy-3-(2-imidazolyl)isoindolinones (IIIa-f)

Compound	mp, °C	IR spectra, ν, cm^{-1} in Nujol		IR spectra, ν, cm^{-1} in DMSO	Found, %			Empirical formula	Calc., %			Yield, %
		C=O	O–H	C=O	C	H	N		C	H	N	
IIIa	201–202*	1677	3290	1708	61.3	4.7	19.7	$C_{11}H_9N_3O_2$	61.4	4.2	19.5	93
IIIb	187–188	1678 1667	3255 3160	1700	62.9	4.7	18.5	$C_{12}H_{11}N_3O_2$	62.9	4.8	18.3	96
IIIc	186–187	1678	3160	1699	65.0	5.5	17.6	$C_{13}H_{13}N_3O_2$	64.2	5.4	17.3	91
IIId	199–200	1675	3187	1700	65.7	5.9	16.4	$C_{14}H_{15}N_3O_2$	65.4	5.9	16.3	92
IIIe	202–203*	1670	3147	1695	65.1	6.2	15.8	$C_{14}H_{15}N_3O_2$	65.4	5.9	16.3	96
IIIg	196–197	1676	3196	1699	71.2	4.9	13.5	$C_{18}H_{15}N_3O_2$	70.8	5.0	13.8	85
IIIh	190–191	1679	3193	1705	70.2	4.3	14.3	$C_{17}H_{13}N_3O_2$	70.1	4.5	14.4	93
IIIf	205–206*	1689	3183	1706	70.8	5.1	13.5	$C_{18}H_{15}N_3O_2$	70.8	5.0	13.8	95

*With decomposition.

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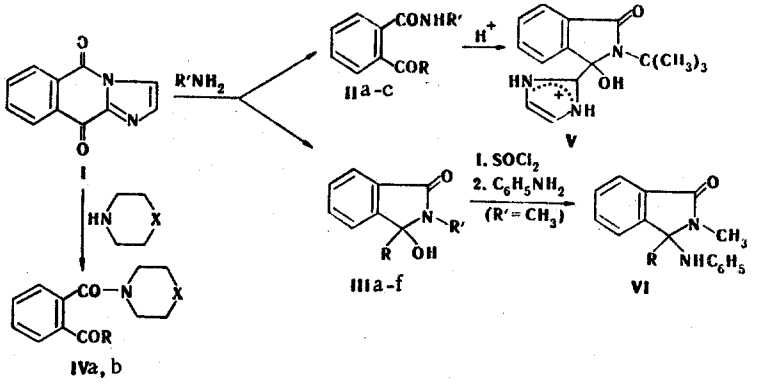
The aim of the present research was to study the structure and ring–chain isomeric transformations of 2-(2-imidazolylcarbonyl)benzamides, i.e., to ascertain the effect of the imidazole substituent on the relative stabilities of the open and ring isomers. Protonation of the imidazole ring makes it possible to easily change the electrophilicity of the carbon atom of the keto group by increasing the −I effect of the substituent attached to it. It seemed of interest to ascertain the effect of this change in the electron density in the keto group on intramolecular nucleophilic addition to it.

In a recent study [2] Regel and Büchel synthesized compounds from imidazo[1,2-b]isoquinoline-5,10-dione (I) with ammonia and primary aliphatic or aromatic amines and characterized them as 2-(2-imidazolylcarbonyl)benzamides (II).

We have established that the reaction of I with ammonia, primary n- and sec-alkylamines, and aromatic amines leads to ring isomers of amides, viz., hydroxyisoindolinones IIIa-f (Table 1). N-Phenylphthalimide is formed with aniline in refluxing dimethylformamide (DMF), and this constitutes evidence for cleavage of the C–C bond and splitting out of a molecule of imidazole from hydroxyisoindolinone IIIh under such severe conditions.



II—IV, VI R=2-imidazolyl; II a $R'=t\text{-}C_4H_9$; b R′=1-adamantyl; c R′= $=C(CH_3)_2CH_2C(CH_3)_3$; III a R′=H; b $R'=CH_3$; c $R'=C_2H_5$; d $R'=C_3H_7$; e $R'=i\text{-}C_3H_7$; f $R'=4\text{-}CH_3C_6H_4$; g $R'=C_6H_5CH_2$; h $R'=C_6H_5$; IV a X=CH_2; b X=O

The reaction of I with tert-alkylamines in refluxing acetonitrile gives N-(tert-alkyl)-benzamides IIa-c (Table 2). An increase in the volume of the substituent attached to the nitrogen atom in the order tert-butyl < adamantyl < 1,1,3,3-tetramethylbutyl is accompanied by a decrease in the reactivity of the amine: the tert-alkylamides are obtained in 44, 31, and 10% yields, respectively, when the reactions are carried out under approximately identical conditions. Thus, bulky tert-alkyl substituents, because of steric shielding of the nitrogen atom, hinder intramolecular nucleophilic addition of the amide N–H group to the C=O bond, and N-(tert-alkyl)amides in the crystalline state have open structure II (see [1, 3]). The IR spectra (Fig. 1) of crystalline N-(tert-alkyl)amides IIa-c (Table 2) contain ketone C=O (1660-1666 cm^{-1}), amide I (1632-1636 cm^{-1}), and amide II (1533-1538 cm^{-1}) bands and a characteristic narrow amide N–H band (3300-3330 cm^{-1}). In the spectrum of a solution in DMSO the amide I band is shifted to the high-frequency side and merges with the ketone C=O band — one overall band at 1650 cm^{-1} is observed. The individual ketone C=O and amide I bands are also present in the spectra of crystalline N,N-disubstituted benzamides IVa,b (Table 2). They are also overlapped in the spectra of solutions in DMSO.

Only one C=O band at 1670-1689 cm^{-1} is observed in the IR spectra (Fig. 2) of crystalline hydroxyisoindolinones IIIa-f (Table 1) (it is split into a doublet in the spectrum of the 2-methyl-substituted compound), and there is also a characteristic broad O–H band at 3147-3290 cm^{-1}. In solution in DMSO the C=O band, because of cleavage of the intermolecular C=O···H–O hydrogen bonds, is shifted 20-30 cm^{-1} to the high-frequency side, and its frequency (Table 1) is in good agreement with the literature data on the spectra of other 3-hydroxyisoindolinones [1, 3, 4].

A comparison of the IR spectra of N-(tert-alkyl)amides II with the spectra of the compounds described in [2] as N-(n-alkyl, isoalkyl, aryl)-2-(2-imidazolylcarbonyl)benzamides with open structures makes it possible to conclude that the latter, despite the data in [2], have ring structure III in the crystalline state and in solutions in DMSO. We were unable to study the IR spectra of isoindolinones III in other solvents because of their low solubilities.

TABLE 2. 2-(2-Imidazolylcarbonyl)benzamides (IIa-c, IVa-b)

Compound	mp, °C	IR spectra, ν, cm^{-1}						Found, %			Empirical formula	Calc., %			Yield, %
		in Nujol				in DMSO									
		ketone C=O	amide C=O	amide II	amide N–N	C=O	amide II	C	H	N		C	H	N	
IIa	222—223*	1660	1636	1533	3330	1648	1544	66.6	6.8	15.1	$C_{15}H_{17}N_3O_2$	66.4	6.3	15.5	44
IIb	224—225*	1666	1632	1538	3323	1650	1543	72.1	6.7	12.3	$C_{21}H_{23}N_3O_2$	72.2	6.6	12.0	31
IIc	206—207*	1660	1632	1537	3303	1655	1546	70.3	8.3	13.0	$C_{19}H_{25}N_3O_2$	69.7	7.7	12.8	10
IVa	186—187*	1651	1615	—	3220†	1623 1640 sh	—	68.3	6.0	14.8	$C_{16}H_{17}N_3O_2$	67.8	6.1	14.8	85
IVb	164—166	1655	1612	—	3210†	1629	—	63.4	5.7	15.0	$C_{15}H_{15}N_3O_2$	63.2	5.3	14.7	84

*With decomposition.
†Imidazole N–H.

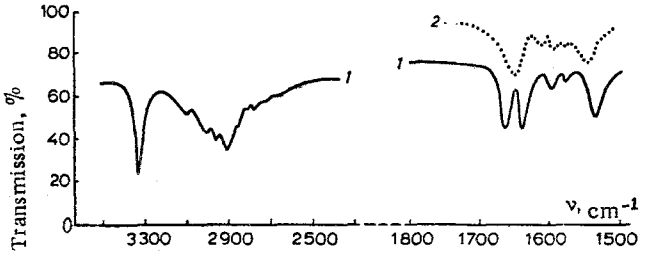


Fig. 1. IR spectrum of N-(tert-butyl)-2-(2-imidazolylcarbonyl)benzamide (IIa): 1) in Nujol; 2) solution in DMSO.

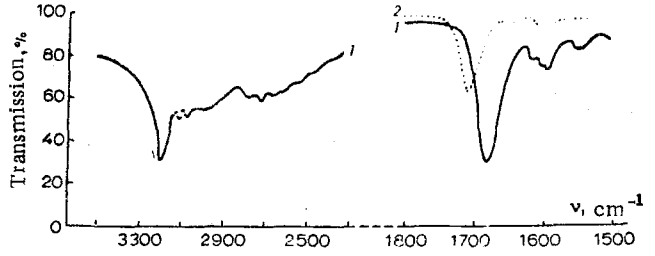


Fig. 2. IR spectrum of 2-phenyl-3-hydroxy-3-(2-imidazolyl)isoindolinone (IIIh): 1) in Nujol; 2) solution in DMSO.

The N–H absorption of the imidazole ring shows up in the IR spectra of crystalline II, III, and 2-benzoylimidazole (VII) [5] in the form of several weakly expressed bands and monotonic absorption at 2600-3100 cm^{-1} (Figs. 1 and 2); this is explained [6] by the formation of intermolecular hydrogen bonds between the imidazole rings. Imidazole N–H absorption is observed in the spectra of crystalline IVa,b and VI in the form of a separate band at 3200 cm^{-1}, and this constitutes evidence for the different character of the intermolecular association.

Isoindolinone VI was synthesized by successive treatment of isoindolinone IIIb with thionyl chloride and a mixture of aniline and triethylamine (see [7]). The IIIb → VI conversion serves as chemical confirmation of the structure of isoindolinones III, since it is known [8] that 2-acylbenzamides with open structures are converted to 2-acylbenzonitriles by the action of thionyl chloride.

An intense absorption band at 290 nm is observed in the UV spectra of solutions (Table 3) of N-(tert-alkyl)amides IIa-f. This band is also present in the spectra of N,N-disubstituted amides IVa,b (∿300 nm) and in the spectrum of 2-benzoylimidazole (VII). This band can be used as an analytical band for the study of the II ⇄ III tautomeric equilibrium in various solvents, since absorption in this region is absent in the spectrum of ring isomer IIIb.

TABLE 3. UV Spectra of 2-(2-Imidazolylcarbonyl)benzamides (IIa,c, IVa), 2-Methyl-3-hydroxy-3-(2-imidazolyl)isoindolinone (IIIb), and 2-Benzoylimidazole (VII)

Compound	Solvent	λ_{max}, nm	lg ε
IIa	Chloroform	293	4.11
IIa	Dioxane	292	4.08
IIa	5 N HCl in dioxane	270 inflection	3.62
IIa	Ethanol	292	3.78
IIa	5 N HCl in ethanol	260 inflection	3.56
IIc	Dioxane	293	4.08
IIIb	5 N HCl in ethanol	260 inflection	3.48
IVa	Chloroform	303	4.16
IVa	Dioxane	299	4.14
IVa	Ethanol	298	4.16
VII	Dioxane	303	4.01
VII	Ethanol	298	4.15
VII	5 N HCl in ethanol	282	4.18

The decrease in the intensity of this band in the spectrum of IIa in ethanol as compared with the spectra of solutions in dioxane and chloroform constitutes evidence for the existence of the II ⇄ III (R' = tert-C_4H_9) tautomeric equilibrium. The results of a quantitative study of the II ⇄ III tautomeric equilibrium in various solvents by UV spectroscopy will be set forth in a separate communication.

The identification of both the II and III isomers by means of PMR spectroscopy is due primarily to the difference in the chemical shifts of the imidazole protons. Thus, the signals of the protons of the imidazole ring (7.06 and 7.4 ppm) in the PMR spectrum of amide IIa in d_6-DMSO are shifted to weaker field as compared with isoindolinone IIIb (6.77 and 7.06 ppm); this is explained by the effect of the electron-acceptor keto group attached to the imidazole ring in amide IIa. This is in agreement with the spectrum of 2-benzoylimidazole (VII), in which the imidazole protons give a broad signal at 7.43 ppm.

Protonation of the imidazole nitrogen atom in amide IIa leads to IIa → V intramolecular cyclization. Thus, the IR spectrum of crystalline hydrochloride V contains only one isoindolinone C=O band, and amide II and amide N–H bands are absent. A 20 nm hypsochromic shift of the band at 292 nm with a considerable decrease in its intensity is observed in the UV spectrum of amide IIa in a 5 N solution of HCl in dioxane (Table 3). The UV spectrum of amide IIa in a 5 N solution of HCl in ethanol is identical to the spectrum of isoindolinone IIIb in the same solvent; that is evidence for the IIa → V cyclization under these conditions. This is also confirmed by the fact that the spectrum of 2-benzoylimidazole (VII) in a 5 N solution of HCl in ethanol contains intense absorption at 282 nm.

Protonation of the imidazole ring evidently increases the electrophilicity of the carbon atom of the keto group to such an extent that intramolecular nucleophilic addition of the amide group to it, even with such a bulky substituent attached to the nitrogen atom as a tert-butyl group, becomes possible.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol and hexachlorobutadiene and of solutions in DMSO (c $2.5 \cdot 10^{-2}$ M, l = 0.011 cm) were recorded with a Specord 75 IR spectrometer. The UV spectra of solutions of the compounds in ethanol, dioxane, and chloroform (c $5 \cdot 10^{-5}$ M, l = 1 cm) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 0.01 M solutions of the compounds in d_6-DMSO were obtained with a Bruker Physik WH-90 DS spectrometer; the operating frequency was 90 MHz, and the internal standard was hexamethyldisiloxane.

The authors thank R. B. Kampare for recording the PMR spectra.

The results of elementary analysis are presented for all of the synthesized isoindolinones III and amides II and IV, since their melting points (with decomposition) differ considerably from those indicated in [2].

General Method for the Synthesis of 3-Hydroxy-3-(2-imidazolyl)isoindolinones (IIIa-g, Table 1) and 2-(2-Imidazolylcarbonyl)benzamides (IVa,b, Table 2). A 10-mmole sample of the amine (in the synthesis of IIIa, 3 ml of concentrated ammonium hydroxide) was added to a hot

solution of 1 g (5 mmole) of I [2] in 30 ml of acetonitrile, and the precipitate that formed after 12 h was separated, washed with acetonitrile, dried, and recrystallized from DMF.

PMR spectrum of isoindolinone IIIb, δ: 2.76 (s, 3H, CH_3), 6.77 and 7.06 (two s, 2H, imidazole protons), 7.27 (s, 1H, OH), 7.30-7.70 (m, 4H, aromatic protons), and 12.44 ppm (s, 1H, NH).

2-Aryl-3-hydroxy-3-(2-imidazolyl)isoindolinones (IIIf,h, Table 1). A mixture of 1 g (5 mmole) of I and 10 mmole of aniline or p-toluidine was heated at 100°C for 1 h, during which it became homogeneous and then solidified. The solid mass was treated with 10 ml of boiling acetonitrile or ethanol, and the precipitate was separated, washed, and recrystallized from DMF.

N-(tert-Alkyl)-2-(2-imidazolylcarbonyl)benzamides (IIa-c, Table 2). A mixture of 1 g (5 mmole) of I and the corresponding tert-alkylamine (20 mmole of tert-butylamine, 5 mmole of 1-aminoadamantane, or 10 mmole of 1,1,3,3-tetramethylbutylamine) in 40 ml of acetonitrile was refluxed for 18-20 h (the reaction with tert-butylamine was carried out in a sealed ampul), after which the precipitate was separated and recrystallized from DMF to give amides IIa,b. In the synthesis of amide IIc unchanged starting I was separated initially, after which workup of the filtrate gave amide IIc, which was recrystallized from acetonitrile.

PMR spectrum of amide IIa, δ: 1.14 [s, 9H, $C(CH_3)_3$], 7.06 and 7.40 (two s, 2H, imidazole protons), 7.55 (s, 4H, aromatic protons), 7.98 (s, 1H, CONH), and 13.30 ppm (s, 1H, NH)

2-(tert-Butyl)-3-hydroxy-3-(2-imidazolyl)isoindolinone Hydrochloride (V). A 0.27-g (1 mmole) sample of amide IIa was dissolved at room temperature in 2 ml of concentrated hydrochloric acid, after which 1 ml of water was added, and the mixture was cooled to 0°C. The precipitate was separated, washed successively with 1 ml of cold water, acetonitrile, and ether, and dried in vacuo to give 0.22 g (73%) of a product with mp 226-227°C (dec.). IR spectrum (in Nujol): 1670 (C=O); 2980 and 2560 cm^{-1} (two broad bands). Found: C 59.2; H 6.2; Cl 12.0; N 13.5%. $C_{15}H_{17}N_3O_2 \cdot HCl$. Calculated: C 58.5; H 5.9; Cl 11.5; N 13.7%.

2-Methyl-3-phenylamino-3-(2-imidazolyl)isoindolinone (VI). A mixture of 0.46 g (2 mmole) of IIIb and 1.5 ml of thionyl chloride was heated at 60°C for 30 min, after which 20 ml of methylene chloride was added, and the resulting solution was evaporated in vacuo. The residue was dissolved in 15 ml of methylene chloride, and the solution was added with stirring to a solution of 0.36 ml (4 mmole) of aniline and 0.56 ml (4 mmole) of triethylamine in 10 ml of methylene chloride. After 12 h, the mixture was washed with water in a separatory funnel, and the organic layer was separated, washed with magnesium sulfate, and filtered. The filtrate was evaporated in vacuo, and the residue was recrystallized from benzene–hexane to give 0.5 g (83%) of a product with mp 210-212°C. IR spectrum: 1685 (C=O), 3353 (N–H;, 3195 (imidazole N–H) (in Nujol), and 1705 cm^{-1} (C=O) (in dioxane). Found: C 71.3; H 5.4; N 18.6%. $C_{18}H_{16}N_4O$. Calculated: C 71.0; H 5.3; N 18.4%.

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