The Chemistry of 2*H*-3,1-Benzoxazine-2,4-(1*H*)dione (Isatoic Anhydride) 3. One Step Synthesis of 2,3-Dihydro-4,1,6-benzoxadiazonine-5,7-(1*H*,6*H*)diones

Sandor Barcza, Gary M. Coppola and Michael J. Shapiro*

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

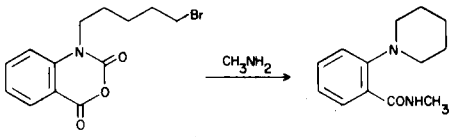
Received September 18, 1978

Reactions of *N*-haloalkylisatoic anhydrides with amines to produce piperidinobenzamides (**2**), pyrrolidinobenzamides (**4** and **5**), and 2,3-dihydro-6-methyl-4,1,6-benzoxadiazonine-5,7-(1*H*,6*H*)diones (**10**) are described. Spectral data are also discussed.

J. Heterocyclic Chem., 16, 439 (1979).

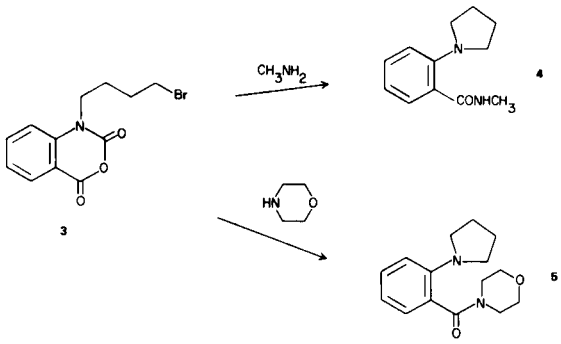
Reactions of isatoic anhydride (1) with various nucleophiles have been reported in the literature (2,3). Complex ring systems can be produced readily if the appropriately *N*-substituted isatoic anhydride is allowed to react with a wisely chosen nucleophile (3). In this publication we would like to report the investigations into the reactions of *N*-haloalkylisatoic anhydrides with various primary and secondary amines.

In compounds where there is a 5-carbon chain with a terminal reactive halogen (*e.g.*, **1**), the reaction with methyl amine produces *N*-methyl-3-piperidinobenzamide (**2**) in moderate yield.



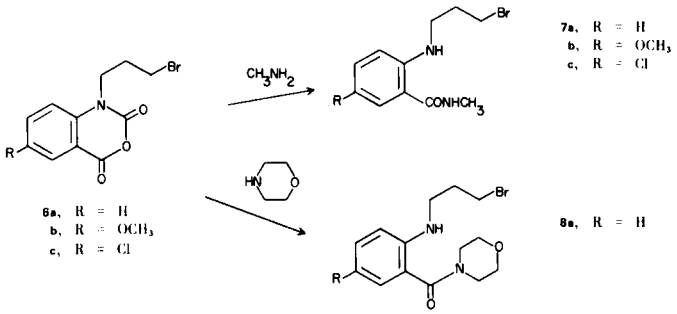
1 2

In analogous reactions where the isatoic anhydride nitrogen bears a 4-carbon methylene chain (**3**), the products resulting from its treatment with methylamine or morpholine are the corresponding 2-pyrrolidine benzamides (**4** and **5**).



3 4 5

When *N*-(3-bromopropyl)isatoic anhydride (**6**) (4) was allowed to react with methylamine or morpholine as in the previous examples, no cyclization products were produced. The only products isolated were the corresponding anthranilamides (**7a-c** and **8a**).

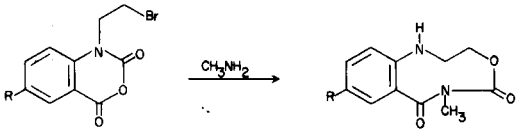


6a, R = H
b, R = OCH_3
c, R = Cl

7a, R = H
b, R = OCH_3
c, R = Cl

8a, R = H

The most interesting results in this series of reactions were obtained when *N*-(2-bromoethyl)isatoic anhydrides (**9a-c**) were treated with methylamine. Along with a small portion of the expected anthranilamide, the major portion of the reaction mixture was found to be the aryl substituted 2,3-dihydro-6-methyl-4,1,6-benzoxadiazonine-5,7-(1*H*,6*H*)dione (**10a-c**), a new ring system.



9a, R = H
b, R = OCH_3
c, R = Cl

10a, R = H
b, R = OCH_3
c, R = Cl

The proposed mechanism of the reaction involves the standard hetero ring opening of the isatoic anhydride with methylamine which proceeds through **A** to form **B** (Scheme I). Instead of decarboxylating to produce the anthranilamide, the carboxylate anion is internally trapped by the halo alkyl function to yield **C** (5). The oxazolidine ring undergoes nucleophilic attack by the amide nitrogen to yield **D** in which the carbon-nitrogen bond is ruptured resulting in the formation of **10**.

The infrared spectra of these type of compounds exhibit characteristic absorption at 3480-3440 cm^{-1} (N-H), 1700-1685 and 1650-1640 cm^{-1} which are attributed to the carbonyl frequencies. The N-H signal in the nmr spectrum (*e.g.*, **10a**) appears as a broad triplet at

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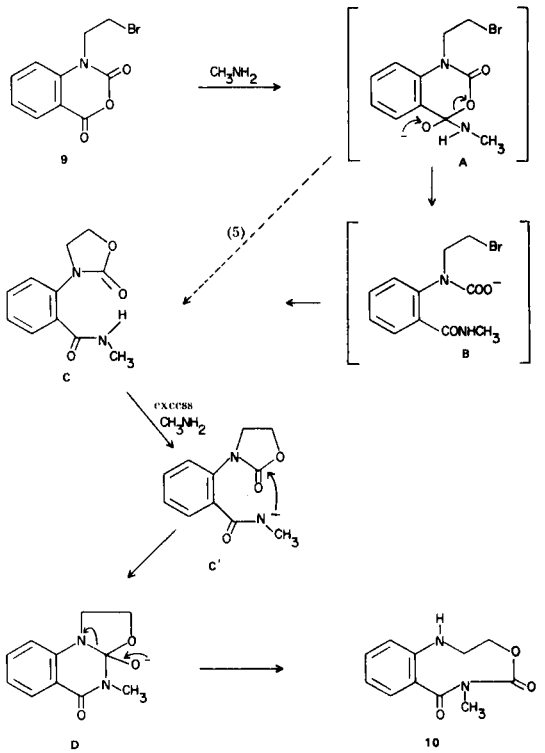
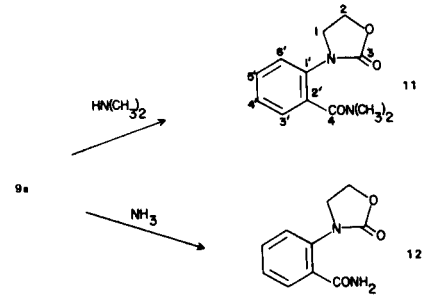
Scheme I



δ 4.9 and one methylene appears as a multiplet at δ 3.7 suggesting that these two functions are adjacent to each other. The second methylene is observed at δ 4.2 as a triplet as expected while the methyl signal falls as a sharp singlet at δ 3.3

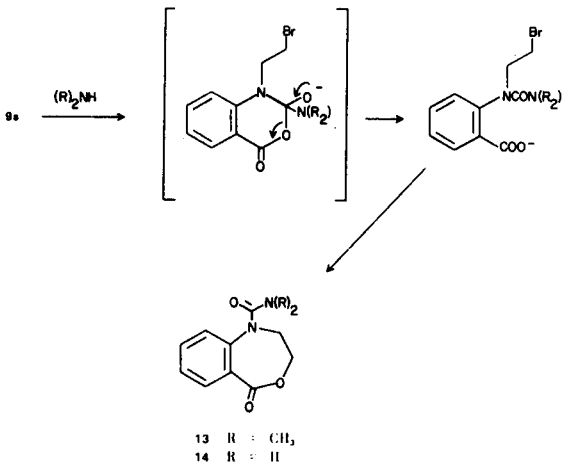
To help support our mechanism the synthesis of a compound of type **C** was needed. Since the elusive intermediate **C** is produced when the reaction is carried out with a primary amine, the possibility of the formation of **C** where the amide nitrogen is fully substituted, thus eliminating the nucleophilic ring opening of the oxazolidine ring, was investigated. Treatment of **9a** with dimethylamine under the same conditions as in the synthesis of **10** afforded oxazolidine **11** in good yield. Surprisingly, analogous treatment of **9a** with ammonia also afforded an oxazolidine (**12**) instead of a ring system of type **10**. The latter maybe a result of the lower basicity and solubility of ammonia in the reaction medium, and



consequent insufficient formation of anion **C'**.

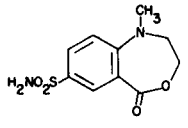
The possibility of an alternate mode of reaction arises when one considers that in the presence of an excess of amines, isatoic anhydrides undergo alternate ring cleavage reactions to produce *o*-uramidobenzoic acids (6,7). This concept, when applied to the reaction of **9a** with ammonia or dimethylamine may produce compounds of type **13** and **14** by the mechanism shown (Scheme II).

Scheme II



The mode of reaction to produce **11** and **12** or **13** and **14** could not be readily deduced by interpretation of either ir or proton nmr spectra. The final results were obtained on analysis of carbon-13 data, which indicated that **11** and **12** were indeed the correct structures.

The carbon-13 nmr shift data and assignments are given in Table I. Assignments were made *via* consideration of chemical shifts and spectral fingerprints of the aromatic carbon signals (8,9). Unfortunately, these data were not sufficient to distinguish between structures **12** and **14**. There was strong evidence from the long range proton carbon coupling constants that the structure was not the 7-membered ring. Model compound **15** (10) clearly showed a very complex coupling pattern for the ester carbonyl resonance whereas in **12** a doublet (J = 3 Hz) was observed.



The strongest evidence in favor of structure **12** rests with deuterium exchange of the labile N-H protons and the increase in T_1 concomitant with this interchange for the lowest field carbonyl carbon (*ca.*, 50% reduction in peak intensity (11)). Furthermore, a decrease in signal intensity is observed for the adjacent aromatic non-

protonated carbon of *ca.*, 25%. The confirmation of structure **11** follows from the substituent shifts expected upon methylation of the amine.

In conclusion, in the above reactions of haloalkyl isatoic anhydrides with amines, as a function of sidechain length, a two-carbon chain enjoys both entropy and enthalpy advantage for immediate *O*-alkylation. The three-carbon chain is less entropy favored to *O*-alkylate and not enthalpy favored to *N*-alkylate. In turn, the four- and five-carbon chains are relatively favored in *N*-alkylation. As a function of amine, only methylamine has the ability to carry intermediate **C** *via* anion **C'** to the medium-sized ring product **10**. The latter lacks the usual transannular destabilization by axial atoms because most of the ring members are sp^2 hybridized.

Table 1

Carbon-13 Chemical Shifts for **11** and **12** (a)

Assignment	**11**	**12**
1	47.7	48.1
2	62.5	62.8
6'	126.9	127.6
4'	127.1	127.6
3'	127.9	129.4
5'	130.1	131.4
2'	134.2	134.4
1'	135.6	136.5
3	156.6	157.1
4	168.9	169.8
CH_3	38.7	
CH_3	34.4	

(a) In ppm from TMS.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60 or EM-360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s - singlet, d = doublet, t - triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.*, 1 molar in deuteriodimethylsulfoxide in 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deterium lock to the solvent; spectral width of 5120 Hz; a pulse width of 25 μs, corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra 8K time-domain data points were used. All shifts reported are referenced to internal TMS, and are estimated to be accurate to ± 0.05 ppm.

Deuteration of compound **12** was accomplished by adding 1.1 mole equivalents of deuterium oxide and 5 mole % of deuteriotrifluoroacetic acid. A blank experiment was performed using water and trifluoroacetic acid for comparison.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

N-Methyl-2-piperidinobenzamide (**2**).

Into a solution of 4.0 g. of *N*-(5-bromopentyl)isatoic anhydride (**1**) (3) in 50 ml. of dioxane was bubbled anhydrous methylamine for 5 minutes. The reaction mixture was then stirred at room temperature for an additional 10 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product which was then crystallized from methylene chloride/ether to yield 0.8 g. of **2** (hydrobromide) (21%), m.p. 245-247°.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot HBr$: C, 52.2; H, 6.4; N, 9.4. Found: C, 52.0; H, 6.2; N, 9.3.

The hydrobromide salt of **2** was dissolved in water, made basic with dilute sodium bicarbonate and extracted into methylene chloride. The organic solution was dried over sodium sulfate and evaporated to furnish the free base of **2** as an oil; ir (chloroform): 3200, 1660 cm^{-1}; nmr (deuteriochloroform): δ 9.9 (m, 1), 8.2 (m, 1), 7.2 (m, 3), 3.0 (d, 3), 2.8 (m, 4), 1.6 (m, 6); ms: (70 eV) m/e 218 (M+).

N-Methyl-2-pyrrolidin-1-ylbenzamide (**4**).

Into a suspension of *N*-(4-bromobutyl)isatoic anhydride (**3**) in 250 ml. of dioxane was bubbled anhydrous methylamine for 5 minutes. The reaction mixture was then stirred at room temperature for an additional 10 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 5.4 g. of **4** (79%). An analytical sample was crystallized from methylene chloride/ether, m.p. 127-130°; ir (chloroform): 3460, 1655 cm^{-1}; nmr (deuteriochloroform): δ 7.6-6.6 (m, 5), 3.1 (m, 4), 2.8 (d, 3), 1.8 (m, 4); ms: (70 eV) m/e 204 (M+).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.6; H, 7.9; N, 13.7. Found: C, 70.4; H, 7.9; N, 13.6.

4-(2-Pyrrolidin-1-ylbenzoyl)morpholine (**5**).

A mixture of 4.4 g. of **3** and 2.6 g. of morpholine in 100 ml. of dioxane was stirred at room temperature for 15 minutes and then at 60° for 30 minutes. The resulting precipitate was filtered from the reaciton mixture and the solvent from the filtrate was removed under reduced pressure. The residue was chromatographed on a column of silica gel using 5% methanol/chloroform to elute the product which was then crystallized from pentane to yield 2.7 g. of **5** (70%), m.p. 80-83°; ir (chloroform): 1630 cm^{-1}; nmr (deuteriochloroform): δ 7.4-6.5 (m, 4), 4.0-3.0 (m, 12), 1.9 (m, 4).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.2; H, 7.7; N, 10.8. Found: C, 69.2; H, 7.3; N, 10.7.

N-(3-Bromopropyl)-5-methoxyisatoic Anhydride (**6b**).

To a solution of 13.5 g. of 5-methoxyisatoic anhydride in 200 ml. of dimethylacetamide was added 3.4 g. of sodium hydride (50%, pentane washed) in portions. After stirring at room temperature for 20 minutes, 30.0 g. of 1,3-dibromopropane was added and the resulting mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure, then cold water was added to the residue. The mixture was extracted

into methylene chloride, dried over sodium sulfate and evaporated to furnish an oil which was crystallized from ether to yield 9.0 g. of **6b** (41%), m.p 105-109°; ir (potassium bromide): 1775, 1660 cm^{-1}; nmr (DMSO): δ 7.4 (m, 3), 4.1 (t, 2), 3.8 (s, 3), 3.6 (t, 2), 2.1 (m, 2).

The material did not analyze satisfactorily and was carried on to the next step without further purification.

N-(3-Bromopropyl)-5-chloroisatoic Anhydride (**6c**).

The reaction was performed similar to the one described for the preparation of **6b** and the product, **6c**, was isolated in 19% yield, m.p. 126-129°; ir (chloroform): 1800, 1750 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (d, 1), 7.75 (m, 1), 7.3 (d, 1), 4.2 (m, 2), 3.55 (t, 2), 2.3 (m, 2).

Anal. Calcd. for $C_{11}H_9BrNO_3$: C, 41.5; H, 2.9; N, 4.4. Found: C, 42.0; H, 3.3; N, 4.6 (reanalysis of carbon did not improve the values).

2-[(3-Bromopropyl)amino]-*N*-methylbenzamide (**7a**).

Into a solution of 15 g. of *N*-(3-bromopropyl)isatoic anhydride (4) (**6a**) in 250 ml. of dioxane was bubbled anhydrous methylamine for 5 minutes. The reaction mixture was then stirred at room temperature for an additional 10 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product, 13.8 g. of **7a** (96%). An analytical sample was crystallized from ether/pentane, m.p. 54-58°; ir (chloroform): 3480, 3340, 1650 cm^{-1}; nmr (deuteriochloroform): δ 7.6-6.4 (m, 6), 3.3 (m, 4), 2.9 (d, 3), 2.1 (m, 2).

Anal. Calcd. for $C_{11}H_{15}BrN_2O$: C, 48.7; H, 5.6; N, 10.3; Br, 29.5. Found: C, 49.2; H, 5.8; N, 10.0; Br, 29.9 (reanalysis of carbon did not improve the value).

2-[(3-Bromopropyl)amino]-5-methoxy-*N*-methyl Benzamide (**7b**).

The reaction was performed similar to the one described for the preparation of **7a** and the product, **7b**, was isolated as an oil in 61% yield.

Anal. Calcd. for $C_{12}H_{17}BrN_2O_2$: C, 47.9; H, 5.7; N, 9.3. Found: C, 47.4; H, 5.5; N, 9.7 (reanalysis of carbon did not improve the values).

2-[(3-Bromopropyl)amino]-5-chloro-*N*-methyl Benzamide (**7c**).

The reaction was performed similar to the one described for the preparation of **7a** and the product, **7c**, was isolated in 90% yield, m.p. 98-102°; ir (chloroform): 3480, 3350, 1655 cm^{-1}; nmr (deuteriochloroform): δ 7.8-6.2 (m, 5), 3.5 (m, 4), 2.9 (d, 3), 2.2 (m, 2).

Anal. Calcd. for $C_{11}H_{14}BrClN_2O$: C, 43.2; H, 4.6; N, 9.2; Br, 26.1. Found: C, 43.0; H, 4.7; N, 9.2; Br, 26.0.

4-[2-[(3-Bromopropyl)amino]benzoyl]morpholine (**8a**).

A mixture of 4.0 g. of **6a** and 2.5 g. of morpholine in 100 ml. of dioxane was stirred at 50° for 20 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 3.5 g. of **8a** (76%). An analytical sample was crystallized from ether/pentane, m.p. 58-61°; ir (chloroform): 3400, 1630 cm^{-1}; nmr (deuteriochloroform): δ 7.4-6.5 (m, 4), 5.2 (m, 1), 3.7-3.1 (m, 12), 2.2 (m, 2).

Anal. Calcd. for $C_{14}H_{19}BrN_2O_2$: C, 51.4; H, 5.9; N, 8.6; Br, 24.4. Found: C, 51.9; H, 5.7; N, 8.7; Br, 24.1 (reanalysis of carbon did not improve the value).

N-(2-Bromoethyl)-5-methoxyisatoic Anhydride (**9b**).

To a solution of 21.0 g. of 5-methoxyisatoic anhydride in 200 ml. of dimethylacetamide was added 5.3 g. of sodium hydride (50%, pentane washed) in portions. The solution was stirred at room temperature for 90 minutes at which time 42 g. of 1,2-dibromoethane was added and the resulting mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and cold water was added to the residue. The mixture was extracted into methylene chloride, dried over sodium sulfate, and evaporated to furnish 10.5 g. of **9b** (32%). An analytical sample was crystallized from methylene chloride/ether, m.p. 158-161°; ir (potassium bromide): 1790, 1720 cm^{-1}; nmr (DMSO): δ 7.5 (m, 3), 4.4 (t, 2), 3.85 (s, 3), 3.7 (t, 2).

Anal. Calcd. for $C_{11}H_{10}BrNO_4$: C, 44.0; H, 3.4; N, 4.7; Br, 26.6. Found: C, 44.3; H, 3.6; N, 4.7; Br, 26.8.

N-(2-Bromoethyl)-5-chloroisatoic Anhydride (**9c**).

The reaction was performed similar to the one described for the preparation of **9b** and the product, **9c**, was isolated in 20% yield, m.p. 161-164°; ir (potassium bromide): 1790, 1735 cm^{-1}; nmr (DMSO): δ 8.1-7.5 (m, 3), 4.5 (t, 2), 3.7 (t, 2).

Anal. Calcd. for $C_{10}H_7BrClNO_3$: C, 39.4; H, 2.3; N, 4.6. Found: C, 39.2; H, 2.6; N, 4.5.

2,3-Dihydro-4,1,6-benzoxadiazonine-5,7-(1*H*,6*H*)dione (**10a**).

Into a suspension of 10.0 g. of **9a** in 200 ml. of dioxane was bubbled anhydrous methylamine for 10 minutes. The reaction mixture was then stirred at room temperature for an additional 25 minutes. The solvent was removed under reduced pressure and the residue was crystallized from chloroform to yield 3.2 g. of **10a** (39%), m.p. 166-168°; ir (Nujol): 3480, 1685, 1640 cm^{-1}; nmr (DMSO): δ 8.2-7.1 (m, 4), 4.9 [t (broad), 1], 4.2 (t, 2), 3.7 (m, 2), 3.3 (s, 3).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 60.3; H, 5.6; N, 12.7.

2,3-Dihydro-9-methoxy-4,1,6-benzoxadiazonine-5,7-(1*H*,6*H*)dione (**10b**).

The reaction was performed similar to the one described for the preparation of **10a** and the product, **10b**, was isolated in 30% yield, m.p. 158-161°; ir (potassium bromide): 3480, 1700, 1650 cm^{-1}; nmr (DMSO): δ 7.55-7.2 (m, 3), 4.6 [t (broad), 1] 4.15 (t, 2), 3.8 (s, 3), 3.7 (m, 2), 3.3 (s, 3).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.6; N, 11.2. Found: C, 57.3; H, 5.6; N, 10.8.

9-Chloro-2,3-dihydro-4,1,6-benzoxadiazonine-5,7-(1*H*,6*H*)dione (**10c**).

The reaction was performed similar to the one described for the preparation of **10a** and the product, **10c**, was isolated in 27% yield, m.p. 191-194°; ir (potassium bromide): 3440, 1700, 1650 cm^{-1}; nmr (DMSO): δ 7.9-7.4 (m, 3), 4.9 [t (broad), 1] 4.2 (t, 2), 3.75 (m, 2), 3.3 (s, 3).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_3$: C, 51.9; H, 4.4; N, 11.0; Cl, 13.9. Found: C, 52.1; H, 4.7; N, 11.3; Cl, 14.0.

N,N-Dimethyl-2-(2-oxo-3-oxazolidinyl)benzamide (**11**).

Into a solution of 6.0 g. of **9a** in 150 ml. of dioxane was bubbled anhydrous dimethylamine for 10 minutes. The reaction mixture was then stirred at room temperature for an additional 30 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product which was crystallized from methylene chloride/ether to yield 2.7 g. of **11** (52%), m.p. 103-105°; ir (chloroform): 1760, 1630 cm^{-1}; nmr

(deuteriochloroform): δ 7.4 (m, 4), 4.7-3.9 (m, 4), 3.1 (s, 3), 2.95 (s, 3); ms: (70 eV) m/e 234 (M+).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.0; N, 12.0. Found: C, 61.5; H, 6.0; N, 11.7.

2-(2-Oxo-3-oxazolidinyl)benzamide (**12**).

Into a solution of 8.0 g. of **9a** in 150 ml. of dioxane was bubbled anhydrous ammonia for 10 minutes. The reaction mixture was then stirred at room temperature for an additional 30 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 5% methanol/chloroform to elute the product, 3.7 g. of **12** (61%). An analytical sample was crystallized from chloroform, m.p. 152-155°; ir (potassium bromide): 3440, 3170, 1760, 1740, 1680 cm^{-1}; nmr (DMSO): δ 7.9-7.2 (m, 6), 4.6-3.8 (m, 4); ms: (70 eV) m/e 206 (M+).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.3; H, 4.9; N, 13.6. Found: C, 57.9; H, 4.9; N, 13.7.

Acknowledgment.

The authors wish to thank S. N. DiCataldo for measuring the nmr spectra, A. D. Kahle for running the carbon-13 nmr spectra, Robert Clark for running the mass spectra and W. J. Bonkoski and associates for performing the microanalyses.

REFERENCES AND NOTES

(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 name whereas Chemical Abstracts subscribes to the latter. We have adopted the Chemical Abstract numbering system for substituted isatoic anhydrides, but we feel that it will be easier to read if we use the expression "*N*-substituted isatoic anhydride" rather than "*N*-substituted-2*H*-3,1-benzoxazine-2,4(1*H*)dione".

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(4) G. E. Hardtmann, G. Koletar and O. R. Pfister, *J. Heterocyclic Chem.*, **12**, 565 (1975).

(5) Formation of **C** from **A** may even occur in a concerted fashion, with the entropy-privileged involvement of the C_2 side chain, to alkylate the $=O^{\delta-}$ immediately, without any lifetime of a $N\text{-}COO^-$ species **B**.

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