C_5H, C_5H'), 3.08 (octet, C_5H'); the O and N are considered to be trans; mass spectrum *m/e* (rel intensity) 242 (26), 186 (22), 161 (98), 160 (100), 103 (90), 82 (46), 77 (49), 55 (19); ir 3.5–4.7 and 5.2–6.1 (H bond), 2.8 μ (OH).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.79; N, 11.57. Found: C, 69.55; H, 5.93; N, 11.47.

1-Cyclopentyl-3-phenyl-5-hydroxypyrazole (13).—A mixture of 4.0 g (0.0018 mol) of **4** and 0.1 g of 5% platinum on charcoal was stirred in 95% ethanol under hydrogen at 1 atm and 23°. Hydrogen uptake ceased at 440 ml after 5 hr. After filtration of the catalyst and evaporation of the solvent, 3.8 g (95%) of the solid **13** was obtained. A recrystallization of the product from a benzene–ethanol mixture gave an analytical sample: mp 207–208°; pmr ($CDCl_3$) δ 7.20–7.84 (m, C_3 C_6H_5), 5.81 (s, pyrazole C_4H), 4.68 (m, cyclopentyl C_1H), 1.98 (m, cyclopentyl methylenes); mass spectrum *m/e* (rel intensity) 228 (22), 173 (73), 160 (100), 103 (7), 77 (7); ir 3.5–4.7 and 5.2–6.1 μ (H bond).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.87; H, 6.82; N, 12.08.

8-Phenyl-1,4-methano-1,2,3,4-tetrahydropyrazolo[1,2-*a*]-pyridazin-6-one (15).—The title compound was prepared by the previously reported procedure,[6] mp 149–151° (lit.[6] mp 148–149°).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.34; H, 6.29; N, 12.39. Found: C, 74.30, H, 6.30; N, 12.60.

Registry No.—**4**, 14181-57-8; **5**, 34347-69-8; **6**, 34347-70-1; **7**, hydroxyl, 34347-71-2; **7**, oxo, 34347-79-0; **8**, hydroxyl, 34347-72-3; **8**, oxo, 34347-80-3; **9**, 34347-73-4; **10**, 34347-74-5; **11**, 34347-75-6; **13**, 34347-76-7; **14**, 34347-81-4; **15**, 14181-60-3.

Acknowledgment.—The authors wish to acknowledge the assistance of the National Science Foundation in providing the Department with a Cary 14 spectrophotometer.

Mechanism of the Transformation of 2,4-Dihydroxy-1,4-benzoxazin-3-ones and 2-Hydroxy-2-methyl-4-methoxy-1,4-benzoxazin-3-one to 2-Benzoxazolinone

EDWARD E. SMISSMAN,* MICHAEL D. CORBETT,[1] NEIL A. JENNY, AND ODD KRISTIANSEN

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

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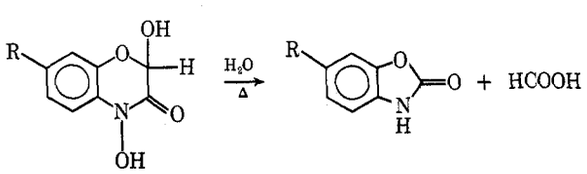
The formation of 2-benzoxazolinones from 2,4-dihydroxy-1,4-benzoxazin-3-ones and from 2-hydroxy-2-methyl-4-methoxy-1,4-benzoxazin-3-one is discussed. A previously proposed mechanism is criticized and a plausible mechanism is offered.

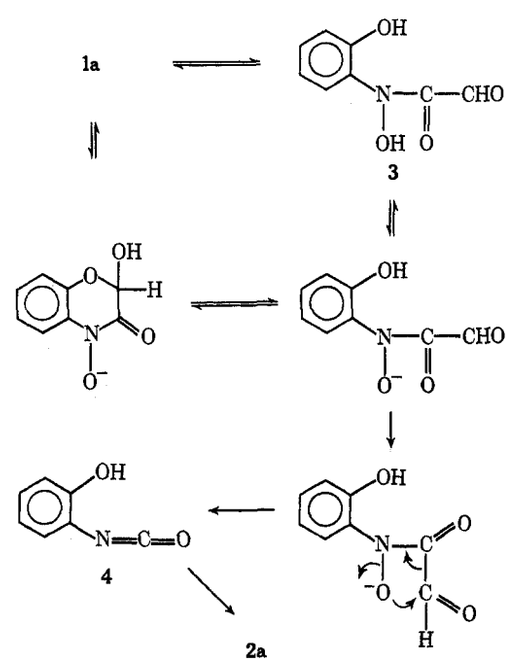
To date, the only reported hydroxamic acids from higher plants are those which are derivatives of 2,4-dihydroxy-1,4-benzoxazin-3-one (**1a**).[2] These compounds and products obtained from their rearrangement have been termed "Resistance Factors," since they are found in several varieties of crop plants and exhibit antifungal and insectistat properties.[3,4]



1 **2**

a, R = H
b, R = OCH_3

When **1** is heated in aqueous or alcoholic solution, the corresponding 2-benzoxazolinone (**2**) is rapidly formed with the liberation of formic acid, which has been established to arise from C-2.[5] The conversion of **1a** to **2a** was proposed to proceed *via* the isocyanate **4**.[6] This mechanism assigns no role to the phenolic hydroxyl group prior to the cyclization step (**4** → **2a**). Therefore, it would be assumed that isocyanate formation would occur independent of the presence of the phenolic hydroxyl function.



Under the conditions utilized for the formation of 2-benzoxazolinone (**2a**) from 2,4-dihydroxy-1,4-benzoxazin-3-one (**1a**), neither *N*-phenylglyoxylohydroxamic acid (**5**) nor *N*-phenyl-α,α-dichloroacetohydroxamic acid (**6**) gave the product expected from an isocyanate intermediate. *N*-Phenylglyoxylohydroxamic acid (**5**) could be transformed to aniline in 36% yield when it was refluxed with aqueous sodium bicarbonate solution, and a small amount of *sym*-diphenylurea (**7**) was isolated from *N*-phenyl-α,α-dichloroacetohydroxamic acid (**6**) after treatment with aqueous sodium hydroxide at room temperature. The products obtained would be

(1) Taken in part from the dissertation presented by M. D. Corbett, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) R. T. Coutts, *Can. J. Pharm. Sci.*, **2**, 27 (1967).

(3) S. D. Beck and E. E. Smissman, *Ann. Entomol. Soc. Amer.*, **54**, 53 (1961).

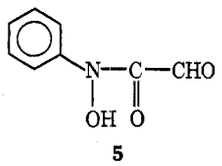
(4) J. A. Klun and T. A. Brindley, *J. Econ. Entomol.*, **59**, 711 (1966).

(5) E. Honkanen and A. I. Virtanen, *Acta Chem. Scand.*, **15**, 221 (1961).

(6) J. Bredenberg, E. Honkanen, and A. I. Virtanen, *ibid.*, **16**, 135 (1962).

expected to arise from the normal hydrolysis of hydroxamic acids.[7] These findings also indicate that the breakdown of the hydroxamic acid **5** requires more drastic conditions than those involved in the transformation of 2,4-dihydroxy-1,4-benzoxazin-3-one (**1a**) to 2-benzoxazolinone (**2a**).

The possibility that the phenolic hydroxyl of the ring-opened compound **3** or the ether oxygen of the parent compound **1** could participate in the rearrangement led to an investigation of other plausible mechanisms. It was found that the oxidized analog of **1a**, 4-hydroxy-1,4-benzoxazine-2,3-dione (**8**), also rearranged to the benzoxazolinone **2a**. Thus the hydroxamic acid **9**,[8] which can be considered to be an open-chain analog of **8** with the phenolic hydroxyl protected as an ether, was subjected to rearrangement conditions. This compound was stable to continuous heating at 70° in either water or ethanol and further demonstrates the need for a free phenolic hydroxyl to facilitate the reaction. The possibility that the ring oxygen in **1a** and **8** is only involved by its role in increasing the electron density at the hydroxamate nitrogen is eliminated by the failure of this reaction to proceed, since the phenolic ether would be expected to have an electronic effect similar to that of the free phenolic hydroxyl in **3**. If the only requirement for the transformation to occur is the attack of the hydroxamate hydroxyl on the carbonyl of the open-chain intermediate **3**, one could reasonably expect **9** to decompose in a similar manner to give products derived from the isocyanate **10**.



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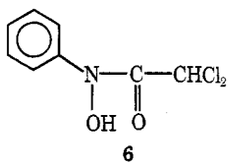

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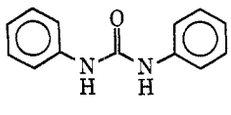

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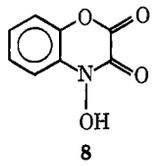

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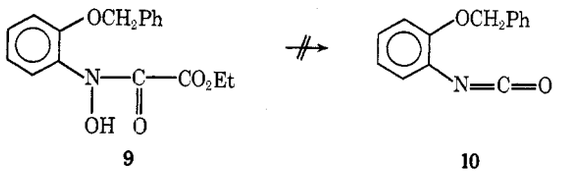


9 **10**

In order to ascertain the role of the N–O bond in the rearrangement, 2-methyl-2,4-dihydroxy-1,4-benzoxazin-3-one (**11**) and 2-methyl-2-hydroxy-4-methoxy-1,4-benzoxazin-3-one (**12**) were prepared by the sequences depicted in Schemes I and II, respectively.

The hydroxamic acid **11** was difficult to purify, since it decomposed readily to 2-benzoxazolinone (**2a**) as expected. However, its positive ferric chloride test, spectral characteristics, and hydrogenolysis to the lactam **16**, which is stable, gave proof for its structure. The rates of decomposition of **1a** and **11** appear to be similar.

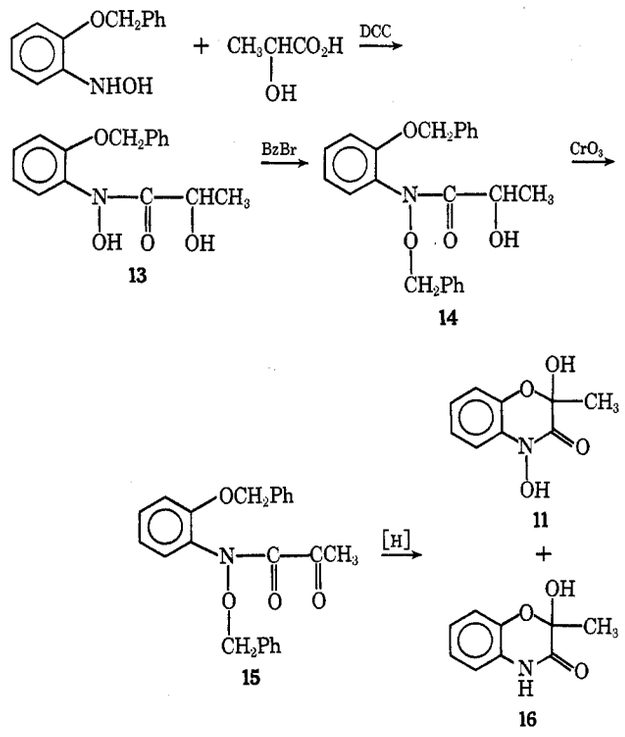
The lactam **16** was found to be stable to prolonged heating in hydroxylic solvents. This indicates that the hydroxamate oxygen is of definite importance to the decomposition reaction.

Heating the hydroxamate methyl ester **12** in water at 55° causes rapid decomposition to 2-benzoxazolinone (**2a**) with the loss of acetic acid. The decomposition of **12** followed first-order kinetics with a half-life of 24 min. This is a faster rate than that for the decomposition of **1a**.[6]

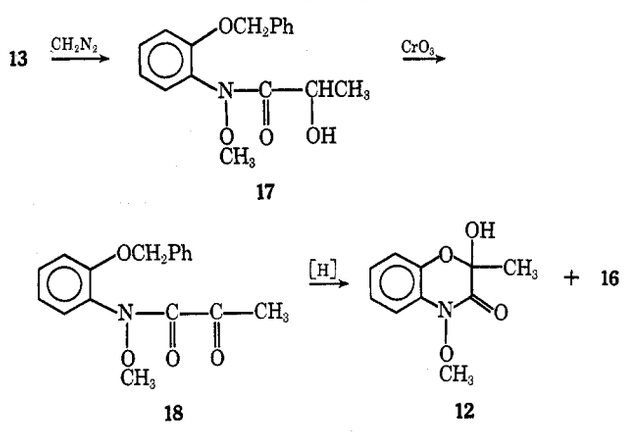
The decomposition of **12** to **2a** did not proceed *via* demethylation to **11**. This was established by the absence of color development when a concentrated ethanolic solution of **12** containing 2% ferric chloride was heated at 50°.

The observed stabilities of the hydroxamic acids **5**, **6**, and **9** indicates that a phenolic hydroxyl group is involved in the decomposition of **1a**, **11**, and **12** to **2a**. The necessity of the hydroxamic acid hydroxyl and a carbonyl group α to the hydroxamate system in order for the rearrangement to occur had been reported previously[6] and was supported by the results obtained in this investigation.

SCHEME I



SCHEME II



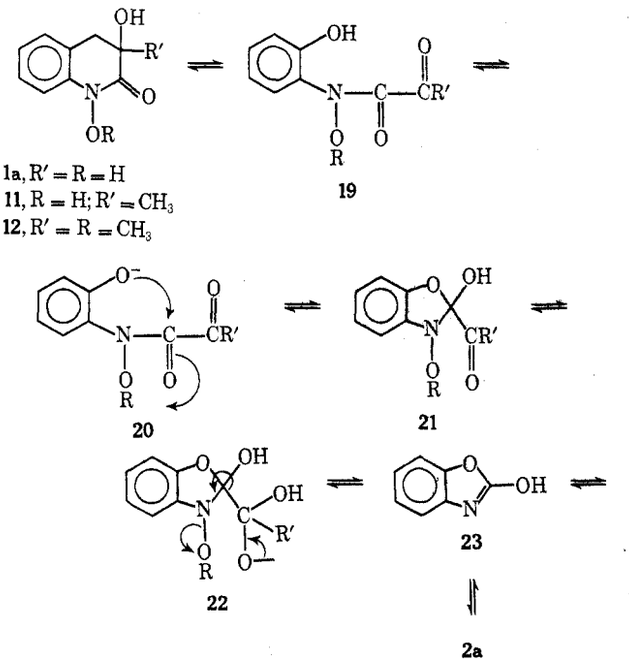
(7) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966.

(8) E. E. Smissman and M. D. Corbett, *J. Org. Chem.*, **37**, 1847 (1972).

The observation which negates the mechanism proposed originally[6] is the fact that the methyl ester **12** undergoes decomposition to **2a** even more rapidly than do the free hydroxamic acids **1a** and **11**.

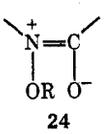
Based on the above findings a more plausible mechanism for this decomposition is offered (Scheme III).

SCHEME III



In this mechanism, intermediate **21** is in equilibrium with the parent benzoxazine system through the open forms **19** and **20**. The equilibrium concentration of **21** would be expected to be quite low. The attack of hydroxide ion or water on the carbonyl carbon of **21** followed by the loss of an acid anion with a concomitant displacement of –OR from nitrogen in **22** would afford **23**, a tautomer of **2a**. Such a transformation is analogous to eliminative decarboxylation.

In this mechanism no intermediate isocyanate is involved. The rate-determining step is the attack of hydroxide ion at the carbonyl group of **21**, followed by a rapid loss of an acid anion. The intermediate **21** is proposed as the rate-determining species, since it is observed that the methyl ester **12** decomposes more rapidly than **1a** or **11**. The concentration of **21** would be expected to be greater when R = methyl than when R = H, since there would be a lower contribution of the resonance form **24**. When R = H, this charge-



24

separated species is stabilized by intramolecular hydrogen bonding, whereas when R = methyl this cannot occur. The decreased contribution of resonance **24** would allow for increased interaction of the phenolic hydroxyl group with the hydroxamate carbonyl function to give **21**.

The hydroxyl or alkoxy group on the hydroxamate nitrogen serves only as a facile leaving group and not a nucleophilic function.

Further investigations of the kinetics of this decomposition with regard to the alkyl or aryl substituent at C-2 and the nature of the leaving group at N-4 are underway.

Experimental Section[9]

***N*-[*o*-(Benzyloxy)phenyl]lactohydroxamic Acid (13).**—To 85% lactic acid (6.3 g, 0.06 mol) dissolved in 20 ml of THF and cooled to −25° was rapidly added dicyclohexylcarbodiimide (14.4 g, 0.07 mol) in 30 ml of THF. The cold solution was stirred until a precipitate began to form, after which *o*-(benzyloxy)phenylhydroxylamine (6.0 g, 0.028 mol) in 40 ml of THF cooled to −25° was added in several portions in the course of 2 min. The mixture was stirred and cooled for 1 hr and allowed to warm to 25°. The mixture was filtered and the solid was washed with 100 ml of Et_2O. The combined filtrates were cooled by the addition of ice and extracted twice with 30 ml of ice-cold 5% NaOH. The combined base extracts were washed with 50 ml of Et_2O and carefully neutralized at 0° with 3 *N* HCl. This aqueous mixture was extracted twice with 50 ml of Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and the solvent was removed to give a dark oil which crystallized from Et_2O to give an amorphous gray solid. Recrystallization (Me_2CO–Et_2O) gave 2.5 g (29%) of **13** as a white, amorphous solid: mp 114.5–116.0°; violet color with $FeCl_3$ in EtOH; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.93; H, 6.25; N, 4.78.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-benzyllactohydroxamic Acid (1).**—*N*-[*o*-(Benzyloxy)phenyl]lactohydroxamic acid (**13**, 4.6 g, 0.016 mol), benzyl bromide (3.1 g, 0.018 mol), and anhydrous K_2CO_3 (2.2 g, 0.016 mol) in 120 ml of Me_2CO were stirred under N_2 and heated to reflux for 6 hr. The solvent volume was reduced to 50 ml and the residue was shaken with 150 ml of Et_2O and 60 ml of H_2O. The ethereal solution was dried (Na_2SO_4) and the solvent was removed to produce an oil which crystallized from Et_2O to give 4.9 g (82%) of **14** as white crystals, mp 89.5–91.4°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.14; H, 6.30; N, 3.56.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-benzylpyruvohydroxamic Acid (15).**—To *N*-[*o*-(Benzyloxy)phenyl]-*O*-benzyllactohydroxamic acid (**14**, 2.3 g, 0.006 mol) in 40 ml of Me_2CO cooled to 5° was added dropwise 8 *N* reagent[10] until the orange color of the oxidant persisted. Excess oxidant was destroyed by the addition of several milliliters of *i*-PrOH. The reaction mixture was combined with 100 ml of Et_2O and washed with 50 ml of H_2O, 50 ml of 5% $NaHCO_3$, and 50 ml of H_2O. The solution was dried (Na_2SO_4) and the solvent was removed to yield an oil which crystallized from EtOH to give 1.8 g (80%) of white needles, mp 86.5–88.0°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.59; H, 5.64; N, 3.73. Found: C, 73.28; H, 5.78; N, 3.38.

2,4-Dihydroxy-2-methyl-1,4-benzoxazin-3-one (11).—*N*-[*o*-(Benzyloxy)phenyl]-*O*-benzylpyruvohydroxamic acid (**15**, 0.75 g, 0.002 mol) was hydrogenated at 25° under 1-atm pressure in 30 ml of EtOH with 500 mg of 5% Pd/C as the catalyst. The reaction was stopped after the consumption of the theoretical amount of H_2 (0.004 mol). The catalyst was removed by filtration and the solvent was removed to give a thick oil. Chromatography on 40 g of silica gel gave **11** as the last component off the column. Removal of $CHCl_3$ gave a brown solid. Recrystallization (Et_2O–C_6H_6) yielded 20 mg (5.2%) of **11** as a white, amorphous solid, mp 132–135°, blue color with $FeCl_3$ in EtOH; spectral data are consistent with the assigned structure but the elemental analysis was not within the acceptable limits because of a small amount of an unknown colored contaminant

(9) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and *HA-100* spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 144.

which could not be removed. Compound **11** could be converted to **16** by further hydrogenolysis.

Fractions immediately preceding those containing **11** yielded **2-hydroxy-2-methyl-1,4-benzoxazin-3-one** (**16**) as a brown solid. Recrystallization (EtOH–C_6H_6) gave fine white crystals (35 mg, 10%), mp 186.5–188°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.61; H, 4.99; N, 7.72.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-methyllactohydroxamic Acid** (**17**).—Approximately 1.4 g (0.033 mol) of ethereal CH_2N_2 was generated and added to a solution of *N*-[*o*-(benzyloxy)phenyl]-lactohydroxamic acid (**13**, 2.0 g, 0.007 mol) in 50 ml of Et_2O which was cooled in an ice bath. The yellow solution was maintained at 0–4° until the evolution of N_2 ceased and the yellow solution was allowed to stand at 25° for 2 hr. Several drops of HOAC were added to the solution to ensure that all the CH_2N_2 had been destroyed. An additional 50 ml of Et_2O was added and the solution was washed with 20 ml of cold 5% NaOH and twice with 30 ml of H_2O. The solution was dried (Na_2SO_4) and the solvent was removed to give an oil which crystallized from 10 ml of Et_2O to give 1.8 g (85%) of **17** as white crystals, mp 86.5–88.0°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.64. Found: C, 67.61; H, 6.65; N, 4.84.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-methylpyruvohydroxamic Acid** (**18**).—To *N*-[*o*-(benzyloxy)phenyl]-*O*-methyllactohydroxamic acid (**17**, 1.6 g, 0.0054 mol) in 20 ml of Me_2CO cooled to 5° was added dropwise 8 *N* Jones reagent until the orange color of the oxidant persisted. Excess oxidant was destroyed by the addition of several milliliters of *i*-PrOH. The reaction mixture was combined with 100 ml of Et_2O and washed with 80 ml of H_2O, 30 ml of 5% $NaHCO_3$, 40 ml of H_2O, and 30 ml of saturated NaCl solution. The organic solution was dried (Na_2SO_4) and the solvent was removed to give 1.2 g (92%) of **18** as an oil; spectral data are consistent with the assigned structure.

2-Hydroxy-2-methyl-4-methoxy-1,4-benzoxazin-3-one (**12**).—*N*-[*o*-Benzyloxy)phenyl]-*O*-methylpyruvohydroxamic acid (**18**, 1.2 g, 0.004 mol) was hydrogenated at 25° under 1-atm pressure with 500 mg of 5% Pd/C as the catalyst and 60 ml of 95% EtOH as the solvent. The reaction was stopped after the consumption of the theoretical amount of H_2 (0.004 mol). The catalyst was removed by filtration and the solvent was distilled to produce an oil which crystallized from C_6H_6 to give 0.40 g (40%) of **12** as a white solid. Recrystallization (Et_2O) gave white crystals, mp 119.0–121.5°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.23; H, 5.02; N, 6.55.

Degradation of *N*-Phenyl-α,α-dichloroacetohydroxamic Acid (**6**) **and *N*-Phenylglyoxylohydroxamic Acid** (**5**) **under Basic Conditions. A. Preparation of *N*-Phenyl-α,α-dichloroacetohydroxamic Acid** (**6**).—To a solution of 53 g (0.486 mol) of phenylhydroxylamine in 600 ml of anhydrous Et_2O was added in small portions 40 g (0.272 mol) of dichloroacetyl chloride in 75 ml of anhydrous Et_2O. The reaction temperature was maintained at 0–5° while the mixture was allowed to stand for 30 min after the last portion of acetyl chloride had been added. A dark precipitate was removed by filtration and the filtrate was extracted with 1 l. of 3% aqueous $NaHCO_3$. The Et_2O solution was dried ($MgSO_4$) and the solvent was removed to yield 55.8 g (93%) of a yellow solid. The product was recrystallized from a mixture of petroleum ether (bp 60–68°) and Et_2O to give long, white needles, mp 90.5–91°. The ferric chloride test gave an intense red color. Spectral data are consistent with the assigned structure.

Anal. Calcd for $C_8H_7NO_2Cl_2$: C, 43.66; H, 3.31; N, 6.37. Found: C, 43.91; H, 2.92; N, 5.89.

B. Preparation of *N*-Phenylglyoxylohydroxamic Acid (**5**).—To 250 ml of 1.5 *N* aqueous NaOH was added 13.20 g (0.06 mol) of *N*-phenyl-α,α-dichloroacetohydroxamic acid (**6**) at such a rate that the temperature did not rise above 30°. After standing for 2 hr the reaction mixture was extracted with 250 ml of Et_2O (ether extract I). The aqueous phase was acidified with 10% hydrochloric acid and extracted with 6 l. of Et_2O (ether extract II).

Ether extract II was concentrated until a precipitate started to form. The solution was cooled and the precipitate was filtered to yield 1.42 g (14.3%) of a white, crystalline material. The substance gave a positive ferric chloride test. Recrystallization (Et_2O) gave a product with mp 169.5–171°.

Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.05. Found: C, 58.28; H, 4.06; N, 8.30.

Ether extract I was extracted with 5% aqueous HCl. The neutral reaction products remained in the organic phase (ether extract Ia). The basic products were recovered from the aqueous phase by addition of 10% aqueous NaOH until basic and subsequent extraction with ether (ether extract Ib).

Ether extract Ia was evaporated to dryness. The residue consisted of 1.4 g of a brown oil which was purified by chromatography on a neutral aluminum oxide column (2.2 × 27.0 cm) with elution by the following solvent sequence: 100 ml of petroleum ether (fraction 1); 50 ml of petroleum ether (fraction 2); 75 ml of petroleum ether–C_6H_6 (1:1) (fraction 3); 50 ml of petroleum ether–C_6H_6 (1:1) (fraction 4); 100 ml of C_6H_6 (fraction 5); and 50 ml of Et_2O (fraction 6).

Fraction 2 was identified as nitrobenzene by reduction with tin and hydrochloric acid to aniline.

Fraction 3 was identified as azoxybenzene by its melting point and by reduction with magnesium and ammonium chloride to azobenzene.

Fraction 4 was characterized as azobenzene.

Fraction 6 was identified as *sym*-diphenylurea by mixture melting point and from its ultraviolet spectrum.

Ether extract Ib yielded 144 mg of yellow oil after evaporation of solvent. The product gave a crystalline derivative with benzoyl chloride, mp 157–158°, which caused no depression of melting point when mixed with benzanilide.

C. Degradation of *N*-Phenylglyoxylohydroxamic Acid (**5**) **in 5% Aqueous Sodium Bicarbonate Solution.**—Compound **5** (300 mg, 0.018 mol) was dissolved in 150 ml of 5% aqueous $NaHCO_3$ solution. The mixture was brought to boiling and water and steam-volatile materials were allowed to distil. The liquid volume was kept constant by gradual addition of water and a steady stream of nitrogen was through the apparatus during the reaction. The distillation was continued until all steam-volatile materials had been removed. Concentrated HCl was added to the aqueous suspension of the steam-volatile fraction until the HCl concentration reached 5%. The mixture was then extracted with 200 ml of Et_2O. The extract was dried ($MgSO_4$) and the solvent was removed. The residue consisted of 20 mg of yellow oil which was identified as nitrobenzene by reduction to aniline. The acidic, aqueous solution was made alkaline and extracted with 1 l. of Et_2O. The Et_2O solution was washed and dried and the solvent was evaporated to yield 61 mg (36%) of aniline, characterized as benzanilide.

Stabilities of Analogs in Hydroxylic Solvents.—Uv absorption spectra (Table I) were obtained on a Beckman Model DB recording spectrophotometer.

TABLE I

Compd	Solvent	Maxima, mμ	ε
11	H_2O	280	4700
		254	7300
16	H_2O	278	3800
		251	6900
12	H_2O	278	3300
		253	5800

No change in the uv spectra of compound **16** was observed after heating at 55° for at least 4 hr. The uv spectra of compounds **11** and **12** changed rapidly on heating to give a different absorption curve with maximum absorption at 270 mμ (2-benzoxazolinone λ_{max} = 270 mμ). 2-Benzoxazolinone (**2a**) was isolated from heated solutions of **11** and **12**, and identified by comparison of its ir spectrum with that of authentic 2-benzoxazolinone (**2a**).

A kinetic analysis of the decomposition of **12** was performed at 40°. The decrease in absorption at 253 mμ was recorded for a period of 6 hr. The reaction follows first-order kinetics for the first 40 min in Sorenson's phosphate buffer (pH 7.0)[11] with a half-life computed to be 24 min.

Registry No.—**2a**, 59-49-4; **5**, 34282-43-4; **6**, 34282-

(11) K. Diem and C. Lentner, "Documenta Geigy," J. R. Geigy S. A., Basle, 1970, p 280.

44-5; **11**, 34282-45-6; **12**, 34282-46-7; **13**, 34282-47-8; **14**, 34282-48-9; **15**, 34282-49-0; **16**, 34282-50-3; **17**, 34282-51-4; **18**, 34282-52-5.

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The Syntheses of 4-Acylamido-1,4-benzoxazine-2,3-diones and 4-(*p*-Toluenesulfonamido)-1,4-benzoxazine-2,3-dione

EDWARD E. SMISSMAN* AND MICHAEL D. CORBETT[1]

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

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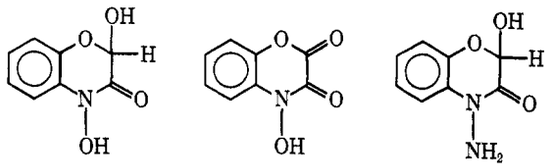
A general synthetic method for the synthesis of 4-acylamido-1,4-benzoxazine-2,3-diones (**8**) is described. Ortho-substituted hydrazines can be prepared by acid hydrolysis of the appropriate mesoionic sydnone. *o*-Benzyloxyphenylhydrazine hydrochloride (**4**) was prepared in this manner and acylated on the terminal nitrogen. The 1-(*o*-benzyloxyphenyl)-2-acylhydrazine (**5**) was treated with ethyl oxalyl chloride to give 1-(*o*-benzyloxyphenyl)-1-ethyloxalyl-2-acylhydrazine (**6**) which on hydrogenation afforded **8**. The synthesis of 4-(*p*-toluenesulfonamido)-1,4-benzoxazine-2,3-dione (**20**) was accomplished by the addition of sodium *p*-toluenesulfinite to the diazonium salt prepared from *o*-benzyloxyaniline. The resulting diimide **17** was reduced to the corresponding hydrazine **18**, which was treated with ethyl oxalyl chloride to afford 1-(*o*-benzyloxyphenyl)-1-ethyloxalyl-2-(*p*-toluenesulfonyl)hydrazine (**19**). This compound on hydrogenolysis of the benzyl protecting group cyclized to give **20**.

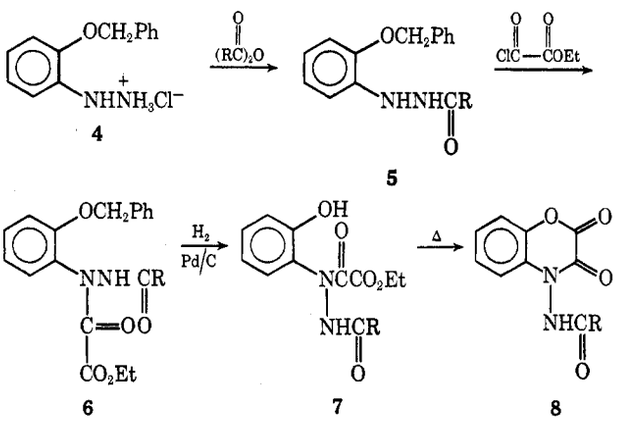
In view of the interesting chemistry and biological activity of the naturally occurring hydroxamic acids having the basic structure 2,4-dihydroxy-1,4-benzoxazin-3-one (**1**),[2-4] a study of the 4-amino analogs **3** and their derivatives was initiated.



1 **2** **3**

The preparative procedure utilized the acylation of *o*-benzyloxyphenylhydrazine (**4**) with either acetic anhydride or trifluoroacetic anhydride to afford the monoacylhydrazides **5a** and **5b**. The monoacylation of phenylhydrazines with anhydrides has been shown to occur at the terminal nitrogen.[5] The treatment of **5a** and **5b** with ethyl oxalyl chloride afforded the diacyl hydrazides **6a** and **6b**, respectively. Hydrogenolysis of **6a** produced a single product as determined by tlc analysis on silica gel. A crystalline compound, **8a**, was obtained when the oil produced by the hydrogenolysis of **6a** was heated in benzene. The nmr spectrum of the oil is consistent with structure **7**.

In the above sequence *o*-benzyloxyphenylhydrazine (**4**) was required as a starting material. *o*-Benzyloxyaniline hydrochloride (**9**) was prepared and converted to the corresponding diazonium salt, but the conventional method for the reduction of diazonium salts utilizing stannous chloride was found to be inapplicable in this case. Ek and Witkop[6] have also reported an unsuccessful attempt to reduce this diazonium salt



4 **5** **6** **7** **8**

a, R = CH_3
b, R = CF_3

by the stannous chloride method, but Clerc-Bory[7] reported that this method gave a 72% yield of the desired product. Clerc-Bory also reported the melting point of this material to be 191°, which is 43° higher than the melting point of the product we obtained by an alternate route. Utilizing stannous chloride we also obtained a material melting at 191° but it would not undergo acylation with acetic anhydride.

The acidic hydrolysis of mesoionic sydnones provided an alternate route for the preparation of ortho-substituted hydrazines.[8,9] 3-(*o*-Benzyloxyphenyl)sydnone (**12**) was prepared in good yield by cyclization of the nitroso intermediate **11**. This cyclization was found to proceed readily with the use of trifluoroacetic anhydride, while other dehydrating agents gave lower yields of **12**.[10] The hydrolysis of **12** with hot aqueous hydrochloric acid was accompanied by considerable tar formation, but, when dioxane–water was employed as the solvent, hydrolysis proceeded rapidly at room temperature with a minimum of decomposition.

The hydrazides **8** are the amino analogs of 4-hydroxy-1,4-benzoxazine-2,3-dione (**2**) which has properties

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