Synthesis of 5*H*-Benzoxazolo[3,2-*a*]quinazolin-5-ones

Dong Han Kim

Research Division, Wyeth Laboratories, Inc., Box 8299, Philadelphia, PA 19101

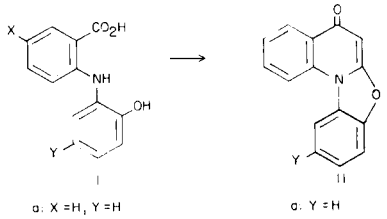
Received August 12, 1980

5*H*-Benzoxazolo[3,2-*a*]quinazolin-5-ones (Xa-d) were synthesized in excellent yields from *N*-(2-hydroxyphenyl)anthranilic acids (Ia-d) and cyanogen bromide. The synthesis was based on the mechanistic consideration of the reactions of salicylic acid with cyanogen bromide previously reported in the literature. A versatile alternative route to these novel heterocyclic compounds was through thermal cyclization of *N*-(2-benzoxazolyl)-2-fluorobenzamides (XIII) obtained by reacting 2-fluorobenzoyl chloride with 2-aminobenzoxazoles. The reaction of Xb with ethanol in the presence of potassium hydroxide gave an ethoxyquinazolinone (XVII). Similarly, the alkaline hydrolysis of Xb afforded an quinazolindione (XVIII).

J. Heterocyclic Chem., **18**, 287 (1981).

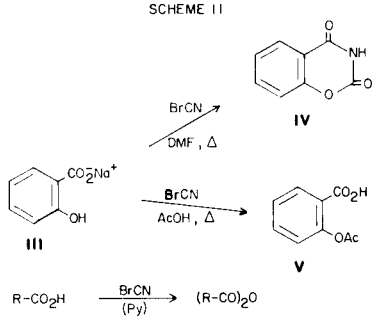
Previously we reported that treatment of *N*-(2-hydroxyphenyl)anthranilic acids (I) with refluxing acetic anhydride yields the novel tetracyclic 5*H*-benzoxazolo[3,2*a*]-quinolin-5-ones (II, Scheme I) in good yield (1). Efforts to extend the work have resulted in the synthesis of a series of new tetracyclic heterocycles. In this report we wish to describe the preparation of 5*H*-benzoxazolo[3,2-*a*]quinazolin-5-ones.

SCHEME I



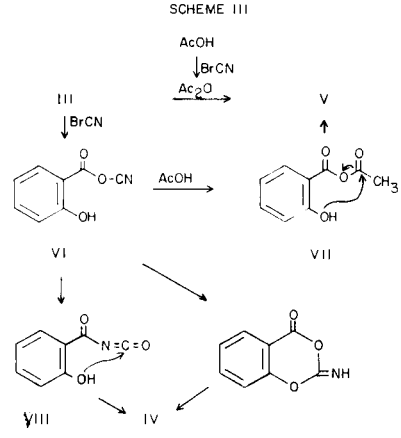
In 1965, Thyagarajan and Rajagopalan (2,3) reported that whereas the treatment of cyanogen bromide with sodium salicylate in refluxing dimethylformamide afforded 2*H*-1,3-benzoxazine-2,4-(3*H*)dione (IV), the same reaction carried out in acetic acid gave acetylsalicylic acid (V, Scheme II). No mechanistic explanation was offered.

SCHEME II



More recently, Ho and Wong (4) obtained anhydrides when alkylcarboxylic acids were allowed to react with cyanogen bromide in the presence of pyridine at room temperature. As suggested by Ho and Wong, the initial reaction in the above transformations most probably involves the formation of the aroyl cyanate VI as a labile intermediate. In an inert reaction medium such as dimethylformamide, the latter intermediate isomerizes to give the aroyl isocyanate VIII, which would undergo an internal cyclization to form the product IV (5, Scheme III). The above explanation is supported by a recent report by Christophersen and Carlsen (6), who have isolated aroyl thiocyanates from the reaction of salts of certain thiobenzoic acids and cyanogen bromide at low temperature and have shown that these compounds have a pronounced tendency to isomerize to aroyl isothiocyanates. However, an alternative mechanistic route which involves the cyclization of VI followed by a Dimroth type rearrangement (7) to IV (8,9) may not be ruled out. When there is a large excess of an acid present the aroyl cyanate (VI) reacts with the carboxylic acid to give VII, and subsequent intramolecular acyl migration would give V (Scheme III).

SCHEME III



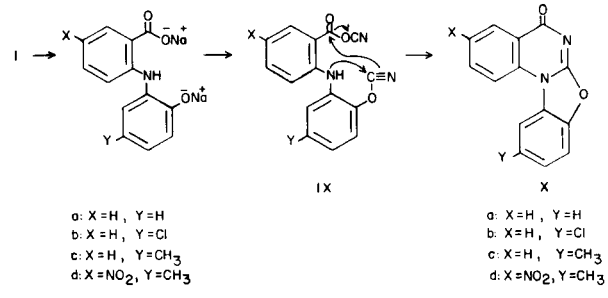
Alternatively, cyanogen bromide may rapidly react with acetic acid in the presence of sodium cation to afford acetic anhydride (4) which then effects the acetylation on salicylic acid to give V. In fact, in support of the explanation, treatment of salicylic acid with an equivalent amount

0022-152X/81/020287-05$02.25

of acetic anhydride in refluxing acetic acid gave V in 53% yield. This postulation may also explain the reported (2) formation of 4-(acetyloxy)benzoic acid upon treatment of the sodium salt of 4-hydroxybenzoic acid with cyanogen bromide in boiling acetic acid (10).

In view of the above mechanistic consideration of the reaction of cyanogen bromide with carboxylic acids and reported reaction of cyanogen bromide with 2-amino-4-chlorophenol to yield 2-amino-5-chlorobenzoxazole (11), it was thought that treatment of the disodium salt of I with two moles of cyanogen bromide would yield benzoxazolo-[3,2-*a*]quinazolin-5-one *via* consecutive double cyclizations of the intermediate IX which would be formed first (Scheme IV). Indeed, when an experiment was carried out under the above conditions, Xb was the product isolated in a quantitative yield.

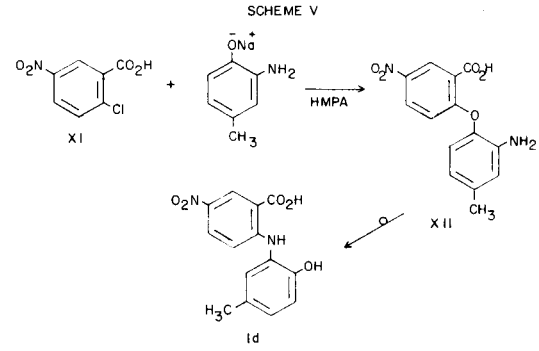
SCHEME IV



Starting materials Ia-c were prepared from 2-bromobenzoic acid and appropriately substituted 2-aminophenol under Ulmann condensation reaction conditions (1). In the preparation of Id, the chloro group of 2-chloro-5-nitrobenzoic acid (XI) was sufficiently activated that it was readily displaced by the sodium salt of 2-amino-4-methylphenol at room temperature overnight, giving 2-(2-amino-4-methylphenoxy)-5-nitrobenzoic acid (XII) in an almost quantitative yield. The latter structure was supported by its nmr (DMSO-d_6) spectrum, which exhibited an exchangeable broad singlet at δ 5.95 ppm integrated for 3 protons ($\overset{+}{N}H_3$) aside from the expected methyl (δ 2.20) and aromatic proton signals. The aryl ether XII was con verted into the required Id under Smiles rearrangement conditions (12). The compound thus obtained showed a very broad proton magnetic resonance signal (DMSO-d_6) corresponding to two hydrogens at δ 10.0 ppm and a singlet at δ 10.25 ppm which integrated for one proton. These signals disappeared upon treatment with deuterium oxide (Scheme V).

The disodium salt of *N*-(5-chloro-2-hydroxyphenyl)anthranilic acid (Ib) was reacted with an excess of cyanogen bromide (13) at room temperature followed by brief refluxing to ensure the completion of the reaction to afford analytically pure Xb in quantitative yield. The structural

SCHEME V

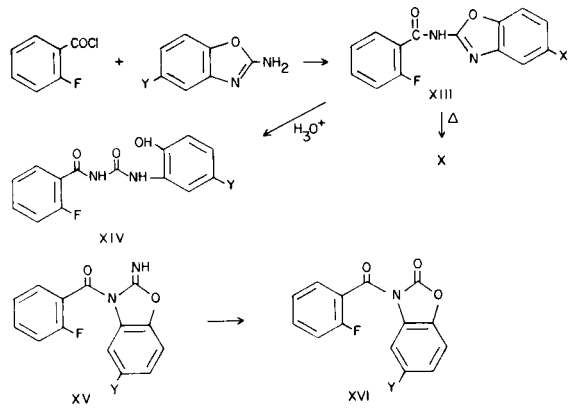


assignment was supported by spectral data and combustion analysis: the infrared spectrum of the compound showed a carbonyl absorption band at 6.03 μ, and the uv spectrum obtained in ethanol solution resembled closely that of IIb (1) showing absorption maxima at mμ (ϵ) 221 (3.62 x 10^4), 234 (2.93 x 10^4), 247 (shoulder, 2.04 x 10^4), 265 (0.55 x 10^4), 276 (0.43 x 10^4), 285 (0.58 x 10^4), and 310 (1.66 x 10^4). Other examples of the new ring system which were synthesized in similar fashion were Xa,c,d. An alternative structure, 12*H*-benzoxazolo[2,3-*b*]quinazolin-12-one is highly unlikely since the melting point of Xa (297-298° dec.) differs significantly from the reported melting point of the isomer (253-253.5° dec.) prepared from anthranilic acid and 2-chlorobenzoxazole (14).

An alternative synthesis of X starting with 2-amino-5-chlorobenzoxazole (11,14) and 2-fluorobenzoyl chloride provided an additional evidence for the assigned structure. When the latter two compounds were allowed to react in the presence of triethylamine, there was obtained *N*-(5-chloro-2-benzoxazolyl)-2-fluorobenzamide (XIIIb) which showed a carbonyl absorption band at 5.28 μ in its infrared spectrum and an exchangeable nmr signal at δ 12.30 ppm (1H) as a broad singlet. In agreement with the structural assignment, acidic hydrolysis of the product gave *N*-(5-chloro-2-hydroxyphenylaminocarbonyl)-2-fluorobenzamide (XIVb). The infrared spectrum of the hydrolysis product showed two carbonyl absorption bands at 5.85 and 5.93 μ, and the nmr spectrum (DMSO-d_6) exhibited three exchangeable signals at δ 10.50 (1H, very broad singlet), 10.91 (1H, singlet), and 11.13 ppm (1H, broad singlet). The elemental analysis agreed with the formula XIIIb + water. A possible alternative structure, XVb for the benzoylation product was eliminated since XVb would be expected to give XVIb rather than XIVb under the acidic condition (15).

Although Sam, *et al.* (14), showed that methylation of 2-amino-5-chlorobenzoxazole with methyl iodide takes place exclusively at the 3-position to give 5-chloro-2-imino-3-methylbenzoxazole, acetylation of 2-aminooxazoles has been reported to occur at the 2-amino group (16), in compatible with the present observation. When XIIIb was heated above its melting point a cyclization reaction took

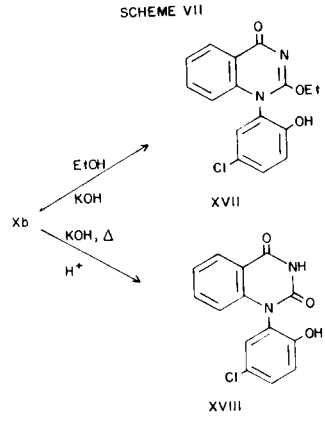
SCHEME VI



place giving a product identical in every respect to the product (Xb) obtained from the reaction of Ib with cyanogen bromide. Similarly, thermal cyclization of XIIIa, which was obtained from 2-fluorobenzoyl chloride and 2-aminobenzoxazole, afforded Xa. This synthetic route involving thermal cyclization of *N*-benzoxazolylfluorobenzamides not only confirms the assigned structure for the reaction product of cyanogen bromide with *N*-(2-hydroxyphenyl)anthranilic acids, but also presents a versatile alternative approach for the preparation of variously substituted benzoxazolo[3,2-*a*]quinazolin-5-ones.

When Xb was allowed to react with ethanol in the presence of potassium hydroxide a ring cleavage occurred, giving 1-(5-chloro-2-hydroxyphenyl)-2-ethoxy-4(1*H*)quinazolinone (XVII) in 55% yield. The treatment of Xb with hot aqueous potassium hydroxide solution followed by acidification gave 1-(5-chloro-2-hydroxyphenyl)-2,4-(1*H*, 3*H*)quinazolinedione (XVIII, Scheme VII).

SCHEME VII



EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. Uv absorption spectra were obtained with a Perkin-Elmer Model 450 Uv-visible spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories. The reported yields may be improved under optimal reaction conditions.

N-(2-Hydroxy-5-methylphenyl)anthranilic Acid (Ic).

2-Bromobenzoic acid (63 g.) was dissolved in a freshly prepared sodium methoxide-methanol solution (6.9 g. of sodium in 250 ml. of absolute methanol) and the solution thus obtained was evaporated to dryness under reduced pressure. The residual sodium salt was dissolved in 210 ml. of 1-butanol and the solution was heated to 100°. The heating source was removed and 2-amino-*p*-cresol (70 g.) was added, followed by the addition of copper powder (2.0 g.). The resulting mixture was stirred for 10 minutes, then refluxed for 40 minutes. Saturated aqueous sodium bicarbonate solution (100 ml.) and sodium carbonate (7.5 g.) were added. The 1-butanol was removed by steam distillation. The distillation residue was filtered under suction and the filter cake was washed repeatedly with water. The filter residue was extracted with about 2.5 liters of saturated aqueous sodium bicarbonate solution by stirring the mixture at room temperature overnight, then filtering under suction. The filtrate was acidified to approximately *p*H 3 by careful addition of concentrated hydrochloric acid. The precipitate that separated was collected on a filter and washed several times with water. Two recrystallizations from ether and petroleum ether gave 11.4 g. (15%) of analytically pure product, m.p. 185-187°; ir: 6.02 (CO).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.96; H, 5.39; N, 5.39.

2-(2-Amino-4-methylphenoxy)-5-nitrobenzoic Acid (XII).

Sodium hydride (9.6 g. of a 50% dispersion in oil) was washed 3 times with pentane, then suspended in 60 ml. of hexamethylphosphoramide. The mixture was chilled in ice and 12.3 g. of 2-amino-*p*-cresol was added in small portions to the cold mixture, followed by careful addition of 20 g. of 2-chloro-5-nitrobenzoic acid. The resulting mixture was stirred under nitrogen at ice-bath temperature for 1.5 hours, then at room temperature overnight. To the black reaction mixture was cautiously added about 10 ml. of aqueous hexamethylphosphoramide solution (1:1 by volume), followed by 200 ml. of water. The aqueous solution thus obtained was washed 3 times with chloroform, then acidified to about *p*H 5 with dilute hydrochloric acid. The precipitate that separated was collected on a filter and washed 5 times with water. The yellow-tinted product weighed 29 g. (100%). Two recrystallizations from ethanol gave a product of analytical purity. The sample started to char at around 300° and decomposed at 320°; ir: μ 5.78 (CO).

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.29; H, 4.39; N, 9.41.

N-(2-Hydroxy-5-methylphenyl)-5-nitroanthranilic Acid (Id).

A mixture of XII (1.0 g.), sodium hydroxide (1.0 g.) and water (100 ml.) was heated under reflux for 1 hour, then cooled to room temperature. Neutralization of the alkaline solution to about *p*H 5 with dilute hydrochloric acid caused separation of an orange precipitate. The precipitate was collected on a filter and washed several times with water, yielding 1.0 g. (100%) of product, m.p. 263-265°; ir: μ 5.98 (CO). (Note: Neutralization should be carried out while hot with vigorous stirring, otherwise, a jelly-like material was obtained. High concentration also gives the product in jelly-like form).

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.23; H, 4.04; N, 9.60.

N-(5-Chloro-2-benzoxazolyl)-2-fluorobenzamide (XIIIb).

To a stirring mixture of 2-amino-5-chlorobenzoxazole (25 g.) and benzene (500 ml.) was added 2-fluorobenzoyl chloride (24 g.) and triethylamine (17 g.). The resulting mixture was stirred at room temperature for 30 minutes, heated under reflux for 1 hour, and then allowed to cool to room temperature. The resulting precipitate was col-

lected on a filter and the filter residue was washed with benzene, then with water. Recrystallization from ethanol gave 10.7 g. (25%) of product, m.p. 195-198°.

Anal. Calcd. for $C_{14}H_8ClFN_2O_2$: C, 57.84; H, 2.77; N, 9.64. Found: C, 57.86; H, 2.67; N, 9.66.

Hydrolysis of XIIIb to *N*-(5-Chloro-2-hydroxyphenylaminocarbonyl)-2-fluorobenzamide (XIVb).

A mixture of XIIIb (0.3 g.) and 2*N* hydrochloric acid (15 ml.) was heated on a steam bath for 1 hour, then chilled in ice. The precipitate that separated was collected on a filter and washed with water. Recrystallization of the crude product from ethanol gave a sample with m.p. 230-232°. The sample showed a positive ferric chloride test.

Anal. Calcd. for $C_{14}H_{10}ClFN_2O_3$: C, 54.47; H, 3.27; N, 9.08. Found: C, 54.51; H, 3.32; N, 8.96.

N-(2-Benzoxazolyl)-2-fluorobenzamide (XIIIa).

To a stirring mixture of 2-aminobenzoxazole (7 g.), triethylamine (5 g.) and benzene (200 ml.) was slowly added 2-fluorobenzoyl chloride (8 g.). The resulting mixture was stirred at room temperature. The precipitate that separated was collected on a filter and washed with benzene. The combined filtrate and washings were evaporated on a rotary evaporator under reduced pressure to give an oil. Addition of anhydrous ether caused the oil to crystallize. The precipitate was collected on a filter and washed repeatedly with ether, giving 6.9 g. (53%) of product, m.p. 153-156°. Recrystallization from tetrahydrofuran improved the m.p. to 162-164°; ir: μ 3.06 and 6.07.

Anal. Calcd. for $C_{14}H_9FN_2O_2$: C, 65.62; H, 3.54; N, 10.94. Found: C, 65.60; H, 3.47; N, 10.86.

A mixture of XIIIa (0.4 g.), 2*N* hydrochloric acid (50 ml.), and ethanol (3 ml.) was heated on a steam bath with occasional swirling for 1 hour, then chilled in ice. A precipitate was collected on a filter and washed several times with water, giving 0.35 g. of crude*N*-(2-hydroxyphenylaminocarbonyl)-2-fluorobenzamide. The product, after purification by dissolution in very dilute aqueous sodium hydroxide solution, filtration, and reprecipitation by acidification of the filtrate with dilute hydrochloric acid, had m.p. 205-207°; ir: μ 5.87 and 5.99.

Anal. Calcd. for $C_{14}H_{11}FN_2O_3$: C, 61.31; H, 4.04; N, 10.22. Found: C, 61.29; H, 3.92; N, 10.19.

10-Chloro-5*H*-benzoxazolo[3,2-*a*]quinazolin-5-one (Xb).

Method A.

Sodium hydride (1.4 g. of a 57% dispersion in oil), washed 3 times with pentane prior to use, was suspended in tetrahydrofuran (250 ml.) and chilled. To the cold suspension was added *N*-(5-chloro-2-hydroxyphenyl)-anthranilic acid (4.0 g.). The resulting mixture was stirred under nitrogen at 0° for 10 minutes to produce a dark green solution. Cyanogen bromide (4.9 g.) dissolved in tetrahydrofuran (80 ml.) was added at once. The reaction mixture was stirred at 0° for 1 hour and at room temperature for 2 hours and was then allowed to set at room temperature overnight.

The mixture was refluxed for 0.5 hour, then cooled. A precipitate was collected on a filter and washed several times with tetrahydrofuran. The filter residue was triturated several times with water, collected on a suction filter, and washed with ethanol, giving 4.1 g. (100%) of product, m.p. 346-348°.

Anal. Calcd. for $C_{14}H_7ClN_2O_2$: C, 62.12; H, 2.61; N, 10.35. Found: C, 62.03; H, 2.78; N, 10.22.

Method B.

N-(5-Chloro-2-benzoxazolyl)-2-fluorobenzamide (0.4 g.) was placed in a test tube and fused for about 5 minutes using a gas burner. The evolution of hydrogen fluoride gas was observed. After cooling, the solid mass was crushed to powder and triturated with hot tetrahydrofuran, giving 0.2 g. (54%) of product, m.p. 344° dec. The mixture m.p. with the sample prepared by Method A was not depressed.

5*H*-Benzoxazolo[3,2-*a*]quinazolin-5-one (Xa).

Method A.

Compound Xa was obtained by the procedure used for the preparation of Xb from *N*-(2-hydroxyphenyl)anthranilic acid (2.3 g.), sodium hydride (57% oil dispersion, 0.94 g.), and cyanogen bromide (3.3 g.), using tetrahydrofuran (200 ml.) as the reaction medium. The product (1.95 g., 85%) had m.p. 297-298° dec.

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 70.81; H, 3.45; N, 11.68.

Method B.

A small amount of *N*-(2-benzoxazolyl)-2-fluorobenzamide (XIIIa) was placed in a test tube and heated in an open flame about 260° for 7 minutes. Once started, the reaction became exothermic. The melt was allowed to solidify on standing. The solid mass was crushed to powder and triturated with tetrahydrofuran, giving Xa with m.p. 298° dec. The mixture m.p. with the sample prepared by Method A was not depressed.

10-Methyl-5*H*-benzoxazolo[3,2-*a*]quinazolin-5-one (Xc).

This compound was prepared from *N*-(2-hydroxy-5-methylphenyl)-anthranilic acid (2.4 g.), sodium hydride (50% oil dispersion, 0.72 g.), and cyanogen bromide (3.2 g.) following the procedure used for the preparation of Xb. The product yield was 2.5 g. (100%), m.p. 300-301° dec.

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.72; H, 3.91; N, 10.82.

10-Methyl-3-nitro-5*H*-benzoxazolo[3,2-*a*]quinazolin-5-one (Xd).

This compound was prepared as described for the preparation of Xa from 2-[(2-hydroxy-5-methylphenyl)amino]-5-nitrobenzoic acid (5.8 g.), sodium hydride (50% oil dispersion, 1.92 g.) and cyanogen bromide (6.54 g.). The product, yield 3.3 g. (56%), did not melt below 350°.

Anal. Calcd. for $C_{15}H_9N_3O_4$: C, 61.02; H, 3.07; N, 14.23. Found: C, 61.21; H, 3.04; N, 14.48.

1-(5-Chloro-2-hydroxyphenyl)-2-ethoxy-4-(1*H*)quinazolinone (XVIII).

A mixture of Xb (5.4 g.), ethanol (200 ml.), and potassium hydroxide (1.5 g.) was heated under reflux for 1 hour, then evaporated to dryness on a rotary evaporator under reduced pressure. The residue was dissolved in water (*ca.* 200 ml.) and filtered. Acidification of the filtrate to about *p*H 5 with dilute hydrochloric acid caused separation of a precipitate, which was collected on a filter and washed with water. The filter residue was then recrystallized from ethanol with charcoal treatment, giving 3.5 g. (55%) of product. Another recrystallization from ethanol gave an analytical sample, m.p. 319-323° dec.; ir: μ 6.10 (CO).

Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.13; N, 8.85. Found: C, 60.80; H, 4.20; N, 8.83.

1-(5-Chloro-2-hydroxyphenyl)-2,4-(1*H*,3*H*)quinazolinedione Hemihydrate (XIX).

A mixture of Xb (2.0 g.) and 5% aqueous sodium hydroxide solution (30 ml.) was heated on a steam bath with occasional shaking for 2 hours. The reaction mixture was filtered and the filtrate was made acidic by addition of concentrated hydrochloric acid, whereby a precipitate separated. The mixture was chilled in ice and the precipitate was collected on a filter and washed with water. Purification by dissolving in dilute aqueous sodium hydroxide solution and reprecipitation by acidification with dilute hydrochloric acid gave 1.7 g. (77%) of product. The product melted at 170-175° with effervescence. On further heating it solidified at *ca.* 190°, then melted at 260°; ir: μ 5.90 (CO) and 5.98 (CO).

Anal. Calcd. for $C_{14}H_9ClN_2O_3 \cdot \frac{1}{2}H_2O$: C, 56.48; H, 3.39; N, 9.41. Found: C, 56.34; H, 3.57; N, 9.33.

Reaction of Salicylic Acid with Acetic Anhydride in Acetic Acid.

A mixture of salicylic acid (1.38 g.), acetic anhydride (1.1 g.), and acetic acid (20 ml.) was heated under reflux for 15 minutes, then evaporated on

a rotary evaporator under reduced pressure. The residue (a mixture of salicylic acid and acetylsalicylic acid) was sublimated *in vacuo* at 56° to remove the unreacted salicylic acid. The crude product obtained was recrystallized twice from water giving 0.94 g. (53%) of acetylsalicylic acid, which showed ir and nmr spectra identical with those of the authentic sample.

REFERENCES AND NOTES

(1) D. H. Kim, R. A. Fieber, A. A. Santilli and S. C. Bell, *J. Heterocyclic Chem.*, **11**, 703 (1974).

(2) B. S. Thyagarajan and K. Rajagopalan, *Tetrahedron Letters*, 729 (1965).

(3) B. S. Thyagarajan and K. Rajagopalan, *Chem. Ind. (London)*, 1931 (1965).

(4) T-L. Ho and C. M. Wong, *Synth. Commun.*, **3**, 63 (1973).

(5) One of the referees informed the author that they have also arrived at essentially the same conclusion as one described here regarding the intermediacy of the aroyl isocyanate in the formation of benzoxazinedione from a different set of experiments (Ph.D. Thesis submitted to the University of Madras, India by K. Rajagopalan, 1966).

(6) C. Christophersen and P. Carlsen, *Tetrahedron*, **32**, 745 (1976).

(7) D. J. Brown, Amidine Rearrangements (The Dimroth Rearrangements), in "Mechanisms of Molecular Migrations", Vol. 1, B. S. Thyagarajan, Ed., Interscience Publishers, New York, N.Y., 1968, pp. 209-245.

(9) K. Lempert and G. Doleschall, *Tetrahedron Letters*, 781 (1963).

(10) The gas generated during the reaction may not be carbon dioxide, as originally claimed (2), but rather hydrogen cyanate.

(11) T. Nagano, M. Itoh and K. Matsumura, *J. Am. Chem. Soc.*, **75**, 2770 (1953).

(12) A. A. Levy, H. C. Rains and S. Smiles, *J. Chem. Soc.*, 3264 (1931).

(13) More than 2 equivalent amounts of cyanogen bromide was used in order to avoid the inconvenience associated with weighing the exact amount needed for the reaction. Such excess did not appear to affect the reaction or the product. The excess reagent was readily removed from the product by washing.

(14) J. Sam, J. N. Plampin and G. I. Poos, *J. Org. Chem.*, **23**, 1500 (1958).

(15) J. Sam and J. N. Plampin, *J. Pharm. Sci.*, **53**, 538 (1964).

(16) G. Crank and M. J. Foulis, *J. Med. Chem.*, **14**, 1075 (1971).