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3-(HETARYLAMINO)- AND 3-[(HETARYLMETHYL)AMINO]-ISOQUINOLIN-1(2H)-ONES

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The reaction of 2-(cyanomethyl)benzoic acid with amines RNH_2 (R = Ar, Het, CH_2Ar, CH_2Het) leads to the formation of the corresponding 3-NHR-isoquinolin-1(2H)-ones. When R = CH_2Ar and CH_2Het, there is a side reaction involving hydrolysis of the hydrolytically-unstable intermediates, derivatives of 2-(2-amino-2-iminoethyl)benzoic acid, leading to 2-R-isoquinoline-1,3(2H,4H)-diones.

Keywords: amidines, 3-aminoisocarbostyryl, 2-(arylmethyl)- and 2-(hetarylmethyl)isoquinoline-1,3(2H,4H)-diones, 3-hetarylaminoisoquinolin-1(2H)-ones, 3-(hetarylmethyl)aminoisoquinolin-1(2H)-ones, homo-phthalimide, 2-(cyanomethyl)benzoic acid.

Interest in the chemistry of derivatives of 3-aminoisoquinolin-1(2H)-one (3-aminoisocarbostyryl) has increased in recent years with the discovery that some of these compounds have valuable biological activity [1-4]. The introduction of an additional heterocyclic fragment into the molecule may considerably expand the spectrum of biological action of these compounds. A convenient method for the synthesis of noncondensed 3-aminoisocarbostyryls based on the reaction of 2-(cyanomethyl)benzoic acid (**1**) with amines, has previously been used for the preparation of 3-benzylamino- [5], dialkylamino- [6], and arylaminoisocarbostyryls [6-8]. In the present work, this approach has been expanded to hetaryl- and (hetarylmethyl)amines.

Heating mixtures of 2-(cyanomethyl)benzoic acid (**1**) with hetarylamines in high-boiling solvents such as 1,2-dichlorobenzene, 1:1 DMF-1,2-dichlorobenzene, and DMF for 3-8 h leads to the formation of 3-(hetarylamino)isoquinolin-1(2H)-ones **2a-m** (Scheme 1). The reaction product yield depends on the solvent. The choice of the solvent is a function of the solubility of the starting amine in it. The highest yields of isoquinolones **2a-m** (50-70%) are achieved using chlorobenzene. The effect of the hetaryl substituent on the reaction result is less pronounced. However, a trend is noted toward increasing yields of product **2** with increasing basicity of the amine. For example, the yields of 3-pyridylamino derivatives **2d**,**e** were 63-68%, while the yields for diazinamino derivatives **2a,b**,**f** were only 35-51%. The structure of 3-amino-isocarbostyryls **2a-m** was supported by IR and ^{1}H NMR spectroscopy (Tables 1 and 2).

A characteristic feature of the ^{1}H NMR spectra of isoquinolones **2** is the finding of singlets for H(2), H(3), and 3-NH group (Table 2). The signal for 3-NH observed in a broad range from 6.7 to 11.5 ppm is the most sensitive to the nature of the hetaryl substituent. This signal is shifted downfield with increasing electron-withdrawing properties of the Het substituent. The Het substituent has the same but less pronounced effect on the signals for H(2) (10.5-13.0 ppm) and H(4) protons (5.2-6.4 ppm).

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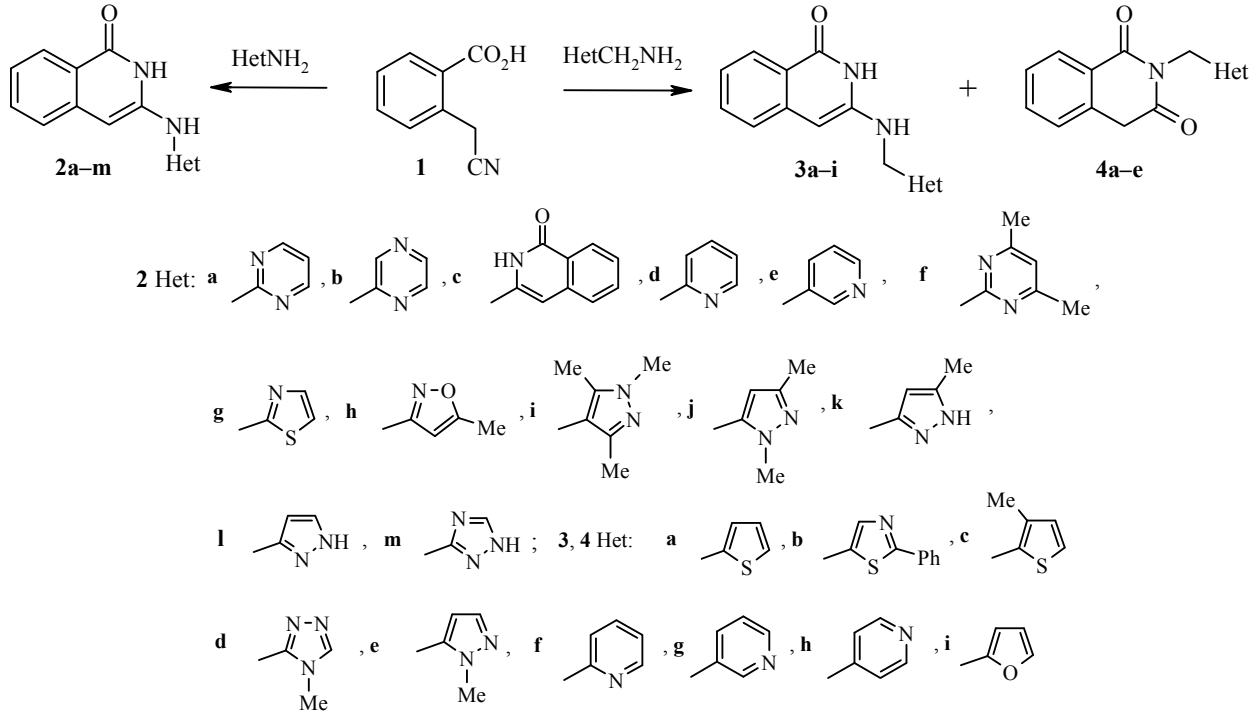
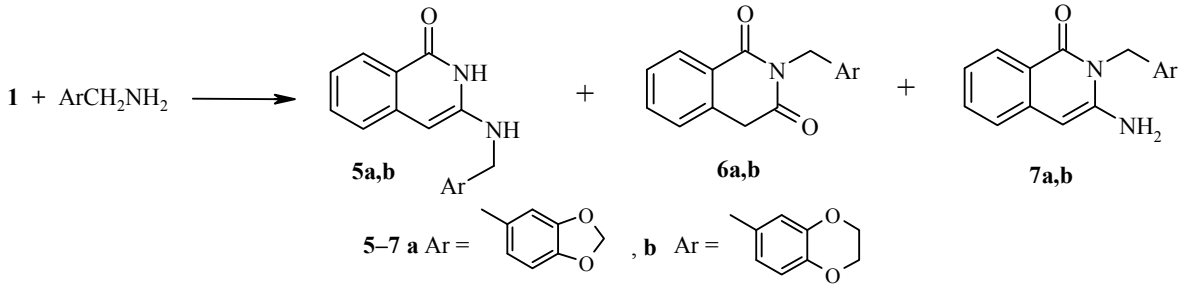
Scheme 1



The reaction of acid **1** with (hetarylmethyl)amines under the same conditions with 1,2-dichlorobenzene or 1:3 DMF-1,2-dichlorobenzene as solvent has a more complex course. Thus, the reaction with aminomethyl derivatives of thiophene, 1,3-thiazole, pyrazole, and 1,3,4-triazole in all cases yielded a mixture of two reaction products in almost equal amounts (~1.15:1.00). The major component was a 3-[(hetarylmethyl)amino]isoquinolin-1(2H)-one **3a-e**, while the minor component was a 2-(hetarylmethyl)isoquinoline-1,3(2H,4H)-dione **4a-e** (Scheme 1). The use of (pyridylmethyl)amines and (2-furylmethyl)amine gave only isoquinolones **3f-i** in good yield (53-69%). All these products **3** and **4** were isolated from the reaction mixtures as pure compounds by recrystallization with the exception of dione **4e**, whose formation was established using ^{1}H NMR spectroscopy and LC/MS (*m/z* 256 $[M+1]^+$ (100%)]. The spectral properties of the 3-NHHet (**2**) and 3-NHCH$_2$Het isoquinolone derivatives **2** are generally similar (Tables 1 and 2). The difference of the ^{1}H NMR spectra of the 3-NHCH$_2$Het derivatives **3** is seen in the upfield position of the signal for proton of 3-NH group (5.4-6.3 ppm) in comparison with the analogous proton in 3-NHHet derivatives **2** (6.7-11.4 ppm) and the formation of an A_2X spin system formed by 3-NH with the CH_2 protons with coupling constant 5.5-6.0 Hz. The nature of the Het substituent has no significant effect on the position of the signals for H(2) (10.5-10.8 ppm) and H(4) (5.3-5.6 ppm). The ^{1}H NMR spectra of homophthalimide derivatives **4a-e** (Table 2) have two singlets for the NCH_2 protons at 5.1-5.2 ppm and for the C(4)H_2 protons at 4.2 ppm, while their IR spectra have carbonyl group stretching bands at 1709-1723 and 1664-1667 cm^{-1}. The IR spectra of products **2** and **3** show one $\nu_{C=O}$ band at 1650-1675 cm^{-1} and, furthermore, ν_{NH} bands at 3165-3406 cm^{-1}, which are lacking in the spectra of homophthalimides **4**.

Thus, the result of the reaction of acid **1** with (hetarylmethyl)amines (Scheme 1) depends on the nature of the Het substituent. Arylamines, similar to hetarylamines studied in our laboratory, react with acid **1** to give exclusively 3-(arylamino)isocarbostyryls of type **2** [5-8]. Of the (arylmethyl)amines, only benzylamine has been used in this reaction. In this case, 3-benzylaminoisocarbostyryl of type **3** was obtained in 70% yield [5]. Thus, it was of interest to study the reaction of acid **1** with other (arylmethyl)amines, of which (1,3-benzodioxol-5-ylmethyl)amine and (2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amine were selected. In both cases, a mixture of three products was obtained (Scheme 2). The major components were the corresponding 3-(arylmethylamino)isoquinolin-1(2H)-ones **5a**,**b** obtained in 42-47% yield and 2-(arylmethyl)isoquinoline-

Scheme 2



1,3(2H,4H)-diones **6a**,**b** obtained in 32-34% yield. The composition and structure of products **5** and **6** were in good accord with the spectral and elemental analysis data. 3-Amino-2-(arylmethyl)isoquinolin-1(2H)-ones **7a**,**b** were also obtained in these reactions in small amounts (up to 11% yield). The formation of products such as **7** was not previously noted in the reactions of acid **1** with amines. Isoquinolone **7b** was isolated from the product mixture by recrystallization. The composition and structure of this product was established by elemental analysis as well as IR and ^{1}H NMR spectroscopy. The IR spectrum of isoquinolone **7b** shows stretching bands for the primary amino group at 3412 and 3333 cm^{-1}. The ^{1}H NMR singlet at 5.91 ppm, which exchanges with D_2O, was assigned to this group protons. The broadening of the N(2)CH_2 group signal is probably the result of steric hindrance to rotation about the N(2)–C and C–C(6') single bonds in isoquinolone **7b**. The presence of isoquinolone **7a** as the third product of the reaction of (1,3-benzodioxol-5-ylmethyl)amine with acid **1** is suggested by us on the basis of the thin-layer chromatographic and LC/MS data for this reaction mixture.

Thus, under similar conditions (9:1, benzene–EtOH) relative chromatographic mobility of the mixture components **5a, 6a, 7a** and **5b, 6b, 7b** is similar: The R_f values of compounds **5a** and **6a** (0.71 and 0.70, respectively), and compounds **5b** and **6b** (0.91 and 0.90, respectively) insignificantly. But in the case of compounds **7a** and **7b**, they are much lower (0.58 and 0.69). A LC/MS analysis of the product mixture obtained from (1,3-benzodioxol- 5-ylmethyl)amine and acid **1** showed three fractions: 1) a product with *m/z* 296 $[M+1]^+$ corresponding to dione **6a** (35% of the mixture), 2) a product with *m/z* 295 $[M+1]^+$ corresponding to isoquinolone **5a** (51% of the mixture), and 3) a product with *m/z* 295 $[M+1]^+$ corresponding to the supposed product **7a** (10% of the mixture).

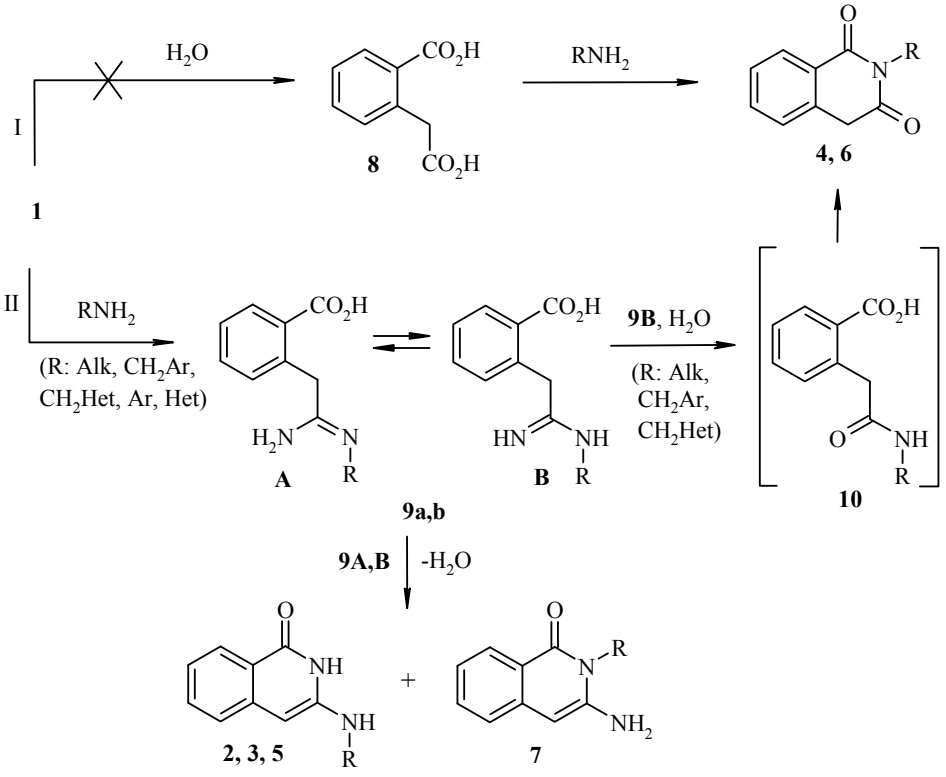
The formation of 2-substituted homophthalimides **4** and **6** from acid **1** eliminated during the formation and (hetarylmethyl)amines and (arylmethyl)amines (Schemes 1 and 2) is probably a consequence of hydrolysis of isoquinolones **3** and **5**.with the participation of water Thus, when the reaction of acid **1** with (1-methyl-1H-pyrazol-5-yl-methyl)amine and (2-furylmethyl)amine proceeds under conditions providing for the removal of water from the reaction medium, the yields of products **3e** and **3i** were markedly increased (from 49 to 72% for **3e** and from 67 to 78% for **3i**).

Methods have been reported for the preparation of homophthalimide derivatives based on the reaction of homophthalic acid (**8**) or its anhydride with amines [9, 10]. There has been only one report on the preparation of a 2-alkylhomophthalimide from cyanoacid **1** [11] but this reaction was carried out in a sulfuric acid solution, i.e., under conditions facilitating hydrolysis of the cyano group. The resistance of acid **1** to hydrolysis in neutral media upon heating in aqueous 1,2-dichlorobenzene or aqueous DMF and the independence of the yield of homophthalimide derivatives on the nature of the amine indicate that diones **4** and **6** are formed not from acid **8** (through pathway I) but from the product of the reaction of acid **1** with the amine (through pathway II) as shown in Scheme 3, which summarizes our results and literature data on the reaction of acid **1** with various amines (the numbering of the compounds in the present work is shown in Scheme).

The formation of intermediate amine **9** with possible tautomeric forms **A** and **B** was shown by us in the reaction of acid **1** with (pyridine-2-ylmethyl)amine and (5-methyl-1H-pyrazol-3-yl)amine. Thus, acids **9a** and **9b**, respectively were isolated only 10-15 min after the onset of heating of mixtures of these reagents. The composition and structure of acids **9** were shown by elemental analysis as well as IR and ^{1}H NMR spectroscopy.

The ^{1}H NMR spectrum of **9a** has signals for the amidine fragment protons at 11.09 and 8.61 ppm, which exchange with D_2O, in addition to the OH group proton signal at 12.15 ppm. The methylene group proton signal at 4.52 ppm is seen as a doublet with $J = 4.0$ Hz, which indicates the formation of amidine **9a** in form **B**. The spectrum of acid **9b** has only one signal for the amidine fragment protons at 10.53 ppm, which is strongly broadened due to rapid exchange of these protons between the two nitrogen atoms in tautomeric forms **A** and **B** (the existence of such forms is characteristic for asymmetrical amidines [12, 13]). Thus, the formation of a mixture of isomeric products **5** and **7** using (dialkoxybenzyl)amines described above may be attributed to the cyclization of tautomeric forms **A** and **B** of intermediate amidines **9**.

Scheme 3



9 a R = pyrid-2-ylmethyl, **b** R = 3-methyl-1H-pyrazol-5-yl

Examples are found in the literature for an effect of the nature of the substituent at the nitrogen atom in acyclic amidines on their resistance to hydrolysis [13]. Our results indicate that amidines **9** with R = CH_2Ar and CH_2Het undergo hydrolysis more readily than amidines with R = Ar and Het. These compounds hydrolyze upon heating with water and are converted to amides of homophthalic acid **10**, which may cyclize to give homophthalimide derivatives **4** and **6** (pathway II) [11, 14, 15]. Thus, we find a definite dependence of the resistance to hydrolysis of amidines **9** on the inductive effect of substituent R. The resistance to hydrolysis of amidines **9** increases with increasing electron-withdrawing capacity of R. This hypothesis is supported by the finding that when R = CH_2Het (Het = 2-pyridyl, 3-pyridyl, 4-pyridyl, or 2-furyl), the corresponding homophthalimide derivatives **4f-i** are not formed in detectable amounts.

The inductive effect of the substituent and its bulk affect the major direction for the conversion of amidines **9**, namely, cyclization, as indicated both by our findings and literature data The direction of the reaction of electrophilic reagents with amidines, to which we may assign amidine cyclization, depends on the nature of the substituents at the nitrogen atoms and less regioselectivity is found for alkylamidines than for

arylamidines [12, 13, 16]. When R = Ar, Het [7, 8], CH_2Ph [5], CH_2Ar, and CH_2Het, the major product of the reaction of acid **1** with amines RNH_2 is 3-NHR-isocarbostyryls **2, 3**, and **5**. The cyclization of intermediate amidines **9** clearly proceeds at the more basic and less shielded unsubstituted nitrogen atom. If R is an alkyl group, which is a stronger electron donor and less bulky substituent, amidines cyclize at the nitrogen atom bound to this alkyl group to give exclusively 2-alkyl-3-aminoisocarbostyryl **7** [17]. A similar 2-methyl-substituted product was also obtained in the reaction of the methyl ester of acid **1** with methylamine [18, 19]. In the case of (arylmethyl)amines studied in this work, the large bulk of the aryl substituent is the factor determining the low yields of 2-(arylmethyl) derivatives **7a**,**b** and the predominant formation of 3-(arylmethyl)-

TABLE 1. IR Spectra of Compounds **2-7**

Compound	ν, cm^{-1}
2a	3171 (NH), 3047, 1667 (C=O), 1645, 1583, 1443, 1407, 783
2b	3220 (NH), 3126 (NH), 1673 (C=O), 1633, 1614, 1552, 1505, 1340, 1147, 1007, 800, 716
2c	3216 (NH), 3053, 1653 (C=O), 1608, 1552, 1348, 1150, 1010, 783, 755, 680
2d	3200 (NH), 3109 (NH), 3053, 1661 (C=O), 1608, 1580, 1547, 1488, 1438, 1334, 1147, 766
2e	3250 (NH), 3165 (NH), 2997, 1653 (C=O), 1642, 1606, 1583, 1550, 1421, 1284, 803, 750
2f	3227 (NH), 3160 (NH), 3059, 1650 (C=O), 1614, 1550, 1494, 1435, 1365, 1343, 1155, 819, 783
2g	3232 (NH), 3130 (NH), 2980, 1659 (C=O), 1614, 1519, 1471, 1345, 1172, 1152, 1127, 803, 691
2h	3243 (NH), 3145 (NH), 3070, 1664 (C=O), 1620, 1522, 789, 708
2i	3333 (NH), 3305 (NH), 2840, 1661 (C=O), 1633, 1552, 1477, 1426, 1323, 1150, 792
2j	3378 (NH), 3064, 1667 (C=O), 1647, 1566, 1555, 1474, 1424, 1261, 1010, 814, 750
2k	3221 (NH), 1656 (C=O), 1614, 1555, 1510, 1180, 1147, 1015, 828, 769
2l	3300 (NH), 3244 (NH), 3171 (NH), 3092, 1662 (C=O), 1606, 1544, 1508, 1477, 1351, 1178, 1138, 1015, 817, 763
2m	3220 (NH), 3194 (NH), 3120 (NH), 2897, 1666 (C=O), 1607, 1553, 1501, 1470, 1347, 1288, 1148, 971, 777, 743, 706
3a	3274 (NH), 3222 (NH), 3097, 1658 (C=O), 1635, 1607, 1564, 792, 775, 709
3b	3344 (NH), 3109, 1673 (C=O), 1642, 1580, 1519, 1152, 1004, 761, 685
3c	3354 (NH), 3177 (NH), 3057, 1661 (C=O), 1650, 1635, 1610, 1590, 1555, 1475, 1421, 1316, 1190, 1151, 775
3d	3250 (NH), 3210 (NH), 3036, 1659 (C=O), 1639, 1606, 1586, 1541, 1480, 1435, 1323, 1220, 1186, 1152, 764
3e	3356 (NH), 3187, 1670 (C=O), 1634, 1608, 1569, 1485, 1354, 1326, 1200, 1155, 783
3f	3328 (NH), 3064, 1670 (C=O), 1639, 1611, 1592, 1555, 1424, 1189, 772
3g	3406 (NH), 2846, 1675 (C=O), 1634, 1606, 1555, 1491, 1427, 774, 713
3h	3395 (NH), 3277 (NH), 3170, 3008, 1659 (C=O), 1631, 1608, 1555, 1482, 1424, 775
3i	3395 (NH), 3053, 1681 (C=O), 1664, 1631, 1295, 778, 741
4a	2930, 1709 (C=O), 1664 (C=O), 1462, 1427, 1382, 1337, 1323, 1253, 1214, 1130, 741, 721
4b	3098, 2891, 1712 (C=O), 1667 (C=O), 1463, 1382, 1362, 1343, 1253, 1228, 1161, 1004, 971, 769, 741, 694
4c	3098, 1712 (C=O), 1667 (C=O), 1463, 1373, 1329, 1248, 1228, 741
4d	3131, 1723 (C=O), 1664 (C=O), 1415, 1385, 1351, 1329, 1236, 1172, 979, 850, 789, 744
5a	3378 (NH), 3350 (NH), 1667 (C=O), 1645, 1502, 1435, 1250 (C–O), 1189, 1035, 929, 780
5b	3328 (NH), 3216 (NH), 1659 (C=O), 1631, 1508, 1309, 1287 (C–O), 1069, 775
6a	2913, 1714 (C=O), 1667 (C=O), 1491, 1443, 1385, 1365, 1343, 1253 (C–O), 1029, 970, 750
6b	2974, 1709 (C=O), 1659 (C=O), 1588, 1510, 1379, 1331, 1309, 1289 (C–O), 1071, 962, 750
7b	3412 (NH_2), 3333 (NH_2), 2930, 1659 (C=O), 1625, 1575, 1510, 1315, 1071 (C–O), 803

TABLE 2. ^{1}H NMR Spectra of Compounds **2-7**

Compound	δ, ppm (*J*, Hz)					
	N(2)H (1H, s)	3-NH (1H)	ArH	H-4 (1H, s)	NCH_2 (2H)	Other signals
1	2	3	4	5	6	7
2a	12.01	10.23 (s)	8.61 (2H, d, ^3J = 5.0, H-4',6'); 8.06 (1H, d, ^3J = 8.0, H-8); 7.57 (1H, t, ^3J = 8.0, H-6); 7.47 (1H, d, ^3J = 8.0, H-5); 7.24 (1H, t, ^3J = 8.0, H-7); 7.02 (1H, t, ^3J = 5.0, H-5')	6.49	—	—
2b	11.93	10.04 (s)	8.28 (1H, s, H-3'); 8.23 (1H, m, H-5'); 8.09 (1H, d, ^3J = 5.0, H-6'); 8.06 (1H, d, ^3J = 8.0, H-8); 7.57 (1H, t, ^3J = 8.0, H-6); 7.51 (1H, d, ^3J = 8.0, H-5); 7.25 (1H, t, ^3J = 8.0, H-7)	6.36	—	—
2c*	11.29 (2H)	8.00 (br. s)	8.06 (2H, d, ^3J = 8.0, H-8,8'); 7.57 (2H, t, ^3J = 8.0, H-6,6'); 7.50 (2H, d, ^3J = 8.0, H-5,5'); 7.27 (2H, t, ^3J = 8.0, H-7,7')	6.17 (2H)	—	—
2d	12.95	9.87 (s)	8.25 (1H, d, ^3J = 4.5, H-6'); 8.04 (1H, d, ^3J = 8.0, H-8); 7.71 (1H, t, ^3J = 8.0, H-4'); 7.53 (1H, t, ^3J = 8.0, H-6); 7.45 (1H, d, ^3J = 8.0, H-5); 7.19 (1H, t, ^3J = 8.0, H-7); 6.92 (2H, m, H-3',5')	6.07	—	—
2e	10.90	8.42 (s)	8.18 (1H, d, ^3J = 4.5, H-6'); 8.13 (1H, s, H-2'); 8.04 (1H, d, ^3J = 8.0, H-8); 7.57 (1H, d, ^3J = 8.0, H-4'); 7.52 (1H, t, ^3J = 8.0, H-6); 7.43 (1H, d, ^3J = 8.0, H-5); 7.32 (1H, m, H-5'); 7.21 (1H, t, ^3J = 8.0, H-7)	6.07	—	—
2f	12.43	10.24 (s)	8.04 (1H, d, ^3J = 8.0, H-8); 7.54 (1H, t, ^3J = 8.0, H-6); 7.43 (1H, d, ^3J = 8.0, H-5); 7.21 (1H, t, ^3J = 8.0, H-7); 6.79 (1H, s, H-5')	6.35	—	2.37 (6H, s, $2CH_3$)
2g	12.01	11.14 (s)	8.06 (1H, d, ^3J = 8.0, H-8); 7.56 (1H, t, ^3J = 8.0, H-6); 7.49 (1H, d, ^3J = 8.0, H-5); 7.38 (1H, m, H-5'); 7.23 (1H, t, ^3J = 8.0, H-7); 7.08 (1H, m, H-4')	6.22	—	—
2h	10.64	9.16 (s)	8.02 (1H, d, ^3J = 8.0, H-8); 7.55 (1H, t, ^3J = 8.0, H-6); 7.48 (1H, d, ^3J = 8.0, H-5); 7.23 (1H, t, ^3J = 8.0, H-7); 6.49 (1H, s, H-4')	6.07	—	2.35 (3H, s, CH_3)
2i	10.51	6.73 (s)	7.92 (1H, d, ^3J = 8.0, H-8); 7.37 (1H, t, ^3J = 8.0, H-6); 7.18 (1H, d, ^3J = 8.0, H-5); 7.01 (1H, t, ^3J = 8.0, H-7)	5.02	—	3.66 (3H, s, 1'-CH_3); 2.08 (3H, s, 3'-CH_3); 1.98 (3H, s, 5'-CH_3)
2j	10.90	8.22 (s)	7.98 (1H, d, ^3J = 8.0, H-8); 7.47 (1H, t, ^3J = 8.0, H-6); 7.35 (1H, d, ^3J = 8.0, H-5); 7.13 (1H, t, ^3J = 8.0, H-7); 5.56 (1H, s, H-4')	5.94	—	3.59 (3H, s, 1'-CH_3); 2.12 (3H, s, 3'-CH_3)
2k	12.07	11.54 (s)	7.96 (1H, d, ^3J = 8.0, H-8); 7.47 (1H, t, ^3J = 8.0, H-6); 7.35 (1H, d, ^3J = 8.0, H-5); 7.08 (1H, t, ^3J = 8.0, H-7); 5.66 (1H, s, H-4')	5.94	—	9.07 (1H, s, H-1'); 2.20 (3H, s, CH_3)
2l	12.39	11.43 (s)	7.97 (1H, d, ^3J = 8.0, H-8); 7.69 (1H, d, ^3J = 1.5, H-5'); 7.47 (1H, t, ^3J = 8.0, H-6); 7.36 (1H, d, ^3J = 8.0, H-5); 7.10 (1H, t, ^3J = 8.0, H-7); 5.90 (1H, d, ^3J = 1.5, H-4')	6.01	—	9.08 (1H, s, H-1')
2m	13.72	11.15 (s)	8.48 (1H, s, H-5'); 8.02 (1H, d, ^3J = 8.0, H-8); 7.54 (1H, t, ^3J = 8.0, H-6); 7.42 (1H, d, ^3J = 8.0, H-5); 7.18 (1H, t, ^3J = 8.0, H-7)	6.40	—	9.64 (1H, s, H-1')
3a	10.47 (br. s)	5.97 (t, ^3J = 6.0)	7.91 (1H, d, ^3J = 8.0, H-8); 7.41 (2H, m, H-6,5'); 7.24 (1H, d, ^3J = 8.0, H-5); 7.11 (1H, d, ^3J = 3.0, H-3'); 7.03 (1H, t, ^3J = 8.0, H-7); 6.97 (1H, m, H-4')	5.51	4.50 (d, ^3J = 6.0)	—
3b	10.62	6.09 (t, ^3J = 5.5)	7.95 (2H, d, ^3J = 7.0, H-2",6"); 7.91 (1H, d, ^3J = 8.0, H-8); 7.60 (1H, s, H-4'); 7.50 (3H, m, H-3",4",5"); 7.42 (1H, t, ^3J = 8.0, H-6); 7.27 (1H, d, ^3J = 8.0, H-5); 7.01 (1H, t, ^3J = 8.0, H-7)	5.54	4.45 (d, ^3J = 5.5)	—

TABLE 2 (continued)

1	2	3	4	5	6	7
3c	10.46	5.88 (t, ^3J = 5.5)	7.92 (1H, d, ^3J = 8.0, H-8); 7.45 (1H, t, ^3J = 8.0, H-6); 7.33 (1H, d, ^3J = 4.0, H-5'); 7.28 (1H, d, ^3J = 8.0, H-5); 7.05 (1H, t, ^3J = 8.0, H-7); 6.89 (1H, d, ^3J = 4.0, H-4')	5.51	4.40 (d, ^3J = 5.5)	2.24 (3H, s, CH_3)
3d	10.61	6.14 (t, ^3J = 5.5)	8.43 (1H, s, H-5'); 7.91 (1H, d, ^3J = 8.0, H-8); 7.44 (1H, t, ^3J = 8.0, H-6); 7.26 (1H, d, ^3J = 8.0, H-5); 7.04 (1H, t, ^3J = 8.0, H-7)	5.58	4.48 (d, ^3J = 5.5)	3.66 (3H, s, CH_3)
3e	10.45	5.91 (t, ^3J = 5.5)	7.91 (1H, d, ^3J = 8.0, H-8); 7.43 (1H, t, ^3J = 8.0, H-6); 7.32 (1H, d, ^3J = 2.0, H-3'); 7.27 (1H, d, ^3J = 8.0, H-5); 7.03 (1H, t, ^3J = 8.0, H-7); 6.24 (1H, d, ^3J = 2.0, H-4')	5.53	4.37 (d, ^3J = 5.5)	3.80 (3H, s, CH_3)
3f	10.78	6.29 (t, ^3J = 5.5)	8.56 (1H, d, ^3J = 5.0, H-6'); 7.90 (1H, d, ^3J = 8.0, H-8); 7.78 (1H, d, ^3J = 7.5, H-4'); 7.40 (2H, m, H-6,3'); 7.30 (1H, t. d, ^3J = 7.5, ^3J = 5.0, H-5'); 7.21 (1H, d, ^3J = 8.0, H-5); 7.01 (1H, t, ^3J = 8.0, H-7)	5.38	4.41 (d, ^3J = 5.5)	—
3g	10.58 (br. s)	6.07 (br. s)	8.61 (1H, s, H-2'); 8.47 (1H, m, H-6'); 7.91 (1H, d, ^3J = 8.0, H-8); 7.78 (1H, m, H-4'); 7.38 (2H, m, H-6,5'); 7.22 (1H, d, ^3J = 8.0, H-5); 7.01 (1H, t, ^3J = 8.0, H-7)	5.42	4.36 (br. s)	—
3h	10.63 (br. s)	6.12 (t, ^3J =5.5)	8.52 (2H, d, ^3J = 4.5, H-2',6'); 7.91 (1H, d, ^3J = 8.0, H-8); 7.41 (1H, t, ^3J = 8.0, H-6); 7.36 (2H, m, H-3',5'); 7.18 (1H, d, ^3J = 8.0, H-5); 7.02 (1H, t, ^3J = 8.0, H-7)	5.31	4.39 (d, ^3J = 5.5)	—
3i	10.47 (br. s)	5.40 (t, ^3J = 5.5)	7.91 (1H, d, ^3J = 8.0, H-8); 7.62 (1H, m, H-5'); 7.43 (1H, t, ^3J = 8.0, H-6); 7.27 (1H, d, ^3J = 8.0, H-5); 7.03 (1H, t, ^3J = 8.0, H-7); 6.42 (2H, m, H-3',4')	5.50	4.30 (d, ^3J = 5.5)	—
4a	—	—	8.05 (1H, d, ^3J = 8.0, H-8); 7.65 (1H, t, ^3J = 8.0, H-6); 7.46 (1H, t, ^3J = 8.0, H-7); 7.37 (2H, m, H-5,5'); 7.07 (1H, d, ^3J = 3.0, H-3'); 6.98 (1H, m, H-4')	4.19 (2H)	5.17 (s)	—
4b	—	—	8.09 (1H, d, ^3J = 8.0, H-8); 7.88 (2H, d, ^3J = 8.0, H-2",6"); 7.65 (1H, t, ^3J = 8.0, H-6); 7.48-7.40 (5H, m, H-5,7,3",4",5"); 7.37 (1H, s, H-4')	4.22 (2H)	5.21 (s)	—
4c	—	—	8.06 (1H, d, ^3J = 8.0, H-8); 7.65 (1H, t, ^3J = 8.0, H-6); 7.47 (1H, t, ^3J = 8.0, H-7); 7.37 (1H, d, ^3J = 8.0, H-5); 7.26 (1H, d, ^3J = 5.0, H-5'); 6.77 (1H, d, ^3J = 5.0, H-4')	4.20 (2H)	5.12 (s)	2.31 (3H, s, CH_3)
4d	—	—	8.37 (1H, s, H-5'); 8.05 (1H, d, ^3J = 8.0, H-8); 7.70 (1H, t, ^3J = 8.0, H-6); 7.50 (1H, t, ^3J = 8.0, H-7); 7.43 (1H, d, ^3J = 8.0, H-5)	4.25 (2H)	5.13 (s)	3.70 (3H, s, CH_3)
4e*[2]	—	—	8.06 (1H, d, ^3J = 8.0, H-8); 7.66 (1H, t, ^3J = 8.0, H-6); 7.48 (1H, t, ^3J = 8.0, H-7); 7.41 (1H, d, ^3J = 8.0, H-5); 7.28 (1H, d, ^3J = 2.0, H-3'); 6.20 (1H, d, ^3J = 2.0, H-4')	4.23 (2H)	5.15 (s)	3.85 (3H, s, CH_3)
5a	10.48	5.91 (t, ^3J = 5.5)	7.89 (1H, d, ^3J = 8.0, H-8); 7.40 (1H, t, ^3J = 8.0, H-6); 7.22 (1H, d, ^3J = 8.0, H-5); 7.00 (1H, t, ^3J = 8.0, H-7); 6.95 (1H, s, H-4'); 6.87 (2H, m, H-6',7')	5.40	4.20 (d, ^3J = 5.5)	5.98 (2H, s, OCH_2O)
5b	10.48	5.90 (t, ^3J = 5.5)	7.88 (1H, d, ^3J = 8.0, H-8); 7.45 (1H, t, ^3J = 8.0, H-6); 7.22 (1H, d, ^3J = 8.0, H-5); 7.01 (1H, t, ^3J = 8.0, H-7); 6.87 (1H, s, H-5'); 6.83 (2H, m, H-7',8')	5.39	4.16 (d, ^3J = 5.5)	4.20 (4H, s, $O(CH_2)_2O$)
6a	—	—	8.04 (1H, d, ^3J = 8.0, H-8); 7.66 (1H, t, ^3J = 8.0, H-6); 7.47 (1H, t, ^3J = 8.0, H-7); 7.38 (1H, d, ^3J = 8.0, H-5); 6.88 (1H, s, H-4'); 6.81 (2H, m, H-6',7')	4.21 (2H)	4.94 (s)	5.94 (2H, s, OCH_2O)
6b	—	—	8.04 (1H, d, ^3J = 8.0, H-8); 7.65 (1H, t, ^3J = 8.0, H-6); 7.47 (1H, t, ^3J = 8.0, H-7); 7.38 (1H, d, ^3J = 8.0, H-5); 6.79 (1H, s, H-4'); 6.75 (2H, m, H-6',7')	4.21 (2H)	4.91 (s)	4.17 (4H, s, $O(CH_2)_2O$)
7b	—	5.91 (2H, s)	7.95 (1H, d, ^3J = 8.0, H-8); 7.41 (1H, t, ^3J = 8.0, H-6); 7.21 (1H, d, ^3J = 8.0, H-5); 7.01 (1H, t, ^3J = 8.0, H-7); 6.75 (1H, d, ^3J = 8.0, H-7'); 6.70 (2H, m, H-5',8')	5.66	5.19 (br. s)	4.18 (4H, s, $O(CH_2)_2O$)

* The ^{1}H NMR spectral data agree with the data of Deady and Quazi [23].

*[2] ^{1}H NMR spectral data from a 5:1 mixture of **3e** and **4e** obtained by excluding the proton signals of isoquinolone **3e**.

aminoisocarbostyryls **5a**,**b**. Since the reaction of acid **1** with benzylamine leads exclusively to product **5** [5], the presence of electron-donor substituents in the aromatic fragment of the (arylmethyl)amines increases the likelihood of formation isocarbostyryls **7**.

TABLE 3. Physicochemical Properties and Elemental Analysis Data of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	S		
1	2	3	4	5	6	7	8
2a	$C_{13}H_{10}N_4O$	65.33 / 65.54	4.18 / 4.23	23.54 / 23.52	—	232-233	38
2b	$C_{13}H_{10}N_4O$	65.50 / 65.54	4.17 / 4.23	23.51 / 23.52	—	297-298	51
2d	$C_{14}H_{11}N_3O$	70.79 / 70.87	4.61 / 4.67	17.73 / 17.71	—	> 280 (dec)	68
2e	$C_{14}H_{11}N_3O$	70.81 / 70.87	4.60 / 4.67	17.71 / 17.71	—	202-203	63
2f	$C_{15}H_{14}N_4O$	67.58 / 67.65	5.25 / 5.30	21.05 / 21.04	—	281-282	35
2g	$C_{12}H_9N_3OS$	59.18 / 59.24	3.68 / 3.73	17.28 / 17.27	13.20 / 13.18	272-273	71
2h	$C_{13}H_{11}N_3O_2$	64.66 / 64.72	4.56 / 4.60	17.44 / 17.42	—	245-246	49
2i	$C_{15}H_{16}N_4O$	67.10 / 67.15	5.95 / 6.01	20.87 / 20.88	—	243-244	68
2j	$C_{14}H_{14}N_4O$	66.08 / 66.13	5.50 / 5.55	22.05 / 22.03	—	218-219	58
2k	$C_{13}H_{12}N_4O$	64.92 / 64.99	4.98 / 5.03	23.31 / 23.32	—	262-263 (dec)	47
2l	$C_{12}H_{10}N_4O$	63.65 / 63.71	4.40 / 4.46	24.78 / 24.77	—	227-228	57
2m	$C_{11}H_9N_5O$	58.09 / 58.14	3.93 / 3.99	30.82 / 30.82	—	308-310 (dec)	38
3a	$C_{14}H_{12}N_2OS$	65.54 / 65.60	4.68 / 4.72	10.95 / 10.93	12.53 / 12.51	177-178	46
3b	$C_{19}H_{15}N_3OS$	68.39 / 68.45	4.48 / 4.53	12.61 / 12.60	9.60 / 9.62	244-245	47
3c	$C_{15}H_{14}N_2OS$	66.60 / 66.64	5.18 / 5.22	10.38 / 10.36	11.87 / 11.86	175-175.5	39
3d	$C_{13}H_{13}N_5O$	61.11 / 61.16	5.07 / 5.13	27.44 / 27.43	—	283-284	45
3e	$C_{14}H_{14}N_4O$	66.08 / 66.13	5.48 / 5.55	22.05 / 22.03	—	208-209	49
3f	$C_{15}H_{13}N_3O$	71.65 / 71.70	5.17 / 5.21	16.73 / 16.72	—	196-197	53
3g	$C_{15}H_{13}N_3O$	71.66 / 71.70	5.15 / 5.21	16.74 / 16.72	—	166-167	69
3h	$C_{15}H_{13}N_3O$	71.69 / 71.70	5.16 / 5.21	16.72 / 16.72	—	197-198	64
3i	$C_{14}H_{12}N_2O_2$	69.91 / 69.99	4.97 / 5.03	11.65 / 11.66	—	141-142 (dec)	67
4a	$C_{14}H_{11}NO_2S$	65.28 / 65.35	4.28 / 4.31	5.44 / 5.44	12.45 / 12.46	137-138	40
4b	$C_{19}H_{14}N_2O_2S$	68.15 / 68.24	4.16 / 4.22	8.39 / 8.38	9.61 / 9.59	142-143	41
4c	$C_{15}H_{13}NO_2S$	66.37 / 66.40	4.75 / 4.83	5.18 / 5.16	11.85 / 11.82	152-153	35
4d	$C_{13}H_{12}N_4O_2$	60.85 / 60.93	4.67 / 4.72	21.88 / 21.86	—	227-228	42
5a	$C_{17}H_{14}N_2O_3$	69.30 / 69.38	4.75 / 4.79	9.54 / 9.52	—	244-245	47
5b	$C_{18}H_{16}N_2O_3$	70.08 / 70.12	5.18 / 5.23	9.11 / 9.09	—	186-187	42
6a	$C_{17}H_{13}NO_4$	69.10 / 69.15	4.38 / 4.44	4.73 / 4.74	—	163-164	32

TABLE 3 (continued)

1	2	3	4	5	6	7	8
6b	$C_{18}H_{15}NO_4$	69.82 69.89	4.83 4.89	4.55 4.53	—	153-154	34
7b	$C_{18}H_{16}N_2O_3$	70.06 70.12	5.08 5.23	9.10 9.09	—	208-209	11
9a	$C_{15}H_{15}N_3O_2$	66.85 66.90	5.58 5.61	15.61 15.60	—	229-230	34
9b	$C_{13}H_{14}N_4O_2$	60.38 60.45	5.41 5.46	21.71 21.69	—	231-232 (dec)	62

* Crystallization solvents: 2-propanol for **2a,i-l, 3d, 4d,** and **7b**, DMF for **2b,d-h**, and **9a**, acetic acid for **2m**, ethanol for **3a-c,e-i, 4a-c, 5a,b, 6a,b**, and **9b**.

The heterocycle in 3-aminoisocarbostyryl isoquinolines undergoes opening upon heating with base or under acid hydrolysis conditions [17, 20, 21]. We have found that products **2, 3**, and **5** are stable upon heating in 2 N ethanolic NaOH, while heating these products in 2 N hydrochloric acid gives a mixture of homophthalic acid **8** and the hydrochloride of the corresponding alkylamine or hetarylamine as shown by elemental analysis and NMR spectroscopy.

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer Spectrum BX spectrometer for KBr pellets. The ^{1}H NMR spectra were taken on a Varian Mercury-400 spectrometer at 400 MHz for **2-7** and a Bruker Avance DRX 500 spectrometer at 500 MHz for **9**. In all cases, DMSO-d_6 was the solvent and TMS was the internal standard. The melting points were determined on a Boetius block and not corrected. The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates and by LC/MS on an Agilent 1100 Series instrument with an Agilent LC/MSD SL detector (the sample was introduced in a TFA matrix). Electron impact mass spectrometry was employed. The R_f values were determined on Silufol UV-254 plates with 9:1 benzene–ethanol as the eluent. Column chromatography was carried out using Silica Gel 4600 and 7:3 chloroform–ethanol as the eluent. The physicochemical and elemental analysis data are given for compounds **2-7** and **9** in Table 3.

A sample of 2-(cyanomethyl)benzoic acid **1** was obtained according to a standard procedure [22], while 3-aminoisoquinolin-1(2H)-one was obtained according to Goya et al. [18]. Commercial samples of all the hetaryl-, (hetaryl)methyl-, and (arylmethyl)amines were obtained from Enamine.

3-(Hetarylamino)isoquinolin-1(2H)-ones 2a,b,f,k-m (General Method). A suspension of acid **1** (1.61 g, 10.0 mmol) and hetarylamine (10.5 mmol) (hereafter in the syntheses of all **2-7** and **9**, the indicated molar amounts of the reagents were used) was prepared in 1:1 mixture 1,2-dichlorobenzene–DMF (10 ml) and heated at reflux for 3-4 h. The solvent was evaporated in vacuum. The solid residue was recrystallized from 2-propanol or DMF to give **2a,b,f,k-m.**

3-[(1-Oxo-1,2-dihydroisoquinolin-3-yl)amino]isoquinolin-1(2H)-one (2c). A suspension of acid **1** and 3-aminoisoquinolin-1(2H)-one in DMF (10 ml) was heated at reflux for 5 h and then cooled. The precipitate formed was filtered off, washed with DMF, and recrystallized from DMF. The yield of product **2c** was 1.03 g (34%), mp >310°C (DMF) (mp >300°C (dec.) [23]).

3-(Hetarylamino)isoquinolin-1(2H)-ones 2d,e,g-j (General Method). A suspension of acid **1** and the corresponding hetarylamine in 1,2-dichlorobenzene (10 ml) was heated at reflux for 7-8 h and then cooled. The precipitate formed was filtered off, washed with ethanol, and recrystallized from 2-propanol or DMF to give products **3d,e**,**g-j**.

3-[(2-Thiophen-2-ylmethyl)amino]isoquinolin-1(2H)-one (3a), 3-[(3-Methylthiophen-2-ylmethyl)-amino]isoquinolin-1(2H)-one (3c), 2-(Thiopen-2-ylmethyl)isoquinoline-1,3(2H,4H)-dione (4a), and 2-(3-Methylthiophen-2-ylmethyl)isoquinoline-1,3(2H,4H)-dione (4c). A suspension of acid **1** and (thiophen-2-ylmethyl)amine or (3-methylthiophen-2-ylmethyl)amine in 1,2-dichlorobenzene (10 ml) was heated at reflux for 5 h and then cooled. The precipitate formed was filtered off and washed with ethanol to give a mixture of products **3a** and **4a** or of products **3c** and **4c**, respectively. These mixtures were separated by column chromatography.

3-[(2-Phenyl-1,3-thiazol-5-ylmethyl)amino]isoquinolin-1(2H)-one (3b) and 2-(2-Phenyl-1,3-thiazol- 5-ylmethyl)isoquinoline-1,3-(2H,4H)-dione (4b). A suspension of acid **1** and (2-phenyl-1,3-thiazol-5-yl-methyl)amine in 1,2-dichlorobenzene-DMF (3:1, 10 ml) was heated at reflux for 7 h and then cooled. The precipitate formed was filtered off, washed with ethanol, and separated into **3b** and **4b** by column chromatography.

3-[(4-Methyl-4H-1,2,4-triazol-3-ylmethyl)amino]isoquinolin-1(2H)-one (3d) and 2-(4-Methyl-4H-1,2,4-triazol-3-ylmethyl)isoquinoline-1,3(2H,4H)-dione (4d). The procedure for the preparation of **3b** and **4b** was used for the reaction of acid **1** and (4-methyl-4H-1,2,4-triazol-3-ylmethyl)amine. Cooling of the reaction mixture gave a precipitate, which was recrystallized twice from 2-propanol to give product **4d**. The filtrate was evaporated and the residue was recrystallized from 2-propanol to give product **3d**.

3-[(1-Methyl-1H-pyrazol-5-ylmethyl)amino]isoquinolin-1(2H)-one (3e). A. The method for the synthesis of **3b** was used for the reaction of acid **1** and (1-methyl-1H-pyrazol-5-ylmethyl)amine to give a mixture, which, upon cooling, gave an oily precipitate. LC/MS analysis indicated that 70% of the precipitate consisted of a 5:1 mixture of **3e** and **4e**. The solution was decanted and evaporated. The residue was recrystallized from ethanol to give product **3e**.

B. A suspension analogous to that described in procedure A was heated at reflux for 7 h in a flask equipped with a Dean-Stark trap and then cooled. The precipitate formed was filtered off and washed with ethanol to give 1.83 g (72%) product **3e**.

3-[(Pyridylmethyl)amino]isoquinolin-1(2H)-ones 3f-h (General Method). A suspension of acid **1** and the corresponding pyridylmethylamine in 10 ml 3:1 1,2-dichlorobenzene–DMF was heated at reflux for 7-8 h and then cooled. The precipitate formed was filtered off, washed with ethanol, and recrystallized twice from ethanol to give product **3f-h**.

3-[(2-Furylmethyl)amino]isoquinolin-1(2H)-one (3i). A. A suspension of acid **1** and 2-furylmethyl-amine in 10 ml 1,2-dichlorobenzene was heated at reflux for 5 h and then cooled. The precipitate of product **3i** formed was filtered off, washed with ethanol, and recrystallized twice from ethanol.

B. A suspension analogous to that in procedure A was heated at reflux for 5 h in a flask equipped with a Dean-Stark trap and then cooled. The precipitate formed was filtered off and washed with ethanol to give 1.87 g (78%) product **3i**.

3-[(1,3-Benzodioxol-5-ylmethyl)amino]isoquinolin-1(2H)-one (5a) and 2-(1,3-Benzodioxol-5-yl-methyl)isoquinoline-1,3(2H,4H)-dione (6a). A suspension of acid **1** and (1,3-bezodioxol-5-ylmethyl)amine in 10 ml 1,2-dichlorobenzene was heated at reflux for 5 h and then cooled. The precipitate formed was filtered off, washed with ethanol, and subjected to column chromatography to give **5a** (R_f 0.71) and **6a** (R_f 0.70).

3-[(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)amino]isoquinolin-1(2H)-one (5b), 2-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)isoquinoline-1,3(2H,4H)-dione (6b), and 3-Amino-2-(2,3-dihydro-1,4-benzo-dioxin-6-ylmethyl)isoquinolin-1(2H)-one (7b). Products **5b-7b** were obtained according to the procedure for the synthesis of **5a** and **6a** using (2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amine. The precipitate was recrystallized twice from ethanol to give product **6b** (R_f 0.91). The filtrate was evaporated and the residue was recrystallized from ethanol to give product **5b** (R_f 0.90). The filtrate after recrystallization of **5b** was evaporated and 10 ml diethyl ether was added to the residue. The precipitate formed was recrystallized from a small amount of 2-propanol to give product **7b** (R_f 0.69).

2-[2-Imino-2-(pyridin-2-ylmethyl)amino]ethylbenzoic Acid (9a). A suspension of acid **1** and (pyridine-2-ylmethyl)amine in 1,2-dichlorobenzene–DMF (3:1, 5 ml) was heated at reflux for 10 min. After cooling, the precipitate formed was filtered off, washed with ethanol, and recrystallized twice from DMF to give acid **9a**. IR spectrum, ν, cm^{-1}: 3200 (br., OH, NH). 3002, 1678 (C=O), 1653 (C=N), 1592, 1538, 1435, 1382, 761. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.15 (1H, br. s, OH); 11.09 (1H, br. s, =NH); 8.61 (1H, br. s, $CH_2N\underline{H}$); 8.53 (1H, d, ^3J = 5.0, H-6'); 7.75 (1H, t, ^3J = 7.5, H-4'); 7.62 (1H, d, ^3J = 8.0, H-6); 7.33-7.17 (5H, m, H-3, H-4, H-5, H-3', H-5'); 4.52 (2H, d, ^3J = 4.0, $C\underline{H}_2NH$); 3.92 (2H, s, $C\underline{H}_2Ar$).

2-[2-Imino-2-(3-methyl-1H-pyrazol-5-yl)amino]ethylbenzoic acid (9b). Acid **9b** was obtained according to the procedure for the synthesis of acid **9a** using (3-methyl-1H-pyrazol-5-yl)amine. IR spectrum, ν, cm^{-1}: 3240 (br., OH, NH), 2960, 1669 (br., C=O), 1581, 1553, 1384, 1020, 809, 758, 726. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.60 (1H, s, OH); 10.53 (2H, br. s, NH_2); 9.20 (1H, s, NH pyrazole); 7.63 (1H, d, ^3J = 8.0, H-6); 7.36-7.25 (3H, m, H-3, H-4, H-5); 5.79 (1H, s, H-4'); 3.96 (2H, s, $C\underline{H}_2Ar$); 2.22 (3H, s, CH_3).

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