Studies of the Reactions of Amines with Sulfur Trioxide. IV.[1] One-step Synthesis of N-substituted Imidobissulfates from Amines[2]
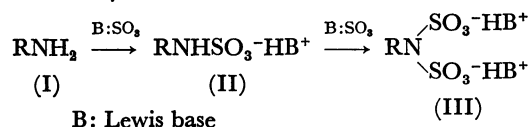
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(Received February 18, 1974)

The scope and limitations of a one-step synthesis of N-substituted imidobissulfates, $RN(SO_3K)_2$ (R=Me, Et, n-Pr, iso-Pr, n-Bu, iso-Bu, sec-Bu, tert-Bu, $n\text{-}C_6H_{13}$, cyclo-C_6H_{11}, $PhCH_2$-, $PhCH_2CH_2$-, $PhCH(CH_3)$-, or Ph), starting from amines and the sulfur trioxide–triethylamine complex are described. The yields are generally good (55—90%). However, with aniline only a poor (13%) yield was obtained. With tert-butylamine, tert-butylamidosulfate was obtained quantitatively instead of the expected tert-butylimidobissulfate. Bis(cyclohexylammonium) salts of the imidobis(sulfuric) acids are prepared, and their properties are briefly recorded.

In a preceding paper[1] we described a new synthesis of N-substituted imidobissulfates (III)[3] by the N-sulfonation of the corresponding amidosulfates (II)[3] with various sulfonating agents, particularly with the 2-picoline–sulfur trioxide addition compound. In general, N-substituted amidosulfates are readily prepared by the interaction of amines (I) with a variety of sulfonating agents,[4] such as chlorosulfuric acid, pyridine–sulfur trioxide, or sulfur trioxide–trimethylamine. Therefore, the reaction of amines with a suitable sulfonating agent appears to provide a more convenient synthetic route to a wide variety of N-substituted imidobissulfates (III).

$$RNH_2 \xrightarrow{B:SO_3} RNHSO_3^-HB^+ \xrightarrow{B:SO_3} RN\begin{array}{l} SO_3^-HB^+ \\ SO_3^-HB^+ \end{array}$$

$$\text{(I)} \qquad\qquad \text{(II)} \qquad\qquad\qquad \text{(III)}$$

B: Lewis base

However, only a few reports on the formation of N-substituted imidobissulfates in the reaction of amines with a sulfonating agent have been recorded. Reitz et al.[5] first suggested that benzylimidobissulfate might have been formed in the action of the pyridine–sulfur trioxide complex on benzylamine. Recently, Vrba and Allan[6] have described briefly the preparation of phenylimidobissulfate (aniline-N,N-disulfonate) by the reaction of a 1 mol equiv. of aniline with a 2 mol equiv. of the 2-picoline–sulfur trioxide complex in chloroform at 0 °C for 1 hr. Very recently, sulfatoethyl- and sulfatopropylimidobissulfates have been prepared[7] in yields of 72.3 and 53.0% respectively by the N-sulfonation of 2-hydroxyethyl- and 3-hydroxypropylamines with pyridine–sulfur trioxide in pyridine. We have shown[8] that, under appropriate conditions, methylimidobissulfate can be obtained as the main product in the gas-phase reaction of methylamine with sulfur trioxide.

We wish now to report a one-step synthesis of N-substituted imidobissulfates by the N-sulfonation of amines with sulfur trioxide–triethylamine. Unlike the complexes of sulfur trioxide with pyridine bases conventionally used in the early work, sulfur trioxide–triethylamine is much more stable and can conveniently be stored in a refrigirator for long periods of time without decomposition.[9] In addition, the latter complex is fairly soluble in the solvents commonly used for the reaction, such as chloroform, 1,2-dichloroethane, and pyridine bases.[9]

Synthesis. The general procedure simply involves adding an amine to a solution of sulfur trioxide–triethylamine in 2-picoline and allowing the reaction mixture to stand at room temperature for 1—3 days. For each reaction, 6—10 mmol of an amine and a 5—10% molar excess of the sulfonating agent were usually used. After the reaction, the solvent was removed.

The product was then converted into the potassium salt by adding aqueous potassium hydroxide. No difficulty was encountered in separating the imidobissulfate from the amidosulfate which was always formed, generally in a small quantity (except for tert-butyl-, 1-phenylethyl-, and phenylamidosulfates). Thus, the imidobissulfate was easily separated from the amidosulfate by extracting the latter with methanol. In the case of cyclohexylimidobissulfate, the separation was best achieved by the use of 85 wt% methanol.

First, we examined the effect of changes in the reaction time and the temperature on the product yields. The results are illustrated in Fig. 1 and Table 1. When n-butylamine was used as a substrate, the reaction at room temperature was unexpectedly rapid and was virtually complete in 2 hr; a 70% yield of n-butylimidobissulfate was obtained. However, increasing the reaction time to 23 hr improved the yield to 80%. On the other hand, the reaction at 80 °C led to considerably lower yields (50—65%). In the
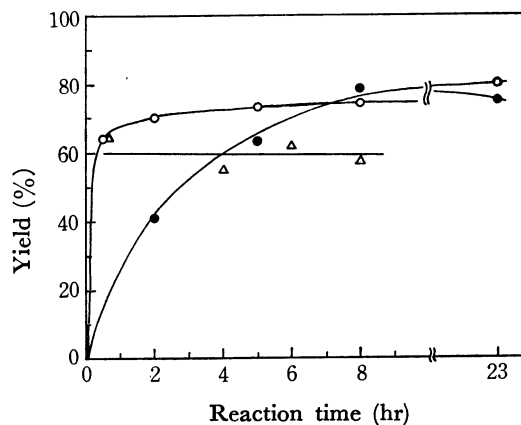

Fig. 1. Effects of reaction time and temperature on the yield of n-butylimidobissulfate.

n-Butylamine, 6—10 mmol; n-Butylamine: sulfur trioxide–triethylamine molar ratio was ~1:2.1.
● −5 °C; ○ 25—30 °C; △ 75—85 °C.

TABLE 1. EFFECTS OF REACTION TIME AND TEMPERATURE ON THE YIELD OF IMIDOBISSULFATES

R	pK_a	Amount (mmol)	$(C_2H_5)_3$-N-SO$_3$ (mmol)	Temp (°C)	Time (hr)	Yield[a] (%)
sec-Bu	10.56[b]	7.0	15.2	25—30	23	65
sec-Bu		7.5	22.3	25—30	46	80
cyclo-C$_6$H$_{11}$	10.64[b]	6.4	13.4	28—30	49	60
cyclo-C$_6$H$_{11}$		6.3	13.4	25—30	72	65
PhCH(CH$_3$)		5.6	11.6	26—27	47	35
PhCH(CH$_3$)		7.5	15.9	25—30	82	55
PhCH(CH$_3$)		56.6	113.0	85—95	3	39
PhCH(CH$_3$)		5.9	12.5	85—95	8	4

a) Yields are based on the starting amine and corrected for the purity of the isolated imidobissulfate.
b) N. F. Hall and M. R. Sprinkle, *J. Amer. Chem. Soc.*, **54**, 3469 (1932).

case of bulky amines such as *sec*-butylamine, cyclohexylamine, and 2-phenylethylamine, a much longer reaction period (47—82 hr) was required. The yields ranged from 55 to 80% when the reaction was conducted at room temperature. It is noteworthy, however, that the reaction at 90 °C with 1-phenylethylamine as a substrate led to very low yields.

The results with the other amines as substrates are summarized in Table 2.

Benzyl- and 2-phenylethyl- as well as primary alkylimidobissulfates were obtained in yields of 80—93%

TABLE 2. SYNTHESIS OF *N*-SUBSTITUTED IMIDOBISSULFATES BY THE *N*-SULFONATION OF AMINES WITH SULFUR TRIOXIDE–TRIETHYLAMINE[a]

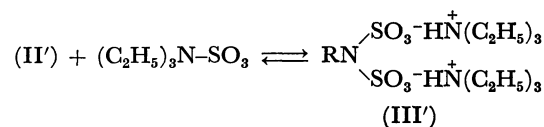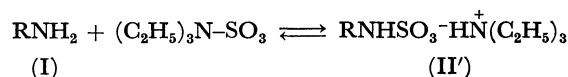| R	pK_a	Amount (mmol)	$(C_2H_5)_3$-N-SO$_3$ (mmol)	Time (hr)	Yield[b] (%)
CH$_3$	10.62[f]	98.2	211.6	23	92
C$_2$H$_5$	10.63[f]	6.5	13.8	23	89
n-C$_3$H$_7$	10.53[f]	8.1	16.5	47	90
iso-C$_3$H$_7$	10.63[f]	7.4	15.7	47	75
n-C$_4$H$_9$	10.61[g]	12.6	24.9	23	80
n-C$_4$H$_9$		6.2	13.8	47	82
iso-C$_4$H$_9$	10.43[g]	8.4	17.5	23	85
tert-C$_4$H$_9$	10.45[f]	7.4	15.8	46	0[c]
n-C$_6$H$_{13}$	10.64[g]	5.8	12.8	48	82
PhCH$_2$	9.34[h]	6.1	12.4	47	83
PhCH$_2$CH$_2$	9.83[h]	6.5	13.8	23	63
Ph	4.58[i]	6.8	14.9	71	13[d,e]

a) Experiments were carried out at room temperature (25—30 °C). b) Yields are based on the starting amine and corrected for the purity of the isolated products. c) *tert*-Butylamidosulfate was obtained quantitatively. d) Isolated main product was the corresponding amidosulfate. e) Isolated as the sodium salt. Anal. Found: N, 4.70; S, 21.50%. Calcd for C$_6$H$_5$O$_6$NS$_2$Na$_2$: N, 4.71; S, 21.58%. f) H. K. Hall Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957). g) C. W. Hoerr and M. R. McCorkle, *ibid.*, **65**, 328 (1943). h) B. M. Wepster, *Rec. Trav. Chim. PaysBas*, **71**, 1171 (1952). i) N. F. Hall and M. R. Sprinkle, *J. Amer. Chem. Soc.*, **54**, 3469 (1932).

after a 23-to 48-hr reaction at room temperature. The use of a large excess of sulfur trioxide–triethylamine does not improve the yields, but has a deleterious effect on the product isolation in a pure state. This procedure also works well on a larger (0.1-mol) scale.

Some attempts to prepare *tert*-butylimidobissulfate by this method were unsuccessful, but *tert*-butylamidosulfate was obtained instead in a nearly quantitative yield. A model shows that the amidosulfate is too sterically hindered to undergo further *N*-sulfonation.

Aniline afforded phenylimidobissulfate in only a poor yield.[11] In this case, the main product was phenylamidosulfate. The low yield of the former compound is most probably due to the low basicity of the amido nitrogen of the latter.

The *N*-sulfonation of primary amines with sulfur trioxide–triethylamine proceeds as is shown in the Scheme. The data described above can best be explained by assuming that an equilibrium exists between amidosulfate (II′) and bis(triethylammonium) imidobissulfate (III′). (1) The temperature, (2) the steric requirement of a substituent on the nitrogen, (3) the basicity of the amido nitrogen, and (4) the basicity of the tertiary amine (triethylamine in this case) forming a sulfur trioxide addition compound are important factors governing the equilibrium and, therefore, the yield of III′.

$$RNH_2 + (C_2H_5)_3N-SO_3 \rightleftharpoons RNHSO_3^- \overset{+}{H}N(C_2H_5)_3$$
(I)   (II′)

$$(II') + (C_2H_5)_3N-SO_3 \rightleftharpoons RN \begin{matrix} SO_3^- \overset{+}{H}N(C_2H_5)_3 \\ SO_3^- \overset{+}{H}N(C_2H_5)_3 \end{matrix}$$
(III′)

Scheme.

The differences in the product yields as well as in the rate of reaction seem to be ascribable mainly to steric factors. Evidently, a large steric requirement of a substituent on the nitrogen atom, as in cyclohexylamine and 2-phenylethylamine, hinders the attack of the bulky sulfonating agent on the amido nitrogen of II′ by blocking the line of approach. Steric strain due to crowding at the imido nitrogen plays an important role in determining the stabilities of III′ and, hence, the position of the equilibrium between II′ and III′. Thus, at higher temperatures, the equilibrium shifts towards II′.

Preparation and Properties of the Bis(cyclohexylammonium) Salts. Amine salts of unsubstituted imidobis(sulfuric) acid were first prepared by Boatman and Sisler.[12] The procedure involves heating diammonium imidobissulfate with an amine in liquid ammonia, water, or an alcohol solution. Free imidobis(sulfuric) acid readily undergoes the hydrolytic cleavage of the sulfur-nitrogen bond in the aqueous solution; hence, it has not hitherto been isolated.[13] Its salts also undergo ready acid-catalyzed hydrolysis.[14] However, Nakano and Yamaguchi[15] have recently prepared eleven bis(tertiary ammonium) salts of unsubstituted imidobis(sulfuric) acid. Their procedure can successfully be applied to the preparation of the bis(cyclohexylammo-
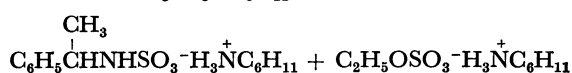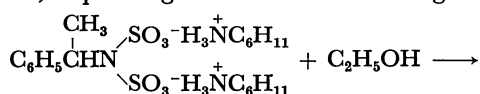
TABLE 3. BIS(CYCLOHEXYLAMMONIUM) IMIDOBISSULFATES

$$RN\left(SO_3^-H_3N^+-\left\langle H\right\rangle\right)_2$$

R	Mp (°C)ᵃ⁾	Recryst. solvent	Analysis (%) N Found (Calcd)	Analysis (%) S Found (Calcd)	Imido-group equiv. Found	Imido-group equiv. (Calcd)
CH_3	195—197.5	iso-PrOH	10.80 (10.79)	16.22 (16.46)	399	(389.5)
C_2H_5	181.5—182.5	iso-PrOH	10.40 (10.41)	15.98 (15.89)	406	(403.6)
n-C_3H_7	184—184.5	EtOH	10.17 (10.06)	15.38 (15.36)	426	(417.6)
iso-C_3H_7	142—143.5	H_2O	10.16 (10.06)	15.33 (15.36)	432	(417.6)
n-C_4H_9	182.5	EtOH	9.84 (9.74)	14.73 (14.86)	451	(431.6)
iso-C_4H_9	177—178.5	EtOH	9.83 (9.74)	14.66 (14.86)	443	(431.6)
sec-C_4H_9	138.5—140	EtOHᵈ⁾	9.71 (9.74)	14.75 (14.86)	450	(431.6)
n-C_6H_{13}	154.5—155.5	EtOH	9.16 (9.14)	13.78 (13.95)	472	(459.7)
Cyclohexyl	b)	H_2O	8.97 (9.18)	13.76 (14.01)	475	(457.7)
$PhCH_2$	212—212.5	H_2O	9.05 (9.03)	13.58 (13.77)	476	(465.6)
$PhCH(CH_3)$	c)	EtOHᵈ⁾	8.88 (8.76)	13.35 (13.37)	513	(479.7)

a) In all cases, the melting points depended on the rate of heating, since thermal decomposition (effervescence) occurred on heating. b) Apparent shrinking occurred at 184.5 °C (placed in the bath at 178 °C). However, no definite melting was observed up to 250 °C. c) An indication of melting was observed at 114—126 °C and a meniscus was formed at 140—150 °C. d) Recrystallization was achieved by dissolving the product in ethanol at room temperature, filtering the solution, and setting aside overnight in a refrigirator (−27 °C).

nium) salts of the primary alkyl-substituted imidobis-(sulfuric) acid from the potassium salts obtained above, whereas in the case of sterically-strained sec-alkyl-, cycloalkyl-, and 1-phenylethylimidobissulfates, considerable hydrolysis occurs. This disadvantage can, however, be overcome by a direct cation-exchange procedure (see the Experimental section). This procedure can be conducted at room temperature, since the ion-exchange process is carried out under neutral conditions.

The bis(cyclohexylammonium) salts so obtained are summarized in Table 3. All the salts are non-hygroscopic, colorless crystals; they are soluble in water, methanol, and ethanol, and practically insoluble in acetone, ether, and ethyl acetate. The stabilities of the N-substituted imidobissulfates are dependent on the basicity of the salt-forming bases as well as on the magnitude of the internal strain due to the steric crowding at the imido nitrogen. Thus, primary alkyl- and benzylimidobissulfates can be recrystallized without appreciable degradation from boiling water or ethanol containing a few drops of cyclohexylamine, although prolonged heating (15—30 min) led to a complete decomposition. On the other hand, bis(cyclohexyl-ammonium) 1-phenylethylimidobissulfate decomposed almost instantly in boiling ethanol to afford ethyl sulfate and 1-phenylethylamidosulfate. All the salts also decomposed partially or completely at their melting points, depending on the rate of heating.

$$C_6H_5CHN\overset{CH_3}{\underset{}{\Big\langle}}\overset{SO_3^-H_3\overset{+}{N}C_6H_{11}}{\underset{SO_3^-H_3\overset{+}{N}C_6H_{11}}{}} + C_2H_5OH \longrightarrow$$

$$C_6H_5\overset{CH_3}{\underset{}{C}}HNHSO_3^-H_3\overset{+}{N}C_6H_{11} + C_2H_5OSO_3^-H_3\overset{+}{N}C_6H_{11}$$

The trans-sulfonation and thermal decompositions of the imidobissulfates are currently being studied and will soon be reported.

Experimental

The melting points were measured in sealed capillaries and corrected. The infrared spectra were recorded for potassium bromide discs on a JASCO IR-S spectrometer. The 1,2-dichloroethane was dried over calcium chloride, distilled, and stored over a molecular sieve (type 3A). The triethylamine and 2-picoline were dried by distillation from potassium hydroxide pellets and stored over a molecular sieve (type 3A). The methylamine (anhydrous) was supplied in a cylinder by the Nitto Chemical Industry, Ltd. The other amines were commercially available and were used without further purification.

Preparation of Triethylamine–Sulfur Trioxide Complex.   The complex was prepared by adding triethylamine to a solution of sulfur trioxide in 1,2-dichloroethane at from −5 to 10 °C; mp 90.5—93 °C (from water) (lit,[16] 91.5°); ν_{SO_3} 1055 (s), ν_{SO_3} 1290 (s), δ_{CH} 1400 (m), 1447 (m), and 1465 (m) cm⁻¹.

General Procedure for the Sulfonation of Amines with Sulfur Trioxide–Triethylamine.   The quantities of the amine and the sulfur trioxide adduct used for each reaction are given in Tables 1 and 2. The appropriate amine in dry 2-picoline(10ml) was added, drop by drop, to a stirred solution of the sulfur trioxide–triethylamine complex in dry 2-picoline (20 ml). Stirring was continued for five min., and then the mixture was allowed to stand at a given temperature (−5 to 5 °C and 25—30 °C) or heated at 85—95 °C. The solvent was evaporated off under reduced pressure at a bath temperature below 50 °C, and the residue was dissolved cautiously in cold water (25 ml), neutralized with a potassium hydroxide solution, and treated with charcoal. The filtrate was then evaporated to dryness under reduced pressure, and the residue was extracted with methanol[17] (40—60 ml). The residual solid was dissolved in water (20 ml), and a barium acetate solution (5%) was added until no more precipitate was formed. The filtered solution was evaporated to dryness under reduced pressure; the residue was extracted with methanol (30 ml), filtered, and washed with methanol to give the product (92—99% purity, as calculated from the imido-group equivalent[18]).

Conversion into the Bis(cyclohexylammonium) Salts. (a) An ice-cold solution of the potassium salt (0.7 g in 10 ml) was passed through a column of Amberlite IR-120 (H⁺ form) which had been externally cooled to —5—0 °C. The eluate was immediately neutralized with an excess of aqueous cyclohexylamine, and the solution was evaporated to dryness at a temperature below 40 °C while kept alkaline. The residue was recrystallized from an appropriate solvent (see Table 3).

(b) A solution of the potassium salt was passed through a column of Amberlite IR-120 (cyclohexylammonium-salt form), and the eluate was evaporated to dryness. The products so obtained were sufficiently pure for practical purposes. Purer products may be obtained by recrystallization from ethanol containing a drop of cyclohexylamine (room temperature→—27 °C).

We wish to thank the Nitro Chemical Industry, Ltd. for its gift of anhydrous methylamine.

References and Footnotes

1) Part III. F. Kanetani and H. Yamaguchi, *Yuki Gosei Kagaku Kyokai Shi*, **32**, 460 (1974).

2) Presented in part at the 29th Annual Meeting of the Chemical Society of Japan, Hiroshima, October 10—14, 1973.

3) Although the names imidodisulfonic acid (also called amine disulfonic acid) or imidodisulfuric acid (used for indexing by the Chemical Abstracts Service), and sulfamic acid have conventionally been used, we prefer the names imidobis(sulfuric) acid and amidosulfuric acid respectively, for they are more consistent with the naming of the imido and amido derivatives of sulfuric acid.

4) A. Dorlars, "Methoden der Organischen Chemie," 4. Aufl., Bd. XI/2, ed. by Eugen Müller, Georg Thieme Verlag, Stuttgart (1958), pp. 645—687.

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10) Recently, thermal degradation of di(tertiary ammonium) salts of unsubstituted imidobis(sulfuric) acid into amidosulfate and a tertiary amine–sulfur trioxide adduct has been reported: H. Yamaguchi and T. Fujii, *Nippon Kagaku Kaishi*, **1973**, 2157.

11) It was stated that the pyridine–sulfur trioxide complex is ineffective for the formation of phenylimidobissulfate whereas 2-picoline–sulfur trioxide yields the desired product (see Ref. 6).

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14) a) H. H. Sisler and L. A. Audrieth, *J. Amer. Chem. Soc.*, **60**, 1947 (1938); b) G. J. Doyle and N. Davidson, *ibid.*, **71**, 3491 (1949).

15) K. Nakano and H. Yamaguchi, *Kogyo Kagaku Zasshi*, **67**, 1878 (1964).

16) F. Beilstein and E. Wiegand, *Ber.*, **16**, 1264 (1883).

17) In all cases, the corresponding amidosulfates were isolated from the methanol solution. They were identified by comparing the IR spectra and melting points of their dibutylammonium salts with those of authentic sample (see Ref. 1).

18) F. Kanetani and H. Yamaguchi, *Yuki Gosei Kagaku Kyokai Shi*, **30**, 539 (1972).