Ester.—To a solution of benzoylphenylalanine N-hydroxysuccinimide ester (240 mg, 0.66 mmol) in 20 ml of tetrahydrofuran at 0°, hydrazine hydrate (150 mg, 3 mmol) in 5 ml of methanol was added at 0°. Precipitation of product was noted immediately. After 2 hr, the solvent was removed under a stream of nitrogen at room temperature. After addition of water to remove N-hydroxysuccinimide, filtration, and drying over P_2O_5, 160 mg (85%) of chromatographically pure paterial was obtained, $[\alpha]^{25}D$ −45.7° (*c* 1, dimethylformamide).

C. Racemization by Methanol.—Benzoyl-L-phenylalanine succinimide ester (250 mg) was boiled in 20 ml of methanol for 20 min. Evaporation of solvent gave completely racemized starting material as determined by infrared spectroscopy thin layer chromatography, and polarimetry. No methanolysis took place under these conditions.

Benzyloxycarbonyl-L-phenylalanine Succinimide Ester.—The crude product was obtained in 68% yield by the dicyclohexylcarbodiimide method. Recrystallization from ethyl acetate–hexane gave a first crop of 1.8 g (45%) of crystalline material, mp 136–138.5°, $[\alpha]^{25}D$ −21.5° (*c* 1.5, tetrahydrofuran).

Anal. Calcd for $C_{21}H_{20}O_6N_2$: C, 63.63; H, 5.08; N, 7.07. Found: C, 63.53; H, 5.33; N, 6.93.

Racemization by Methanol.—The succinimide active ester (250 mg) was boiled for 20 min in methanol and then the solvent was removed at room temperature. The product was washed with hexane and filtered. Infrared and thin layer analyses showed no methanolysis, $[\alpha]^{25}D$ −19.4° (*c* 1.5, tetrahydrofuran).

Instruments and Apparatus.—All measurements of optical activity were made on a Model 80 Rudolph polarimeter equipped with a Model 200A oscillating polarizer. Monochromatic light was obtained by a prism monochromator equipped with an independent Xenon light source (Hanovia 901B). Center-fill, 2-dm polarimeter tubes with a bore of 3 mm in diameter were used (Polarimeter tube type 14, catalogs of O. C. Rudolph and Sons, Caldwell, N. J.). The temperature of the tube compartment was kept constant at 25 ± 0.2° by a circulating pump connected to a constant-temperature bath. The voltage applied to the photoelectric cell was controlled by a Keithley Voltage Supply Model 240.

High-resolution nuclear magnetic resonance spectral measurements were made with the Cary A-60 megacycle instrument at room temperature and resonances are expressed in units relative to tetramethylsilane as an internal standard.

Infrared spectra were determined with a Perkin-Elmer Model 132, 21, or 521 spectrophotometer from Nujol mulls or potassium bromide pellets.

Registry No.—2-Phenyl-L-4-benzyloxazolone, 5874-61-3; benzoyl-L-phenylalanine methyl ester, 3005-61-6; benzoyl-L-phenylalanine hydrazide, 23912-50-7; benzoylphenylalanine *t*-butyloxycarbonyl hydrazide, 23912-51-8; benzoylphenylalanine phenylhydrazide, 23912-53-0; benzoylphenylalanine dimethylhydrazide, 23912-54-1; benzoylphenylalanine *p*-nitrophenylhydrazide, 23912-55-2; benzoyloxycarbonyl-L-phenylalanine *p*-nitrophenylhydrazide, 23912-56-3; L-phenylalanine *p*-nitrophenylhydrazide hydrobromide, 23912-57-4; benzoyl-L-phenylalanine *o*-methoxyphenylhydrazide, 23912-58-5; benzoyloxycarbonyl-L-phenylalanine *o*-methoxyphenylhydrazide, 23912-59-6; L-phenylalanine *o*-methoxyphenylhydrazide hydrobromide, 23912-60-9; benzoylphenylalanine hydroxamic acid, 23912-61-0; benzoylphenylalanine N-hydroxypiperidine ester, 23967-35-3; *o*-(benzoylphenylalanyl)-N,N-diethylhydroxylamine, 23912-62-1; N-methyl-N-(benzoylphenylalanyl)-O-methylhydroxylamine, 23912-63-2; benzoylphenylalanine N-hydroxysuccinimide ester, 23912-64-3; benzyloxycarbonyl-L-phenylalanine succinimide ester, 3397-32-8.

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Reaction of Aldehydes with N-Hydroxybenzenesulfonamide. Acetal Formation Catalyzed by Nucleophiles

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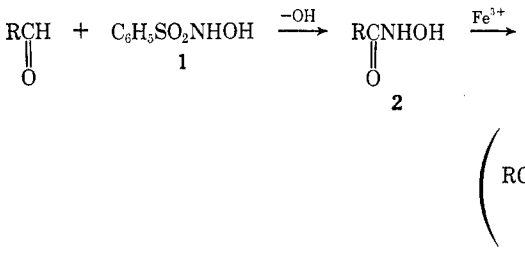
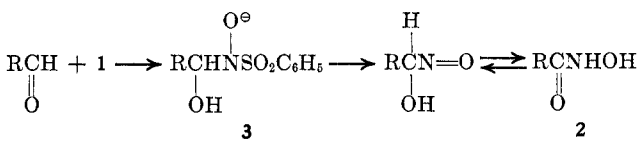
The reaction of N-hydroxybenzenesulfonamide (**1**) with aldehydes was studied. In the presence of strong base, hydroxamic acids are formed. In methanol in the absence of base, rapid acid catalysis by **1** takes place, leading to dimethyl acetals. In this manner acetal formation or hydrolysis can be catalyzed by the mild acids **1** or its O-benzyl ether **6**. Treatment of **1** or **6** with base does not appear to furnish nitrenes, as indicated by lack of reaction with olefins.

The reaction of aldehydes with N-hydroxybenzenesulfonamide (**1**) under basic conditions constitutes the basis for a well-known spot test used in the qualitative identification of aldehydes.[1] This test, known as the Angeli–Rimini test, involves the formation of a hydroxamic acid **2** which forms characteristically colored complexes with ferric ions.[2]



purple color

A proposed mechanism for hydroxamic acid formation involves the following scheme.[3] Alternatively, 1,2 elimination of benzenesulfinic acid from **3** would lead to **2**.



Since α-elimination reactions have been used to generate nitrenes,[4] we considered the possibility that the

(1) F. Feigl, "Spot Tests In Organic Chemistry," 2nd ed, Elsevier Publishing Co., New York, N. Y., 1966, p 196.

(2) A. Angeli, *Gazz. Chim. Ital.*, **26** (II), 17 (1896); E. Rimini, *ibid.*, **31** (II), 84 (1901).

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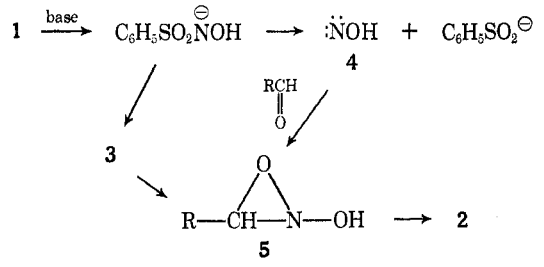
above reaction may involve the intermediacy of an N-hydroxynitrene **4** which attacks the carbonyl group to give **5**. Alternately, nucleophilic attack of the anion of **1** on the C=O could take place followed by ring closure to an N-hydroxyoxaziridine **5** which would ring open to **2**. Our past interest in the introduction of nitrogen functions into organic molecules[5] and in small-ring heterocycles[6] suggested a study of the reaction of N-hydroxybenzenesulfonamide (**1**) with C=O and C=C systems. During this study we discovered a facile synthesis and hydrolysis of acetals catalyzed by **1**.



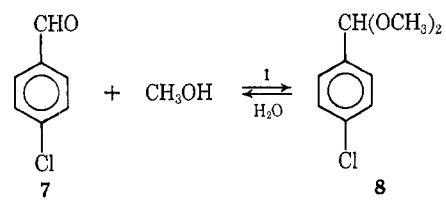
Results and Discussion

We were able to confirm the fact that aldehydes react with **1** in the presence of NaOH in ethanol–water or DMSO or even better with $NaOCH_3$ in methanol to produce hydroxamic acids **2** in fair to good yields. Acidic work-up furnished benzenesulfinic acid as a by-product in 96% yield. Ketones react much slower under these reaction conditions and lead in poor yield to N-hydroxyamides.[7]

Attempts to add **4** to olefins such as cyclohexene or dihydropyran by treatment with **1** or its O-benzyl ether

$C_6H_5SO_2NHOCH_2C_6H_5$
6

6 with various bases were unsuccessful. Unexpectedly, we found that slow addition of sodium methoxide in methanol to a solution of *p*-chlorobenzaldehyde (**7**) and N-hydroxybenzenesulfonamide (**1**) in methanol gave rise to the dimethyl acetal **8** in good yield. It soon became obvious that aldehydes reacted readily with methanol in the presence of 1 equiv of **1** within 10–15 min at room temperature even in the absence of sodium methoxide to form dimethyl acetals (see Table I). This was surprising since the pK_a of **1** is approximately 9.[8] We were able to show that N-hydroxybenzenesulfonamide (**1**) as well as its ether **6** behave as powerful nucleophilic catalysts in this reaction.



(5) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967); A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968), and references cited therein.

(6) A. Hassner and F. W. Fowler, *ibid.*, **90**, 2869 (1968); A. Hassner, G. J. Mathews, and F. W. Fowler, *ibid.*, **91**, 5046 (1969).

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TABLE I

FORMATION OF DIMETHYL ACETALS WITHIN 15 MIN IN METHANOL IN THE PRESENCE OF 1 EQUIV OF **1**

Aldehyde	% yield of acetal[a]
Benzaldehyde	87
p-Chlorobenzaldehyde (**7**)	85
p-Methylbenzaldehyde	86
p-Methoxybenzaldehyde	77
2,4,6-Trimethylbenzaldehyde	45
p-Dimethylaminobenzaldehyde	
1-Heptanal	89
Cinnamaldehyde	85
Cyclohexanone	75
Benzyl methyl ketone	33

[a] Usually determined from the nmr spectrum of the crude product. In the case of **7**, the acetal was isolated and compared with authentic sample.

Neither benzenesulfonamide nor other weak acids such as phenols catalyze the acetal formation. Acetic acid, a much stronger acid ($pK_a = 4.75$) is considerably poorer than **1** in catalyzing acetal formation (see Table II). The effectiveness of **1** as a catalyst in acetal

TABLE II

EFFECT OF ACIDS ON DIMETHYLACETAL FORMATION FROM *p*-CHLOROBENZALDEHYDE (**7**) IN METHANOL AT 25°

Acid (equiv)[a]	pK_a	Reaction time, min	% yield[b] **7**	% yield[b] **8**
HCl (1.0)	<1	15		85
HCl (0.1)	<1	15		80
Acetic acid (1.0)	4.75	15	95	5
		60	86	12
p-Nitrophenol (1.0)	6.85	15	79	
1 (1.0)	9.26	15		80
1 (0.1)	9.26	15	11	89
6 (1.0)	~9	15	24	68
Phenol (1.0)	9.85	15	80	
Benzenesulfonamide (1.0)	>10	2,400	89	
2-Pyridone (1.0)		15	90	

[a] All reactions were carried out and worked up as described for the use of **1**. [b] The yields were calculated from the nmr spectrum of the crude product.

production appears comparable with that of hydrochloric acid and 0.1 equiv of the **1** is sufficient to accomplish dimethyl acetal formation within 15 min. That this mild acid serves only in a catalytic capacity can be shown by the recovery of N-benzyloxybenzenesulfonamide (**6**) in 94% yield after assuming its role in the conversion of *p*-chlorobenzaldehyde to its acetal **8** in 85% yield.

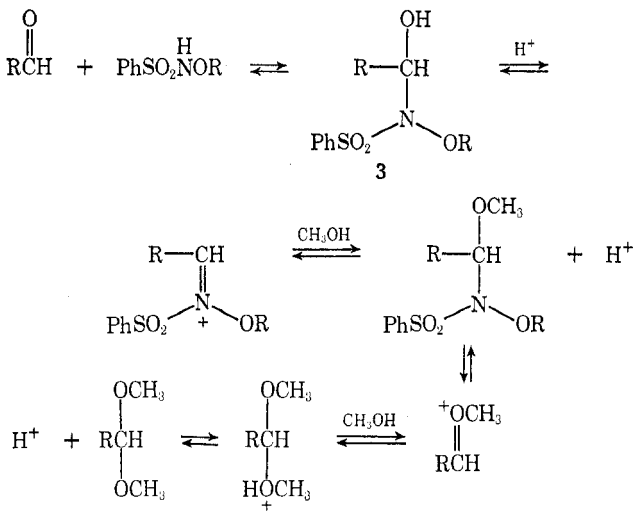
N-Hydroxybenzenesulfonamide (**1**) also serves as a mild acid catalyst in the hydrolysis of **8** to **7** in dioxane–water at 25°. The reagent **1** is stable to methanol but unstable to base at room temperature and is converted to benzenesulfinic acid (isolated) and nitrous oxide. The latter was identified by mass spectrometry.

The conversion of ketones to dimethyl ketals in the presence of **1** is slower than that of aldehydes. Cyclohexanone and benzyl methyl ketone gave dimethyl ketals in 75 and 33% yield, respectively, but cyclopentanone did not react within 15 min.

Aldehydes that contain basic functions, such as *p*-dimethylaminobenzaldehyde and 3-pyridinecarboxaldehyde, do not give acetals under the conditions mentioned.

Though the exact nature of the function of **1** or **6** are not yet understood, the acid catalysis must involve assistance by the N oxygen and is probably related to the strong nucleophilic character of **1**. Nucleophiles with an electronegative atom adjacent to the nucleophilic atom, such as hydroxylamine or hydrazine, are unusually efficient nucleophiles toward carbonyl groups.[9]

A plausible pathway in which **1** or **6** acts as a good nucleophile as well as a good leaving group is suggested below. It also explains the unexpected formation of acetals from methanol and aldehydes in the presence of hydroxylamine–hydroxylamine hydrochloride buffer.[10] In the presence of strong base, loss of benzenesulfinic acid from **3** leads to formation of hydroxamic acids.



An alternative mechanism in which **1** or **6** act as an acid and a base is unlikely since 2-pyridone, which can act in this manner,[11] does not catalyze acetal formation. On the other hand, hydroxylamine and its derivatives have been reported to catalyze hydrolysis of esters by attack on the carbonyl group.[12]

Experimental Section

Formation of *p*-Chlorobenzenehydroxamic Acid.—To an ice-cooled solution of 365 mg (2.1 mmol) of N-hydroxybenzenesulfonamide (**1**) in methanol, 2.18 ml (4.2 mmol) of a 1.93 *M* sodium methoxide–methanol solution was added dropwise with stirring. Then 281 mg (2 mmol) of *p*-chlorobenzaldehyde (**7**) dissolved in 2 ml of methanol was added, and the reaction mixture was warmed to room temperature and stirred an additional 2 hr. The solution was concentrated under vacuum, diluted with 100 ml of ether, and extracted twice with 2 *M* NaOH. The organic phase yielded 45 mg (16%) of slightly impure starting material. The aqueous phase was acidified with concentrated HCl to pH 7–8 and extracted twice with ethyl acetate. The dried solution ($MgSO_4$) was concentrated giving 225 mg (68%) of *p*-chlorobenzenehydroxamic acid: mp 193–195° dec; ir (KBr) 3250 (N—H), 2700 (broad, O—H), 1600 (C=O), 1550, 1090, 895, 845 cm^{-1}; nmr DMSO-d_6 τ 2.8 (broad, s, 1), 0.65 (broad, s, 1), 2.34 (m, 4).

If the reaction was carried out using 2 equiv of 2 *N* NaOH in ethanol–water (2:1), 35% pure hydroxamic acid was obtained together with of a mixture of **7** and its acetal **8** (*ca.* 45%).

Using DMSO–water (1:1) instead of ethanol–water as a solvent system led to isolation of 15% **7** and 82% *p*-chlorobenzenehydroxamic acid, mp 193–195° dec, lit.[13] mp 185°.

Acid-Catalyzed Formation of *p*-Chlorobenzaldehyde Dimethyl Acetal (8).—A solution of 281 mg (2 mmol) of *p*-chlorobenzaldehyde (**7**) and 365 mg (2.1 mmol) of N-hydroxybenzenesulfonamide (**1**) in 8 ml of absolute methanol was let stand for 15 min at room temperature, diluted with 50 ml ether, and extracted two times with 10 ml of 2 *M* NaOH solution. The ethereal extract was washed twice with NaCl solution, dried ($MgSO_4$), and concentrated giving 298 mg [bp 104–106° (0.2 mm), lit.[14] bp 125.5°–126.5° (35 mm) (80%)] of the dimethyl acetal **8**: nmr $CDCl_3$ τ 2.61 (s, 4), 4.64 (s, 1), 6.70 (s, 6); mass spectrum (70 eV) *m/e* (relative intensity) 188 (2) and 186 (6) for M^+, 157 (33) and 155 (100) for M − OCH_3, 141 (8) and 139 (25) for M − 47, 113 (6) and 111 (18) for M − $HC(OCH_3)_2$, 91 (35).

Acid-Catalyzed Hydrolysis of 8.—A solution of 2 mmol of acetal **8** and 2 mmol of **1** in 40 ml of dioxane–water (1:1) was allowed to stand for 5 hr at 25°. Work-up gave *p*-chlorobenzaldehyde (**7**) in nearly quantitative yield identified by ir and nmr.

Reactivity of N-Hydroxybenzenesulfonamide (1). A. Reaction with Sodium Methoxide.—To a solution of 346.4 mg (2 mmol) of **1** in 5 ml of methanol was added 113 mg (0.21 mmol) of $NaOCH_3$ at room temperature with stirring. A precipitate of colorless crystals appeared which dissolved after about 30 min. After another 2 hr the methanol was evaporated giving colorless crystals of sodium benzenesulfinate. This salt was acidified with 2 *N* HCl, and the benzenesulfinic acid was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and concentrated giving 209 mg (74%) of benzenesulfinic acid: mp 81–83° (lit.[15] 85°); ir $CHCl_3$ 2500 (broad, O—H), 1090 cm^{-1} (S=O).

B. Reaction with Methanol.—N-Hydroxybenzenesulfonamide (**1**) was recovered unchanged upon standing in methanol (0.25 *M* solution) for 1 hr at 25°. After 45 hr impure **1** was recovered.

Reaction of 7 with N-Benzoxybenzenesulfonamide (6).—A solution of 281 mg of *p*-chlorobenzaldehyde (**7**) and 1 equiv of **6** in methanol was allowed to stand for 30 min and worked up as described under formation of acetal **8**. The neutral fraction consisted of 85% **8** and 15% **7** as indicated by nmr. From the basic fraction there was isolated N-benzoxybenzenesulfonamide (**6**), 94% yield, mp 103–105°.

Registry No.—**1**, 599-71-3; **7**, 104-88-1; benzaldehyde, 100-52-7; *p*-methylbenzaldehyde, 104-87-0; *p*-methoxybenzaldehyde, 123-11-5; 2,4,6-trimethylbenzaldehyde, 487-68-3; *p*-dimethylaminobenzaldehyde, 100-10-7; 1-heptanol, 111-71-7; cinnamaldehyde, 104-55-2.

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