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SYNTHESIS AND RING–CHAIN ISOMERISM OF ACID CHLORIDES AND AMIDES OF 2-(2-PYRIDYL AND 2-QUINOLYLCARBONYL)-BENZOIC ACIDS

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The reaction of 2-(2-pyridylcarbonyl)benzoic acid with thionyl chloride affords an unexpected product of the intramolecular acylation of the pyridine nitrogen atom, namely, 6,11-dioxo-6,11-dihydrobenzo[b]quinolizinium chloride. At the same time, 2-(2-quinolylcarbonyl)benzoic acid forms the expected cyclic acid chloride, namely, 3-(2-quinolyl)-3-chlorophthalide in this reaction. Both compounds acylate ammonia and primary amines, including those with bulky alkyl groups (tert-butyl, 1-adamantyl, and 1,1,3,3-tetramethylbutyl) with the formation of 2-R-3-hydroxy-3-(2-pyridyl- or 2-quinolyl)isoindolines. The protonation of the pyridine nitrogen atom of N-(1,1,3,3-tetramethylbutyl)-2-(2-pyridylcarbonyl)benzamide, obtained in the open amide form, is accompanied by the closing of the isoindolinone ring; the deprotonation is accompanied by ring opening.

We previously proposed [1, 2] an original method for the isolation of a series of 2-pyridyl- and 2-quinolylcarbonylarenecarboxylic acids. The synthesis and study of the structure and tautomeric conversions of chlorides and amides of two of these acids, now readily available, provide the continuation of investigations on the production of ring–chain equilibrium systems of ketocarboxylic acids and their derivatives, having a nitrogen-containing heterocycle as the substituent at the keto group, and the study of the influence of the N-protonation of this heterocycle on the ring–chain equilibrium.

The action of thionyl chloride on 2-(2-pyridylcarbonyl)benzoic acid (I) yielded [3] 6,11-dioxo-6,11-dihydrobenzo[b]-quinolizinium chloride (II). It is known [4, 5] that 2-acylbenzoyl chlorides exist, for the most part, in the stable cyclic form of 3-R-3-chlorophthalides. The stable open isomers of 2-acylbenzoyl chlorides are only obtained in those cases where the carbonyl group is sterically shielded by the substituent (2-mesityl, 9-anthryl). Therefore, the chloride (II) is an interesting exception, where the stable cyclic form is formed as a result of the intramolecular acylation of the nitrogen atom of the pyridine ring. As was also expected, the chloride (II) possesses increased reactivity in relation to the attack of the CON^+ group by the nucleophilic reagent in comparison with 3-R-3-chlorophthalides. It was shown in a preliminary communication [3] that the solution of the chloride (II) occurring when it is heated in polar organic solvents (acetic acid, acetonitrile, nitromethane, and DMSO) is accompanied by its isomerization to 3-(2-pyridyl)-3-chlorophthalide (III). It was shown afterwards that 3-hydroxy-3-(2-pyridyl)phthalide hydrochloride (IV), i.e., a protonated cyclic form of the acid (I), is a product of the conversion of the chloride (II); this was also confirmed by the direct synthesis (I) → (IV) [2]. On a hypothetical basis, the formation of the hydrochloride (IV) occurs as a result of the interaction of the chloride (II) with traces of water contained in the organic solvent. Only equimolar amounts of the chloride (II) and water thereby enter into the reaction. In consequence of this, after the addition of a molecule of water with the opening of the azaquinone ring and the subsequent new cyclization, the reaction is completed at the stage of the formation of the hydrochloride (IV), which does not undergo the cleavage of a molecule of hydrogen chloride with the conversion to the acid (I). When an excess amount of water acts on the chloride (II), it is hydrolyzed quantitatively to the acid (I) [3] (see top of the following page).

When the chloride (II) reacts with ammonia and a series of primary aliphatic and aromatic amines, the C=O group connected with the quaternized nitrogen atom undergoes nucleophilic attack; the amides thereby formed in the reaction medium are cyclized to their ring isomers — 2-substituted 3-hydroxy-3-(2-pyridyl)isoindolinones (Va-f, h, i) (Table 1). The IR spectra

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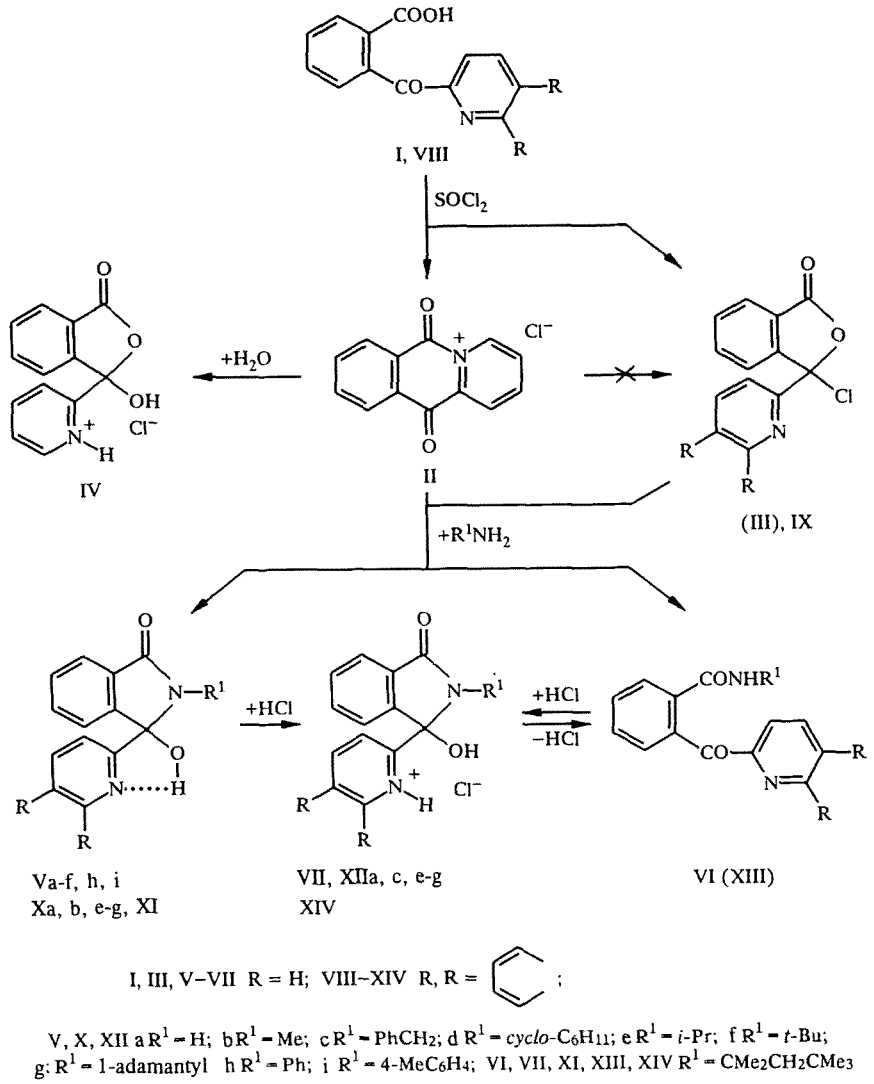

I, III, V–VII R = H; VIII–XIV R, R = ;

V, X, XII a R^1 = H; b R^1 = Me; c R^1 = $PhCH_2$; d R^1 = *cyclo*-C_6H_{11}; e R^1 = *i*-Pr; f R^1 = *t*-Bu; g: R^1 = 1-adamantyl h R^1 = Ph; i R^1 = 4-MeC_6H_4; VI, VII, XI, XIII, XIV R^1 = $CMe_2CH_2CMe_3$

of the compounds (Va-f, h, i) contain only one band of the C=O group of the isoindolinone, which is shifted toward high frequencies in the dioxane solution. The spectra of the crystalline substances also contain broad bands of the associated OH groups which, in general, gives the spectral picture also characteristic of other isoindolinones of an analogous structure [5, 6]. The reaction of the chloride (II) with 1,1,3,3-tetramethylbutylamine affords N-(1,1,3,3-tetramethylbutyl)-2-(2-pyridylcarbonyl)benzamide (VI). The IR spectrum of the amide (VI) contains the band of the C=O group of the ketone, the amide-I and amide-II bands, and the characteristic narrow band of the stretching vibrations of the NH group. Within the limits of sensitivity of the method of IR spectroscopy, ring–chain tautomeric equilibrium between the open amide form and the hydroxyisoindolinone form was not detected in the solution in dioxane.

The protonation of the nitrogen atom of the pyridine ring in the molecule of the amide (VI) leads to the cyclization (VI) → (VII). Thus, the IR spectrum of the hydrochloride of 2-(1,1,3,3-tetramethylbutyl)-3-hydroxy-3-(2-pyridyl)isoindolinone (VII) has the band of the C=O group of the isoindolinone; the bands of the amide-II and the NH of the amide group are absent. The deprotonation of compound (VII) by aqueous ammonia is accompanied by the opening of the ring (VII) → (VI).

Therefore, using this example, the cyclization of a 2-aroylbenzamide to 3-hydroxyisoindolinone was first accomplished with a bulky substituent at the nitrogen atom such as 1,1,3,3-tetramethylbutyl. We previously established that the ability of N-(tert-alkyl)-2-aroylbenzamides to form the ring form of 3-hydroxyisoindolinone on account of the addition of the amide group to the keto group decreases according to the extent of the increase in the steric volume of the substituent at the nitrogen atom in the series tert-butyl < 1-adamantyl < 1,1,3,3-tetramethylbutyl [7-10]. Until the present, the intramolecular cyclization of the 2-aroylbenzamide to 3-hydroxyisoindolinone was only successful in the cases of the tert-butyl or 1-adamantyl substituent at the nitrogen atom.

TABLE 1. Characteristics of the 2-Substituted 3-Hydroxy-3-(2-pyridyl)isoindolinones (Va-f, h, i)

Compound	Empirical formula	mp, °C*	R_f (acetone–hexane)	IR spectrum, ν, cm^{-1}			Yield, %*2
				crystalline substances		solutions in dioxane	
				C=O	OH, NH	C=O	
Va	$C_{13}H_{10}N_2O_2$	176...178	0,29 (1 : 1)	1710	3275, 3045	1719	32
Vb	$C_{14}H_{12}N_2O_2$	172...173	0,46 (1 : 1)	1672	3278	1707	46
Vc	$C_{20}H_{16}N_2O_2$	124...125	0,42 (1 : 2)	1698	3060	1714	73
Vd	$C_{19}H_{20}N_2O_2$	152...153	0,39 (2 : 3)	1695	3060	1708	71
Ve	$C_{16}H_{16}N_2O_2$	167...169	0,62 (1 : 1)	1678	3140	1706	57
Vf	$C_{17}H_{18}N_2O_2$	171...172	0,42 (2 : 3)	1690	3090	1704	66
Vh	$C_{19}H_{14}N_2O_2$	196...197	0,67 (1 : 1)	1715	3320, 3050	1718	80
Vi	$C_{20}H_{16}N_2O_2$	180...181	0,64 (1 : 1)	1702	3030	1714	63

*The compounds were purified by recrystallization as follows: (Va, i) from ethanol, (Vb) from the mixture benzene–hexane, (Vc-f) from 50% ethanol, and (Vh) from benzene.

*2The yields are shown for the recrystallized substances.

In contrast to the acid (I), 2-(2-quinolylcarbonyl)benzoic acid (VIII) forms the acid chloride of the "ordinary" cyclic structure, 3-(2-quinolyl)-3-chlorophthalide (IX), in the reaction with thionyl chloride. The condensed benzene ring, more precisely the 8-H of the quinoline ring, probably produces steric prevention of the intramolecular acylation of the nitrogen atom in the quinoline substituent. The IR spectrum of the chlorophthalide (IX) contains only one C=O band at approximately 1800 cm^{-1}, which is also characteristic of chlorolactones of an analogous structure [5].

The reaction of the chlorophthalide (IX) with ammonia, benzylamine, and isopropylamine, as well as a series of tert-alkylamines, led to the exclusive isolation of ring isomers of amides — 2-substituted 3-hydroxy-3-(2-quinolyl)isoindolinones (Xa, c, e-g), (XI) (Table 2). It was established by the method of IR spectroscopy that the compounds (Xa, c, e-g) and (XI) occur in the cyclic form of the isoindolinones both in the crystalline state and in the solutions in dioxane, and that, within the limits of sensitivity of the method of IR spectroscopy, tautomeric equilibrium between the ring and open amide forms was not detected. In that case, ring isomers of amides not only with bulky tert-butyl and 1-adamantyl substituents at the nitrogen atom [compounds (Xf, g)], but also the 2-(1,1,3,3-tetramethylbutyl)-3-hydroxy-3-(2-quinolyl)isoindolinone (XI), which is first observed in the series of 2-aroylbenzamides, are successfully obtained.

Compound (XI) undergoes thermal isomerization to the open form of the N-(1,1,3,3-tetramethylbutyl)amide of 2-(2-quinolylcarbonyl)benzoic acid (XIII); this also explains the indistinct melting temperature of the compound (XI). The isomerization is not completely accomplished; the equilibrium mixture of the open and ring isomers (XI) ⇄ (XIII) is isolated. This is confirmed by the IR spectrum, where bands of the C=O of the ketone (1680 cm^{-1}), the amide-I (1650 cm^{-1}), and amide-II (1536 cm^{-1}) are observed besides the C=O band of the isoindolinone (1700 cm^{-1}); the band of the associated group of the OH is retained (3340 cm^{-1}), and the band of the NH group appears (~3390 cm^{-1}).

With the object of obtaining derivatives, soluble in water, to be screened for biological activity, the synthesis of the hydrochlorides was accomplished by the action of hydrogen chloride on the compounds (Xa, c, e-g) and (XI). It was thereby established that the hydrochlorides (XIIa, c, e-g) and (XIV) have the ring structure of isoindolinones.

In comparing the IR spectra of the crystalline isoindolinones (Va-f, h, i), (Xa, c, e-g), and (XI) (Tables 1 and 2), it can be observed that hydrogen bonds of two types are formed in the crystalline state. The intermolecular OH...C=O bonds, generally characteristic of 3-hydroxyisoindolinones, pertain to the first type [5]. The compounds (Vb, e) and (Xa, e) pertain to

TABLE 2. Characteristics of the 2-Substituted 3-Hydroxy-3-(2-quinolyl)isoindolinones (Xa, c, e-g), (XI), and Their Hydrochlorides (XIIa, c, e-g) and (XIV)

Compound	Empirical formula	mp, °C*	R_f (ethyl acetate–CCl_4)	IR spectrum, ν, cm^{-1}			Yield, %*2
				crystalline substances		Solutions in dioxane	
				C=O	OH, N^+H	C=O	
Xa	$C_{17}H_{12}N_2O_2$	190...191	0,33 (2 : 1)	1694	3272 broad,	1724	61
Xc	$C_{24}H_{18}N_2O_2$	150...151	0,56 (1 : 1)	1704	3236	1710, 1698	69
Xe	$C_{20}H_{18}N_2O_2$	140...141	0,53 (1 : 1)	1678, 1640	3468, 3395, 3148	1698	60
Xf	$C_{21}H_{20}N_2O_2$	194...195	0,59 (1 : 1)	1690, 1682	3332	1706	50
Xg	$C_{27}H_{26}N_2O_2$	218...219	0,85 (1: 1)	1692	3288	1704	53
XI	$C_{25}H_{28}N_2O_2$	184...186	0,67 (1 : 1)	1698	3340	1702	31
XIIa	$C_{17}H_{12}N_2O_2$ · HCl	140...142 (decomp.)		1728	3452, 3336, 3100, 2796		97
XIIc	$C_{24}H_{18}N_2O_2$ · HCl	157 (decomp.)		1682, 1672	3204 broad. 2900...2700 broad.		81
XIIe	$C_{20}H_{18}N_2O_2$ · HCl	150 (decomp.)		1702	3000...2700 broad.		98
XIIf	$C_{21}H_{20}N_2O_2$. · HCl	200...202 (decomp.)		1677, 1665	3457, 3097 broad.		75
XIIg	$C_{27}H_{26}N_2O_2$ · HCl	138 (decomp.)		1685, 1668	3120 broad.		98
XIV	$C_{25}H_{28}N_2O_2$ · HCl	110 (decomp.)		1698, 1680, 1664	3560, 3392, 3056, 2956, 2912. 2856		98

*The compounds were purified by recrystallization as follows: (Xa, c, e-g) and (XI) from ethanol, and (XIIa, c, f) from the mixture abs. ethanol–abs. ether.

*2The yields are shown for the recrystallized substances.

this group; in their spectra, the shift in the frequency of the C=O band in the transition from the crystalline state to the solutions in dioxane comprises 20-38 cm^{-1}. The intra- or intermolecular hydrogen bonds with the participation of the nitrogen atom of the pyridine or quinoline substituent (OH...N) pertain to the second type. The compounds (Va, c, d, f, h, i), (Xc, f, g), and (XI) pertain to this group; in their spectra, the $\Delta\nu_{C=O}$ = 3-16 cm^{-1}. Confirmation of the stated information is provided by the shift of the C=O band of the isoindolinone toward low frequencies in the transition from the crystalline isoindolinones (Xc, f, g) to their hydrochlorides (XIIc, f, g), which is determined by the reorganization of the hydrogen bonds from the O–H...N to the OH...O=C in the crystalline hydrochlorides (XIIc, f, g). In some cases, the reorganization of the hydrogen bonds was even observed in the recrystallization. For example, in the spectrum of the crystalline isoindolinone (Vd), precipitated with water from the dioxane solution, the C=O bands were observed at 1679 and 1667 cm^{-1} (OH...O=C), but it was observed at 1695 cm^{-1} (OH...N) after the recrystallization.

EXPERIMENTAL

The IR spectra were taken on the Specord M-80 instrument using suspensions in mineral oil and hexachlorobutadiene and in solutions of dioxane with the concentration of $2.5 \cdot 10^{-2}$ M. The monitoring of the course of reactions and the purity of the substances was accomplished by the method of TLC using plates of silica gel type Silufol UV-254, the eluent of acetone–hexane and ethyl acetate–carbon tetrachloride, and the development in UV light and with iodine.

The data of the elemental analysis for C, H, N, and Cl correspond with the calculated data.

The 6,11-dioxo-6,11-dihydrobenzo[b]quinolizinium chloride (II) was obtained by the method of [3].

2-Unsubstituted and 2-Methyl-3-hydroxy-3-(2-pyridyl)isoindolinones (Va, b) (Table 1). To the suspension of 2 mmoles of the chloride (II) in 15 ml of acetonitrile is added, dropwise with stirring at 20°C in the course of 5 min, the solution of 5 mmoles of ammonia or methylamine in 5 ml of acetonitrile. The reaction mixture is stirred for 2 h, maintained at 20°C for 15-20 h, and then poured into 50 ml of water. The aqueous solution is saturated with sodium chloride and extracted with chloroform (2 × 40 ml). After the separation of the organic layer, it is dried over magnesium sulfate; the solvent is evaporated in vacuo, and the residue is recrystallized.

2-Substituted 3-Hydroxy-3-(2-pyridyl)isoindolinones (Vc-f, h, i) (Table 1). To the suspension of 4 mmoles of the chloride (II) in 30 ml of acetonitrile are added 4 mmoles of the corresponding amine, and then the solution of 4 mmoles of triethylamine in 10 ml of acetonitrile is added dropwise with the stirring at 20°C. The reaction mixture is stirred for 2 h, held at 20°C for 15-20 h, and then poured into 150 ml of water. The precipitated residue is filtered off, washed with water, dried, and recrystallized. If required, the solution is clarified by the addition of activated carbon.

N-(1,1,3,3-Tetramethylbutyl)-2-(2-pyridylcarbonyl)benzamide (VI) ($C_{21}H_{26}N_2O_2$). To the suspension of 0.49 g (2 mmoles) of the chloride (II) in 15 ml of acetonitrile is added, dropwise with stirring at 20°C in the course of 5 min, the solution of the mixture of 0.26 g (2 mmoles) of 1,1,3,3-tetramethylbutylamine and 0.28 ml (2 mmoles) of triethylamine in 5 ml of acetonitrile. The reaction mixture is stirred for 2 h and maintained at 20°C for 15-20 h, prior to the separation of the residue and the pouring of the filtrate into 100 ml of water. The precipitated residue is filtered off, washed with water, and recrystallized from 20-25 ml of 50% ethanol with the addition of activated carbon. Colorless crystals of the amide (VI) are obtained; the yield is 0.35 g (52%). The mp is 167-168°C, and the R_f is 0.40 (the 1:2 mixture of acetone–hexane). The IR spectrum in a thin layer, given in cm^{-1}, is as follows: 3378, 3054, 2956, 2932, 2908, 2870, 1672, 1638, 1588, and 1534. The IR spectrum in dioxane, given in cm^{-1}, is as follows: 1687, 1661, 1586, and 1529.

Hydrochloride of 2-(1,1,3,3-Tetramethylbutyl)-3-hydroxy-3-(2-pyridyl)isoindolinone (VII) ($C_{21}H_{26}N_2O_2 \cdot HCl$). The amide (VI) (0.17 g, 0.5 mmole) is dissolved with heating in 5 ml of abs. dioxane. The solution is cooled to 40-50°C prior to the addition of 5 ml of abs. ether saturated with dry hydrogen chloride. Then, 20-25 ml more of pure abs. ether are added, and the mixture is maintained at 0°C for 15-20 h. The residue is filtered off, washed with abs. ether, and dried in vacuo. Compound (VII) is obtained with the yield of 0.15 g (80%); it has the mp 143-145°C (decomp.). The IR spectrum, given in cm^{-1}, is as follows: 3075, 3030 (broad band, OH), 2952, 2873, 2750, 2340 (N^+H), 1685, and 1603.

Isomerization (VII) → (VI). Compound (VII) (0.15 g, 0.4 mmole) and 5 ml of concentrated aqueous ammonia are stirred at 20°C for 1 h. The residue is separated, washed with water, and dried. Compound (VI) is obtained with the yield of 0.13 g (96%), and it is identical in all characteristics to the sample of (VI) obtained previously.

3-(2-Quinolyl)-3-chlorophthalide (IX) ($C_{17}H_{10}ClNO_2$). The acid (VIII) (0.56 g, 2 mmoles) [2] and 0.44 ml (6 mmoles) of thionyl chloride are boiled for 1 h in 10 ml of abs. benzene (or 2 ml of thionyl chloride without the solvent). The reaction mixture is concentrated in vacuo, and the chlorophthalide (IX), obtained in the form of an oil, can be utilized for further reactions with amines without isolation in the crystalline form. Using the recrystallization from the mixture of benzene–hexane, colorless crystals of the chlorophthalide (IX) are obtained. The yield is 0.56 g (93%), and the mp is 94-96°C. The IR spectrum in a thin layer, given in cm^{-1}, is as follows: 3572, 3064, 1794, 1622, 1594, 1564, and 1502. The IR spectrum in dioxane, given in cm^{-1}, is as follows: 1802, 1620, 1596, 1573, and 1504.

2-Substituted 3-Hydroxy-3-(2-quinolyl)isoindolinones (Xa, c, e-g) and (XI) (Table 2). To the solution of 2 mmoles of the chlorophthalide (IX) in 6 ml of abs. dioxane are added, with stirring, 10 ml of aqueous ammonia [for the isolation of compound (Xa)] or the mixture of 2 mmoles of the corresponding amine and 2 mmoles of triethylamine in 4 ml of abs. dioxane [for the isolation of compounds (Xc, e-g) and (XI)]. The reaction mixture is maintained for 15-20 h at 20°C [additional heating on a water bath for 1 h is performed in the synthesis of compound (XI)], and the mixture is then poured into 50 ml of water [into 50 ml of the 5% solution of sodium carbonate in the case of the compounds (Xe) and (XI)]. The residue is separated and recrystallized from ethanol prior to the isolation of the compounds (Xa, c, e-g) and (XI) as colorless crystalline substances.

Hydrochlorides (XIIa, c, e-g) and (XIV) (Table 2). The compounds (Xa, c, e-g) and (XI) (0.2 g) are dissolved in 5 ml of abs. dioxane. To the solution obtained are added 10 ml of abs. ether saturated with dry hydrogen chloride. The residue is separated, washed with abs. ether, and dried in vacuo prior to the isolation of colorless crystals of the hydrochlorides (XIIa, c, e-g) and (XIV). If required, the hydrochlorides are recrystallized from the mixture abs. ethanol–abs. ether.

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