The Synthesis of *o*-Amino-*N*-substituted Benzamides and 3-Substituted 2,4(1*H*,3*H*)-Quinazolinediones from Isatoic Anhydride

Richard L. Jacobs

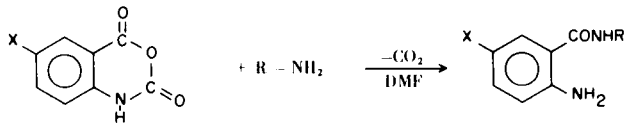
Toledo Laboratory, Sherwin Williams Chemicals, A Division of the Sherwin-Williams Company

The reaction of isatoic anhydride with sterically hindered amines in DMF or DMSO, and subsequent treatment of the *o*-amino-*N*-substituted benzamides thus produced with phosgene, gives high yields of 2,4(1*H*,3*H*)-quinazolinediones with branched alkyl groups in the 3-position.

In connection with a general study of the chemistry of isatoic anhydride and heterocyclic compounds which are readily prepared from it, we became interested in 2,4-(1*H*,3*H*)-quinazolinediones with branched alkyl groups in the 3-position. The literature contains many reports (1-14) describing the synthesis of 3-substituted 2,4(1*H*,3*H*)-quinazolinediones.

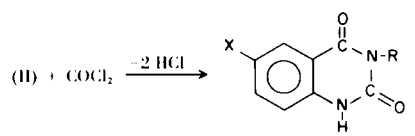
Of many procedures, only three (1a,7c,8a) appear to be applicable to the synthesis of 2,4(1*H*,3*H*)-quinazolinediones with branched alkyl groups in the 3-position. However, in these instances there are major drawbacks, including the need for expensive starting materials, as well as lengthy reaction periods and yields of the desired products are generally poor.

The present paper describes a simple, economical, and versatile synthesis which produces the desired compounds in good yields. In the course of this work, an improved procedure for the preparation of *o*-amino-*N*-substituted benzamides was developed. The following equation illustrates the reactions involved.



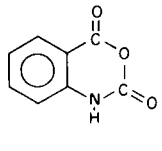
X = H, Cl, NO_2

(I) (II)



(III)

The literature contains several references (15) to the synthesis of *o*-amino-*N*-substituted benzamides by reaction of isatoic anhydride (I) with amines. In general, two types of products are produced during the reaction.



(I)

(II) (IV)

Staiger and Wagner (15c) found that formation of (IV) was favored by bulkiness in the amine, and by a high mole ratio of amine to (I). By contrast, simple straight chain amines, and a low mole ratio of amine to (I), favored the formation of (II).

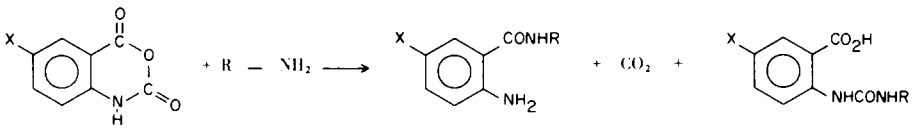
Staiger and Miller (15d) suggested steric hindrance as a possible explanation for the favored formation of (IV) in the case of sterically hindered amines. That such an explanation is not entirely responsible for the results obtained, is indicated by our work in DMF, DMAC and DMSO with (I) and sterically hindered amines.

Although different solvents, including DMF, have been used in this reaction, no striking effect has ever been attributed to the reaction solvent. In our hands, a significant increase in the yield of (II) was found, when DMF, DMAC, or DMSO was employed as the reaction solvent (Table I).

For example, the reaction of isatoic anhydride with *sec*-butylamine in water produced *o*-amino-*N*-*sec*-butylbenzamide in a maximum yield of 77.1%. Under identical reaction conditions, except that DMF was used in place of water, the yield of *o*-amino-*N*-*sec*-butylbenzamide was increased to 97.0%. A still more dramatic effect was found in the reaction of isatoic anhydride with *t*-butyl-

TABLE I

o-Amino-*N*-substituted Benzamides



(I) (II) (IV) (a)

No.	X	R (c)	Reaction Temp. °C	Amine Addition Time-Hours	Total Reaction Time-Hours	Solvent	% Yield of II (b)	Formula	Calcd. %	Found %	M.p., °C
1	H	*sec*-butyl	45-48 (d)	1	7	water	77.1	$C_{11}H_{16}N_2O$	C 68.72 H 8.39 N 14.57	68.62 8.29 14.31	112.5-113.5
2	H	*sec*-butyl	45-48	1	6	98% water 2% DMF (e)	81.3				
3	H	*sec*-butyl	45-49	1	3	Xylene	69.8				
4	H	*sec*-butyl	45-48	1	3	98% Xylene 2% DMF	93.2				
5	H	*sec*-butyl	45-46.3	0.5	3	DMF	97				
6	H	*sec*-butyl	45-49	1	3.5	DMAC (e)	95.2				
7	H	*t*-butyl	49-49	1	2.5	water	8.5 (k)	$C_{11}H_{16}N_2O$	N 14.57	14.39	124-125.5
8	H	*t*-butyl	35-40	0.5	3	DMF	72.6				
9	H	*t*-butyl	31-38	0.5	(g)	DMSO (e)	65				
10	H	isopropyl	17-21	0.1	7	water	74.7 (h)	$C_{10}H_{14}N_2O$	C 67.38 H 7.92 N 15.72	67.31 7.81 15.67	145-146
11	H	isopropyl	48-50	1	4	water	83.5 (i)				
12	H	isopropyl	35-36	2	4	DMF	94.2 (j)				
13	H	*o*-ethylphenyl	136-138	0.75	3.5	DMF	13.3	$C_{15}H_{16}N_2O$	E. Wt. (f) 240	E. Wt. 248	138.8-141
14	H	2′,6′-di-ethylphenyl	135-139	0.5	15	DMF	0.0	$C_{17}H_{20}N_2O$			
15	H	3-heptyl	35-41	0.75	6.5	DMF	89.8	$C_{14}H_{22}N_2O$	C 71.8 H 9.4	72.0 9.3	94-95.5
16	H	2-octyl	42.5-43	1	4.5	DMF	95	$C_{15}H_{24}N_2O$	C 72.54 H 9.74	72.58 9.61	86.5-88

17	H	2-methyl-cyclohexyl	38.40	1	5	DMF	92.5	$C_{14}H_{20}N_2O$	C 72.37 H 8.68	72.34 8.74	127.5-128.5
18	H	branched hexadecyl	45-45	0.5	3.5	DMF	97.5	$C_{23}H_{40}N_2O$	C 76.61 H 11.18	76.40 11.00	64.5-66.5
19	Cl	*sec*-butyl	47-48	1	4.5	DMF	94	$C_{11}H_{15}ClN_2O$	Cl 15.64	15.64	144.5-145.1
20	NO_2	morpholino	45-47	1	5	DMF	93.5	$C_{11}H_{13}N_3O_4$	C 52.58 H 5.22 N 16.72	52.65 5.24 16.40	193-194
21	H	(1-naphthyl)-ethyl (1)	45-46	2	7	DMF	94.6	$C_{19}H_{18}N_2O$	C 78.59 H 6.25 N 9.65	78.56 6.18 9.85	201-202
22	H	cyclopropyl	39-40	1.5	3.5	DMF	86.9	$C_{10}H_{12}N_2O$	C 68.16 H 6.86	67.96 6.87	152-152.5
23	H	2-heptyl	25.5-29	1	5	DMF	98.3	$C_{14}H_{22}N_2O$	C 71.75 H 9.46	72.08 9.55	100-102.5
24	H	tetrahydro-furfuryl	20-24	0.3	2	DMF	73	$C_{12}H_{16}N_2O_2$	C 65.43 H 7.32	65.61 7.44	69-71
25	H	propargyl	22-40	0.25	2.5	DMF	94	$C_{10}H_{10}N_2O$	C 68.94 H 5.79	68.70 5.91	99-100.5
26	H	*n*-heptyl	45-48	1	3.5	DMAC (m)	99	$C_{14}H_{22}N_2O$	C 71.75 H 9.46 N 11.9	71.64 9.47 11.6	67.5-69
27	H	*n*-octyl	49-49	1	2.5	DMSO (n)	99	$C_{15}H_{24}N_2O$	C 72.54 H 9.74 N 11.27	72.75 9.60 11.12	66.5-67.5
28	Cl	2-diethyl-aminoethyl	47-48	2	4.5	DMF	80	$C_{13}H_{20}ClN_3O$	C 57.88 H 7.47 N 15.58	57.99 7.52 15.61	155-157/1 mm
29	NO_2	phenyl	70-80	0.1	4	dioxane	82	$C_{13}H_{11}N_3O_3$	N 16.34	16.01	201-203
30	Cl	3,4-dichloro-phenyl	135-155	0.1	2	none	75.3	$C_{13}H_9Cl_3N_2O$	C 49.47 H 2.88	49.32 2.88	161-162
31	Cl	phenyl	134-150	0.1	2	none	77	$C_{13}H_{11}ClN_2O$	C 63.29 H 4.49	63.52 4.64	151-153
32	NO_2	3-chloro-phenyl	80-100	0.1	24	dioxane	86.4	$C_{13}H_{10}ClN_3O_3$	C 53.53 H 3.46 N 14.41	53.50 3.61 14.23	231-232
33	H	2-vinyl oxoethyl	42-47	0.5	5	DMF	80	$C_{11}H_{14}N_2O_2$	C 64.06 H 6.84 N 13.58	64.18 6.90 13.77	61-62.5

TABLE I - Continued

No.	X	R (c)	Reaction Time °C	Amine Addition Time-Hours	Total Reaction Time-Hours	Solvent	% Yield of II (b)	Formula	Calcd. %	Found %	M.p., °C
34	H	3-methoxy-propyl	46.49	1	2.5	DMF	95.6	$C_{11}H_{16}N_2O_2$	C 63.48 H 7.75	63.29 7.90	46.5-47.3
35	H	*t*-butoxy-carbonylamino	52-60	1	5	DMF	78.5	$C_{12}H_{17}N_3O_3$	C 57.36 H 6.82 E. Wt. (f) 251	57.21 6.9 E. Wt. 256	143-144
36	H	carbethoxy-amino	48-50	0.5	10	DMF	37.9	$C_{10}H_{13}N_3O_3$	C 53.78 H 5.83	53.80 5.78	115-116

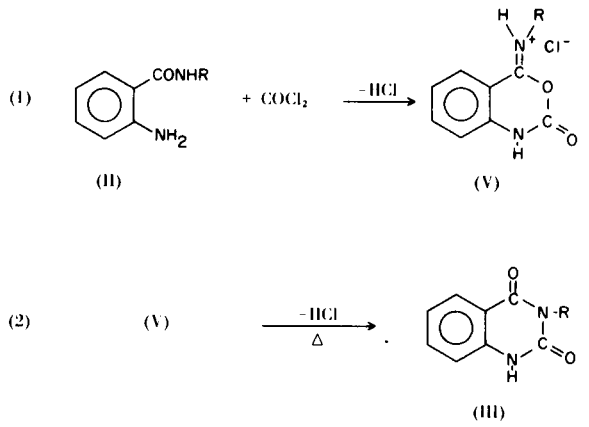
(a) In general, the yield of IV is the difference between 100% yield of II and actual yield of II. (b) With water as solvent, the highest yield of II reported is 33.66% (ref. 14c). (c) Overall mole ratio of amine to I was 1:1. (d) This temperature was maintained until carbon dioxide evolution ceased. (e) DMF = Dimethylformamide; DMAC = Dimethylacetamide; DMSO = Dimethylsulfoxide. (f) Equivalent Weight as determined by nitrite titration. (g) Set aside overnight at room temperature. (h) In this experiment the isatoic anhydride was added to the isopropylamine. (i) The highest yield reported (14c) is 65%. (j) Actual yield probably quantitative, since no trace of IV could be found, also II has slight water solubility. (k) When this reaction was carried out in the presence of *t*-butylamine hydrochloride, the yield increased to 37.5%. (l) The amine used was *d*-Resoline-A obtained from Chemtron Corporation. (m) 97.3% yield in DMF. (n) 98.4% yield in DMF

amine. In water, the maximum yield of *o*-amino-*N*-*t*-butylbenzamide was 8.5%, whereas in DMF a 73.5% yield was isolated. Similar results were obtained in DMSO and DMAC.

Whether the DMF is exerting a catalytic effect or merely a solvent effect (16) upon the reaction of isatoic anhydride with amines, or whether a combination of these effects is responsible for the observed increase in yields of *o*-amino-*N*-substituted benzamide is not known at present.

The formation of 2,4(1*H*,3*H*)-quinazolinediones with branched alkyl groups in the 3-position was readily accomplished by reacting the corresponding *o*-amino-*N*-substituted benzamides with phosgene (17). In general, yields of 80-85% are easily achieved (see Table II), even when the branched alkyl group is *t*-butyl.

The reaction probably occurs in two steps, as shown below (18).



The first step occurs spontaneously, and is exothermic in nature. The second step occurs only slowly unless the reaction mixture is heated above ambient temperature and is especially rapid in the vicinity of 100°. The end of the reaction is signaled by the end of hydrogen chloride evolution.

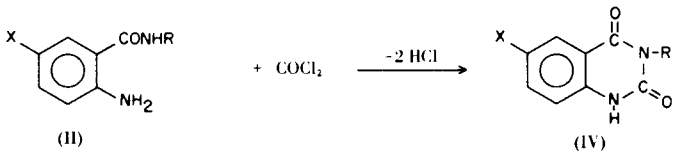
When a known procedure (8b) was modified by substituting *o*-amino-*N*-isopropylbenzamide for *o*-amino-3,5-dichlorobenzamide, and reacting with a substantially equimolar proportion of ethyl chloroformate in *p*-dioxane as a solvent, no 3-isopropyl-2,4(1*H*,3*H*)-quinazolinedione was formed. In another instance, *o*-amino-*N*-isopropylbenzamide was reacted by the known method with a large excess of ethyl chloroformate at reflux and again, no 3-isopropyl-2,4(1*H*,3*H*)-quinazolinedione was formed.

Instead, in both of the above instances, a nearly quantitative yield of *o*-carbethoxyamino-*N*-isopropylbenzamide (19) was obtained.

We were able to make the desired 3-isopropyl-2,4-(1*H*,3*H*)-quinazolinedione, from *o*-carbethoxyamino-*N*-isopropylbenzamide, using a modification of the method

TABLE II

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



(II) (IV)

Reaction Conditions (a)

No.	X	R	Reaction Time-Hours	Temperature-°C At Start of Phosgene Addition	At End of Phosgene Addition	% Yield	M.p. °C	Product - IV Formula	Calcd. %	Found %
1	H	isopropyl	6	21	38	86.3	187-188.5	$C_{11}H_{12}N_2O_2$	C 64.70 H 5.87	64.74 5.85
2	H	isopropyl	3	23	42	93 (b)	187-188			
3	H	*sec*-butyl	3	21	39	83	131-132.5	$C_{12}H_{14}N_2O_2$	C 66.00 H 6.47	66.04 6.47
4	H	*t*-butyl	3	19	38.5	75.2	192-192.5	$C_{12}H_{14}N_2O_2$	Ref. (8a)	
5	H	2-methyl-cyclohexyl	2	22	35	99.6	209-212	$C_{15}H_{18}N_2O_2$	C 69.74 H 7.0	69.9 7.1
6	H	2-octyl	4	22.5	34	82	82-85	$C_{16}H_{22}N_2O_2$	C 70.0 H 8.1	70.0 8.3
7	H	*o*-ethylphenyl	5.5	24	41	87.2	272.5-277.5	$C_{16}H_{14}N_2O_2$	C 72.2 H 5.3	72.5 5.3
8	H	2-ethylhexyl	2	22	38	74	145-146	$C_{16}H_{22}N_2O_2$	C 70.0 H 8.08	69.8 7.97
9 (c)	H	branched tetradecyl	2.5	21	38.5	66	72.5-80.5	$C_{22}H_{34}N_2O_2$	C 73.70 H 9.57	73.81 9.57
10 (c)	H	branched hexadecyl	5.5	19.5	37	83	85.5-88.5	$C_{24}H_{38}N_2O_2$	C 74.5 H 9.9	74.1 9.8
11	H	3-heptyl	4.5	25	39	66.1	80-83	$C_{15}H_{20}N_2O_2$	C 69.2 H 7.74	69.3 7.70
12	H	2-heptyl	3	24	39	89.6	101.5-102.5	$C_{15}H_{20}N_2O_2$	C 69.2 H 7.74	69.1 7.75
13	H	2-carboxylphenyl	2	22.5	37	57	296.5-298 dec	$C_{15}H_{10}N_2O_4$	C 63.82 H 3.57	63.73 3.54

TABLE II—Continued

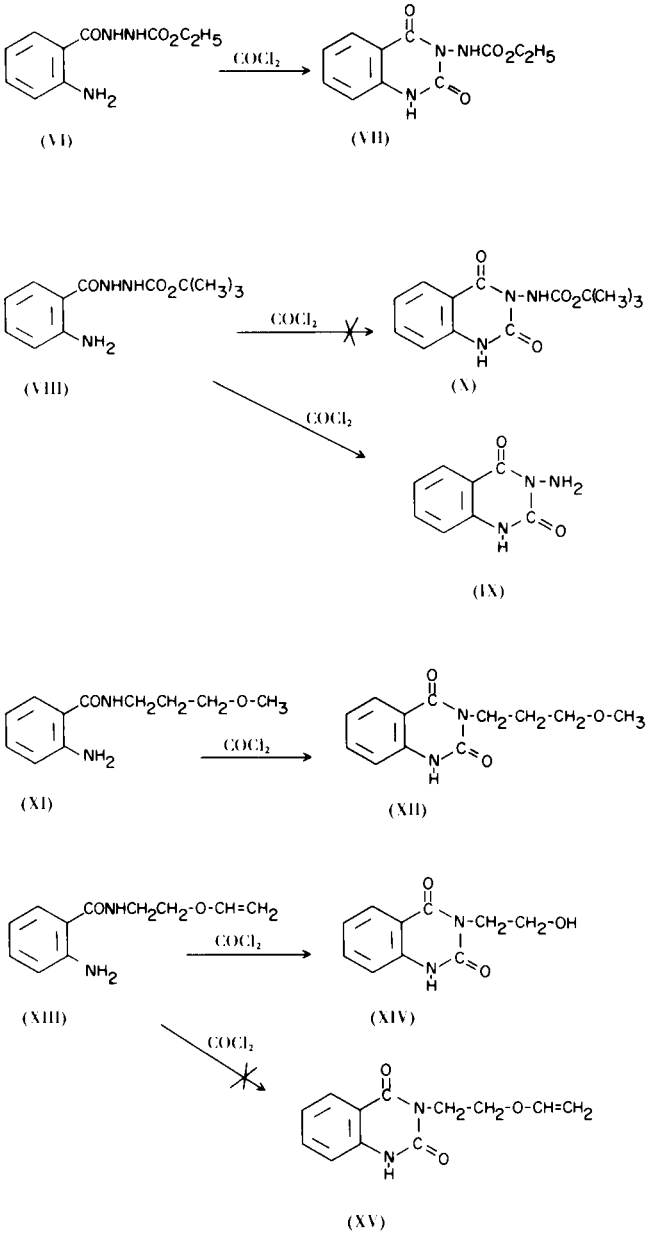
14 (d)	H	*o*-methylamino-*N*-isopropylbenzamide	73	18.5	38	67.4 (e)	131.5-132.5	$C_{12}H_{14}N_2O_2$	C 66.0 H 6.46 N 12.84	65.9 6.44 12.54
15		tetrahydro-furfuryl	4.5	23	42	64	202-205	$C_{13}H_{14}N_2O_3$	C 63.4 H 5.7	63.7 5.9
16	H	propargyl	4.5	24	41	87	239-240.5	$C_{11}H_8N_2O_2$	C 65.9 H 4.0	65.6 4.3
17	H	cyclopropyl	8	23	36	49.5	212-213	$C_{11}H_{10}N_2O_2$	C 65.34 H 4.98	64.90 5.07
18	NO_2	phenyl	2	21	37	85.5	296.5-298	$C_{14}H_9N_3O_4$	C 59.36 H 3.20 N 14.84	59.47 3.22 14.82
19	Cl	3,4-dichlorophenyl	5	21	37.5	62.7	366-367	$C_{14}H_7Cl_3N_2O_2$	C 49.22 H 2.07	49.35 2.21
20	Cl	phenyl	3	22	36	63.3	308-309	$C_{14}H_9ClN_2O_2$	C 61.66 H 3.33	61.22 3.34
21	H	3-methoxypropyl	4.5	25	45	70	145.5-147	$C_{12}H_{14}N_2O_3$	C 61.52 H 6.02 N 11.96	61.64 6.41 11.51
22	H	carbethoxyamino	5	22	39	82.3	225.5-227	$C_{11}H_{11}N_3O_4$	C 53.01 H 4.45	52.83 4.27

(a) Phosgene was bubbled through a dry dioxane solution of II at the rate of one-half gram per minute - overall mole ratio of phosgene to II was 1:1. After the phosgene addition the reaction mixture was heated and maintained at 100° until the evolution of hydrogen chloride stopped - usually one to five hours. The resulting solution was then cooled to 20-25° and quenched into water to precipitate the product. (b) The major portion of the dioxane was removed *in vacuo* prior to quenching of the reaction mixture into water. In general, yields averaged 5-10% higher than those shown in the table if this concentration procedure were followed. (c) A mixture of isomers. (d) Prepared from *N*-methylisatoic anhydride and isopropylamine. (e) This result contrasts sharply with the report by Hayao, *et al.* (20), who found that phosgene did not ring close *o*-methylamino-*N*-[3-(4-phenyl-1-piperazinyl)propyl]benzamide.

developed by Sheibley (8a). But such a technique is not recommended since it is tedious and yields are only fair.

In addition we observed that merely heating the dry *o*-carbethoxyamino-*N*-isopropylbenzamide to temperatures 80-100° above its melting point and holding the material at these elevated temperatures for long periods of time would also give the desired 3-isopropyl-2,4(1*H*,3*H*)-quinazolinedione in moderate yield, but again the method cannot be recommended as a convenient procedure (20).

In the course of this investigation, several unusual reactions occurred during the phosgene ring closure phase. For example, whereas (VI) reacted smoothly to give (VII) in 82.3% yield, (VIII) produced (IX) in 57.4% yield with no (X) being observed.



In another instance, whereas (XI) proceeded readily to (XII) in 70% yield, (XIII) afforded a 78.6% yield of (XIV) with no (XV) being observed.

It should be pointed out that the transformation of (XIII) into (XIV) may require the presence of an HCl-acceptor, for in the absence of a material like triethylamine, a vigorous exothermic reaction occurs between (XIII) and phosgene producing viscous black tars.

EXPERIMENTAL (21)

o-Amino-*N*-*sec*-butylbenzamide [(II), R = *sec*-butyl].

General Procedure.

The preparation of *o*-amino-*N*-*sec*-butylbenzamide well demonstrates the general procedure followed in the synthesis of those compounds listed in Table I. A one liter flask was charged with 163.1 g. (1.0 mole) of isatoic anhydride (recrystallized from DMF) and 500 ml. of DMF (dried over molecular sieves). The above solution was warmed to 44° and held at 45-50° while 74.6 g. (1.02 mole) of *sec*-butylamine dissolved in 200 ml. of DMF was added dropwise (22) in the course of one hour. The reaction mixture was maintained at 45-50° until carbon dioxide evolution had ceased (usually 2-5 hours). The reaction mixture was poured into 4200 ml. of water and the resulting aqueous slurry adjusted to *p*H 9 with 50% sodium hydroxide solution. The product was removed by filtration, washed free of caustic with 5 x 200 ml. portions of water and dried in air under infrared lamps. In this manner, a 94.9% yield of *o*-amino-*N*-*sec*-butylbenzamide, m.p. 112.5-113.5° was obtained.

3-*sec*-Butyl-2,4(1*H*,3*H*)-quinazolinedione [(IV), R = *sec*-butyl].

General Procedure.

The synthesis of 3-*sec*-butyl-2,4(1*H*,3*H*)-quinazolinedione well illustrates the general technique followed in the preparation of compounds shown in Table II. A 500 ml. flask was charged with 38.4 g. (0.2 mole) of *o*-amino-*N*-*sec*-butylbenzamide and 350 ml. of dioxane (dried over molecular sieves). Phosgene (23) was then introduced at a rate of 0.5 g. per minute, until a total of 19.8 g. (0.20 mole) had been added. During this addition period, the reaction temperature increased from 21° to 39°. The phosgene addition tube was replaced by a glass stopper and the reaction mixture heated to reflux (24) and maintained at reflux for 2.5 hours. The resulting solution was cooled to 20-25° and poured into one liter of cold water. The resulting slurry was filtered and the product washed free of acid with 4 x 100 ml. portions of cold water, and air dried under infrared lamps. There was obtained an 83% yield of 3-*sec*-butyl-2,4(1*H*,3*H*)-quinazolinedione, m.p. 131-132.5°.

3-*t*-Butyl-2,4(1*H*,3*H*)-quinazolinedione (4).

Procedure A.

A 250 ml. flask was charged with 6.9 g. (0.05 mole) of anthranilic acid, 15.4 g. (0.10 mole) of *N*,*N*′-di-*t*-butylcarbodiimide (25), and 50 ml. of anhydrous benzene. The resulting slurry was stirred at 25° for one hour, heated to reflux and held there for four hours. The resulting clear yellow solution was cooled to 20-25° and set aside overnight. The benzene was removed under reduced pressure and 150 ml. of an ethanol-sulfuric acid mixture (10% sulfuric acid by weight) added to the concentrated residue and the resulting mixture heated to reflux and held there for four hours. The

solvent was again removed under reduced pressure and the concentrated product poured into 500 ml. of ice water. The crude product, 5.3 g., was removed by filtration and recrystallized from methanol, m.p. 170-195°. Repeated recrystallizations failed to improve upon this melting point range. An examination of this material by infrared techniques indicated the presence (max. amount 5%) of some 3-*t*-butyl-2,4(1*H*,3*H*)-quinazolinedione.

Procedure B.

Following the procedure described by Gadekar, *et al.* (8b), we obtained a 91% yield of crude *o*-carbethoxyamino-*N*-*t*-butylbenzamide (26), m.p. 137-160° (recrystallization from ethanol gave material with a m.p. of 159-160° [lit. (8b) m.p. 161-163°]. Subsequent treatment of this material with ethanolic potassium hydroxide at reflux, afforded a 58% yield of crude 3-*t*-butyl-2,4(1*H*,3*H*)-quinazolinedione, m.p. 195-196° [lit. (8b) m.p. 198-199°].

Substitution of *o*-amino-*N*-isopropylbenzamide for *o*-amino-*N*-*t*-butylbenzamide in this reaction resulted in the formation of 3-isopropyl-2,4(1*H*,3*H*)-quinazolinedione in 60% yield.

3-(2-Hydroxyethyl)-2,4(1*H*,3*H*)-quinazolinedione (XIV).

A 500 ml. flask was charged with 20.6 g. (0.1 mole) of *o*-amino-*N*-(2-vinyloxyethyl)benzamide, 20.2 g. (0.2 mole) of triethylamine and 350 ml. of dry dioxane. Phosgene (23) was then added at a rate of 0.5 g. per minute, until a total of 9.9 g. (0.1 mole) had been added. During phosgenation, the reaction temperature increased from 22-64°. The phosgene addition tube was replaced by a glass stopper and the reaction mixture heated to reflux and held at reflux for three hours. The resulting slurry was cooled to 80° and the triethylamine hydrochloride removed by filtration. The dioxane filtrate was carbon treated, filtered and the dioxane removed under reduced pressure. The residue was recrystallized from methanol to give 3-(2-hydroxyethyl)-2,4(1*H*,3*H*)-quinazolinedione, m.p. 250.5-252.5°, in 78.6% yield.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.25; H, 5.06; N, 13.38.

3-Amino-2,4(1*H*,3*H*)-quinazolinedione (IX).

A 500 ml. flask was charged with 25.1 g. (0.1 mole) of *o*-amino-*N*-[(*t*-butoxycarbonyl)amino]benzamide and 350 ml. of dioxane (dried over molecular sieves). Phosgene (23) was then introduced at a rate of 0.5 g. per minute, until a total of 9.9 g. (0.1 mole) had been added. During phosgenation, the reaction temperature increased from 18° to 42°. The phosgene addition tube was replaced by a glass stopper and the reaction mixture heated to reflux and held at reflux for five hours. The resulting slurry was cooled to 20° and filtered. Recrystallization from ethanol gave a 57.4% yield of 3-amino-2,4(1*H*,3*H*)-quinazolinedione, m.p. 291.5-293°.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.26; H, 3.99; N, 23.82.

Preparation of 3-Isopropyl-2,4(1*H*,3*H*)-quinazolinedione from *o*-Carbethoxyamino-*N*-isopropylbenzamide.

To a stirred solution of 25 g. (0.14 mole) of *o*-amino-*N*-isopropylbenzamide in 500 ml. of anhydrous dioxane was added 15.2 g. (0.14 mole) of ethyl chloroformate. The addition required 34 minutes and a rise in temperature from 22° to 30° was observed. The resulting yellow slurry was heated to reflux and held there for five hours, cooled to 25° and poured into 1250 ml. of water. The product was removed by filtration and air dried under infrared lamps. There was obtained 25.6 g. of *o*-carbethoxyamino-*N*-isopropylbenzamide, m.p. 105-109°. (Recrystallization from methanol gave material with a m.p. of 106.5-107.5°.)

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.36; H, 7.33; N, 11.30.

This material was held at 155° for three hours and then at 185° for three hours to produce 3-isopropyl-2,4(1*H*,3*H*)-quinazolinedione in 50% yield, m.p. 187-188°. The infrared spectrum of this material was identical in every respect with that of material prepared by the general procedure, from phosgene and *o*-amino-*N*-isopropylbenzamide.

Preparation (27) and Isolation of (V), with R = Isopropyl.

Phosgene was introduced into a solution of 3.56 g. (0.02 mole) of *o*-amino-*N*-isopropylbenzamide dissolved in 100 ml. of dioxane, until 3 g. (0.03 mole) of phosgene had been absorbed. The reaction mixture was kept at 20° by external cooling throughout the phosgene addition period and for one hour thereafter. The solid which formed during the reaction was removed, washed with 25 ml. of cold dioxane, and dried under reduced pressure at 20-25°. The dry solid, m.p. 179-181° was examined by infrared techniques and its spectrum found to be in agreement with the structure shown above for (V). Upon continued standing at 20-25°, (V) liberated hydrogen chloride. Heating a sample of (V) in refluxing dioxane for three hours, resulted in the formation of 3-isopropyl-2,4(1*H*,3*H*)-quinazolinedione in 70% yield.

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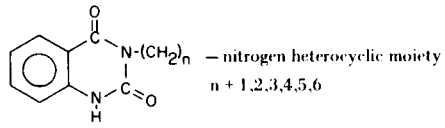
(16) DMF is the best solvent for isatoic anhydride, dissolving 28.9 g./100 g. of solution at 25°.

(17) After the present work was completed, reports appeared [S. Hayao, U. S. Patent 3,274,194 (1966); S. Hayao, *et al.*, *J. Med. Chem.*, **8**, 807 (1965)] describing the use of phosgene in the preparation of 3-(4-aryl-1-piperazinylalkyl)-2,4(1*H*,3*H*)-quinazolinediones. The 3-substituent in this instance is a nitrogen containing heterocyclic moiety connected to the 3-position of the 2,4(1*H*,3*H*)-quinazolinedione by a straight chain hydrocarbon linkage.



Because of the presence of the nitrogen heterocyclic moiety, the ring closure with phosgene yields hydrochloride salts of the 3-substituted 2,4(1*H*,3*H*)-quinazolinediones which must then be treated with a base to free the 3-substituted 2,4(1*H*,3*H*)-quinazolinedione.

(18) A close analogy is to be found in work reported in British Patent 1,060,741 (1967).

(19) Such structures have recently been patented, S. Gadekar, U. S. Patent 3,252,986 (1966), as central nervous system depressants.

(20) S. Hayao, *et al.*, *J. Med. Chem.*, **8**, 807 (1965) have also noted that heating an *o*-carboxyamino-*N*-substituted benzamide at high temperatures results in ring closure to 3-substituted 2,4(1*H*,3*H*)-quinazolinediones, although in this instance the starting materials and final products were hydrochloride salts.

(21) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer and all compounds prepared had infrared spectra which agreed with the assigned structures. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tennessee.

(22) The tip of the dropping funnel should extend well below the surface of the isatoic anhydride-DMF solution, in order to minimize plugging of the funnel by amine carbonate (produced by reaction of the amine with liberated carbon dioxide).

(23) A rotometer was used to measure and control the rate of phosgene addition. The phosgene addition tube should extend well below the surface of the dioxane solution. Soon after phosgene addition was started, the formation of solids was noted.

(24) During the heat-up period, at about 80°, rapid hydrogen chloride evolution occurred and by 88°, all solids had dissolved.

(25) Prepared by the method of Coles and Levine, U. S. Patent 2,942,025 (1960).

(26) By carrying this reaction out in dioxane, using a 1:1 mole ratio of reactants, we obtained a 98% yield of nearly pure product, m.p. 158-159°. Recrystallization from ethanol gave material of m.p. 160-161°.

(27) The preparation and characterization of (V) was carried out by Dr. R. L. Hively.

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