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NEW METHOD OF SYNTHESIZING PYRIDYL- AND QUINOLYLCARBONYLARENECARBOXYLIC ACIDS

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UDC 547.589.5'824'831.8:541.62

An original method has been developed for the synthesis of a number of pyridyland quinolylcarbonylarenecarboxylic acids by condensing anhydrides of aromatic dicarboxylic acids with picolinic and quinaldic acids. The characteristics of the IR spectra of the compounds synthesized are given, and their ring-chain equilibrium transformations are discussed. It has been shown that the protonation of the nitrogen atom of the heterocycle stabilizes the cyclic form.

We have previously detected the stabilization of the ring form of 2-(imidazol-2-ylcarbonyl)benzamides by the protonation of the imidazole ring [1, 2]. It appeared of interest to investigate the influence of this effect on ring-chain equilibrium systems of keto carboxylic acids and their derivatives having other nitrogen heterocycles attached to the keto group.

The aim of the present work was to synthesize and investigate pyridyl- and quinolylcarbonylarenecarboxylic acids.

2-(2-Pyridylcarbonyl)benzoic acid (Ia) has long been known, but the methods previously used for its preparation [3, 4] involve many stages and are laborious. We [5] have obtained the acid (Ia) by condensing phthalic anhydride with picolinic acid at the temperature of decarboxylation of the latter (160-165°C) in a high-boiling organic solvent (nitrobenzene, benzonitrile, cymene, diethyleneglycol diethyl ether). This method is favorably distinguished from those known previously [3, 4] by the fact that it is a single-stage process, by the use of readily available reactants, and by the simplicity of its practical performance.

We have studied the possibility of expanding the boundaries of this method by using carboxylic acids of other nitrogen heterocycles, and also the anhydrides of other aromatic dicarboxylic acids. Thus, in the analogous reaction of naphthalic and diphenic anhydrides with

A. Ya. Pel'she Riga Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1231-1234, September, 1984. Original article submitted October 10, 1983; revision submitted January 31, 1984.



picolinic acid, 8-(2-pyridylcarbonyl)-1-naphthoic acid (Ib) and 2'-(2-pyridylcarbonyl)biphenyl-2-carboxylic acid (Ic) were obtained. The reaction of phthalic, naphthalic, and diphenic anhydrides with quinaldic acid, when the reaction conditions given above were observed, led to the synthesis of, respectively, 2-(2-quinolylcarbonyl)benzoic acid (Id), 8-(2-quinolylcarbonyl)-1-naphthoic acid (Ie), and 2'-(2-quinolylcarbonyl)biphenyl-2-carboxylic acid (If).

The method that we have proposed is a modification of the Hammick reaction [6] in which aromatic dicarboxylic acid anhydrides are used as the carbonyl components in place of aldehydes or ketones. The yields of the acids (Ia-f) ranged between 24 and 43% (Table 1). It was impossible to increase the yields by changing the temperature conditions of the reaction, the solvents, and the ratios of the reactants. It is obvious that the carbanions formed in the decarboxylation of the picolinic and quinaldic acids and attacking the C=O group of the dicarboxylic acid anhydride undergo the competing reaction of protonation with the formation of pyridine and quinoline.

The acids (Ia-f) synthesized may exist in three isomeric forms: open, A; cyclic, B; and betaine, C. To determine the structures of the acids (Ia-f) in the crystalline state and in solution we used the method of IR spectroscopy. The IR absorption bands of the acids (Iaf) in the form of crystalline compounds and their solutions in dioxane are given in Table 1.

In the IR spectra of the 2-(2-pyridyl- and 2-quinolylcarbonyl)benzoic acids (Ia, d), the ring form of which is produced by the closure of a five-membered lactone ring, in the crystalline state absorption bands of the C=O groups of the carboxy and ketone groupings are observed, which confirms their open structure (IaA and IdA). The appearance in the spectra of the acids (Ia, d) in dioxane solution of - besides the above-mentioned bands - the band of the C=O group of a five-membered hydroxylactone [7] indicates the existence of the tautomeric equilibrium A  $\stackrel{>}{\downarrow}$  B.

In the IR spectra, taken both for the crystalline substances and for dioxane solutions, of the 8-(2-pyridyl- and 2-quinolylcarbonyl)-1-naphthoic acids (Ib, e), the ring forms of which are obtained by the closure of a six-membered lactone ring, there is, in each case, only one absorption band of a C=O group (in solution, a shift of this band toward higher frequencies by  $30-40 \text{ cm}^{-1}$  is observed). The absence of a ketonic C=O band, and also the presence in each spectrum of the characteristic band of an OH group at 3225 and  $3270 \text{ cm}^{-1}$ , respectively, for the acids (Ib) and (Ib) (see [8]) permits the conclusion that these acids exist both in the crystalline state and in solution in the ring form of 3-hydroxy-3-(2-pyridyl- and 2-quinolyl)perinaphthalides [(IbB and (IEB)].

In the IR spectra of the 2'-(2-pyridy1- and 2-quinolylcarbony1)bipheny1-2-carboxylic acids (Ic, f), the ring form of which can be produced by the closure of a 7-membered lactone ring, both in the crystalline state and in dioxane solution the absorption bands are observed of carboxylic and ketonic C=O groups, and there is no absorption of a lactone C=O group, which confirms their open structures [(IcA), (IfA)].

The protonation of the nitrogen atoms in the proline and quinoline rings in the molecules of the acids (Ia) and (Ib) leads to the formation of a protonated cyclic form. Thus, in the IR spectra of the hydrochlorides of acids (IIa) and (IId) taken for the crystalline substances there is, in each case, only one absorption band of the C=O group of a five-mem-

TABLE	1.	Characteristics	of	the	Acids	(Ia-f)	

1		IR spectrum, cm <sup>-1</sup>										Calou			
Compound	mp, °C (from eth- anol)	in Nujol, vC=0		in dioxane, vC=0			Found, %			Empiric <b>al</b>	lated, %			~	
		lactone	carboxyl	ketone	lactone	carboxyl	ketone	С	н	N	formu <b>la</b>	с	н	N	Yield.
Ia	229—230† decomp		1689	1681	1775	1715	1689								38
lb ∫c	167 - 168 149 - 150	1689	 1715	1673	1729	 1736	 1673	73,5 75,1	4,0 4,3	4,5 4,2	C <sub>17</sub> H <sub>11</sub> NO <sub>3</sub> C <sub>19</sub> H <sub>13</sub> NO <sub>3</sub>	73,6 75,2	4,0 4,3	5,1 4,6	40 28
١d	225—226, decomp.	-	1690	1671	1778	1720	1684	73,8	4,4	4,9	$C_{17}H_{11}NO_3$	73,6	4,0	5,1	43
le I f	179—180 185—186	1715	1706	1670	1732	 1726	1670	77,2 78,2	4,2 4,5	4,5 4,1	$\begin{array}{c} C_{21}H_{13}NO_{3}\\ C_{23}H_{15}NO_{3} \end{array}$	77,1 78,2	4,0 4,3	4,3 4,0	43 24

\*The yields of compounds (Ib, c, e, and f) are given with allowance for the recovered unchanged anhydride. +mp 229-232°C, decomp. [3].

TABLE 2. Characteristics of the Hydrochlorides of the Acids (IIa-f)

Hydro- chlorides	mp, °C	II meetruth cm <sup>-1</sup>	Found, %				Empirical	Calculate, %				d, %
of the com- pounds	(decomp.)	ik spectrum, cm	с	н	CI	N	formu <b>la</b>	С	Н	CI	N	Yiel
Ha	185—187	3040, 2830, 2520, 1788, 1608, 1528	59,2	4,1	13,6	5,2	C <sub>13</sub> H9NO3∙ ∙ HCl	59,2	3,8	13,5	5,3	98
IIb	215-217	3410, 3030, 2650, 1734, 1605, 1584,	65,1	4,1	11,3	4,2	C <sub>17</sub> H <sub>11</sub> NO <sub>3</sub> · · HCl	65,1	3,9	11,3	4,5	96
IIc	186—190	1516 3368, 2858, 2547, 1687, 1599, 1563,	67,0	4,4	10,2	4,3	C₁9H₁3NO3 · • HCl	67,2	4,2	10,4	4,1	86
IId	182—183	1521 3420, 2980, 2500, 1782, 1633, 1597,	64,7	4,3	11,0	4,2	C <sub>17</sub> H <sub>11</sub> NO <sub>3</sub> · · HCl	65,1	3,9	11,3	4,5	93
IIe	196—198	$ \begin{array}{c}     3420, 3065, 2955, \\     2690, 1736, 1637, \\     1500, 1535, 1500 \end{array} $	68,7	4,2	9,8	3,6	$\begin{array}{c} C_{21}H_{13}NO_3 \cdot \\ \cdot HCl \end{array}$	69,3	3,9	9,8	3,9	93
IIf	156	1590, 1555, 1509 3390, 2842, 1685 sh., 1675, 1630, 1592, 1566, 1540	70,6	4,3	9,6	3,5	C <sub>23</sub> H <sub>15</sub> NO₃ · • HCl	70,9	4,1	9,1	3,6	84

bered lactone, the bands of carboxylic and ketonic C=O groups being absent, which confirms the ring structure D.

This example shows that the protonation of the pyridine and quinoline rings considerably facilitates the closure of the 5-membered hydroxylactone ring — obviously because of the increase in the electrophilicity of the carbon atom of the keto group (see [1, 2]).

The hydrochlorides of the other acids (IIb, c, e, and f) were also synthesized (Table 2). Judging from the IR spectra of the crystalline compounds, the hydrochloride of (IIb) is a cyclic structure and those of (IIc and f) are open structures, although the presence in the spectra of the hydrochlorides of (IIc and f) of an absorption band in the region of the stretching vibrations of an OH group (3390-3370 cm<sup>-1</sup>) may indicate the presence of the cyclic form.

Thus, we have developed a convenient one-stage method for obtaining pyridyl- and quinolylcarbonylarenecarboxylic acids, which are difficultly accessible by other methods of synthesis [3, 4].

## EXPERIMENTAL

IR spectra were taken on IKS-14A and Specord 75 IR spectrophotometers using mulls in paraffin oil (Nujol) and hexachlorobutadiene, and also solutions in dioxane,  $c = 2.5 \cdot 10^{-2}$  M.

2-(2-Pyridylcarbony1)benzoic Acid (Ia, Table 1). A mixture of 12.3 g (0.1 mole) of picolinic acid and 29.6 g (0.2 mole) of phthalic anhydride in 100 ml of nitrobenzene was heated at 100°C with stirring until a homogeneous solution had been formed. Then the temperature was raised to 160-165°C and the reaction mixture was kept at this temperature, with stirring, until the evolution of carbon dioxide had ceased — about 3 h. After cooling and keeping at room temperature for 10-12 h, the precipitate that had deposited was filtered off and was washed with nitrobenzene and then with benzene and was dried to give gray crystals of the acid (Ia). The filtrate was extracted with 6 N hydrochloric acid, and the aqueous layer was separated off, decolorized with activated carbon, and neutralized with 10% sodium carbonate solution to pH 4-5, and it was then saturated with sodium chloride. The resulting precipitate was filtered off, washed with water, and dried. The two precipitates obtained were dried and recrystallized from ethanol to give the acid (Ia) in the form of colorless crystals.

8-(2-Pyridyl- and 2-Quinolylcarbonyl)-1-naphthoic acids (Ib, e, Table 1), and 2'-(2pyridyl- and 2-quinolylcarbonyl)biphenyl-2-carboxylic acids (Ic, f, Table 1) were obtained from 0.01 mole of picolinic or quinaldic acids and 0.01 mole of naphthalic anhydride in 10 ml of nitrobenzene (Ib, c) or from 0.1 mole of picolinic or quinaldic acid and 0.1 mole of diphenic anhydride in 100 ml of nitrobenzene (Ic, f). After the reaction had ceased and the reaction mixture had been kept at room temperature for 10-12 h, the precipitate of unchanged naphthalic or diphenic anhydride was filtered off. The filtrate was extracted with 6 N hydrochloric acid, and the aqueous layer was separated off, decolorized with activated carbon, and neutralized with 10% sodium carbonate solution to pH 4.5, and it was then saturated with sodium chloride. The resulting precipitate was filtered off, washed with water, and dried to give one of the acids (Ib, c, e, and f).

2-(2-Quinoly1carbony1)benzoic Acid (Id, Table 1). This was obtained from 0.01 mole of quinaldic acid and 0.02 mole of phthalic anhydride in 10 ml of nitrobenzene in a similar manner to the synthesis of (Ia).

General Method for the Synthesis of the Hydrochlorides of the Acids (IIa-f, Table 2). With heating, 0.5 g of one of the acids (Ia-f) was dissolved in 20 ml of absolute dioxane, and dry hydrogen chloride was bubbled through the solution until it was saturated, after which 20 ml of absolute ether was added. After cooling, the resulting precipitate was filtered off, washed with absolute ether, and dried in a vacuum desiccator.

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