[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Schmidt Reaction: Experimental Conditions and Mechanism

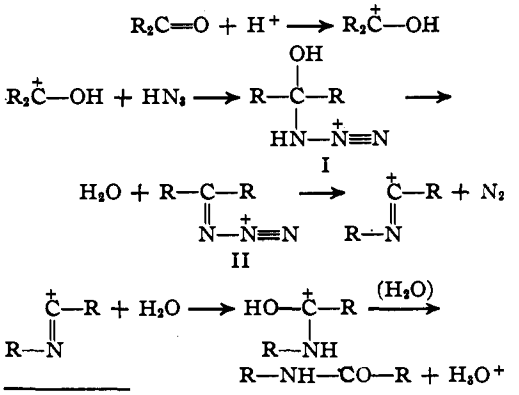
BY PETER A. S. SMITH

In 1944[1] we proposed a mechanism for the amination of the benzene ring by hydrazoic acid involving the radical NH or NH_2^+. On the other hand, we felt that the amination of carbonyl compounds by the same reagents, known as the Schmidt reaction,[2] proceeded by a carbonium ion mechanism,[3] but publication has been withheld pending more complete experimental confirmation. Recently, Newman proposed essentially the same mechanism,[4] and it seemed desirable, therefore, to present our work as it now stands. A review of other mechanisms which have been proposed for the Schmidt reaction through 1945 is available elsewhere.[2] Since then an oxatriazole intermediate has been suggested.[5]

The stoichiometry of the Schmidt reaction is represented by

$$R{-}CO{-}R + HN_3 = R{-}NH{-}CO{-}R + N_2$$

The reaction is carried out with the aid of at least equimolar quantities[2] of catalysts which are strong Lewis acids.[6] The mechanism now proposed consists of the formation of a carbonium ion from the carbonyl group and the acid catalyst; this is the initial step recently proposed by Sanford, Blair, Arroya and Sherk[7] for an otherwise somewhat different mechanism. The carbonium ion and hydrogen azide form a transitory intermediate (I), which loses water and undergoes *trans* rearrangement with loss of nitrogen, as detailed below.



$$R_2C{=}O + H^+ \longrightarrow R_2\overset{+}{C}{-}OH \qquad (1)$$

$$R_2\overset{+}{C}{-}OH + HN_3 \longrightarrow \underset{\text{I}}{R{-}\underset{HN-\overset{+}{N}\equiv N}{\overset{OH}{C}}{-}R} \longrightarrow$$

$$H_2O + \underset{\text{II}}{R{-}\underset{N-\overset{+}{N}\equiv N}{\overset{}{C}}{-}R} \longrightarrow \underset{R-N}{\overset{+}{C}}{-}R + N_2 \qquad (2)$$

$$\underset{R-N}{\overset{+}{C}}{-}R + H_2O \longrightarrow HO{-}\underset{R-NH}{\overset{+}{C}}{-}R \xrightarrow{(H_2O)} R{-}NH{-}CO{-}R + H_3O^+ \qquad (3)$$

It can be seen that this mechanism implies: (1) that the occurrence of the Schmidt reaction is dependent upon both the extent to which the carbonyl compound undergoes step (1) and the polarizing power of the particular carbonium ion in step (2); and (2), that insofar as the intermediate (II) has a finite existence, there should be a geometrical effect influencing the apparent "migration aptitudes" of the two groups in unsymmetrical ketones. In this paper a series of Schmidt reactions are described in which the carbonyl compound, the acid catalyst, and the solvent were varied in order to test the first conclusion. The investigation of the second conclusion by determining the ratios of the isomeric amides formed from unsymmetrical ketones is now in progress, and will be the subject of a future communication.

The occurrence and rate of the Schmidt reaction should depend on the equilibrium concentration of carbonium ion produced by step (1) if step (2) is rate-determining. As a first approximation, one may say that the more basic the carbonyl compound and the more acidic the reaction medium, the faster the reaction will go. Our experiments with nineteen carbonyl compounds of different types in solvents of varying basicity and with catalysts of different acid strength bear this out. Only a qualitative agreement would be expected, however, since each carbonium ion will of course have its own specific reaction rate in step (2).

The available data on the basic strengths of carbonyl compounds[8] permit as a rough generalization the assumption of the following order: cycloalkyl ketones > dialkyl ketones > aryl alkyl ketones > diaryl ketones > carboxylic acids. Cycloalkyl and dialkyl ketones were found to undergo the Schmidt reaction even in such basic solvents as water, alcohols, and ethers, but with the less basic types of carbonyl compounds the use of these solvents inhibited the reaction largely or completely.[9] Catalysts which are strong enough acids to bring about the Schmidt reaction with the more basic carbonyl compounds may not be strong enough to be effective with the less basic ones. Thus trichloroacetic acid was found to be an efficient catalyst for alkyl and aryl alkyl ketones, but it was only partially effective on diaryl ketones, and failed completely with all acids but formic. The carboxyl group of trichloroacetic acid itself does not show a measurable tendency to

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[1] R. N. Keller and P. A. S. Smith, THIS JOURNAL, **66**, 1122 (1944).

[2] *Cf.* H. Wolfe, "The Schmidt Reaction," in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946.

[3] P. A. S. Smith, Thesis, "Reaction Mechanisms Involving the Radical NH," University of Michigan, 1944.

[4] (a) M. S. Newman, Organic Chemistry Symposium, Boston, Mass., 1947; (b) M. S. Newman and H. Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

[5] A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., New York, N. Y., 1946, p. 371.

[6] G. N. Lewis, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, N. Y., 1923, p. 142.

[7] J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, THIS JOURNAL, **67**, 1941 (1945).

[8] *Cf.* W. Gordy and S. C. Stanford, *J. Chem. Phys.*, **8**, 170 (1940).

[9] *Cf.* the published observation[10] that the use of ether in place of chloroform reduces the yield of aniline from benzoic acid from 85% to 24%.

[10] L. H. Briggs, G. C. De Ath and S. R. Ellis, *J. Chem. Soc.*, 61 (1942).

form carbonium ions.[11] It is thus understandable that no catalyst was found strong enough to bring about the Schmidt reaction with it; and trichloroacetic acid is accordingly a satisfactory solvent in which to carry out the Schmidt reaction on other carbonyl compounds, using sulfuric acid as the catalyst if necessary. Trifluoroacetic acid has been reported[12] to be similarly resistant.

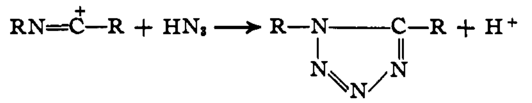
Our experiences lead us to some recommendations about the choice of experimental conditions. In general, the least strongly acid medium which will bring about reaction in a reasonable time gives the purest products. Concentrated aqueous hydrochloric acid has been found to be a useful solvent and catalyst for the reaction with aliphatic ketones; its use minimizes the formation of both tars and tetrazoles. Benzylacetone, for example, gave an 87% yield of mixed amides (consisting of 5% of N-methylphenylpropionamide and 95% of N-(β-phenylethyl)-acetamide when treated with sodium azide in hydrochloric acid, whereas with sulfuric acid[10] a yield of only 62% has been reported. Solutions of hydrogen chloride in alcohol[13] or dioxane are useful with relatively insoluble ketones, but most aliphatic ketones dissolve sufficiently in aqueous acid. While aqueous hydrochloric acid is not strong enough to bring about the Schmidt reaction on the less basic aryl alkyl ketones, the more acid medium provided by molten trichloroacetic acid gives excellent results. Acetophenone, β-acetonaphthone and α-tetralone gave yields of N-aryl amides of 89, 95 and 85%, respectively, whereas yields of 77,[14] 70 and 70%[14] were given by the unnecessarily strong catalyst sulfuric acid; in addition, purification of the products may be more difficult when sulfuric acid is used. Sulfuric acid appears to be the best catalyst for the even less basic diaryl ketones and carboxylic acids, but the use of only two molar equivalents of sulfuric acid with one of the carbonyl compound in trichloroacetic acid as a solvent provides a homogeneous and fluid reaction medium and lessens the danger of sulfonation. Work at present under way indicates that strong aprotic acids, such as aluminum chloride, in inert solvents favor tetrazole formation.

Among numerous applications of the mechanism here presented, which cannot be reviewed here, it is interesting to consider Götzky's[15] observation that benzhydrylidene diazide gives benzanilide in 98% yield when treated with 70% sulfuric acid. This reaction may be formulated in an analogous manner

$$Ar_2C(N_3)_2 \xrightarrow{(H^+)} HN_3 + Ar_2C{=}N{-}\overset{+}{N}{\equiv}N \longrightarrow$$

$$N_2 + Ar{-}N{=}\overset{+}{C}{-}Ar \xrightarrow{(H_2O)} Ar{-}NH{-}CO{-}Ar + H_3O^+$$

The imino-carbonium ion[16] resulting from step (2) may give rise to products other than amides in step (3) if it encounters a species other than water capable of forming a permanent attachment. If it should encounter a second molecule of hydrogen azide, a tetrazole would be produced



If a large quantity of alcohol is present, an imido-ester results instead of an amide. The same type of imino-carbonium ion probably arises[17] in the Beckmann rearrangement of oximes, and it is significant that tetrazoles and imido-esters result from the Beckmann rearrangement also when it is carried out in the presence of azide or alcohols, respectively. Most of the catalysts used in the Schmidt reaction cannot generate an imino-carbonium ion from amides and, accordingly, amides, once formed, do not react further with hydrogen azide. It is expected that we will be able to present a more detailed treatment of tetrazole formation at the completion of present work.

In view of the additional evidence presented by Newman and Gildenhorn, the carbonium ion mechanism seems to be fairly well established. A quantitative study of the rate of the Schmidt reaction as influenced by substrate, solvent, and catalyst is nevertheless felt to be a suitable addition to this work, and has recently been begun.

It was felt of interest to confirm the report[10] that methyl azide does not take part in a Schmidt reaction as does hydrogen azide. No N-methyl products could be detected in experiments with acetophenone, and the principal effect of mixtures of ketones and acids on alkyl azides appeared to be catalysis of their decomposition according to other paths.

Experimental

In the accompanying table the results of a number of Schmidt reactions are summarized. In the method usually employed, powdered sodium azide was added to the mixture of solvent, catalyst, and carbonyl compound. In certain experiments, indicated by a footnote, benzene solutions of hydrogen azide were used. In many experiments where the yield of product would be of little significance or preparative value, yields were not determined. These experiments are listed just before the table, or, for carbonyl compounds which do appear in the table, are mentioned in footnotes. Nitrogen evolution was used as the criterion of reaction in these cases, and the results were confirmed by a qualitative test for the products. All reactions were run at room temperature unless noted otherwise by a footnote. The organic chemicals used were Eastman Kodak Co. products, except monochloro- and trichloroacetic acids, which were Mallinckrodt products, and α-tetralone, phenylacetone, benzylacetone, and cyclohexanone-α-carboxylic ester, which were synthesized

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[11] L. P. Hammett and A. J. Deyrup, THIS JOURNAL, 55, 1900 (1933); M. Ussanovich and V. Tartakovskaya, *J. Gen. Chem.* (*U. S. S. R.*), 16, 1987 (1946); T. Sumarokova and Z. Grishkun, *ibid.*, 16, 1991 (1946).

[12] H. Gilman and R. G. Jones, THIS JOURNAL, 65, 1458 (1943).

[13] The use of alcohols gives rise to imido-esters.

[14] L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, 456 (1937).

[15] S. Götzky, *Ber.*, 64, 1555 (1931).

[16] We are pleased to adopt the nomenclature for carbonium ions suggested by Newman and Gildenhorn, ref. 4.

[17] W. A. Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1936, p. 354, *et seq.*

TABLE I

YIELDS AND PRODUCTS OF SOME SCHMIDT REACTIONS

Carbonyl compd.	Solvent	Cat.	Product	Yield, %
Cyclohexanone	H_2O^b	HCl	ε-Caprolactam	63
Cyclohexanone	CH_3COOH^c	HBr	ε-Caprolactam	56
Cyclohexanone-α-carboxylic ester	H_2O	HCl	α-Aminopimelic acid	20
Benzylacetone	H_2O	HCl	Mixed amides[d]	87
Acetoacetic ester	H_2O	HCl	Glycine·HCl	56
α-Tetralone	Cl_3CCOOH^a		Homodihydrocarbostyryl[e]	85
Acetophenone	CH_3COOH^f	HBr	Acetanilide	21
Acetophenone	Cl_3CCOOH^a		Acetanilide	89
Acetophenone	$C_6H_5NO_2^g$	$AlCl_3$	1-Phenyl-5-methyltetrazole	42[h]
α-Acetonaphthone	Cl_3CCOOH^a		α-Acetnaphthalide	90
β-Acetonaphthone	$Cl_3CCOOH^{a,i}$		β-Acetnaphthalide	95
β-Acetonaphthone	H_2SO_4		β-Acetnaphthalide	55
β-Acetonaphthone	$C_6H_5NO_2^{j,g}$	$AlCl_3$	1-β-Naphthyl-5-methyltetrazole	73[h]
β-Acetonaphthone	$CHCl_3$	$POCl_3$	β-Acetnaphthalide	42
Benzophenone	$Cl_3CCOOH^{a,i}$		Benzanilide	59
Benzophenone	Cl_3CCOOH^a	H_2SO_4	Benzanilide	99
Fluorenone	$Cl_3CCOOH^{a,k}$		Phenanthridone	55
Fluorenone	H_2SO_4		Phenanthridone	99[l,m]
m-Toluic acid	Cl_3CCOOH	H_2SO_4	*m*-Toluidine	43

[a] Temperature between 55 and 65°. [b] Also reacts vigorously in dioxane or ether solution with hydrogen chloride as catalyst. [c] No reaction in acetic acid alone; moderate reaction in acetic acid with trichloroacetic acid as catalyst and in monochloroacetic acid alone; moderate to vigorous reaction in dichloroacetic acid alone and in trichloroacetic acid alone. [d] Consisted of N-β-phenylethylacetamide, 95%, and N-methylphenylpropionamide, 5%, as determined from hydrolysis products. [e] As its trichloroacetic acid salt. [f] No reaction in water or dioxane with hydrogen chloride catalyst. [g] Benzene solution of hydrogen azide used. [h] Based on hydrogen azide; these two preparations will be described in a forthcoming communication. [i] No reaction in dioxane with hydrogen chloride catalyst. [j] Almost no reaction in nitrobenzene with stannic chloride catalyst. [k] No reaction in dioxane, ethanol, or acetic acid with hydrogen chloride or bromide catalyst. [l] This experiment performed by Mr. Jerome Horwitz. [m] A yield of 70% has been obtained by L. P. Walls, *J. Chem. Soc.*, 1405 (1935), by adding an aqueous solution of sodium azide to fluorenone dissolved in sulfuric acid.

by standard procedures. Yields are reported for products purified only to the point where their identity could be definitely established by comparison, usually by mixed melting point, with known samples; in other cases, the products were in turn converted into identifiable derivatives. Following the tabulation, a more detailed description of selected typical experiments is given.

The following carbonyl compounds were treated with sodium azide in the solvents and with the catalysts named, without determining the yields: Methyl ethyl ketone in water or dioxane with hydrogen chloride catalyst reacted at a moderate rate; phenylacetone in aqueous hydrochloric acid reacted vigorously; formic acid alone did not react, nor did it in aqueous hydrochloric acid, but with trichloroacetic acid catalyst it reacted at a moderate rate; acetic acid did not react alone nor with trichloroacetic acid catalyst, but reacted vigorously with hydrogen bromide catalyst; benzoic acid did not react with aqueous hydrochloric acid, but reacted very slowly in molten trichloroacetic acid alone, and moderately rapidly in trichloroacetic acid with sulfuric acid catalyst; molten chloroacetic acid alone reacted very slowly, dichloracetic acid alone reacted slowly, and trichloroacetic alone or with sulfuric acid catalyst reacted not at all.

β-Acetnaphthalide from β-Acetonaphthone: A. With Trichloroacetic Acid.—To a solution of 1.70 g. (0.01 mole) of β-acetonaphthone in 15 g. of trichloroacetic acid at 60° was added 1.0 g. (0.015 mole) of powdered sodium azide all at once. After four hours at 60° with occasional stirring, the mixture was diluted with 75 cc. of water and alkalized with 10 cc. of concd. ammonium hydroxide. The nearly white product was filtered from the cooled solution and washed with water and warm petroleum ether; wt. 1.75 g. (95%), m.p. 125–130°. Recrystallization of a portion from aqueous alcohol gave snow-white crystals, m.p. 132–134° (lit.,[18] 132°).

B. With Sulfuric Acid.—To a solution of 1.70 g. of β-acetonaphthone in 20 cc. of concd. sulfuric acid overlaid with 10 cc. of chloroform was added with stirring 0.9 g. of sodium azide in small portions over a five-hour period. When further addition caused no fresh gas evolution, the pasty mixture was poured on ice, alkalized with concd. ammonium hydroxide, and the organic material was taken up in ether. Evaporation of the extracts left a waxy solid, which was successively extracted with petroleum ether and recrystallized from benzene–petroleum ether. There was obtained 1.02 g. (55%) of impure β-acetamidonaphthalene; the filtrates yielded 0.17 g. (10%) of recovered β-acetonaphthone.

ε-Caprolactam from Cyclohexanone.—To a solution of 2.0 g. of cyclohexanone (0.02 mole) in 10 cc. of concd. hydrochloric acid at room temperature was added 2.0 g. (0.031 mole) of sodium azide in portions as fast as the vigor of the reaction permitted. After standing for several hours, the mixture was distilled to dryness *in vacuo*, and the residue taken up in a little water and alkalized with excess 50% sodium hydroxide solution. The yellow oil which separated was extracted with three portions of chloroform, and the extracts washed with a very little water and evaporated to a mass of crystals; wt. 1.3 g. (63%). Recrystallization from benzene–petroleum ether produced a colorless product, m.p. 63–64° (lit.,[19] 68–70°), with very little loss.

Acetophenone in Acetic Acid with Hydrogen Bromide.—To a solution of 2.4 g. of acetophenone in 15 cc. of 30% hydrogen bromide in acetic acid was added with stirring 1.0 g. of sodium azide in portions over thirty minutes. When the gas evolution subsided, the mixture was poured on ice, neutralized with ammonium hydroxide, and the excess acetophenone was removed by steam distillation. From the cooled residue was obtained 0.18 g. of acetanilide, and, on treatment with bromine water, 0.40 g. of *p*-bro-

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(18) C. Liebermann and F. Scheiding, *Ann.*, **183**, 267 (1876).

(19) O. Wallach, *ibid.*, **312**, 187 (1900).

moacetanilide, m.p. 164–165° (lit.,[20] 167–168°); total yield 21%, based on sodium azide.

Phenanthridone from Fluorenone: A. With Trichloroacetic Acid.—On treatment with the same quantities of reagents under the same conditions as described above for β-acetonaphthone, 1.80 g. of fluorenone yielded 1.08 g. (56%) of crude phenanthridone; m.p. *ca.* 220° with sublimation, and 0.86 g. (48%) of crude recovered fluorenone.

B. **With Sulfuric Acid.**[21]—To a solution of 1.80 g. of fluorenone in 20 cc. of concd. sulfuric acid at room temperature was added with stirring 1.0 g. of sodium azide in portions over half an hour. The mixture was then poured on ice, and the precipitated phenanthridone was filtered off and washed with water and petroleum ether; wt. 1.93 g. (99%), m.p. 290–293° with sublimation (lit.,[22] 293°).

Methyl Azide and Acetophenone.—Solutions of methyl azide in petroleum ether or chloroform were prepared from methyl sulfate and 3.25 g. of sodium azide, according to the method of Dimroth and Wislicenus[23]; the methyl azide was passed in the gas phase through a long tube of soda-lime and potassium hydroxide pellets to remove completely any trace of hydrogen azide. The purity of the product so obtained was confirmed by testing liberal portions with alcoholic silver nitrate and with ferric chloride solution; no opalescence of silver azide was obtained with the first reagent, and no color developed with the second. Mixtures of the methyl azide solutions with 5 cc. of acetophenone and 10 cc. of concd. sulfuric acid foamed vigorously at room temperature. When the reaction subsided, the mixture was poured on ice, and the organic material extracted with ether and steam-distilled. Treatment of the residue in the still-pot with bromine water gave 0.1 to 0.28 g. of *p*-bromoacetanilide in different runs (0.9–2.6%), m.p. 166–168° (lit.,[23] 168°). In an experiment in which aluminum chloride in nitrobenzene was used in place of sulfuric acid, nitrogen evolution was vigorous, but only resinous products were isolated.

Homodihydrocarbostyryl from α-Tetralone.—A mixture of 1.46 g. (0.01 mole) of α-tetralone, 15 g. of trichloroacetic acid, and 1.0 g. (0.015 mole) of sodium azide was heated at 60° for six hours. Pouring the mixture into *ca.* 75 cc. of cold water deposited a brownish, crystalline solid; wt. 2.75 g. (85%), m.p. 109–113°, after washing with water and petroleum ether. Recrystallization from benzene gave an analytical sample; rectangular prisms, m.p. 126°, insol. water and petroleum ether, sol. other organic solvents.

Anal.[24] Calcd. for $C_{10}H_{11}ON \cdot Cl_3CCOOH$: C, 44.45; H, 3.70; Cl, 32.85. Found: C, 44.61; H, 3.88; Cl, 32.67.

This substance could be titrated sharply to a methyl orange end-point, and then left as residue pure homodihydrocarbostyryl, m.p. 139–141° (lit.,[14] 141°), with only mechanical losses. The same addition product was produced at room temperature when equimolar amounts of the components were mixed in concentrated benzene solution.

An attempt to prepare this addition product from α-tetralone oxime by causing it to rearrange in trichloroacetic acid at 60° produced only **α-tetralone oxime trichloroacetate**, silky needles m.p. 113–115°, insol. water and petroleum ether, sol. other organic solvents. Titration with sodium hydroxide to a methyl orange end-point gave an equivalent weight of 323 (calcd. 324.5) and regenerated α-tetralone oxime, m.p. 101–102° (lit.,[25] 102.5–103.5°), with only mechanical losses.

Summary

1. A qualitative study of the effect of solvents and catalysts on the Schmidt reaction has been made.

2. The occurrence of the Schmidt reaction appears to be governed by the acidity of the medium as determined by the acid strength of the catalyst and the basic strength of the solvent, and by the basic strength of the carbonyl compound undergoing the reaction.

3. Some improvements in carrying out the Schmidt reaction are suggested.

4. The factors influencing the Schmidt reaction are correlated with a carbonium ion mechanism.

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[20] H. Hübner, *Ann.*, **209**, 355 (1881).

[21] See footnote *l* in table.

[22] C. Graebe and C. A. Wander, *Ann.*, **276**, 248 (1893).

[23] O. Dimroth and W. Wislicenus, *Ber.*, **38**, 1573 (1905).

[24] Microanalysis by Micro-Tech. Laboratories, Skokie, Illinois.

[25] F. S. Kipping and A. Hill, *J. Chem. Soc.*, **75**, 151 (1899).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Ketoxime-O-sulfonic Acids[1]

BY PETER A. S. SMITH

Recently,[2] Sanford, Blair, Arroya and Sherk reported on the reaction of hydroxylamine-O-sulfonic acid with ketones, finding that aryl alkyl ketones yield the same amide as obtained from the Beckmann rearrangement of the corresponding oxime, and that aliphatic ketones yield only the oximes. An explanation of these facts was suggested involving the addition of hydroxylamine-O-sulfonic acid to the carbonyl group, subsequent loss of sulfuric acid, and final rearrangement of the organic fragment either to an oxime or to an amide. A different course for this reaction was suggested to the writer by an observation by Sommer, Schulz and Nassau[3] that salts of ketoxime-O-sulfonic acids can be made by the interaction of ketones with neutralized aqueous solutions of hydroxylamine-O-sulfonic acid.

If the initial reaction between a ketone and hydroxylamine-O-sulfonic acid is the elimination of water to form a ketoxime-O-sulfonic acid, then an oxime might arise by hydrolysis of the sulfonyl group, or an amide might arise by direct rearrangement of the sulfonic acid, as indicated below. Some amide might also arise by the Beckmann rearrangement of the oxime under the influence of the sulfuric acid produced by the hydrolysis.

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[1] Presented before the Division of Organic Chemistry at the 111th meeting of the American Chemical Society, Atlantic City, April, 1947.

[2] J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, THIS JOURNAL, **67**, 1941 (1945).

[3] F. Sommer, O. F. Schulz and M. Nassau, *Z. anorg. allgem. Chem.*, **147**, 142 (1925).