Convenient Preparation of *N*-Substituted 2-Amino-4*H*-3,1-benzoxazin-4-ones and 3-Substituted 2,4(1*H*,3*H*)-Quinazolinediones

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Room temperature treatment of 2-(3-arylureido)benzoic acids (**1**) and methyl 2-(3-alkyl-, or 3-arylureido)-benzoates (**2**) with concentrated sulfuric acid leads to *N*-substituted 2-amino-4*H*-3,1-benzoxazin-4-ones (**3**) in generally very good yields. The isomeric 3-substituted 2,4(1*H*,3*H*)-quinazolinediones (**4**) are conveniently made in high yield by the action of aqueous-ethanolic sodium hydroxide on **2**.

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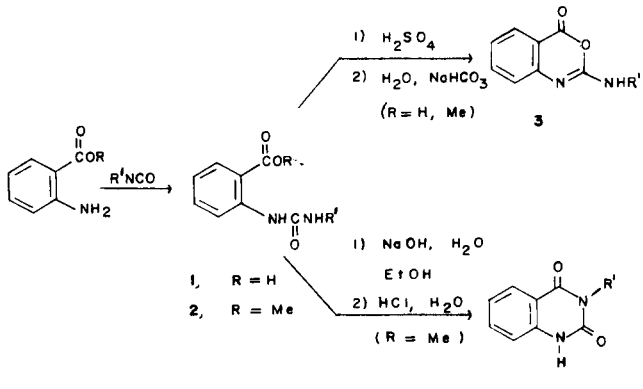
Although individual 2-amino-4*H*-3,1-benzoxazin-4-ones (**3**) have been reported in a number of papers (1-5), a literature search reveals only one general method of preparation of these compounds. This involves cyclodehydration of *o*-ureidobenzoic acids generally by the action of acetic anhydride at 60-140°, in a solvent such as benzene or chlorobenzene and, in some cases, in the presence of a catalytic amount of *p*-toluenesulfonic acid (6).

In the course of a recent investigation of reactions involving anthranilonitrile and ethyl isocyanatoacetate, it was found that 2-(3-ethoxycarbonylmethylureido)benzoic acid (**1f**) is converted into 2-ethoxycarbonylmethylamino-4*H*-3,1-benzoxazin-4-one (**3f**) by the action of concetrated sulfuric acid at room temperature (7). Because of the ease of this transformation, a brief study was undertaken to investigate its possibilities as a general method of preparation of 2-amino-4*H*-3,1-benzoxazin-4-ones (**3**) starting from anthranilic acid. To keep the procedure as simple as possible, it was decided to routinely omit purification of the intermediate *o*-ureidobenzoic acids (**1**).

Treatment of anthranilic acid with an aryl isocyanate in tetrahydrofuran gives 2-(3-arylureido)benzoic acids (**1g-m**) conveniently and in high yield. When the solution of a crude **1** in concentrated sulfuric acid is allowed to stand at room temperature for about one hour and then is diluted with water and neutralized, 2-arylamino-4*H*-3,1-benzoxazin-4-ones (**3g-m**) are obtained in generally excellent yield. In the cases of **3g** and especially **3i** the yield is decreased by the presence in the product of significant amounts of high melting, possibly polymeric material of undetermined structure. Although good yields of the 2-chloroethylamino (**3e**) and 2-ethoxycarbonylmethylamino (**3f**) derivatives may similarly be obtained, preparation of simple alkylamino derivatives (**3b-d**) by this method has not proved satisfactory. The main reason for this is the failure of the first step, *i.e.*, the reaction of anthranilic acid with the less electrophilic alkyl isocyanates, to give good enough results in terms of quantity and quality of crude 2-(3-alkylureido)benzoic acids (**1b-d**). Because of the stated intention to utilize this procedure as an essentially one-pot conversion of anthranilic acid to **3**, this approach to **3b-d** was not pursued further. It was decided, instead, to investigate the analogous sythetic sequence using methyl anthranilate as starting material.

Methyl 2-(3-alkylureido)benzoates (**2b-f**) are obtained in excellent yield and good state of purity by allowing a mixture of methyl anthranilate and an alkyl isocyanate to stand at room temperature until complete solidification. For the more reactive aryl isocyanates, equally good results (**2g-m**) are obtained when the reaction is run in a small amount of ethyl ether. Treatment of crude **2** with concentrated sulfuric acid, as described earlier for **1**, leads to 2-alkylamino (**3b-f**) and 2-arylamino-4*H*-3,1-benzoxazin-4-ones (**3g-m**) in excellent yield (8). Once again, however, **3i** is obtained in not as good a yield.

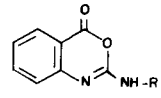
Although the two approaches, *i.e.*, using anthranilic acid or methyl anthranilate as starting material, seem to be comparable with regard to the 2-arylamino derivatives (**3g-m**), the latter approach often gives somewhat better results and is overall the method of choice.



R'		R'	
a	H	g	C_6H_5
b	Et	h	2-Me C_6H_4
c	n-Bu	i	3-Me C_6H_4
d	Cyclohexyl	j	4-Me C_6H_4
e	$ClCH_2CH_2$	k	3-Cl C_6H_4
f	$EtOCCH_2$ (O)	l	4-Cl C_6H_4
		m	2,5-$Cl_2C_6H_3$

Table I

N-Substituted 2-Amino-4*H*-3,1-benzoxazin-4-ones (**3**).



Compound No.	R	% Yield (a) (b)	(c)	Mp °C	Elemental Analysis Calcd. (Found) C	H	N	IR, cm⁻¹ N-H	C=O	C=N	¹H-NMR, ppm (d)
3a	H		93	214-215 dec (e) (f)				3330	1740	1690	7.1-7.4 (m, 2, ArH), 7.6-8.1 (m, 4, ArH, NH_2)
3b	CH_3CH_2		95	169-171 (g)	63.15 (63.36)	5.30 (5.25)	14.73 (14.55)	3300	1740	1640	1.2 (t, 3, CH_3), 3.3 (m, 2, CH_2), 7.0-7.3 (m, 2, ArH), 7.5-7.7 (m, 1, ArH), 7.8-8.1 (m, 2, ArH, NH)
3c	$CH_3(CH_2)_3$		75	127-129 (h)	66.04 (65.88)	6.46 (6.30)	12.83 (12.81)	3300	1740	1630	1.0 (m, 3, CH_3), 1.5 (m, 4, CH_2CH_2), 3.3 (m, 2, CH_2N), 7.0-7.3 (m, 2, ArH), 7.6-7.8 (m, 1, ArH), 7.9-8.1 (m, 2, ArH, NH)
3d	C_6H_{11} (i)		98	207-209 (g)	68.83 (68.96)	6.60 (6.60)	11.47 (11.47)	3280	1730	1630	1.2-2.1[m, 10, $(CH_2)_5$], 3.7 (m, 1, CHN), 7.0-7.2 (m, 2, ArH), 7.5-7.7 (m, 1, ArH), 7.8-8.0 (m, 2, ArH, NH)
3e	$ClCH_2CH_2$	81 (j)	91	143.5-145				3320	1730	1630	3.7 (m, 4, CH_2CH_2), 7.1-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 8.3 (br. t, 1, NH)
3f	$EtOOCCH_2$	70 (k)	87	147-148.5				3340	1760 1730	1620	1.2 (t, 3, CH_3), 4.0 (d, 2, CH_2CO), 4.2 (q, 2, CH_2CH_3), 7.0-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 8.4 (br. t, 1, NH)
3g	C_6H_5	83	98	191-192 (g) (l)				3280	1740	1630	7.1-8.1 (m, 9, ArH), 10.4 (s, 1, NH)
3h	2-$CH_3C_6H_4$	98	88	156-158 (g)	71.42 (71.56)	4.79 (4.77)	11.10 (11.19)	3280	1750	1640	2.3 (s, 3, CH_3), 7.1-8.0 (m, 8, ArH), 9.7 (s, 1, NH)
3i	3-$CH_3C_6H_4$	56	64	180-182 (g)	71.42 (71.58)	4.79 (4.78)	11.10 (11.29)	3260	1730	1630	2.4 (s, 3, CH_3), 6.9-7.4 (m, 4, ArH), 7.6-8.1 (m, 4, ArH), 10.3 (s, 1, NH)
3j	4-$CH_3C_6H_4$	90	95	196-198 (g)	71.42 (71.43)	4.79 (4.79)	11.10 (11.00)	3280	1730	1630	2.3 (s, 3, CH_3), 7.1-7.4 (m, 4, ArH), 7.6-8.1 (m, 4, ArH), 10.3 (s, 1, NH)
3k	3-ClC_6H_4	95	97	212-213 (m) (n)				3290	1740	1650	7.0-7.5 (m, 4, ArH), 7.7-8.1 (m, 4, ArH), 10.5 (s, 1, NH)
3l	4-ClC_6H_4	94	97	230-231.5 (e) (o)	61.66 (61.67)	3.33 (3.36)	10.27 (10.12)	3260	1730	1630	7.2-7.6 (m, 4, ArH), 7.8-8.1 (m, 4, ArH), 10.5 (s, 1, NH)
3m	2,5-$Cl_2C_6H_3$ (i)	98	98	179-181 (g)	54.75 (54.73)	2.63 (2.67)	9.12 (9.17)	3300	1770	1640	6.9-7.8 (m, 7, ArH), 10.0 (s, 1, NH)

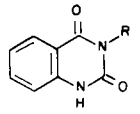
(a) Crude or recrystallized product with melting point within 10° of that of the analytically pure compound. (b) *Via* **1**. (c) *Via* **2**. (d) Solutions in DMSO-$_6$. (e) Recrystallized from ethyl acetate. (f) Lit (1a) mp 212° dec. (g) Recrystallized from benzene. (h) Recrystallized from benzene-petroleum ether (bp 63-75°). (i) Listed in reference 6, but its mp not given. (j) Reference 20. (k) Reference 7. (l) Lit (lb) mp 192-193°. (m) Lit (3) mp 214°. (n) Recrystallized from benzene-ethyl acetate. (o) Lit (6) mp 206-209°.

The parent compound of the series (**3a**), reported to exist in its tautomeric form as 1,2-dihydro-2-imino-4*H*-3,1-benzoxazin-4-one, was first prepared from anthranilic acid and cyanogen bromide (1c). This compound is obtained in 93% yield by treatment of methyl 2-ureidobenzoate (**2a**) (14) with concentrated sulfuric acid, as described earlier.

Structures **3b-m** are consistent with the ir and nmr spectra of the products and are supported by the published melting points of the known members of the series. The carbon, nitrogen double bond of these compounds may be either endo-, or exocyclic (1-5). In the nmr spectra (taken on solutions in DMSO-d_6) of **3b-d** the NH proton signal overlaps signals of aromatic protons, but for **3e-f** this signal appears in the form of a partially resolved, broad triplet (J = 5-6 Hz). On the other hand, the signals of the α-protons of the alkyl group R' of **3b-c** become less complex and exhibit splitting only by the β-protons after treatment of the solution with deuterium oxide. These indications of coupling between the NH proton and the α-protons of the alkyl group are more consistent with an endocyclic C=N bond, as shown in structure **3**, at least when the compounds in question are dissolved in dimethyl sulfoxide. It is noteworthy, in this connection, that even **3a** is believed to exist in its amino tautometic form when in dioxane or dimethyl sulfoxide solution (1c). The C=N infrared stretching band of **3a** has been reported at 1700 cm^{-1} (unconjugated), for the imino, and at 1660 cm^{-1} (con-

Table II

3-Substituted-2,4(1*H*,3*H*)-quinazolinediones (**4**)



Compound No.	R	% Yield (a)	Mp °C	IR, cm^{-1} N-H	IR, cm^{-1} C=O	^{1}H-NMR, ppm (b)
4a	H (c)			3150	1680	7.1-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 11.0 (s, 1, NH), 11.2 (s, 1, NH)
4b	CH_3CH_2	95	195-197 (d)	3220	1700, 1630	1.2 (t, 3, CH_3), 4.0 (q, 2, CH_2), 7.1-7.4 (m, 2, ArH), 7.6-7.7 (m, 1, ArH), 7.8-8.1 (m, 1, ArH), 11.5 (s, 1, NH)
4c	$CH_3(CH_2)_3$	96	153-155 (e)	3350, 3180	1700, 1650	1.0 (m, 3, CH_3), 1.5 (m, 4, CH_2CH_2), 3.9 (m, 2, CH_2N), 7.1-7.3 (m, 2, ArH), 7.5-7.7 (m, 1, ArH), 7.8-8.0 (m, 1, ArH), 11.4 (s, 1, NH)
4d	C_6H_{11}	65	268-270 (f)	3280	1710, 1680	1.1-2.2 [m, 10, $(CH_2)_5$], 4.8 (m, 1, CHN), 7.0-7.3 (m, 2, ArH), 7.5-7.7 (m, 1, ArH), 7.8-8.0 (m, 1, ArH), 11.4 (s, 1, NH)
4e	$ClCH_2CH_2$ (g)	57	193-195	3300, 3180	1710, 1650	3.8 (m, 2, CH_2), 4.3 (m, 2, CH_2), 7.1-7.3 (m, 2, ArH), 7.5-7.7 (m, 1, ArH), 7.8-8.0 (m, 1, ArH), 11.4 (s, 1, NH)
4f	$EtOOCCH_2$ (h)	100	227-228.5	3130, 3180	1730, 1710 1660	1.2 (t, 3, CH_3), 4.2 (q, 2, CH_2CH_3), 4.7 (s, 2, CH_2N), 7.1-7.4 (m, 2, ArH), 7.6-8.0 (m, 2, ArH), 11.6 (s, 1, NH)
4g	C_6H_5	99	276-278 (i)	3350	1720, 1660	7.1-8.1 (m, 9, ArH), 11.6 (s, 1, NH)
4h	2-$CH_3C_6H_4$	97	248-250 (j)	3200	1730, 1650	2.1 (s, 3, CH_3), 7.1-7.4 (m, 6, ArH), 7.6-7.7 (m, 1, ArH), 7.8-8.0 (m, 1, ArH), 11.6 (s, 1, NH)
4i	3-$CH_3C_6H_4$	97	257-258.5 (k)	3250	1720, 1650	2.4 (s, 3, CH_3), 7.1-7.4 (m, 6, ArH), 7.6-7.7 (m, 1, ArH), 7.8-8.1 (m, 1, ArH), 11.6 (s, 1, NH)
4j	4-$CH_3C_6H_4$	97	262-264 (l)	3200	1720, 1640	2.4 (s, 3, CH_3), 7.1-7.4 (m, 6, ArH), 7.6-7.7 (m, 1, ArH), 7.8-8.1 (m, 1, ArH), 11.6 (s, 1, NH)
4k	3-ClC_6H_4	95	266-268 (m)	3220	1720, 1640	7.1-8.1 (m, 8, ArH), 11.8 (s, 1, NH)
4l	4-ClC_6H_4	95	295-296.5 (n)	3200	1710, 1660	7.1-8.1 (m, 8, ArH), 11.7 (s, 1, NH)
4m	2,5-$Cl_2C_6H_3$	88	227-229 (o)	3180	1710, 1670	7.2-8.1 (m, 7, ArH), 10.3-12.0 (br s, 1, NH)

(a) Crude or recrystallized product with melting point within 10° of that of the analytically pure compound. (b) Solutions in DMSO-d_6. (c) Reference 14. (d) Lit (10) mp 198°. (e) Lit (10) mp 156°. (f) Lit (10) mp 270-271°. (g) Reference 20. (h) Reference 7. (i) Lit (11) mp 280-282°. (j) Lit (21) mp 246°. (k) Lit (22) mp 252-252.5°. (l) Lit (11) mp 265-266°. (m) Lit (22) mp 260.5-261.5°. (n) Lit (12) mp 297°. (o) Lit (12) mp 228-230°.

jugated) for the amino form (1c). The appearance of the C=N band in the infrared spectra of **3b-m** at 1630-1650 cm^{-1} provides further support for the endocyclic position of the C=N in these compounds.

With regard to the reaction pathway for the conversion of **1** and **2** into **3** by the action of sulfuric acid, the possibility of a nucleophilic attack by the urea oxygen on the protonated acid or ester carbonyl is unlikely, in view of the earlier observations that heating of **1** or **2** with ethanol and hydrochloric or sulfuric acid yields the corresponding 3-substituted 2,4(1*H*,3*H*)-quinazolinediones (9-12). An attractive speculation is that, in concentrated sulfuric acid, the reaction proceeds by a mechanism involving formation of an acylium ion, which is the actual species undergoing cyclization.

Because of the known formation of 2,4(1*H*,3*H*)-quinolinediones by acid catalyzed, intramolecular condensation of **1** or **2**, it was thought desirable to firmly establish the 4*H*-3,1-benzoxazinone structure of all of the products of the reaction in concentrated sulfuric acid by individual comparison with the authentic isomeric, 3-substituted 2,4(1*H*,3*H*)-quinazolinediones (**4**). The method chosen for the preparation of the latter compounds was the hydroxide ion catalyzed cyclization of methyl 2-(3-alkyl-, or 3-aryl-ureido)benzoates (**2**). This reaction, which is very convenient and gives high yields of products within minutes, does not seem to have attracted much attention as a method of preparation of **4** (13), although it has been used to prepare the parent compound of the series (**4a**) (14), as well as several analogs of **4** containing a heterocyclic, instead of a benzene ring (15). When the corresponding members of the two series (**3** and **4**) were compared, it was found that in no case had a reaction of **1** or **2** in sulfuric acid produced a 2,4(1*H*, 3*H*)-quinazolinedione.

The availability of the two isomeric series of compounds allowed a comparison to be made of their ir and proton

nmr spectra. As was to be expected, the carbonyl stretching bands in the infrared spectra appear at wavenumbers higher by 10-60 cm^{-1} for compounds **3** (lactone-type carbonyls) than for the isomeric **4** (amide and urea carbonyls). Also, the nmr signals of the alkyl α-protons are less deshielded for the benzoxazinones (δ 3.3, 3.3, 3.9, 3.6-3.9, and 4.1 ppm respectively for **3b-f**), than for the quinazolinediones (δ 4.0, 3.9, 4.8, 4.2-4.4, and 4.7 respectively for **4b-f**). Finally, in agreement with the proposed endocyclic position of the C=N bond of compounds **3** (at least in solution), the nmr signals of their NH protons appear at a condiderably higher field (δ ca, 7.8 ppm for **3a**, 7.9-8.4 ppm for **3b-f**, and 9.7-10.5 ppm for **3g-m**) relative to those of the NH protons of compounds **4** (δ11.0, 11.2 ppm for **4a**, 11.4-11.6 ppm for **4b-f**, and 11.6-11.8 ppm for **4g-m**).

EXPERIMENTAL

Melting points were determined in capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer using mineral oil mulls. Proton nmr spectra were obtained on a Varian EM 360 spectrometer using solutions in hexadeuteriodimethyl sulfoxide and tetramethylsilane as internal standard.

2-(3-Arylureido)benzoic Acids (**1g-m**).

The mixture resulting from the addition of 0.015 mole of an aryl isocyanate to a solution of 2.05 g (0.015 mole) of anthranilic acid in 5 ml of dry tetrahydrofuran was allowed to stand until the reaction had been completed (1-6 hours). Addition of petroleum ether (bp 60-80°) followed by filtration yielded the crude **1** in essentially quantitative yield. Alternatively, isolation of **1** was accomplished by evaporation of the solvent at the aspirator.

Methyl 2-(3-Alkyl- and 3-Arylureido)benzoates (**2**).

For **2b-f**, a mixture of 0.020 mole of the alkyl isocyanate and 3.0 g (0.020 mole) of methyl anthranilate was allowed to stand until it had solidified completely (2-5 days).

For **2g-m**, an aryl isocyanate (0.020 mole) was added to a solution of 3.0 g (0.020 mole) of methyl anthranilate in 5 ml of dry ethyl ether and the resulting mixture was allowed to stand for 1-6 hours. It was then warmed on a steam bath to evaporate the solvent and yield the product.

2-Alkylamino- and 2-Arylamino-4*H*-3,1-benzoxazin-4-ones (**3**).

Crude, crushed **1**, or **2** (*ca.* 0.015, or 0.020 mole, respectively) was swirled for a few minutes with 10 ml of concentrated sulfuric acid to obtain a clear solution (16), which was allowed to stand for 1 hour (17). The reaction mixture was then poured into ice-water and neutralized with solid, or saturated aqueous sodium bicarbonate to yield the product, which was collected by filtration, thoroughly washed with water, and air dried. Yields and physical properties of **3** shown in Table I.

3-Alkyl- and 3-Aryl-2,4(1*H*,3*H*)-quinazolinediones (**4b-d,g-m**).

A mixture of *ca.* 0.020 mole of crude **2**, 10 ml (**2b-d**), or 20 ml (**2g-m**) of ethanol, and 10 ml of 10% aqueous sodium hydroxide was swirled on a steam bath until a clear solution had been obtained (2-5 minutes) (18). This was cooled (19), diluted with water, acidified with concentrated hydrochloric acid, and filtered to give the product. Yields and physical properties of **4** are listed in Table II.

Acknowledgement.

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(8) Heating of the sulfuric acid solution does not change the reaction outcome although it seems to decrease the yield somewhat. Thus, when a solution of 0.020 mole of **2k** in 10 ml of concentrated sulfuric acid is heated on a steam bath for 1 hour, an 86% of **3k** is obtained.

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(16) In the case of **2k**, the mixture does not become clear because a new solid starts forming before all of the starting material has dissolved.

(17) For **3a**, the solution in sulfuric acid was allowed to stand for 20 hours, whereas for **3m** 15 ml of sulfuric acid was used and the solution was allowed to stand for 1.5 hour.

(18) In the case of **4d**, the mixture was heated for 15 minutes to obtain a clear solution.

(19) For **4m**, the hot mixture was filtered from a small amount of insoluble solid material.

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