A Rapid Amide Cleavage Assisted by a Neighboring Hydroxylamino Function[1]

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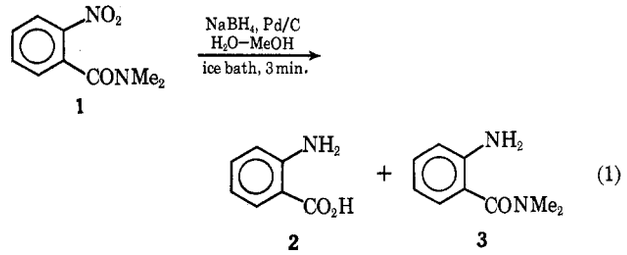
An attempted reduction of *o*-nitro-*N*,*N*-dimethylbenzamide (1) to the amine **3** by subjecting it, over a 3-min period, to an ice-cooled water–methanol solution of sodium borohydride containing suspended palladium on carbon resulted in the production of anthranilic acid (2) in 58% crude yield. The rapid amide cleavage is believed to occur in the intermediate *o*-hydroxylamino-*N*,*N*-dimethylbenzamide (4) by loss of a proton from the hydroxylamino group followed by nucleophilic attack on the carbonyl group to provide 2,1-benzisoxazolone (5), which is then reduced to **2**. Evidence for each of these steps is presented. The cleavage of the amide group of 4 (which can be obtained from some of the reduction reactions) in 0.1 *N* aqueous alkali at room temperature is at least 3.7×10^8 times as fast as that of *N*,*N*-dimethylbenzamide under the same conditions.

In recent years, a number of instances of neighboring group assistance in the cleavage of amides have been reported.[2-4] A few of these involve benzamide cleavage which is assisted by an ortho substituent. One of the earliest examples, reported by Bender and coworkers,[5] is the participation of the *o*-carboxyl group in the hydrolysis of phthalamic acid. Morawetz and Shafer[6] attributed a rate enhancement in the hydrolysis of *o*-carboxyphthalanilic acid to bifunctional catalysis involving the neighboring carboxyl groups of both rings. Bruice and Tanner[7] provided evidence that the *o*-hydroxy groups of salicylamides in their ionized forms enhance the rate of alkaline hydrolysis by exerting a general base catalytic effect. Cohen and Lipowitz[8] showed that the rate of acid hydrolysis of *N*,*N*-dicyclohexylbenzamide was greatly enhanced by the presence of an ortho benzamido group, which appeared to provide nucleophilic assistance to the hydrolysis. We now report another example of an extremely facile cleavage of a *tert*-benzamide and suggest a mechanism which involves nucleophilic assistance by a neighboring hydroxylamino group.

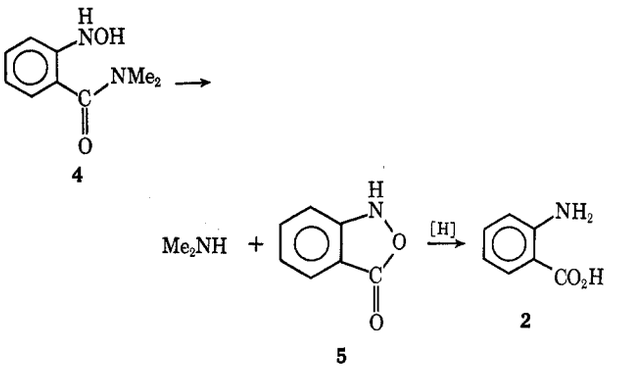
During an attempted reduction of *o*-nitro-*N*,*N*-dimethylbenzamide (1) to the amine by the use[9] of palladium on carbon and sodium borohydride in a water–methanol solution which was cooled in an ice bath, anthranilic acid (2, 58% crude yield) was produced along with the expected *o*-amino-*N*,*N*-dimethylbenzamide (**3**, 26% yield) (eq 1) after a reaction time of only 3 min. The ratio of **2** to **3** produced varied widely



1 2 3 (1)

depending on the exact experimental conditions. It was shown that **3** is not cleaved under the reaction conditions and that the nitro compound **1** is stable in the reaction mixture used provided that the sodium borohydride is not present.

It is thus likely that cleavage of the amide linkage is occurring in a reduction intermediate. A very likely intermediate in the reduction of the nitro compound and one which has the proper structure for neighboring group participation is *o*-hydroxylamino-*N*,*N*-dimethylbenzamide (4). The gross features of a reasonable mechanism are shown.



The first step would presumably be promoted by the alkalinity that develops in sodium borohydride solutions. An analogy for this step is the finding by Bamberger and Pyman[10] that methyl and ethyl *o*-hydroxylaminobenzoate (6) are cleaved in high yield to 2,1-benzisoxazolone (5) at room temperature by the use of 1 *N* sodium hydroxide. Participation of the general type suggested here, albeit in acid solution, has been claimed for the electrochemical reduction of *o*-nitrobenzoic acid and the corresponding amide and ethyl ester (7) in 2–5 *N* sulfuric acid at 60–80°; the product was considered to be 5, but no evidence for its structure was presented.[11] Another analogy is the

(1) This work was supported by Grant GP 22955 from the National Science Foundation.

(2) Reviews of intramolecular participation in the cleavage of carboxylic acid derivatives: M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964); T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, Chapter 1; S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

(3) For a recent review of intramolecular assistance in amide cleavage, see B. C. Challis and J. A. Challis, "The Chemistry of Amides," J. A. Zabicky, Ed., Interscience, New York, N. Y., 1970, pp 833–840. For other examples see footnote 4.

(4) H. Zahn and L. Zürn, *Justus Liebigs Ann. Chem.*, **613**, 76 (1958); T. A. Dobson, M. A. Davis, A. M. Hartung, and J. M. Manson, *Can. J. Chem.*, **46**, 2843 (1968); B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. Soc. Chim. Belg.*, **69**, 616 (1960); P. Crooy and A. Bruylants, *ibid.*, **73**, 44 (1964); J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); A. Signor and E. Bordignon, *ibid.*, **30**, 3447 (1965); W. H. Puterbaugh and C. R. Hauser, *ibid.*, **29**, 853 (1964); E. M. Levi, C. L. Mao, and C. R. Hauser, *Can. J. Chem.*, **47**, 3671 (1969); C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 475 (1969); G. I. Glover, R. B. Smith, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 2003 (1965).

(5) M. L. Bender, *J. Amer. Chem. Soc.*, **79**, 1258 (1957); M. L. Bender, Y. L. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(6) H. Morawetz and J. Shafer, *ibid.*, **84**, 3783 (1962).

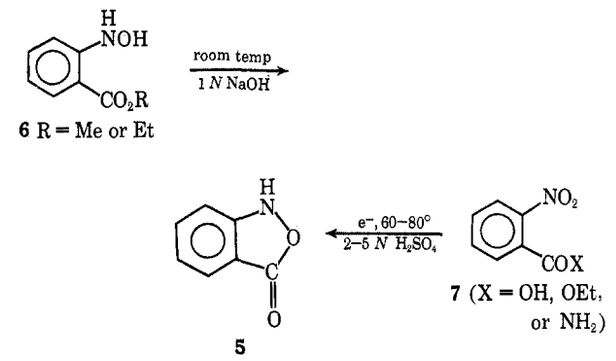
(7) T. C. Bruice and D. W. Tanner, *J. Org. Chem.*, **30**, 1668 (1965).

(8) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **86**, 5611 (1964).

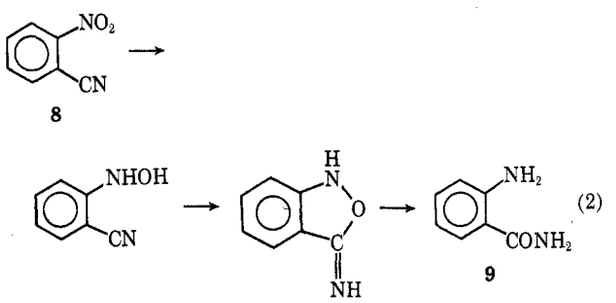
(9) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

(10) E. Bamberger and F. L. Pyman, *Chem. Ber.*, **42**, 2297 (1909).

(11) M. Le Guyader and D. Peltier, *C. R. Acad. Sci.*, **253**, 2544 (1961); M. Le Guyader, A. Tallec, and R. Legoff, *ibid.*, **258**, 6175 (1964); A. Tallec, *ibid.*, **263**, 722 (1966).



conversion of *o*-nitrobenzonitrile (**8**) to *o*-aminobenzamide (**9**) by reduction with Raney nickel; evidence was presented for the reaction scheme shown (eq 2).[12]



In the present work, preliminary support for the intermediate formation of 2,1-benzisoxazolone (**5**) was obtained by isolation of its *N*-acetyl derivative from an acidified reaction mixture in which the reduction of **1** had been performed under conditions similar to those which produced anthranilic acid. The acetyl derivative was identified by comparison of its infrared and mass spectra with those of the acetyl derivative of an independently prepared sample of **5** (see below).

When a different batch of palladium on carbon catalyst was used for the reduction of **1**, it was possible to isolate the unstable proposed intermediate, *o*-hydroxylamino-*N*,*N*-dimethylbenzamide (**4**) in a crude yield of up to 50%. The material had similar spectral properties to those of a sample[13] prepared by the careful reduction of **1** with zinc and ammonium chloride; the procedure used is a modification of that developed by Bamberger and Pyman[10] for the preparation of methyl and ethyl *o*-hydroxylaminobenzoate.

(12) H. Musso and H. Schröder, *Chem. Ber.*, **98**, 1562 (1965).

(13) Since recrystallized samples of this material deteriorate rather rapidly, the purity of the sample obtained by zinc reduction has not been definitely established. It apparently contains some *o*-amino-*N*,*N*-dimethylbenzamide (**3**), since its glpc trace shows only one small peak at the same retention time as the amine; evidently the hydroxylamine does not survive the gas chromatographic conditions. The mass spectrum, obtained utilizing a direct probe, also closely resembles that of **3** except for the presence of a weak parent peak at *m/e* 180 and one of moderate intensity at *m/e* 135, possibly a result of the cyclization to **5** in the mass spectrometer; since it is known that loss of oxygen is a major mode of fragmentation of *N*-arylhydroxylamines, often producing the base peak in the mass spectrum,[14] this spectrum is not surprising.

Fortunately, the infrared spectrum of the crude hydroxylamine is quite different from that of the amine (see Experimental Section). For example, the peaks at 3480 and 3390 cm^{-1} in the spectrum of the amine are not present in that of the hydroxylamine; instead, the latter has a sharp peak at 3584 cm^{-1} and a broad one at 3322 cm^{-1} which are indicative of the hydroxylamino function. Further, the amide absorption of the amine occurs at 1609 cm^{-1} while that of the hydroxylamine is at 1621 cm^{-1}.

The most convincing evidence for the structure of the hydroxylamine is the cleavage to the benzisoxazolone (**5**) in 51% isolated yield (see text).

(14) R. T. Coutts and G. Mukherjee, *Org. Mass Spectrom.*, **3**, 63 (1970).

Evidence for the suggested participation of the hydroxylamino function in the cleavage of the amide group has been obtained by the isolation of 2,1-benzisoxazolone (**5**, 51% yield) from a weakly alkaline (0.1 *N*) aqueous solution of **4** which was allowed to remain at room temperature and then neutralized; the total reaction time was less than 7 min. The benzisoxazolone was identified by its melting point,[10] its mass spectrum (at 15 eV peaks at *m/e* 135, parent and base; 119, P − O; 91, P − CO_2; and 79), infrared spectrum (3311, sharp, N–H; 1773 and 1751 cm^{-1}, 5-ring carbonyl) and nmr spectrum (τ 1.17, broad singlet, one proton, NH; 2.0–2.9, multiplet, 4 aromatic protons), and its conversion to the known *N*-acetyl derivative.

An attempt to monitor the cleavage reaction of **4** in deuterium oxide by infrared spectroscopy failed because of the high rate of the reaction; the spectral scan, which was started 70 sec after mixing (scan rate 80 cm^{-1} per minute from 1300–1800 cm^{-1}), indicated that the amide **4** had been converted to the sodium salt of *o*-hydroxylaminobenzoic acid (the open form of **5** exists in alkaline solution; see Experimental Section). In contrast, a solution of the amide in neutral heavy water gave a spectrum which was clearly that of the uncleaved amide and which did not change during a 0.5-hr period. It is thus apparent that the amide cleavage is base catalyzed. This is consistent with the proposed mechanism, since the anionic form of the hydroxylamino function should be far more nucleophilic than the un-ionized form.

In an attempt to estimate the enhancement of the cleavage rate provided by the hydroxylamino function, *N*,*N*-dimethylbenzamide was subjected to the reaction conditions used to prepare the benzisoxazolone (**5**) from **4**. After 18 days in 0.1 *N* aqueous base at room temperature, 56% of the amide could be recovered unchanged. Thus, the half-life of the hydrolysis is greater than 18 days. Since the half-life of the assisted hydrolysis is less than 7 min, 3.7×10^3 is a minimum factor for the enhancement. In view of the facts that the 7-min figure may be too large by a factor of 2 or 3 and that in the absence of nucleophilic participation an electron-donating ortho substituent would be expected to decrease the rate of alkaline hydrolysis by decreasing the electrophilicity of the carbonyl group[15] and probably by steric hindrance, the actual rate enhancement may be several times this factor.

Finally, it was demonstrated that 2,1-benzisoxazolone (**5**) could be reduced to anthranilic acid (**2**, 76% yield) under the reaction conditions.

Experimental Section

Infrared spectra were determined with a Beckman IR-8 or IR-12 spectrophotometer; sodium chloride cell windows were used throughout except for work in aqueous solution, where calcium fluoride windows were employed. Nmr spectra were determined with a Varian A-60 spectrometer; chemical shifts are expressed in τ values relative to internal tetramethylsilane. Mass spectra were obtained with an LKB-9000 combined gas chromatograph–mass spectrometer at 70 eV, unless otherwise stated; the *m/e* values of major peaks are reported, followed in parentheses by intensity values as percentages of the base peak. Melting points were taken on a Thomas-Kofler micro hot stage and are corrected. Two different lots of Matheson Coleman and Bell 10% Pd/C were used. Micro silicic acid columns were prepared with Mallincrodt TLC-7GF silicic acid.

(15) K. T. Koshy, *J. Pharm. Sci.*, **58**, 560 (1969).

Catalytic Reduction of o-Nitro-N,N-dimethylbenzamide in the Presence of Sodium Borohydride. A. Isolation of Anthranilic Acid.—A solution of 0.97 g (5.0 mmol) of o-nitro-N,N-dimethylbenzamide[16] in 22 ml of water and 3 ml of methanol was rapidly added to a slurry of 0.05 g of 10% Pd/C in an ice-cooled solution of 0.7 g (18 mmol) of sodium borohydride in 15 ml of water. The mixture was stirred for 3 min and the catalyst was removed by filtration. The basic solution was made slightly acidic with 18% hydrochloric acid, extracted with ether, made basic with sodium carbonate, and reextracted with chloroform. The two extracts were separately dried ($MgSO_4$) and the solvents were removed by evaporation to produce 0.40 g (58%) of crude anthranilic acid (**2**) and 0.21 g (26%) of crude o-amino-N,N-dimethylbenzamide (**3**) from the ether and chloroform extracts, respectively. The infrared spectrum of the anthranilic acid strongly resembles that reported.[17] The crude o-amino-N,N-dimethylbenzamide was identified by comparison of its infrared spectrum with that of an authentic sample:[16] ir ($CHCl_3$) 3480 (m), 3390 (m), 3010 (s), 2940 (m), 1609 (vs), 1587 (vs), 1480 (s), 1390 (s), 1300 (m), 1255 (m), 1201 (m), 1151 (m), 1075 (s), and 1058 cm^{-1} (sh). Its mass spectrum is very similar to that of **4** and is presented below under the description of the latter.

Another reaction was performed as above, except at one-half the scale. The mixture was stirred this time for 15 min and the catalyst was then removed by filtration. The basic solution was extracted with chloroform (five 5-ml portions), neutralized with 18% hydrochloric acid, reextracted, acidified, and finally extracted a third time. The acid extract was dried ($MgSO_4$) and concentrated to leave 67 mg of residue, which was partially purified by passage through a micro silicic acid column ($CHCl_3$), and was then sublimed at 100° (0.5 Torr) in a micro sublimator. There was significant decomposition of the residue during sublimation, but the sublimed anthranilic acid consisted of 20.3 mg (5.7% yield) of white crystals, mp 147.0–147.5° (lit.[18] mp 144.9–145.4°; lit.[19] mp 144–145°), whose infrared spectrum matched that reported.[17]

When the aminoamide **3** was subjected to the reaction conditions except that ice cooling was not employed, over 90% of it was recovered. The starting nitro compound was recovered unchanged under these couditions when the sodium borohydride was not present and cooling was not employed.

In another run, using the same quantities of reactants but in a solution of 30 ml of water, 5 ml of methanol, and one drop of 1 *N* sodium hydroxide, less catalyst (0.02 g), and a longer reaction time (1 hr), the yield of crude anthranilic acid was 42% and that of crude aminoamide was 60%. In a third run, in which the solution of nitro compound was added slowly, a 5.7% yield of pure anthranilic acid could be obtained; in this run there was a large basic fraction, the infrared spectrum of which indicated that it was largely a mixture of 2,1-benzisoxazolone and o-hydroxylamino-N,N-dimethylbenzamide. The detection of the former by acetylation of the basic fraction of a similar run is described below.

B. Isolation of N-Acetyl-2,1-benzisoxazolone.—A solution of 1.00 g (5.15 mmol) of the nitroamide in 22 ml of water and 3 ml of methanol was added at a rate of 5 drops/sec to a slurry of 0.04 g of 10% Pd/C in an ice-cooled solution of sodium borohydride (1.0 g, 27 mmol) in 15 ml of water. After the addition, the solution was stirred for 5 min, the catalyst was removed by filtration, and the basic filtrate was acidified with 18% hydrochloric acid and extracted with methylene chloride. Acetic anhydride (1.00 g, 9.8 mmol) was added to the aqueous solution followed by enough sodium acetate to neutralize the solution. The mixture was stirred at room temperature for 1 hr and the white precipitate was removed by filtration and dried in a vacuum desiccator. This material (100 mg, 12% yield) gave a single peak when chromatographed from 140° at a rate of 8°/min on a 10-ft column of 3% OV-17 on Gas-Chrom Q. Its infrared and mass spectra matched those of an authentic sample of N-acetyl-2,1-benzisoxazolone.

C. Isolation of o-Hydroxylamino-N,N-dimethylbenzamide (4).—The procedure in **B** was used except that a different batch of Pd/C was employed. After removal of the catalyst, the basic yellow solution was extracted with methylene chloride (five 5-ml portions) and the extract was dried ($MgSO_4$) and concentrated to yield 372 mg (crude yield 40%) of light yellow oil, the ir spectrum of which matched that of a sample of **4** prepared by reduction of the nitro compound with zinc and ammonium chloride. Addition of hexane to a chloroform solution of the oil resulted in the precipitation of 218 mg (23%) of white solid which discolored in air. It also had the correct ir spectrum. Another similar run yielded 50% of **4** as a crude, light yellow solid.

o-Hydroxylamino-N,N-dimethylbenzamide (4).—Zinc dust (795 mg, 12.1 mmol) was added in small portions over a 5-min period to a vigorously stirred mixture of 6 ml of water and 4 ml of ether containing 388 mg (2.00 mmol) of o-nitro-N,N-dimethylbenzamide and 300 mg (5.60 mmol) of ammonium chloride. The temperature was maintained below 23° by intermittent cooling. The mixture was stirred for an additional 10 min and the zinc oxide and unreacted zinc were removed by filtration. The residue was washed with ether, the water and ether layers were separated, and the aqueous layer was extracted with ether. The combined ether extract was dried ($MgSO_4$) and evaporated to yield 218 mg (crude yield 60%) of yellowish-white solid, the spectroscopic properties of which indicate that it is predominantly o-hydroxylamino-N,N-dimethylbenzamide. Upon glpc, the material exhibited one small peak at the same retention time as the amine; apparently the hydroxylamine is itself not capable of being chromatographed but is contaminated with some of the corresponding amine. The mass spectrum at 15 eV is given in the discussion. That at 70 eV (direct probe) is very similar to that of o-amino-N,N-dimethylbenzamide (**3**) and the two are now compared; the first number in parenthesis is the per cent of the base peak in the spectrum of **4** and the second is the corresponding figure for the spectrum of pure amine (**3**): *m/e* 181 (0.2, 0), 180 (1.3, 0), 164 (36, 36), 163 (7, 12), 137 (2.3, 0), 136 (2, 0.07), 135 (21, 0.4), 121 (8, 12), 120 (100, 100), 119 (12, 12), 92 (46, 51), 91 (9, 5) 65 (32, 33), 64 (12, 5), 52 (12, 3), 51 (5, 1), 50 (5, 1), 46 (5, 1), 44 (21, 23), 41 (5, 2), 39 (13, 7). The following ir spectrum (chloroform solution) of **4** is similar to but distinctly different from that of **3**: 3584 (w, sharp), 3322 (broad), 3003 (s), 2933 (m), 1621 (s), 1504 (m), 1481 (m), 1453 (m, sharp), 1397 (s, sharp), 1350 (w), 1190 (w), 1119 (w), 1071 (m), 1042 cm^{-1} (sh). Nmr: τ 2.6–3.8 (m, 6 H, aromatic and NHOH) and 7.0 (three sharp peaks, separated by about 1 Hz, 6 H, methyls). There is no discernible absorption at about τ 5.75 where the corresponding amine exhibits a peak for amine protons.

Conversion of o-Hydroxylamino-N-N-dimethylbenzamide (4) to 2,1-Benzisoxazolone (5).—A sample of **4** (148.7 mg, 0.825 mmol) was added in one portion to 8.3 ml (0.83 mmol) of *ca.* 0.1 *N* sodium hydroxide solution which was maintained at 23° in a water bath; it dissolved within 1.3 min to give a golden yellow solution. The solution was stirred for an additional 3.2 min, cooled to 10° during 2 min, and made slightly acidic with 18% hydrochloric acid. The white precipitate was immediately removed by filtration and placed under vacuum in a desiccator (dry weight 48.1 mg, mp 104–109° dec) and the filtrate was rapidly extracted with ether (two 5-ml portions). Evaporation of the dried ($MgSO_4$) ether extract yielded 21.7 mg of tan crystals, recrystallization of which from ethanol–water (with noticeable handling losses) gave 8.6 mg of white crystals, mp 106–111° dec (lit.[10] mp for 2,1-benzisoxazolone 112° dec). The combined yield of this fairly pure material is thus 51%: ir ($CHCl_3$) 3311 (w), 3040 (w), 1773 (s), 1751 (s), 1610 (w), 1513 (w), 1473 (w), 1330 (w), 1297 (w), 1149 (w), 1111 (w), 1040 cm^{-1} (m); nmr ($CDCl_3$) τ 2.0–2.9 (m, 4 H, aromatic) and 1.17 (s, broad, 1H, NH); mass spectrum, direct probe, 137 (3.8), 136 (8), 135 (100), 119 (5), 104 (5), 91 (23), 79 (15), 77 (9), 76 (14), 65 (8), 64 (25), 63 (16), 62 (6), 61 (38), 52 (13), 51 (10), 50 (13), 39 (7), 38 (10), 37 (6).

A rapidly prepared solution of the hydroxylamine **4** in D_2O was scanned from 1800 to 1300 cm^{-1} six times over a period of 30 min; the spectra were the same and quite consistent with uncleaved amide: 1616 (vs, sharp), 1540–1440 (broad envelope containing several peaks), 1412 cm^{-1} (w). An entirely different ir spectrum was exhibited by the same material dissolved in 0.1 *N* NaOD in D_2O and it did not change with time; the strongest peaks are considerably broader and less well defined than those in the nonbasic case and they are found at 1625, 1612, 1597, and 1581 cm^{-1}; in addition there is a broad envelope from 1600 to 1350 cm^{-1} which contains peaks at 1570–1550, 1484, 1460, 1412, and 1381 cm^{-1}. The spectrum of 2,1-benzisoxazolone in the

(16) T. Cohen, R. M. Moran, and G. Sowinski, *J. Org. Chem.*, **26**, 1 (1961).

(17) Sadtler Standard Spectra, No. 2703, Sadtler Research Laboratories, Inc., Philadelphia, Pa.

(18) J. M. Sugihara and S. R. Newman, *J. Org. Chem.*, **21**, 1445 (1956).

(19) A. F. Isbell and H. R. Henze, *J. Amer. Chem. Soc.*, **66**, 2096 (1944).

same solution is very similar, but cleaner (of course, the absorptions for dimethylamine would be absent from the latter solution): 1631, 1598, 1551, 1486, 1455, 1380, and 1339 cm^{-1}. It seems clear that the latter two solutions contain sodium *o*-hydroxylaminobenzoate.

Alkaline Hydrolysis of *N*,*N*-Dimethylbenzamide.—A solution of 152.5 mg (1.022 mmol) of *N*,*N*-dimethylbenzamide dissolved in 1 equiv of the same solution of NaOH used for the cleavage of 4 was left at room temperature (*ca.* 23°) for 432 hr and then extracted with CH_2Cl_2 (eight 5-ml portions). The dried extract yielded 85.5 mg (56%) of residue, the infrared spectrum of which was identical with that of the starting amide.

***N*-Acetyl-2,1-benzisoxazolone.**—Acetyl chloride (5 drops) was added to a solution of 18 mg (0.13 mmol) of 2,1-benzisoxazolone in 10 drops of dioxane. The solution was gently warmed over a flame and then cooled. Water was added (crystals formed) and the mixture was extracted with ether. The residue from evaporation of the ether was precipitated from an alcoholic solution with water to give 9.4 mg (44%) of white crystals: mp 116–118° (lit.[10] mp 117.5–118.5°); ir ($CHCl_3$) 3040 (w), 1786 (s), 1704 (s), 1613 (w), 1477 (m), 1464 (s), 1379 (s),1350 (m), 1332 (s), 1299 (w), 1153 (w), 1112 (w), 1074 (w), 1042 (w), 980 cm^{-1} (m, broad); mass spectrum, direct probe (since the peak at *m/e* 43, the acetyl cation, was extremely intense and off-scale, the values in parentheses are percentages of the 135 peak) 178 (6.3), 177 (53.1), 136 (21), 135 (100), 104 (28), 91 (32), 79 (95), 77 (14), 76 (65), 75 (16), 74 (17), 64 (49), 63 (37), 62 (16), 52 (52), 51 (24), 50 (73), 44 (97), 43 (off scale).

Reduction of 2,1-Benzisoxazolone.—2,1-Benzisoxazolone (65.8 mg, 0.488 mmol) was added in small portions to a slurry of 4.1 mg of 10% Pd/C in a solution of 97 mg (2.6 mmol) of sodium borohydride in 3.2 ml of water and 0.28 ml of methanol in an ice bath. After the solution had been stirred for 15 min, the catalyst was removed by filtration, the basic solution was extracted with chloroform (five 1-ml portions), acidified to *ca.* pH 3 with 18% hydrochloric acid, and then extracted again. Evaporation of the solvent from the combined, dried ($MgSO_4$) extract left 50.0 mg (76%) of off-white crystals, mp 143–147°, the infrared spectrum of which matched that reported[17] for anthranilic acid. Sublimation at 100° (0.5 Torr) yielded material of mp 146.5–147.0 (lit.[18] mp 144.9–145.4°; lit.[19] mp 144–145°).

Registry No.—**1,** 2018-71-5; **2,** 118-92-3; **3,** 6526-66-5; **4,** 33047-10-8; **5,** 31499-90-8; **5** *N*-acetyl derivative, 33047-12-0.

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The Reaction Rates of Alkyl Dihydroxybenzoates in a Nucleophilic Fused Salt[1]

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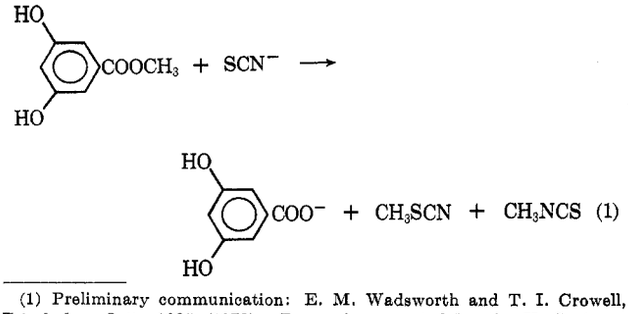
Methyl and ethyl 3,5-dihydroxybenzoates, in molten potassium–sodium thiocyanate eutectic, react by a pseudo-first-order $B_{Al}2$ displacement on the alkyl group to form alkyl thiocyanates and isothiocyanates. The methyl ester, which reacts 49 times as fast as the ethyl at 150°, shows an activation energy of 26 kcal/mol. The product compositions are 96% MeSCN, 4% MeNCS and 54% EtSCN, 46% EtNCS. Methyl 2,4-dihydroxybenzoate reacts similarly except that the 2,4-dihydroxybenzoate ion immediately decarboxylates, evolving 0.5 mol of carbon dioxide per mole of ester and following the rate equation $\ln a/(a - 2x) = 2kt$. Neither the *o*-hydroxyl group nor the decarboxylation accelerates the displacement, as this ester reacts slightly more slowly than the 3,5-dihydroxy compound. The isotope effect is small ($k_{OH}/k_{OD} = 0.97$).

Noting the high nucleophilicity and low melting point of potassium thiocyanate, we initiated a study of nucleophilic displacement reactions in this molten salt, an ionic, aprotic medium which represents the upper concentration limit of a solution. Suitable substrates, undergoing simple displacement reactions with moderate rates at elevated temperatures and containing hydroxyl groups to confer solubility by hydrogen bonding with the solvent[2] are difficult to devise. Benzoic esters with two phenolic hydroxyl groups, however, have these properties. For example, methyl 3,5-dihydroxybenzoate reacts with thiocyanate ion with alkyl–oxygen cleavage, of the type[3] $B_{Al}2$ (eq 1).



Nucleophilic displacements at the saturated carbon atom in ester hydrolysis or alcoholysis can be observed only under the following conditions: (1) special structural features favor alkyl–oxygen cleavage as in the reaction of β-lactones with water[4] or methanol;[5] (2) the competing attack at the carbonyl group ($B_{Ac}2$) is hindered as in methyl 2,4,6-tri-*tert*-butyl benzoate[6] or is designed to be a symmetrical transesterification;[7] (3) the nucleophile is unreactive toward carbonyl groups. The very few examples of this last case include the cleavage of simple methyl esters by trimethylamine[8] and by lithium halides in pyridine[9a] or 2,4,5-collidine.[9b] Thiocyanate ion also belongs to this small group of nucleophiles preferentially attacking the carbon atom of the alkyl group in esters, effecting a slow displacement of the carboxylate ion. Packham and

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