

The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)dione (Isatoic Anhydrides)1. The Synthesis of *N*-substituted 2*H*-3,1-Benzoxazine-2,4(1*H*)diones

Goetz E. Hardtmann*, Gabor Koletar and Oskar R. Pfister

Department of Medicinal Chemistry, Pharmaceutical Division, Sandoz, Inc.,
Route 10, East Hanover, New Jersey 07936

Received December 24, 1974

Three methods for the preparation of *N*-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)diones (isatoic anhydrides) (1) utilizing 2-chloro-, 2-nitrobenzoic acids and *N*-unsubstituted isatoic anhydrides as starting materials, are described.

During the past fifty years 2*H*-3,1-benzoxazine-2,4(1*H*)dione (2), its halo (3), and nitro (4) derivatives have been utilized in the preparation of anthranilamides (5), aminobenzophenones (6), quinazolines (7), quinazoline-diones (8) and a variety of fused heterocyclic ring systems (9). The majority of the reactions described were carried out with *N*-unsubstituted 2*H*-3,1-benzoxazine-2,4(1*H*)diones, but more recently (10,11) simple *N*-alkyl derivatives have also been utilized. While the *N*-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)dione and its 6-nitro and 6-chloro derivatives can be obtained commercially (12), other alkyl derivatives are either unknown or not readily available (13). For the past several years, we have been interested in the chemistry of isatoic anhydrides and wish now to report the synthesis of a variety of 1-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)diones (Chart 1) which in our hands

have become most useful synthetic tools.

The method most generally used (Method A) (14) takes advantage of the ease by which the *N*-sodio derivative of 2*H*-3,1-benzoxazine-2,4-dione (2) is formed on treatment of 1 with sodium hydride. In turn 2 is readily alkylated with alkyl, alkenyl, propargyl and benzyl halides. The use of sodium hydride can often be circumvented by directly reacting the isatoic anhydrides with halides in the presence of potassium or sodium carbonate.

Low yields were encountered when reaction II (Method A) was performed with secondary alkyl halides (e.g. isopropyl iodide yielded only 15% of the product 3, R = isopropyl). For those compounds we found it, in some cases, advantageous to react 2-chlorobenzoic acid sodium salt (4) in the presence of copper powder with secondary amines (Ullmann reaction, Method B, reaction III). The intermediate anthranilic acid (5) was transformed into benzoxazine-2,4-diones by reaction with phosgene. Alternatively the anthranilic acids (5) could also be obtained by catalytic reduction of *o*-nitrobenzoic acids in presence of aldehydes or ketones (Method C) which was followed by immediate treatment of the crude reduction product with phosgene. During reaction V small amounts of dialkylamino anthranilic acids (8) are formed, which are easily separated by filtration of the final product 3 through a small column of activated alumina.

The 2*H*-3,1-benzoxazine-2,4(1*H*)diones prepared by methods A, B and C are listed in Table 1. The broad utility of those has already been demonstrated and in a forthcoming publication we will report about a number of heterocyclic systems, readily accessible from the products described in this publication.

EXPERIMENTAL

All compounds gave satisfactory elemental analyses except as

Chart 1

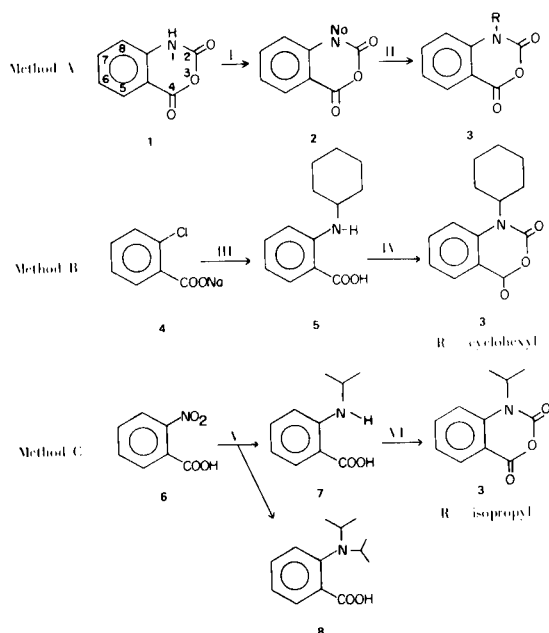
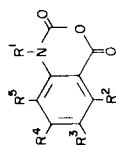


Table I



R ¹	R ²	R ³	R ⁴	R ⁵	M.p. °C	Yield %	Empirical Formula (M. W.)	Elemental Analysis	Procedure
1 Methyl (a)	H	H	H	H	165 dec.				
2 Methyl	H	Cl	H	H	192-195		C ₉ H ₆ NO ₃ Cl (211.61)	Calcd. C 51.1 H 2.9 N 6.6 Found 51.3 3.0 6.6	Cl 16.8 16.4
3 Methyl	H	H	Cl	H	216-218	43	C ₉ H ₆ NO ₃ Cl (211.61)	Calcd. C 51.1 H 2.9 N 6.6 Found 50.7 2.7 6.6	Cl 16.8 16.8
4 Methyl	H	OMe	H	H	228-231	65	C ₁₀ H ₉ NO ₄ (207.18)	Calcd. C 58.0 H 4.4 N 6.8 Found 57.7 4.6 6.9	
5 Methyl	H	OMe	OMe	H	213-217	17	C ₁₁ H ₁₁ NO ₅ (237.21)	Calcd. C 55.7 H 4.7 N 5.9 Found 55.7 4.9 5.9	
6 Methyl	H	-O-CH ₂ -O-	H	H	220-222	86	C ₁₀ H ₇ NO ₅ (221.16)	Calcd. C 54.3 H 3.2 N 6.3 Found 54.3 3.2 6.3	
7 Ethyl	H	H	H	H	121-123	61	C ₁₀ H ₉ NO ₃ (191.20)	Calcd. C 62.8 H 4.8 N 7.3 Found 62.8 4.8 7.2	
8 Ethyl	H	Cl	H	H	143-145	37	C ₁₀ H ₈ NO ₃ Cl (225.63)	Calcd. C 53.2 H 3.6 N 6.2 Found 53.2 3.8 5.8	Cl 15.7 15.5
9 Propyl	H	H	H	H	79-81	44	C ₁₁ H ₁₁ NO ₃ (205.23)	Calcd. C 64.4 H 5.4 N 6.8 Found 64.7 5.8 6.9	
10 Isopropyl	H	H	H	H	117-119	15/63	C ₁₁ H ₁₁ NO ₃ (205.23)	Calcd. C 64.4 H 5.4 N 6.8 Found 64.4 5.8 6.7	
11 Allyl	H	H	H	H	102-104	77	C ₁₁ H ₉ NO ₃ (203.19)	Calcd. C 65.0 H 4.5 N 6.9 Found 65.0 4.6 6.7	
12 2-Propynyl	H	H	H	H	132-134	56	C ₁₁ H ₇ NO ₃ (201.17)	Calcd. C 65.7 H 3.5 N 7.0 Found 65.7 3.8 7.0	
13 2-Propynyl	H	Cl	H	H	163-166	69	C ₁₁ H ₆ NO ₃ Cl (235.63)	Calcd. C 56.1 H 2.6 N 5.9 Found 56.0 2.9 5.8	Cl 15.0 15.7
14 2-Propynyl	H	O-CH ₂ -O	H	H	182-184	23	C ₁₂ H ₇ NO ₅ (245.18)	Calcd. C 58.8 H 2.9 N 5.7 Found 58.4 3.2 5.7	
15 Butyl (b)	H	H	H	H	59-61	80	C ₁₂ H ₁₃ NO ₃ (219.26)	Calcd. C 55.7 H 6.0 N 6.4 Found 65.7 6.1 6.4	

Table I (Continued)

	R ¹	R ²	R ³	R ⁴	R ⁵	M.p. °C	Yield %	Empirical Formula (M.W.)	Elemental Analysis	Procedure	
16	Butyl	H	H	Cl	H	107-110	80	C ₁₂ H ₁₂ NO ₃ Cl (253.70)	Calcd. C 56.8 H 4.8 N 5.5 Found 56.4 5.1 5.4	Cl 14.0 14.6	A
17	3-Butenyl	H	H	H	H	67-70	37	C ₁₂ H ₁₁ NO ₃ (217.22)	Calcd. C 66.4 H 5.1 N 6.5 Found 66.4 5.1 6.4		A
18	2-Butenyl	H	H	H	H	88-91	53	C ₁₂ H ₁₁ NO ₃ (217.22)	Calcd. C 66.4 H 5.1 N 6.5 Found 66.6 5.2 6.4		A
19	2-Methylallyl	H	H	H	H	84-87	15	C ₁₂ H ₁₁ NO ₃ (217.22)	Calcd. C 66.4 H 5.1 N 6.5 Found 66.2 5.1 6.3		A
20	2-Butynyl	H	H	H	H	139-141	51	C ₁₂ H ₉ NO ₃ (215.20)	Calcd. C 67.0 H 4.2 N 6.5 Found 67.3 4.4 6.3		A
21	2-Butynyl	H	Cl	H	H	161-163	20	C ₁₂ H ₈ NO ₃ Cl (249.66)	Calcd. C 57.7 H 3.2 N 5.6 Found 57.4 3.4 5.6	Cl 14.2 13.8	A
22	2-Butynyl (g)	H	O-CH ₂ -O	H	H	218-222	48	C ₁₃ H ₉ NO ₅ (259.21)	Calcd. C 60.2 H 3.5 N 5.4 Found 59.5 3.6 5.3		A
23	Pentyl	H	H	H	H	68-70	49	C ₁₃ H ₁₅ NO ₃ (233.29)	Calcd. C 66.9 H 6.5 N 6.0 Found 66.7 6.9 5.6		A
24	2-Methylbutyl	H	H	H	H	73-75	64	C ₁₃ H ₁₅ NO ₃ (233.29)	Calcd. C 66.9 H 6.5 N 6.0 Found 67.1 6.9 6.2		C
25	3-Methylbutyl	H	H	H	H	74-77	33	C ₁₃ H ₁₅ NO ₃ (233.29)	Calcd. C 66.9 H 6.5 N 6.0 Found 67.0 6.5 6.0		A
26	4-Pentenyl	H	H	H	H	42-45	58	C ₁₃ H ₁₃ NO ₃ (231.24)	Calcd. C 67.5 H 5.7 N 6.1 Found 67.8 5.7 6.0		A
27	4-Pentenyl	H	Cl	H	H	110-114	36	C ₁₃ H ₁₂ NO ₃ Cl (265.71)	Calcd. C 58.8 H 4.6 N 5.3 Found 58.9 4.5 5.0	Cl 13.3 13.1	A
28	4-Pentenyl	H	H	H	H	123-125	10	C ₁₃ H ₁₁ NO ₃ (229.32)	Calcd. C 68.2 H 4.1 N 6.1 Found 67.8 4.3 6.2		A
29	Hexyl	H	H	H	H	57-60	65	C ₁₄ H ₁₇ NO ₃ (247.28)	Calcd. C 68.0 H 6.9 N 5.7 Found 68.1 7.1 5.7		A
30	5-Hexenyl	H	H	H	H	63-66	68	C ₁₄ H ₁₅ NO ₃ (245.27)	Calcd. C 68.6 H 6.2 N 5.7 Found 68.3 6.3 5.6		A
31	2,4-Hexadienyl	H	H	H	H	139-142	45	C ₁₄ H ₁₃ NO ₃ (243.25)	Calcd. C 69.1 H 5.4 N 5.8 Found 69.0 5.3 5.8		A
32	Heptyl	H	H	H	H	60-63	46	C ₁₅ H ₁₉ NO ₃ (261.31)	Calcd. C 68.9 H 7.3 N 5.4 Found 68.8 7.4 5.2		A
33	Octyl	H	H	H	H	47-50	51	C ₁₆ H ₂₁ NO ₃ (275.34)	Calcd. C 69.8 H 7.7 N 5.1 Found 70.0 7.3 5.0		A

Table I (Continued)

	R ¹	R ²	R ³	R ⁴	R ⁵	M.p., °C	Yield %	Empirical Formula (M.W.)		Elemental Analysis			Procedure
34	7-Octenyl	H	H	H	H	66-69	45	C ₁₆ H ₁₉ NO ₃ (273.23)	Calcd. Found	C 70.3 70.5	H 7.0 7.3	N 5.1 5.1	A
35	Cyclopropylmethyl	H	H	H	H	118-121	56	C ₁₂ H ₁₁ NO ₃ (217.22)	Calcd. Found	C 66.4 66.0	H 5.1 5.2	N 6.5 6.3	A
36	Cyclopropylmethyl	H	Cl	H	H	110-114	35	C ₁₂ H ₁₀ NO ₃ Cl (251.68)	Calcd. Found	C 57.3 57.4	H 4.0 4.3	N 5.6 5.3	A
37	Cyclohexyl	H	H	H	H	194-197	28	C ₁₄ H ₁₅ NO ₃ (245.27)	Calcd. Found	C 68.6 68.5	H 6.2 5.8	N 5.7 5.8	B
38	Cyclohexylmethyl	H	H	H	H	121-123	23	C ₁₅ H ₁₇ NO ₃ (259.29)	Calcd. Found	C 69.5 69.2	H 6.6 6.2	N 5.4 5.2	A
39	2-Cyclohexylmethyl	H	H	H	H	103-105	60	C ₁₆ H ₁₉ NO ₃ (273.36)	Calcd. Found	C 70.3 70.6	H 7.0 7.1	N 5.1 5.0	A
40	2-Bromoethyl	H	H	H	H	160-163	26	C ₁₀ H ₈ NO ₃ Br (270.10)	Calcd. Found	C 44.5 44.6	H 3.0 3.2	N 5.2 5.6	Al
41	3-Chloropropyl	H	H	H	H	94-97	16	C ₁₁ H ₁₀ NO ₃ Cl (239.66)	Calcd. Found	C 55.1 55.4	H 4.2 4.2	N 5.8 5.7	Al
42	3-Chloroallyl	H	H	H	H	138-140	39	C ₁₁ H ₈ NO ₃ Cl (237.65)	Calcd. Found	C 55.6 55.4	H 3.4 3.7	N 5.9 5.8	A
43	2-Chloroallyl	H	H	H	H	102-104	26	C ₁₁ H ₈ NO ₃ Cl (237.65)	Calcd. Found	C 55.6 55.5	H 3.4 3.6	N 5.9 5.8	A
44	4-Chlorobutyl	H	H	H	H	73-75	35	C ₁₂ H ₁₂ NO ₃ Cl (253.70)	Calcd. Found	C 56.8 56.9	H 4.8 5.0	N 5.5 5.4	Al
45	4-Chloro-2-butenyl	H	H	H	H	120-123	43	C ₁₂ H ₁₀ NO ₃ Cl (251.68)	Calcd. Found	C 57.3 57.5	H 4.0 4.1	N 5.6 5.6	Al
46	3-Chloro-2-butenyl	H	H	H	H	112-116	58	C ₁₂ H ₁₀ NO ₃ Cl (251.68)	Calcd. Found	C 57.3 57.2	H 4.0 4.3	N 5.6 5.5	A
47	5-Bromopentyl	H	H	H	H	68-70	30	C ₁₃ H ₁₄ NO ₃ Br (312.18)	Calcd. Found	C 50.0 50.1	H 4.5 4.6	N 4.5 4.4	Al
48	Cyanomethyl	H	H	H	H	170-173	37	C ₁₀ H ₆ N ₂ O ₃ (202.18)	Calcd. Found	C 59.4 59.7	H 3.0 3.1	N 13.9 14.1	A
49	Ethoxycarbonylmethyl	H	H	H	H	150-152	65	C ₁₂ H ₁₁ NO ₅ (249.22)	Calcd. Found	C 57.8 57.9	H 4.5 4.6	N 5.6 5.5	A
50	Ethoxycarbonylmethyl	H	Cl	H	H	183-185	37	C ₁₂ H ₁₀ NO ₅ Cl (283.68)	Calcd. Found	C 50.8 51.2	H 3.6 3.5	N 4.9 4.8	A
51	Ethoxycarbonylmethyl	H	O-CH ₂ -O	H	H	162-164	41	C ₁₃ H ₁₁ NO ₇ (293.23)	Calcd. Found	C 53.2 53.3	H 3.8 3.8	N 4.8 4.6	A

Table I (Continued)

	R ¹	R ²	R ³	R ⁴	R ⁵	M.p. °C	Yield %	Empirical Formula (M.W.)	Elemental Analysis	Procedure
52	1-Ethoxycarbonyl	H	H	H	H	62-64	37	C ₁₃ H ₁₃ NO ₅ (263.24)	Calcd. C 59.3 H 5.0 N 5.3 Found 59.2 5.1 5.1	A
53	<i>bis</i> (Ethoxycarbonyl)methyl	H	H	H	H	116-118	22	C ₁₅ H ₁₅ NO ₇ (321.28)	Calcd. C 56.1 H 4.7 N 4.4 Found 56.1 5.0 4.2	A
54	2-Acetoxyethyl	H	H	H	H	128-131	42	C ₁₂ H ₁₁ NO ₅ (249.23)	Calcd. C 57.8 H 4.5 N 5.6 Found 58.4 4.7 5.5	A
55	4-Acetoxy-2-butenyl	H	H	H	H	122-124	34	C ₁₄ H ₁₁ NO ₅ (273.26)	Calcd. C 61.5 H 4.1 N 5.1 Found 61.6 4.3 5.0	A
56	2-Ethoxyethyl	H	H	H	H	61-63	28	C ₁₂ H ₁₃ NO ₄ (235.23)	Calcd. C 61.3 H 5.6 N 6.0 Found 61.0 5.3 5.8	A
57	Acetonyl	H	H	H	H	154-157	73	C ₁₁ H ₉ NO ₄ (219.19)	Calcd. C 60.3 H 4.1 N 6.4 Found 60.1 4.6 6.1	A
58	Pivaloylmethyl	H	H	H	H	140-142	45	C ₁₄ H ₁₅ NO ₄ (261.27)	Calcd. C 64.4 H 5.8 N 5.4 Found 64.4 5.7 5.3	A
59	Dimethylcarbamoymethyl (c)	H	H	H	H	202-205	63	C ₁₂ H ₁₂ N ₂ O ₄ (248.23)	Calcd. C 58.1 H 4.9 N 11.3 Found 58.3 5.1 11.0	A
60	Diethylcarbamoymethyl	H	H	H	H	157-159	51	C ₁₄ H ₁₆ N ₂ O ₄ (276.28)	Calcd. C 60.9 H 5.8 N 10.1 Found 60.8 5.7 10.0	A
61	Dipropylcarbamoymethyl	H	H	H	H	154-156	50	C ₁₆ H ₂₀ N ₂ O ₄ (304.34)	Calcd. C 63.1 H 6.6 N 9.2 Found 62.8 6.4 9.0	A
62	Phenyl (d)	H	H	H	H	177-179	49	C ₁₄ H ₉ NO ₃ (239.22)	Calcd. C 70.3 H 3.8 N 5.9 Found 70.6 3.6 5.8	B
63	<i>p</i> -Fluorophenyl	H	H	H	H	199-201	24	C ₁₄ H ₈ NO ₃ F (257.23)	Calcd. C 65.4 H 3.1 N 5.4 Found 65.5 3.0 5.4	B
64	<i>m</i> -Trifluoromethylphenyl (e)	H	H	H	H	167-169	46	C ₁₅ H ₈ NO ₃ F ₃ (307.23)	Calcd. C 55.6 H 2.6 N 4.6 Found 55.3 2.8 4.3	B
65	Benzyl (f)	H	H	H	H	140-142	75	C ₁₅ H ₁₁ NO ₃ (253.25)	Calcd. C 71.1 H 4.4 N 5.5 Found 71.0 4.2 5.7	A
66	Benzyl	H	CL	H	H	147-149	42	C ₁₅ H ₁₀ NO ₃ Cl (287.70)	Calcd. C 62.6 H 3.5 N 4.9 Found 62.3 3.6 4.7	A
67	Benzyl	H	H	CL	H	165-170	72	C ₁₅ H ₁₀ NO ₃ Cl (287.70)	Calcd. C 62.6 H 3.5 N 4.9 Found 62.4 3.7 4.8	A
68	<i>p</i> -Bromobenzyl	H	H	H	H	175-177	60	C ₁₅ H ₁₀ NO ₃ Br (332.16)	Calcd. C 54.2 H 3.0 N 4.2 Found 54.4 3.1 4.1	A
69	<i>p</i> -Chlorobenzyl	H	H	H	H	129-131	51	C ₁₅ H ₁₀ NO ₃ Cl (287.70)	Calcd. C 62.6 H 3.5 N 4.9 Found 62.1 3.8 5.1	A

Table I (Continued)

R ¹	R ²	R ³	R ⁴	R ⁵	M.p. °C	Yield %	Empirical Formula (M.W.)	Elemental Analysis	Procedure	
70 <i>o</i> -Chlorobenzyl	H	H	H	H	165-167	25	C ₁₅ H ₁₀ NO ₃ Cl (287.70)	Calcd. C 62.6 H 3.5 N 4.9 Found 62.1 3.7 4.6	Cl 12.3 12.6	A
71 <i>p</i> -Fluorobenzyl	H	H	H	H	143-145	52	C ₁₅ H ₁₀ NO ₃ F (271.26)	Calcd. C 66.4 H 3.7 N 5.2 Found 66.3 4.0 5.3	F 7.0	A
72 <i>p</i> -Fluorobenzyl	H	OMe	OMe	H	229-234	38	C ₁₇ H ₁₄ NO ₅ F (331.32)	Calcd. C 61.6 H 4.3 N 4.2 Found 61.3 4.5 4.4	F 5.7 6.2	A
73 <i>p</i> -Fluorobenzyl	Cl	H	H	OMe	174-177	30	C ₁₆ H ₁₁ NO ₄ ClF (335.73)	Calcd. C 57.2 H 3.3 N 4.2 Found 57.3 3.4 4.6	Cl 10.6 10.9	A
74 <i>m</i> -Fluorobenzyl	H	H	H	H	133-136	52	C ₁₅ H ₁₀ NO ₃ F (271.26)	Calcd. C 66.4 H 3.7 N 5.2 Found 66.5 3.8 5.1	F 7.0	A
75 <i>o</i> -Fluorobenzyl	H	H	H	H	151-154	44	C ₁₅ H ₁₀ NO ₃ F (271.26)	Calcd. C 66.4 H 3.7 N 5.2 Found 66.2 4.1 5.0	F 7.0	A
76 <i>p</i> -Methylbenzyl	H	H	H	H	133-135	64	C ₁₆ H ₁₃ NO ₃ (267.27)	Calcd. C 71.9 H 4.9 N 5.2 Found 71.9 5.2 5.2		A
77 <i>m</i> -Trifluoromethylbenzyl	H	H	H	H	137-140	51	C ₁₀ H ₁₀ NO ₃ F ₃ (321.26)	Calcd. C 59.8 H 3.1 N 4.4 Found 59.5 2.8 4.8	F 17.7	A
78 <i>p</i> -Methoxybenzyl	H	H	H	H	138-139	78	C ₁₆ H ₁₃ NO ₄ (283.27)	Calcd. C 67.8 H 4.6 N 5.0 Found 67.9 5.0 4.8		A
79 <i>o</i> -Nitrobenzyl	H	H	H	H	211-213	52	C ₁₅ H ₁₀ N ₂ O ₅ (298.25)	Calcd. C 60.4 H 3.4 N 9.4 Found 60.3 3.7 9.4		A
80 <i>o</i> -Cyanobenzyl	H	H	H	H	184-187	33	C ₁₆ H ₁₀ N ₂ O ₃ (278.28)	Calcd. C 68.1 H 3.6 N 10.1 Found 68.7 3.9 10.0		A
81 <i>o</i> -Methoxycarbonylbenzyl	H	H	H	H	128-131	31	C ₁₈ H ₁₅ NO ₅ (325.34)	Calcd. C 66.4 H 4.7 N 4.2 Found 66.6 4.8 4.2		A
82 2,6-Dichlorobenzyl	H	H	H	H	166-169	52	C ₁₅ H ₉ NO ₃ Cl ₂ (322.14)	Calcd. C 55.9 H 2.8 N 4.3 Found 55.8 3.0 4.6	Cl 22.0 21.8	A
83 3,4-Difluorobenzyl	H	H	H	H	129-132	48	C ₁₅ H ₉ NO ₃ F ₂ (289.24)	Calcd. C 62.3 H 3.1 N 4.8 Found 62.4 3.3 4.8	F 13.1	A
84 3,4-Dimethoxybenzyl	H	H	H	H	172-174	53	C ₁₇ H ₁₅ NO ₅ (313.30)	Calcd. C 65.2 H 4.8 N 4.5 Found 65.4 4.9 4.7		A
85 2,3,4,5,6-Pentafluorobenzyl	H	H	H	H	135-137	58	C ₁₅ H ₆ NO ₃ F ₅ (343.22)	Calcd. C 52.5 H 1.8 N 4.1 Found 52.6 1.9 3.8	F 27.7 28.0	A
86 α -Methylbenzyl	H	H	H	H	146-148	48	C ₁₆ H ₁₃ NO ₃ (267.27)	Calcd. C 71.9 H 4.9 N 5.2 Found 72.1 5.1 5.2		A
87 α -(Methoxycarbonyl)benzyl	H	H	H	H	124-126	10	C ₁₇ H ₁₃ NO ₅ (311.28)	Calcd. C 65.6 H 4.2 N 4.5 Found 65.4 4.1 4.4		A

Table I (Continued)

	R ¹	R ²	R ³	R ⁴	R ⁵	M.p. °C	Yield %	Empirical Formula (M.W.)	Elemental Analysis			Procedure			
88	Phenethyl	H	H	H	H	171-174	42	C ₁₆ H ₁₃ NO ₃ (267.27)	Calcd. Found	C 71.9 72.1	H 4.9 4.9	N 5.2 5.1	A		
89	Cinnamyl	H	H	H	H	152-155	68	C ₁₇ H ₁₃ NO ₃ (279.31)	Calcd. Found	C 73.1 73.1	H 4.7 4.4	N 5.0 4.9	A		
90	3-Phenyl-2-propynyl	H	H	H	H	194-196	34	C ₁₇ H ₁₁ NO ₃ (277.27)	Calcd. Found	C 73.6 73.9	H 4.0 4.0	N 5.1 5.1	A		
91	4-(<i>p</i> -Fluorophenyl)-3-butenyl	H	H	H	H	155-161	28	C ₁₈ H ₁₄ NO ₃ F (311.33)	Calcd. Found	C 69.4 69.0	H 4.5 4.7	N 4.5 4.5	F 6.1 6.0	A	
92	α -Naphthylmethyl	H	H	H	H	214-217	70	C ₁₉ H ₁₃ NO ₃ (303.30)	Calcd. Found	C 75.2 75.6	H 4.3 4.4	N 4.6 4.7	A		
93	Diphenylmethyl	H	H	H	H	144-146	43	C ₂₁ H ₁₅ NO ₃ (339.34)	Calcd. Found	C 76.6 76.5	H 4.6 4.9	N 4.3 4.2	A		
94	2-Furfuryl	H	H	H	H	141-143	54	C ₁₃ H ₉ NO ₄ (243.21)	Calcd. Found	C 64.2 64.3	H 3.7 3.8	N 5.8 5.9	A		
95	2-Thenyl	H	H	H	H	137-140	20	C ₁₃ H ₉ NO ₃ S (259.29)	Calcd. Found	C 60.2 60.2	H 3.5 3.6	N 5.4 5.4	S 12.4 12.6	A	
96	Phenacyl	H	H	H	H	214-216	47	C ₁₆ H ₁₁ NO ₄ (281.26)	Calcd. Found	C 68.3 68.1	H 3.9 4.1	N 5.0 4.7	A		
97	<i>p</i> -Fluorophenacyl	H	H	H	H	207-209	28	C ₁₆ H ₁₀ NO ₄ F (299.27)	Calcd. Found	C 64.2 64.0	H 3.4 3.5	N 4.7 4.7	F 6.3 6.4	A	
98	<i>p</i> -Chlorophenylthiomethyl	H	H	H	H	131-134	30	C ₁₅ H ₁₀ NO ₃ SCl (319.77)	Calcd. Found	C 56.3 56.0	H 3.2 3.2	N 4.4 4.3	S 11.0 11.2	Cl 10.0 10.3	A
99	2-(2,4-Dichlorophenoxy) ethyl	H	H	H	H	164-167	41	C ₁₆ H ₁₁ NO ₄ Cl ₂ (352.12)	Calcd. Found	C 54.5 54.2	H 3.1 3.2	N 4.0 3.8	Cl 20.1 20.5	A	
100	2-Phthalimidoethyl	H	H	H	H	220-225	15	C ₁₈ H ₁₂ N ₂ O ₅ (336.29)	Calcd. Found	C 64.3 64.1	H 3.6 3.8	N 8.3 8.4	A		

(a) Previously prepared by I. M. Heilbron, F. N. Kitchen, E. B. Parkes, G. D. Sutton, *J. Chem. Soc.*, 127, 2167 (1925). (b) Previously prepared British Patent, 1,057,667 (1967); *Chem. Abstr.*, 68, 21717 (1968). (c) Previously prepared by T. Takahashi, I. Satoda, T. Fukai, Y. Matsuo, *Yakugaku Zasshi*, 80, 1579 (1960). (d) Previously prepared by A. A. Santilli and T. S. Ostene, *J. Org. Chem.*, 29, 2717, (1964). (e) Previously prepared by R. A. Scherrer, Belgian Patent 637,515 (1964); *Chem. Abstr.*, 63, 4307 (1965). (f) Previously prepared by W. L. F. Armarego, *J. Chem. Soc.*, 2697 (1961). (g) On repeated CHN analysis the value obtained for carbon deviated from the calculated value. All spectral data are in agreement with the proposed structure.

noted; the spectra (ir, obtained on a Perkin-Elmer Model 137 spectrophotometer, and nmr, on a Varian Model A-60) were in full accord with the proposed structures. Melting points, obtained on a Hoover melting point apparatus, are uncorrected.

Method A. 1-Ethyl-2*H*-3,1-benzoxazine-2,4(1*H*)dione (7).

To a solution of isatoic anhydride (16.3 g., 0.1 mole) in 200 ml. of *N,N*-dimethylacetamide, sodium hydride (4.6 g., 0.11 mole, 57% in mineral oil, washed with pentane) was slowly added and the mixture was stirred for 1 hour at room temperature. Bromoethane (12 g., 0.11 mole) was added and the reaction was allowed to stir for 18 hours at room temperature. About two-thirds of the solvent were then evaporated *in vacuo* and the residue poured into 250 ml. of ice/water. A precipitate formed, which was filtered off, washed with water and dried. On recrystallization from methylenechloride 11.6 g. (61%, m.p. 121-123°) of *N*-ethyl-2*H*-3,1-benzoxazine-2,4(1*H*)dione were obtained.

Method A-1. 1-Haloalkyl-2*H*-3,1-benzoxazine-2,4(1*H*)diones.

Same as Method A, but a threefold excess of the halogen-compound was used to depress formation of a dimeric isatoic anhydride.

Method A-2. *N*-Benzylisatoic Anhydride (65).

Same as Method A, but sodium hydride was replaced by potassium carbonate.

Method B. *N*-Cyclohexyl-2*H*-3,1-benzoxazine-2,4(1*H*)dione (*N*-Cyclohexylisatoic Anhydride) (37).

A suspension of the potassium salt of 2-chlorobenzoic acid (19.4 g., 0.1 mole), cyclohexylamine (15 g., 0.15 mole) potassium carbonate (13.5 g., 0.2 mole) and 1.5 g. of copper powder in *N,N*-dimethylacetamide (150 ml.) were heated under reflux for 6 hours. The mixture was evaporated to dryness and the residue was titrated with hot water (200 ml.). Insoluble material was removed by filtration and the filtrate was cooled to room temperature.

While stirring vigorously a phosgene solution (125 ml., 12.5% in benzene) was added (over a period of one hour) to the filtrate. During this process the final product began to precipitate. The mixture was allowed to stir for an additional 4 hours. The benzene was then removed under reduced pressure and all accumulated precipitate was filtered off. After washing (with water) and drying, the material was recrystallized from methylene chloride to obtain 7.0 g. (28%, m.p. 194-197°) of *N*-cyclohexylisatoic anhydride (37).

Method C. *N*-Isopropylisatoic Anhydride (10).

A solution of 2-nitrobenzoic acid (16.7 g., 0.1 mole) in 250

ml. of acetone was hydrogenated at 50 psi in the presence of palladium/carbon. The catalyst was filtered off and the solvent evaporated. The residue was dissolved in water (400 ml.), containing 8 g. (0.2 mole) of sodium hydroxide and a little solid carbon dioxide was added to buffer the solution. To this mixture phosgene (80 ml., 12.5% solution in benzene, 0.1 mole) was added while stirring. The stirring was continued for 4 hours and the benzene was evaporated under reduced pressure. The precipitate was filtered off, washed with water and dried by suction. The crude material was dissolved in methylene chloride, dried (sodium sulfate) and filtered through a short column of alumina. On partial evaporation of the solvent and addition of diethylether 13.1 g. (63%, m.p. 113-116°) of *N*-isopropylisatoic anhydride was obtained.

REFERENCES

- (1) Throughout this paper the names "isatoic anhydride" and "2*H*-3,1-benzoxazine-2,4(1*H*)dione" are used interchangeably. Commercial sources still prefer the first one whereas Chemical Abstract subscribes to the latter. *We have adopted the Chemical Abstract numbering system*, but we feel that it will be easier for the reader if we say "*N*-unsubstituted isatoic anhydride" rather than "*N*-unsubstituted-2*H*-3,1-benzoxazine-2,4(1*H*)dione".
- (2a) E. Erdmann, *Ber.*, **32**, 2159 (1899); (b) C. R. Hauser, J. T. Adams and R. Levine, *Org. Syn.*, Coll. Vol. 3, John Wiley and Sons, New York, 1960 p. 488.
- (3) Chemistry of Isatoic Anhydride, Comm. Bulletin, Maumee Chemicals, page 1A and 2A.
- (4) Chemistry of Isatoic Anhydride, Comm. Bulletin, Maumee Chemicals, page 3A.
- (5) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959).
- (6) F. S. Statham, *J. Chem. Soc.*, 213 (1951).
- (7) J. Meyer and E. Wagner, *J. Org. Chem.*, **8**, 239 (1943).
- (8) R. P. Staiger, C. L. Moyer, G. R. Pitcher, *J. Chem. Eng. Data*, **8**, 454 (1963).
- (9) E. Späth and N. Platzer, *Ber.*, **68**, 2221 (1935).
- (10a) E. Ziegler, T. Kappe, W. Steiger, *Z. Naturforsch.*, **20b**, 812 (1965); (b) G. E. Hardtmann, B. S. Huegi, J. H. Gogerty, L. C. Iorio and H. W. Barnes, *J. Med. Chem.*, **14**, 878 (1971).
- (11a) D. T. Connor and M. van Strandtmann, *J. Org. Chem.*, **38**, 1047 (1973); (b) M. van Strandtmann, S. Klutchko, M. P. Cohen and J. Shavel, *J. Heterocyclic Chem.*, **9**, 173, (1972).
- (12) Sherwin Williams Chemicals and/or Aldrich Chemicals Co., Inc. Products are sold usually as "isatoic anhydrides".
- (13) H. C. Scarsborough and J. J. Minielli, U. S. Patent 3,119,824 (1964).
- (14) Method A is described in reference 3 on page 7A.