second peak, equivalent in intensity to one proton and differing only little in position from the first four protons, could be a CH proton in the cyclopropane ring. A wide choice of structural features could be held responsible for the doublets at δ 3.6, most likely, an alkyl group adjacent to a quaternary nitrogen. Of the remaining eight protons, the sharp lines at δ 4.7 and 7.3, respectively, are considered to be due to ammonium hydrogen and phenyl protons.

The Reactions of Sulfonamides with Oxalyl Chloride

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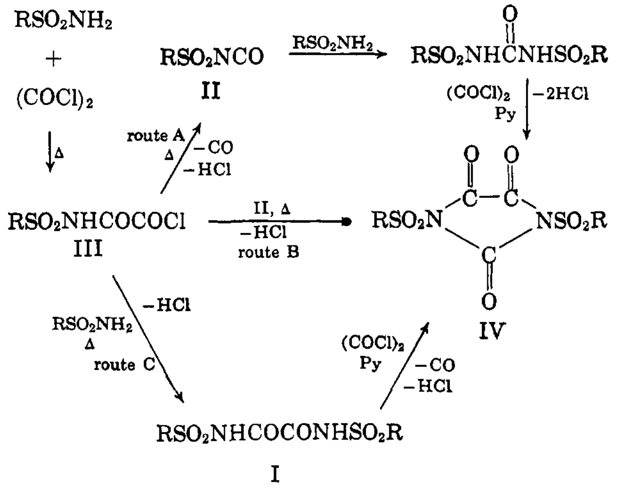
The reactions of aryl and alkyl sulfonamides with oxalyl chloride have been investigated. The uncatalyzed reaction produced sulfonyloxamides or sulfonyloxamoyl chlorides depending on the mole ratio of reactants. In the presence of a tertiary amine catalyst, however, the major products were sulfonylparabanates or mixtures of sulfonyl isocyanate and sulfonyl chloride. Probable mechanisms of these transformations are discussed. Several reactions of the new intermediate oxamoyl chlorides and parabanates are described. The pyrolyses of the latter products represent novel syntheses of sulfonyl isocyanates.

The reaction of oxalyl chloride with 2 moles of benzenesulfonamide has afforded N,N′-bis(benzenesulfonyl)oxamide (Ia)[1-3] in high yield. More complex acylation products such as parabanic acid derivatives[4] were absent. That the reaction may take a more complex course has been shown by investigations in this laboratory. Thus, while Ia was the major product (60%) in the reaction of 1 mole of oxalyl chloride with 1 mole of benzenesulfonamide, benzenesulfonyl isocyanate (IIa) and the oxamoyl chloride (IIIa) were also obtained. Addition of a catalytic amount of pyridine to this reaction mixture, followed by additional heating, gave a 60% yield of N,N′-bis(benzenesulfonyl)parabanate (IVa) and a substantial amount of benzenesulfonyl isocyanate. No bis(benzenesulfonyl)oxamide was recoverable. The same overall result was obtained when pyridine was incorporated in the original reaction mixture.

The oxamoyl chloride (IIIa) was formed in 95% yield by heating benzenesulfonamide with a 4 molar excess of oxalyl chloride. This product was a hygroscopic white solid which formed IVa at the melting point. When heated in *o*-dichlorobenzene, however, IIIa decomposed smoothly to IIa in 81% yield.[5] IIIa exhibited the expected reactivity with water, methanol, and ammonia giving the acid, methyl ester, and amide, respectively.

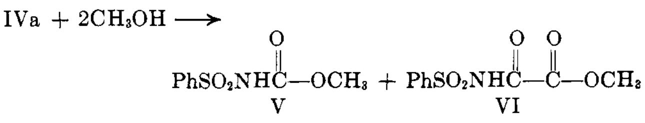
These results are readily explained on the basis of the following competitive reactions in which the oxamoyl chloride III is a key intermediate (Chart I). In route A the independent conversion of III to II in high yield was just described. The formation of the sulfonyl urea from the isocyanate and benzenesulfonamide is a known reaction.[6] Finally, the conversion of N,N′-bisbenzenesulfonylurea to IV by heating with oxaloyl chloride in the presence of pyridine was shown to proceed in 91% yield. The formation of IV at the melting point of III is represented by route B and undoubtedly involves the interaction of III and the intermediate II. The preparation of both III and I in high yields according to route C has been independently accomplished in the absence of a basic catalyst (see Experimental). As mentioned earlier, I is converted to IV by heating with oxaloyl chloride in the presence of pyridine. Although the latter reaction may involve the formation of tetraketopiperazines,[4,7] intermediates of this type were not isolated. It may be concluded, therefore, that each of the reaction steps shown in Chart I has been substantiated and routes A, B, and C probably compete in the formation of IV.

CHART I



a, R = C_6H_5; b, R = p-$CH_3C_6H_4$; c, R = CH_3; d, R = n-C_8H_{17}

The parabanate IVa was readily solvolyzed by warm methanol to give V and VI.



$$\text{IVa} + 2CH_3OH \longrightarrow \underset{\text{V}}{PhSO_2NH\overset{O}{\overset{\|}{C}}{-}OCH_3} + \underset{\text{VI}}{PhSO_2NH\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OCH_3}$$

Both products were identified by isolation and comparison with authentic materials. That V and VI were obtained in essentially equivalent amounts was shown by a comparison of the melting points (91–101°) and infrared spectra of the crude reaction products with an equimolar mixture of pure V and VI. Hot water converted IVa to benzenesulfonamide and oxalic acid. Pyrolysis of the parabanate yielded

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(1) J. M. V. Charante, *Rec. trav. chim.*, **32**, 90 (1913).

(2) R. Adams and W. Reifschneider, *J. Am. Chem. Soc.*, **78**, 3825 (1956).

(3) S. I. Burmistrov, *Ukr. Khim. Zh.*, **24**, 764 (1958).

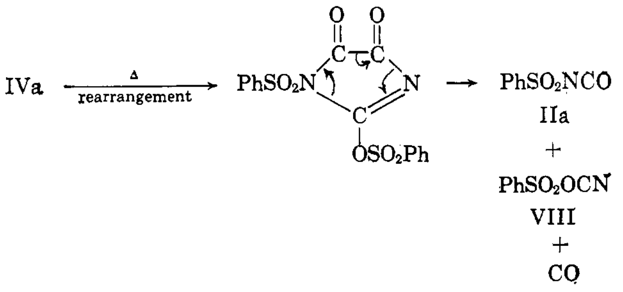
(4) J. T. Bornwater, *Rec. trav. chim.*, **31**, 105 (1912).

(5) A. J. Speziale and L. R. Smith [*J. Org. Chem.*, **28**, 1805 (1963)] have postulated an acyloxamic acid chloride as a possible intermediate in their preparation of acyl isocyanates. Whereas they were unable to isolate such an intermediate (RCONHCOCOCl), the corresponding sulfonyl compounds are isolable.

(6) O. C. Billeter, *Ber.*, **37**, 690 (1904).

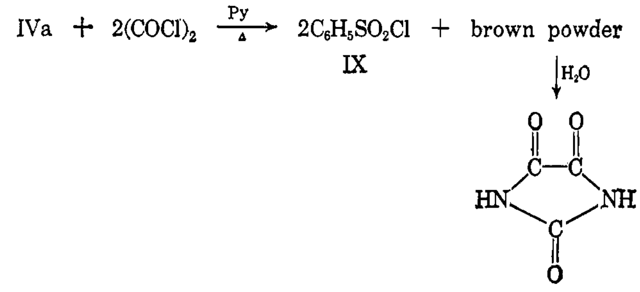
(7) A. T. DeMouilpied and A. Rule, *J. Chem. Soc.*, **91**, 177 (1907).

benzenesulfonyl isocyanate (45%), benzenesulfonic anhydride (VII, 35%), and polymeric material. The following reaction scheme involving the intermediate formation of benzenesulfonyl cyanate (VIII) accounts for the products obtained.



$$2PhSO_2OCN \longrightarrow \underset{\text{VII}}{(PhSO_2)_2O} + (NC{-}O{-}CN)_x$$

The pyridine-catalyzed reaction of benzenesulfonamide with 1.5 moles of oxalyl chloride afforded 45% yields each of benzenesulfonyl isocyanate (IIa) and benzenesulfonyl chloride (IX). The origin of IIa in this transformation must have been from IIIa since under similar reaction conditions IV was cleaved quantitatively to IX by oxalyl chloride. Air-sensitive powders which precipitated from these reaction mixtures reacted with water to form parabanic acid (X) and other unidentified products. Analyses of the powders corresponded roughly to parabanic acid–carbon dioxide complexes contaminated with chlorine-containing constituents. An attempt to prepare compound IVa from benzenesulfonyl chloride and parabanic acid using triethylamine[8] as an acid scavenger was not successful.



X

m-Benzenedisulfonamide and *p,p'*-bis(sulfonamido)-diphenyl ether were too insoluble in oxalyl chloride to undergo reaction. When diglyme was used as a solvent, polymeric products were obtained. The infrared spectra and methanolysis experiments indicate that the polymers have a parabanate structure.

The reactions of oxalyl chloride with aliphatic sulfonamides were more complicated. Thus, equimolar quantities of methanesulfonamide and oxalyl chloride in the absence of catalyst yielded a mixture containing 41% bis(methanesulfonyl)oxamide (Ic), 26% N,N'-bis(methanesulfonyl)parabanate (IVc), and methanesulfonyl isocyanate (IIc). Methanesulfonyloxamoyl chloride (IIIc) was readily prepared in 86% yield by use of an excess of oxalyl chloride. The methyl ester was prepared by methanolysis of the acid chloride. Pyrolysis of IIIc in trichlorobenzene produced a mixture containing 19% Ic, 41% IVc, and 40% IIc. The reaction of methanesulfonamide with 2 moles of oxalyl chloride in the presence of pyridine as a catalyst gave a solid consisting of a mixture of oxamide (Ic) and parabanate (IVc).

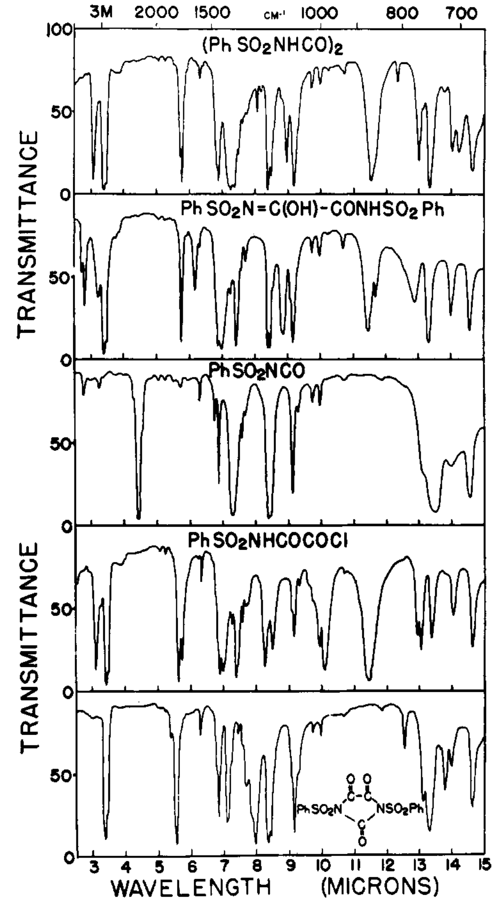


Fig. 1.—Infrared spectra of products. All solids run as mineral oil mull; liquid is neat.

n-Octanesulfonamide was unusual in that strong isocyanate bands were detected shortly after a mixture of the sulfonamide and oxalyl chloride was heated to reflux. Eventually an oil consisting of equimolar quantities of octanesulfonyl isocyanate and octanesulfonyl chloride was isolated as the reaction product.

The parabanate structure of the compounds (IV) prepared in this report is indicated by the lack of imine-type absorption in the 6–7-μ region of the infrared spectrum as well as by elemental analysis. As further support the n.m.r. spectrum of IVc in acetonitrile contained only one sharp peak at 3.47 p.p.m. which is consistent with a symmetrical structure with equivalent methyl groups.

Experimental[9]

Preparation of N,N'-Bis(benzenesulfonyl)oxamide (Ia).—A mixture of 15.7 g. (0.10 mole) of benzenesulfonamide, 14 g. (0.11 mole) of oxalyl chloride, and 150 ml. of ethylene chloride was refluxed for 24 hr. After the first hour oxamide began to precipitate and after 3 hr. isocyanate bands were first detected in the infrared spectrum of the supernatant liquor. The white crystalline bis(benzenesulfonyl)oxamide was collected by filtration

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[8] K. Kawahara, R. Sato, A. Fryita, and R. Miwa, Japanese Patents 13,915 (1961) and 15,783 (1960).

[9] All melting and boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. The n.m.r. spectrum was obtained on a Varian HR-60 n.m.r. spectrometer with tetramethylsilane as reference.

and washed with a little ethylene chloride. The yield of product, m.p. 258° (lit. m.p. 254°,[4] 258.5[3]) was 11.2 g. (61%). The filtrate was concentrated to a semisolid mixture containing benzenesulfonyl isocyanate and benzenesulfonyloxamoyl chloride as evidenced from the infrared spectrum.

Catalyzed Reaction of Benzenesulfonamide with Excess Oxalyl Chloride.—A mixture of 15.7 g. (0.10 mole) of benzenesulfonamide and 14 g. (0.11 mole) of oxalyl chloride was refluxed in 150 ml. of ethylene chloride until hydrogen chloride evolution ceased (5 hr.) and precipitation of oxamide was complete. An additional 6 g. (0.05 mole) of oxalyl chloride and 3 drops of pyridine were then added to the mixture; refluxing was resumed as hydrogen chloride was again evolved. After a few hours, infrared spectra of the precipitate and supernatant liquor indicated the conversion of oxamide into parabanate and the presence of isocyanate in solution. The mixture was finally refluxed overnight and then cooled to room temperature. A light brown amorphous precipitate (6.6 g.) was removed by filtration.

Anal. Calcd. for $C_4H_2N_2O_5$: C, 30.4; H, 1.3; N, 17.7; Cl, 0.0. Found: C, 32.2; H, 1.6; N, 17.8; Cl, 2.0.

This unidentified solid dissolved completely in water with vigorous evolution of a gas and the formation of parabanic acid.

The filtrate was concentrated at reduced pressure and the yellow oily residue (18.5 g.) distilled. The colorless product, 15.5 g., b.p. 71–83° at 1.5 mm., was shown by infrared measurements to be an equimolar mixture of benzenesulfonyl isocyanate (lit.[6] b.p. 130° at 9 mm.) and benzenesulfonyl chloride (lit.[10] b.p. 65.9° at 1.0 mm).

Preparation of N,N′-Bis(benzenesulfonyl)parabanate (IVa) from Benzenesulfonamide.—A mixture of 15.7 g. (0.10 mole) of benzenesulfonamide, 14.0 g. (0.11 mole) of oxalyl chloride, 135 ml. of ethylene chloride, and 4 drops of pyridine was heated at the reflux temperature for 3.5 hr. Isocyanate bands were detected in the infrared spectrum of the supernatant liquor shortly after refluxing was initiated. The precipitated parabanate was recovered from the cooled reaction mixture by filtration and washed with a little methylene chloride. The yield of product, m.p. 225° dec., was 12 g. (61%). An analytical sample was prepared by recrystallization from acetonitrile–ether.

Anal. Calcd. for $C_{15}H_{10}N_2O_7S_2$: C, 45.68; H, 2.56; N, 7.10; S, 16.26. Found: C, 45.69; H, 2.65; N, 7.04; S, 16.48.

The filtrates and mother liquor were concentrated to a nearly colorless semisolid residue weighing 7.6 g. Besides benzenesulfonyl isocyanate, this mixture was found to contain a small amount of N,N′-bis(benzenesulfonyl)urea.

From N,N′-Bis(benzenesulfonyl)urea.—A solution of 6.1 g. (0.018 mole) of the urea derivative (prepared by a known method[11]), 2.5 g. (0.02 mole) of oxalyl chloride, 50 ml. of ethylene chloride, and 1 drop of pyridine was refluxed 65 min. A heavy white precipitate formed after about 55 min. This mixture was cooled in an ice bath and filtered; the solid was washed with cold ethylene chloride to give, after drying under vacuum, 4.2 g. of parabanate IVa, m.p. 219° dec. The combined filtrate and washings were evaporated to dryness under reduced pressure. The resultant pasty solid was triturated with ether to give 2.1 g. of a solid which was shown by infrared analysis to be mostly starting urea contaminated with a small amount of parabanate. The yield of parabanate based on a conversion of 65.5% was 91%.

Solvolysis Reactions of IVa.—The parabanate dissolved in warm aqueous sodium bicarbonate. The product precipitated on acidification of the aqueous solution appeared to be the enol of bis(benzenesulfonyl)oxamide. After remaining overnight at room temperature, the enol changed to the keto form as evidenced by the infrared spectrum (see Fig. 1). Both the enol and keto forms melted at 258°. When refluxed in water IVa yielded oxalic acid and benzenesulfonamide.

Warming the parabanate with excess methanol produces a quantitative yield of an equimolar mixture of methyl benzenesulfonylcarbamate (also prepared from benzenesulfonyl isocyanate and methanol), m.p. 131.0–131.8°,[12] and methyl benzenesulfonyloxamate (also prepared from benzenesulfonyloxamoyl chloride and methanol), m.p. 153.2–153.8° (lit.[3] m.p. 149°). The melting points of the synthetic and authentic mixtures were 91–101° and the infrared spectra were identical in all details.

Oxalyl Chloride Cleavage of IVa.—A mixture of 4 g. (0.01 mole) of IVa, 2.5 g. (0.02 mole) of oxalyl chloride, 40 ml. of ethylene chloride, and 2 drops of pyridine was refluxed for 24 hr. After cooling, the precipitate was collected and washed with methylene chloride. The yield was 1.5 g. of tan amorphous powder. The filtrate was dissolved in ether and the solution was washed with aqueous sodium bicarbonate and then water. After drying over magnesium sulfate, the solvent was removed by distillation. The nearly colorless residue weighed 3.5 g. (100%). The infrared spectra of the product and authentic benzenesulfonyl chloride were identical.

Preparation of Benzenesulfonyloxamoyl Chloride (IIIa).—Benzenesulfonamide, 7.8 g. (0.05 mole), and 34.0 g. (0.27 mole) of oxalyl chloride were stirred at the reflux temperature for 20 hr. Hydrogen chloride was smoothly evolved as the crystalline nature of the solid phase underwent an obvious change in appearance. The white crystalline product weighed 11.5 g. (93%) and melted with decomposition at 150° forming IVa.

Anal. Calcd. for $C_8H_6ClNO_4S$: C, 38.79; H, 2.45; Cl, 14.31. Found: C, 39.04; H, 2.84; Cl, 13.94.

This acid chloride was air sensitive and readily hydrolyzed to oxamic acid hydrate which melted with decomposition at 150–155°, lit.[3] m.p. 155–158°.

Anal. Calcd. for $C_8H_9NO_6S$: C, 38.86; H, 3.68. Found: C, 39.14; H, 3.69.

The oxamoyl chloride reacted readily with methanol to form methyl benzenesulfonyloxamate, m.p. 153.2–153.8°, and with aqueous ammonia to form the amide, m.p. 166° (lit.[3] m.p. 166–167°). The mixture melting points and infrared spectra of the latter products were identical with authentic materials.[3]

Preparation of Benzenesulfonyl Isocyanate (IIa). By Pyrolysis of Benzenesulfonyloxamoyl Chloride.—Dry dichlorobenzene (45 ml.) and 5.9 g. (0.025 mole) of benzenesulfonyloxamoyl chloride were heated at the reflux temperature for 1 hr. The solvent was removed under reduced pressure and the residue was distilled through a Holzmann column. The yield of benzenesulfonyl isocyanate, b.p. 97° at 2.5 mm., was 3.5 g. (81%). The residue, 0.5 g., consisted of a mixture of benzenesulfonamide and N,N′-bis(benzenesulfonyl)oxamide.

By Pyrolysis of N,N′-Bis(benzenesulfonyl)parabanate.—The parabanate (3.74 g., 0.01 mole) was pyrolyzed at 250° under a Holzmann column and colorless benzenesulfonyl isocyanate, b.p. 93° (2.0 mm.), was collected as distillate. The yield was 1.55 g. or 45% of the theoretical amount. The residue (1.7 g.) was extracted with ether to yield 1.1 g. of an ether-soluble, hygroscopic, white solid, m.p. 66–75° (lit.[13] m.p. 60–89° for benzenesulfonic anhydride). A portion of this solid (0.311 g.) was dissolved in ether and the solution was saturated with ammonia gas. The precipitate of crude ammonium benzenesulfonate (0.225 g.) was recovered by filtration, m.p. 267–272° (lit. m.p. 256,[14a] 271–275°[14b]). The ether filtrate yielded 0.123 g. (75%) of benzenesulfonamide, m.p. 147.5–150°. The infrared spectrum was identical with authentic material.

Preparation of *p*-Toluenesulfonyl Isocyanate (IIb).—Using the method described for IIa the pyrolysis of *p*-toluenesulfonyloxamoyl chloride (obtained in 90% yield from the reaction of *p*-toluenesulfonamide with 4 moles of oxalyl chloride), m.p. 133° dec. (remelt 220°), in 100 ml. of *o*-dichlorobenzene gave 6.6 g. (88%) of IIb, b.p. 95–96 at 0.2 mm. (lit.[15] b.p. 115° at 0.4 mm.); 0.5 g. of *p*-toluenesulfonamide; and 0.6 g. of a mixture of the sulfonyl oxamide (Ib) and sulfonylparabanate (IVb).

Preparation of N,N′-Bis(*p*-toluenesulfonyl)parabanate (IVb).—Using the method described for the phenyl analog, 17.1 g. (0.1 mole) of *p*-toluenesulfonamide and 23.5 g. (0.18 mole) of oxalyl chloride gave 10.5 g. (50%) of product, m.p. 215° dec. An analytical sample was obtained by recrystallization from acetonitrile–ether.

Anal. Calcd. for $C_{17}H_{14}N_2O_7S_2$: C, 48.33; H, 3.34; S, 15.18. Found: C, 48.36; H, 3.33; S, 15.03.

Preparation of N,N′-Bis(methanesulfonyl)oxamide (Ic).—A mixture of 9.5 g. (0.10 mole) of methanesulfonamide, 14 g. (0.11 mole) of oxalyl chloride, and 100 ml. of ethylene chloride was refluxed for 5.5 hr. The mixture was concentrated at reduced pressure to about one-half volume and then filtered. After washing with methylene chloride, the residue weighed 8.5 g. The

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(10) D. R. Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).

(11) L. Field and F. A. Grunwald, *J. Am. Chem. Soc.*, **75**, 934 (1953).

(12) *Anal.* Calcd. for $C_8H_9NO_4S$: C, 44.64; H, 4.21; N, 6.51. Found: C, 44.77; H, 4.32; N, 6.30.

(13) L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952).

(14) (a) T. H. Norton, *ibid.*, **19**, 835 (1897); (b) W. Autenrieth and R. Bernheim, *Ber.*, **37**, 3800 (1904).

(15) H. Krzikalla, German Patent 817,602 (1951).

infrared spectra indicated that the filtrate contained isocyanate and that the crude solid was a mixture of sulfonyloxamide and sulfonylparabanate. The solid was boiled with methanol and the insoluble oxamide, 5 g. (41%), was recovered by filtration. Recrystallization from dimethyl acetamide–methanol gave m.p. 291° dec.

Anal. Calcd. for $C_4H_8N_2O_6S_2$: C, 19.67; H, 3.30; S, 26.26. Found: C, 19.4; H, 3.1; S, 25.9.

Concentration of the methanol filtrate yielded 4.0 g. of a mixture from which methyl methanesulfonylcarbamate, m.p. 120.6–121.3°, was isolated.

Anal. Calcd. for $C_3H_7NO_4S$: C, 23.53; H, 4.61; N, 9.15. Found: C, 23.61; H, 4.47; N, 9.09.

Methyl methanesulfonyloxamate, m.p. 103–105°, and a little N,N′-bis(methanesulfonyl)oxamide were also found in the mixture. The yield of methyl esters corresponds to a yield of 26% of N,N′-bis(methanesulfonyl)parabanate in the initial crude reaction product.

Preparation of Methanesulfonyloxamoyl Chloride (IIIc).—Methanesulfonamide, 9.5 g. (0.10 mole), and 63.5 g. (0.50 mole) of oxalyl chloride were refluxed for 0.5 hr., and the mixture was then allowed to remain at room temperature for 1 day. An equal volume of hexane was added, and the precipitate was recovered by filtration. The yield of off-white crystalline product, m.p. 95–100° dec., was 16 g. (86%). The crude product (0.8 g.) was warmed with methanol and 0.05 g. of bis(methanesulfonyl)-oxamide was removed by centrifugation. The methyl ester recovered from the methanol solution melted at 104.5–105.5° after recrystallization from benzene–methanol–petroleum ether.

Anal. Calcd. for $C_4H_7NO_5S$: C, 26.52; H, 3.89; N, 7.73. Found: C, 26.63; H, 4.08; N, 7.79.

Pyrolysis of Methanesulfonyloxamoyl Chloride.—When 9.3 g. (0.05 mole) of methanesulfonyloxamoyl chloride was heated with 50 ml. of trichlorobenzene to 150°, vigorous gas evolution occurred. A solid which appeared during the decomposition remained present even at the maximum temperature reached. Distillation of the entire reaction mixture through a Holzmann column gave 4.3 g. of a mixture of trichlorobenzene and methyl sulfonyl isocyanate which was identified by its infrared spectrum.

The distillation residue was cooled and filtered to give a tan powder, 3.9 g., m.p. 200–220° dec., which appeared, from the infrared spectrum, to contain oxamide (Ic) and parabanate (IVc). Treatment with methanol enabled separation of the oxamide, 19% of theory, m.p. 285–290°. The mixture of esters obtained from the alcohol-soluble portion corresponded to 2.73 g. of parabanate, 41% of theory.

Preparation of N,N′-Bis(methanesulfonyl)parabanate (IVc).—A mixture of 4.76 g. (0.05 mole) of methanesulfonamide, 12.2 g. (0.10 mole) of oxalyl chloride, 100 ml. of ethylene chloride, and 3 drops of pyridine was refluxed for 5.5 hr. After cooling and filtering, there was recovered 4.1 g. of product. The infrared spectrum indicated the major constituent was parabanate contaminated with some oxamide. Methanol treatment of a portion indicated that about 13% of this product was oxamide. The parabanate, m.p. 215° dec., was extracted from the mixture with acetonitrile and precipitated with ether.

Anal. Calcd. for $C_5H_6N_2O_7S_2$: C, 22.22; H, 2.24; S, 23.73. Found: C, 22.18; H, 2.28; S, 23.82.

Reaction of Octanesulfonamide with Oxalyl Chloride.—A mixture of 4.7 g. (0.024 mole) of *n*-octanesulfonamide and 17 g. (0.134 mole) of oxalyl chloride was refluxed 7 hr. *o*-Dichlorobenzene (10 ml.) was added and excess oxalyl chloride was removed by distillation. The mixture was then distilled under reduced pressure. The infrared spectrum of the product, 4.5 g., b.p. 102–104° (1.0 mm.), indicated an equimolar mixture of *n*-octanesulfonyl isocyanate and *n*-octanesulfonyl chloride.[16]

Anal. Calcd.: Cl, 8.1. Found: Cl, 8.5.

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(16) R. B. Scott, Jr., and R. E. Lutz [*J. Org. Chem.*, **19**, 830 (1954)] reported this sulfonyl chloride, b.p. 94° at 1 mm.

The Synthesis of Dehydrocycloheximide and the Conversion of *cis*-2,4-Dimethylcyclohexanone to Its *trans* Isomer[1,2]

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The synthesis of dehydrocycloheximide has been accomplished by the condensation of the enamine of (+)-*trans*-2,4-dimethylcyclohexanone with glutarimide-β-acetyl chloride. It is inferred that, when *cis*-2,4-dimethylcyclohexanone was converted into its enamine, an isomerization occurred with the result that the methyl groups assumed a *trans* relationship. A proposal is presented in an attempt to explain this isomerization.

The determination of the stereochemistry and the attempted syntheses of the glutarimide antibiotics related to cycloheximide have been under investigation in a number of laboratories.[3-6] We now wish to give the complete details of our previously announced synthesis of dehydocycloheximide[7] and to describe certain isomerizations which appear to occur during the preparation of enamines from substituted cyclic ketones.

For the synthesis of dehydrocycloheximide, we elected to combine the two fragments, 2,4-dimethylcyclohexanone (I) and glutarimide-β-acetyl chloride (III). The ketone was activated for condensation by converting it into either the pyrrolidine or piperidine enamine according to the elegant procedure of Stork and co-workers.[8] Thus, when (+)-*trans*-2,4-dimethylcyclohexanone was allowed to react with pyrrolidine in benzene solution, a 78% yield of the desired enamine (II) was obtained. Condensation of II in dioxane solution with glutarimide-β-acetyl chloride (III), followed by hydrolysis with dilute hydrochloric acid gave dehydrocycloheximide in a 25% yield. The fact that the synthetic dehydrocycloheximide (IV) was identical with an authentic sample of dehydrocycloheximide[9] was established by comparison of the optical rotation, ultraviolet and infrared spectra, R_f on thin layer chromatography, and the melting and mixture melting points of the two samples. As reported earlier,[7] when a similar condensation was performed in which the piperidine enamine of (+)-*trans*-2,4-dimethylcyclohexanone was allowed to react with III, a 19% yield of IV was obtained. In addition, the synthesis of (±)-norde-

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(1) The research described in this paper was submitted by V. K. Jain in partial fulfillment of the Ph.D. requirements.

(2) This investigation was supported in part by Research Grant CY-4812 from the National Institutes of Health and in part by a Public Health Service research career program award CA-K6-18718 from the National Institutes of Health.

(3) H. J. Schaeffer and V. K. Jain, *J. Pharm. Sci.*, in press.

(4) B. C. Lawes, *J. Am. Chem. Soc.*, **82**, 6413 (1960).

(5) T. Okuda, M. Suzuki, and Y. Egawa, *J. Antibiotics* (Tokyo), **14A**, 158 (1961); *Chem. Pharm. Bull.* (Tokyo), **11**, 582 (1963).

(6) F. Johnson, W. D. Gurowitz, and N. A. Starkovsky, *Tetrahedron Letters*, 1167 (1962).

(7) H. J. Schaeffer and V. K. Jain, *J. Pharm. Sci.*, **52**, 509 (1963).

(8) G. Stork, A. Brizzolara, H. Landesmann, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(9) E. C. Kornfeld, R. J. Jones, and T. V. Parke, *ibid.*, **71**, 150 (1949).