The Synthesis of Fused Azolones from *ortho*-Substituted Arenecarbohydroxamic Acids

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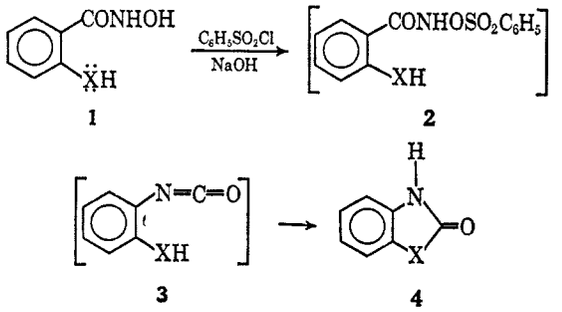
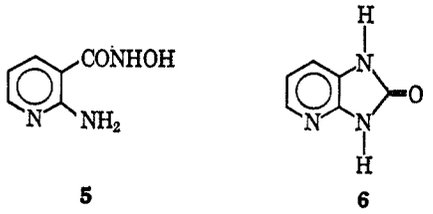
It has been observed that sulfonyl halides convert benzohydroxamic acid into O-phenylcarbamoyl benzohydroxamate,[2] the product of O-acylation of the hydroxamic acid by the expected degradation product, *viz.*, phenyl isocyanate. A cognate reaction on phthalohydroxamic acid (**1**, XH = CONHOH) proved to be somewhat different: one of the hydroxamic acid groups was degraded to an isocyanate, which then N-acylated the neighboring hydroxamic acid to form 3-hydroxy-2,4-quinazolinedione [**4**, X = CON(OH)].[3]



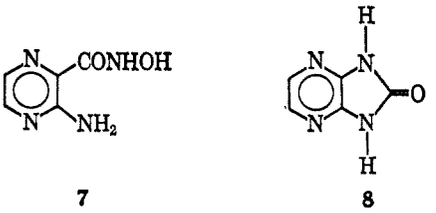
In the present study, anthranilo- and salicohydroxamic acids were subjected to benzenesulfonyl chloride in dilute aqueous sodium hydroxide solution at 25°. In these systems (**1**, XH = NH_2 or OH), it is predictable that the excellent nucleophilicity of the hydroxamate ion[4] would dictate preferential reaction with the acid halide to form an O-sulfonyl hydroxamate (**2**) faster than the sulfonamide or aryl sulfonate. On such a premise and the known rapid degradation[2,5] of **2** to **3**, the reaction sequence took place as anticipated, the final step being the cyclization of **3** to **4**. It was found that benzenesulfonyl chloride converted anthranilohydroxamic acid into 2-benzimidazolone (**4**, X = NH) quantitatively. This synthesis represents a considerable improvement over the Lossen rearrangement of O-benzoyl anthranilohydroxamate previously reported (in unspecified yield).[6] 2-Benzimidazolone was also produced in apparently negligible yield from two less conventional Lossen degradations, from the pyrolyses of either anthranilohydroxamic acid at 150–170° for 7 min[7] or sodium anthranilohydroxamate "until evidence of sublimation was noted."[6] It should be noted that the 2-benzimidazolone was the product of the related Hofmann rearrangements of anthranilamide (34%)[8] and the Curtius rearrangement of anthraniloyl azide (45%).[7]

Salicylohydroxamic acid (**1**, X = OH) reacted quickly with benzenesulfonyl chloride to furnish 2-benzoxazolone (**4**, X = O), in excellent yield. This preparation of 2-benzoxazolone represents an improvement over the one utilizing the "standard" Lossen rearrangement, *via* O-benzoyl salicylohydroxamate,[9] or by the more unusual reaction of salicylohydroxamic acid with thionyl chloride.[10]

In view of the successful application of this modified Lossen rearrangement using sulfonyl halides, the behavior of two heteroaromatic amino hydroxamic acids was examined. The only Lossen type of reaction hitherto reported for 2-aminonicotinohydroxamic acid (**5**) was its pyrolysis at 210–220° for 5 min to give, among other products, a minute quantity of the fused imidazolone, **6**.[7] However, benzenesulfonyl chloride



transformed **5** into **6** in excellent yield. It is of interest to note that the related Hofmann rearrangement on 2-aminonicotinamide[8,11] and the Curtius rearrangement on 2-aminonicotinoyl azide[7,11] afforded **6** in 34%[8] and 96%[7] yield, respectively.



The other example described in this work involved 2-aminopyrazinecarbohydroxamic acid, **7**.[12] Rearrangement of **7** with benzenesulfonyl chloride readily made **8** available in 60–70% yield. Although **8** can be obtained in good yield from the fusion of 2,3-diaminopyrazine with urea at 160° for 2 hr,[13] the synthesis of the diamine is quite tedious whereas the starting material for the present synthesis, 2-amino-3-pyrazinecarboxylic acid is commercially available.[14]

(1) National Science Foundation Trainee.

(2) D. Samuel and B. L. Silver, *J. Amer. Chem. Soc.*, **85**, 1197 (1963), and references quoted therein.

(3) For a review of these reactions, see L. Bauer and C. S. Mahajanshetti, *J. Heterocycl. Chem.*, **4**, 325 (1967).

(4) The "α effect" would make the $-CONHO^-$ group a most effective nucleophile: J. D. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

(5) It is not surprising that the rearrangement of O-benzenesulfonyl benzohydroxamates occur almost spontaneously since it had been demonstrated by R. D. Bright and C. R. Hauser [*ibid.*, **61**, 618 (1939)] that the rate of the Lossen reaction increases with the pK_a of the acid corresponding to the departing anion.

(6) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).

(7) D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 3157 (1959).

(8) A. Dornow and O. Hahmann, *Arch. Pharm.* (Weinheim), **290**, 20 (1957).

(9) A. W. Scott and J. H. Mote, *J. Amer. Chem. Soc.*, **49**, 2545 (1927).

(10) R. Marquis, *Compt. Rend.*, **143**, 1164 (1906).

(11) A. Dornow, German Patent 1,024,974 (1958); *Chem. Abstr.*, **54**, 7748 (1960).

(12) W. B. Wright and J. M. Smith, *J. Amer. Chem. Soc.*, **77**, 3927 (1955).

(13) F. L. Muehlmann and A. R. Day, *ibid.*, **78**, 242 (1956).

(14) Aldrich Chemical Co., Milwaukee, Wis.

Experimental Section[15]

Anthranilohydroxamic Acid.—This procedure consistently gave good results in the synthesis of the hydroxamic acid from ethyl anthranilate. When the published conversion of methyl anthranilate into anthranilohydroxamic acid[16] was applied to ethyl anthranilate in hot ethanol, little hydroxamic acid was isolated.

Sodium ethoxide, prepared from 4.6 g (0.2 g-atom) of sodium in 50 ml of ethanol, was added to a stirred solution of dried hydroxylamine hydrochloride (14.0 g, 0.2 mol) in ethanol (130 ml). After 1 hr the solution was filtered and to the filtrate was added ethyl anthranilate (16.5 g, 0.1 mol) followed by sodium ethoxide, prepared from 2.3 g (0.1 g-atom) of sodium in 50 ml of ethanol. The reaction mixture was stirred at 25° for 2 days. The solid was collected, washed with petroleum ether (bp 30–60°), dissolved in the minimum amount of water, filtered, and acidified with acetic acid. Recrystallization from water yielded the hydroxamic acid in 60% yield, mp 144–145° (lit. mp 142–143°,[14] 149°[6]).

2-Benzimidazolone.—Benzenesulfonyl chloride (14.13 g, 0.08 mol) was added dropwise to a stirred solution of anthranilohydroxamic acid (6.1 g, 0.04 mol) in freshly prepared 5% NaOH solution (64 ml). The reaction mixture was stirred at 25°, maintaining the pH at 8 or above by the addition of 10% NaOH as required. After 2 hr, the presence of the hydroxamic acid group could not be detected by means of the ferric chloride test. The solution was cooled in an ice–water bath and acidified with dilute HCl (1:1) to pH 4. The crystalline product was collected, washed with petroleum ether (bp 30–60°), dried *in vacuo*, and recrystallized from 95% ethanol to give the product (5.09 g, 95%), mp 309–310°, (lit. mp 300°,[6,17,18] 307–308°,[19] 310°,[20,21] 313–316°[7]). Its ir spectrum, melting point, and mixture melting point were identical with that of an authentic sample:[14] ir, 3120 (NH) and 1725 cm^{-1} (C=O); nmr (DMSO), δ 7.0 (s, C_6H_4).

2-Benzoxazolone.—Salicylohydroxamic acid (6.1 g, 0.04 mol) was treated with benzenesulfonyl chloride (7.07 g, 0.04 mol) as described above. After 0.75 hr, at which time the reaction mixture did not give a purple color with ferric chloride, it was treated with 20% NaOH solution (20 ml) and filtered, and the filtrate was acidified with dilute HCl (1:1). The product (4.65 g, 86%, mp 122–125°) was recrystallized from water: mp 131–133° (lit.[9] mp 139°); ir, 3215 (NH) and 1750 cm^{-1} (C=O); nmr (DMSO), δ 7.15 (s, C_6H_4); mass spectrum (70 eV), *m/e* (relative intensity) 136 (9.6), 135 (100), 91 (24), 79 (53), 78 (7.7), 67.5 (5.8), 64 (17.4), 63 (12.5), 53 (6.7), 52 (45), 51 (21), 50 (11.5), 39.5 (7.7), 39 (8.6), 38.5 (4.8), 38 (9.6), 32 (7.7), 28 (26).

2-Oxo-1H,3H-imidazo[4,5-*b*]pyridine.—Benzenesulfonyl chloride (1.06 g, 0.006 mol) was added dropwise to a stirred solution of 2-aminonicotinohydroxamic acid (0.9 g, 0.006 mol) in 10% NaOH (10 ml). After 10 min the reaction mixture was filtered and the filtrate was acidified to pH 6 with dilute HCl (1:2). The solid (0.85 g, mp 259–262°). was recrystallized from 95% ethanol to furnish the pure product (0.58 g, 71%): mp 269–272° (lit. mp 238–239°,[22] 265–266°,[8,11] 270–272°,[7] 274°[23]); ir, 3100 (NH) and 1700 cm^{-1} (C=O); nmr (DMSO), δ 7.93 (d of d, H_6 $J_{4,6}$ = 1.6 Hz), 7.00 (d of d, H_5, $J_{4,5}$ = 7.6 Hz), 7.34 (d of d, H_4, $J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV), *m/e* (relative intensity) 136 (8.34), 135 (100), 108 (4.2), 107 (23), 92 (6.2), 80 (20.8), 79 (5.2), 64 (12.5), 63 (6.2), 55 (5.2), 53 (19.8), 52 (13.5), 39 (7.3), 38 (10.4), 32 (7.3), 28 (26.1).

2-Oxo-1H,3H-imidazo[4,5-*b*]pyrazine.—Benzenesulfonyl chloride (15.90 g, 0.09 mol) was added dropwise to a stirred solution of 2-amino-3-pyrazinecarbohydroxamic acid (14.05 g, 0.09 mol) in 4% NaOH solution (200 ml). The reaction mixture was stirred at 25° for 1 hr, then acidified at 0° to pH 4 with dilute HCl (1:3). The red-brown product (7.95 g, 65%) was recrystallized from water: mp 334–336° (lit.[13] mp 336°); ir, 3480, 3330 (NH) and 1720 cm^{-1} (C=O); nmr (DMSO), δ 7.93 (s); mass spectrum (70 eV), *m/e* (relative intensity) 137 (5.1), 136 (66.8), 109 (7.9), 108 (6.5), 94 (13.5), 81 (9.8), 71 (6.1), 69 (6.5), 66 (10.7), 57 (13.5), 56 (5.6), 55 (10.28), 54 (13.08), 53 (10.7), 44 (7.0), 43 (12.1), 41 (11.7), 40 (5.6), 39 (8.4), 32 (42.5), 28 (100), 27 (7.5).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.03; H, 3.10; N, 41.18.

Registry No.—**4** (X = NH) 615-16-7; **4** (X = O) 59-49-4; **6**, 16328-62-4; **8**, 16328-63-5.

(15) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls (NaCl plates) with a Perkin-Elmer spectrophotometer, Model 337. Nmr spectra were determined with a Varian A-60 spectrometer, calibrated with tetramethylsilane (TMS)(0) and $CHCl_3$(7.28); chemical shifts are reported in parts per million (δ) downfield from internal TMS. Mass spectra were obtained from a Hitachi Perkin-Elmer model RMU-6D spectrometer. The analysis (C, H) was performed by Dr. Kurt Eder, Geneva, Switzerland and that for N by Leo Horner using a Coleman Nitrogen Analyzer.

(16) M. A. Stolberg, W. A. Mosher, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **79**, 2615 (1957).

(17) L. C. Raiford, E. Conrad, and W. H. Coppock, *J. Org. Chem.*, **7**, 346 (1942).

(18) F. Montanari and A. Risaliti, *Gazz. Chim. Ital.*, **83**, 278 (1953).

(19) A. Hartman, *Ber.*, **23**, 1046 (1890).

(20) S. von Niementowski, *Ber.*, **43**, 3012 (1910).

(21) D. G. Crosby and C. Niemann, *J. Amer. Chem. Soc.*, **76**, 4458 (1954).

(22) J. R. Vaughan, Jr., J. Krapcho, and J. P. English, **71**, 1885 (1949).

(23) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

Nitration of 2-Methylthiazole

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Although it is known that 4-methyl- and 5-methylthiazoles undergo nitration[1] with relative ease, 2-methylthiazole has been nitrated only in very low yield (3–4%) through the use of fuming sulfuric acid and potassium nitrate at 330°.[2] The product, mp 131–133°, was reported to be 2-methyl-5-nitrothiazole, but no proof of structure was given. Under milder conditions, Ganapathi and Kulkarni[3] obtained similar yields of what was presumably the same compound. Since we intended to utilize 2-methyl-5-nitrothiazole as an intermediate, the nitration of 2-methylthiazole was investigated using nitronium tetrafluoroborate[4] and the nitrogen tetroxide–boron trifluoride complex.[5,6] These reagents, however, were unstable in the presence of 2 methylthiazole. Nitrogen dioxide was evolved and only low yields[7] (8–19%) of a 2-methyl nitrothiazole, mp 70.5–72.5°, were obtained.[8] This material was homogeneous by glpc and did not appear to be the same compound as that which had been alleged to be 2-methyl-5-nitrothiazole by Babo and Prijs. It was suspected that decomposition of the reagent could be cir-

(1) J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 634.

(2) H. v. Babo and B. Prijs, *Helv. Chim. Acta*, **33**, 306 (1950).

(3) K. Ganapathi and K. D. Kulkarni, *Curr. Sci.*, **21**, 314 (1952); *Proc. Indian Acad. Sci., Sect. A*, **37**, 758 (1953).

(4) G. A. Olah, S. Kuhn, and A. Mlinko, *J. Chem. Soc.*, 4257 (1956).

(5) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Amer. Chem. Soc.*, **77**, 6188 (1955).

(6) The stoichiometry involved in the formation of the complex is believed to be

$$3N_2O_4 + 8BF_3 \longrightarrow 3NOBF_4 + 3NO_2BF_4 + B_2O_3$$

Cf. G. A. Olah and M. W. Meyer in "Friedel-Crafts and Related Reactions," Vol. 1, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1963, pp 124, 125, and 684.

(7) The higher yield was obtained by using the method of R. A. Parent [*J. Org. Chem.*, **27**, 2282 (1962)].

(8) For nucleophilic attack by pyridine on nitronium tetrafluoroborate, *cf.* G. A. Olah, J. A. Olah, and N. A. Overchuk, *J. Org. Chem.*, **30**, 3373 (1965); J. Jones and J. Jones, *Tetrahedron Lett.*, 2117 (1964).