[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY]

The Sulfonic Acids Derived from Pyridine and 2,6-Lutidine and the Corresponding *N*-Oxides[1]

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2-, 3-, and 4-pyridinesulfonic acids were prepared and characterized as the *S*-benzylisothiuronium derivatives. The sulfonic acids were not affected by hydrogen peroxide and glacial acetic acid, but the sodium salts were readily converted into the corresponding *N*-oxides. The chlorine in 2-, 3-, and 4-chloropyridine 1-oxides was easily replaced by $-SO_3Na$ using aqueous sodium sulfite. With 2- and 4-chloropyridine, partial replacement only occurred, but the 3-isomer was unaffected. 4-Bromo-2,6-lutidine with sodium sulfite at 190° gave the corresponding 4-sulfonic acid. Sulfonation of 2,6-lutidine and its *N*-oxide occurred in the 3-position.

Previous papers from this laboratory have described the measurement of the dissociation constants of alkyl-[4] and halopyridines.[5] In connection with an extension to this program it was necessary to obtain specimens of pyridine and 2,6-lutidine monosulfonic acids.

2-Pyridinesulfonic acid was obtained by the nitric acid oxidation of 2-mercaptopyridine,[6,7] itself prepared from 2-bromopyridine and aqueous alcoholic potassium hydrogen sulfide in a sealed tube at 160–170°. A more direct synthesis involved the replacement of a halogen atom in the 2-position of pyridine by $-SO_3Na$. However, with 2-chloropyridine and aqueous alcoholic sodium sulfite at high temperatures, replacement was only partial, while 2-bromopyridine under the same conditions underwent extensive decomposition. As expected from the activating effect of the *N*-oxide linkage, nucleophilic displacement of the halogen in 2-chloropyridine 1-oxide by $-SO_3Na$ occurred more readily, but was accompanied by reduction of the *N*-oxide linkage.

3-Pyridinesulfonic acid was obtained from commercial sodium 3-pyridinesulfonate by passage through a cation-exchange resin. Although an alternate method of synthesis was unnecessary, it was of interest to compare the 2- and 3-chloropyridines in their behavior with sodium sulfite. It was found that 3-chloropyridine was stable to aqueous sodium sulfite under extreme conditions. However, replacement of the halogen did occur with the *N*-oxide derivative. Here the halogen atom is activated toward nucleophilic attack only by the operation of the inductive effect arising from the *N*-oxide linkage. The σ value of the latter (1.59)[8] indicates that it is one of the most powerful electron withdrawing groups known. The 3-pyridinesulfonic acid 1-oxide thus prepared had an infrared spectrum identical with that of the product obtained by the sulfonation of pyridine 1-oxide itself.[9] More recently,[10] it was shown that minor quantities (0.5–1% and 2–2.5%, respectively) of the 2- and 4-sulfonic acids were formed in the sulfonation reaction.

4-Pyridinesulfonic acid was reputedly first prepared by Koenigs and Kinne,[11] who oxidized 4-mercaptopyridine, m.p. 177°, with nitric acid and obtained an acidic material, m.p. 134–135°. Since it was considered unlikely that a sulfonic acid, particularly one with a zwitterionic structure, would have a melting point lower than that of the corresponding mercapto compound, we investigated the effect of other oxidizing agents on 4-mercaptopyridine. We found that oxidation with hydrogen peroxide in barium hydroxide solution and precipitation of the barium from the reaction solution with sulfuric acid led to the isolation of white needles, m.p. 317–318°, whose alkali equivalent and elemental analysis supported the claim that it was 4-pyridinesulfonic acid. Since our original work was completed, the oxidation of 4-mercapto-

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(4) H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

(5) D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3752 (1955).

(6) W. Marckwald, W. Klemm, and H. Trabert, *Ber.*, **33**, 1556 (1900).

(7) A. J. P. van Gastel and J. P. Wibaut, *Rec. trav. chim.*, **53**, 1031 (1934).

(8) H. H. Jaffé, *J. Am. Chem. Soc.*, **76**, 3527 (1954).

(9) H. S. Mosher and F. J. Welch, *J. Am. Chem. Soc.*, **77**, 2902 (1955).

(10) M. van Ammers and H. J. den Hertog, *Rec. trav. chim.*, **78**, 587 (1959).

(11) E. Koenigs and G. Kinne, *Ber.*, **54**, 1357 (1921).

pyridine with nitric acid has been reinvestigated[12-14] and it is concluded that the acidic product, m.p. 134–135°, isolated by Koenigs and Kinne,[11] is a mixture of di-4-pyridyldisulfide dinitrate and 4-pyridinesulfonic acid. The latter was isolated by fractional crystallization of the mixture and the values of the melting points of the specimens of acid isolated in this way were not very different from our value.

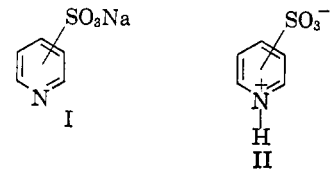
Sodium bisulfite, but not the sulfite, was found to yield sodium 4-pyridinesulfonate (albeit in small yield) when it was heated with aqueous 4-hydroxypyridine to 150°. This reaction may involve intermediates similar to those isolated in the Bucherer and allied reactions.[15]

Nucleophilic replacement of chloride by —SO_3Na occurred when either 4-chloropyridine or its more active *N*-oxide reacted with sodium sulfite. The yield of the product obtained in the first case suggested that the 4-chloropyridine polymerized before reacting.[16,17]

4-Pyridinesulfonic acid 1-oxide did not rearrange under the conditions used for the sulfonation of pyridine 1-oxide[9] to the 3-sulfonic acid and it was concluded that the 4-acid was not an intermediate in the latter sulfonation.

For large scale preparations of 4-pyridinesulfonic acid, we used a modification of a patent by Tiesler,[18] who claimed to have obtained the alkali metal salts of 4-pyridinesulfonic acid when *N*-(4-pyridyl)-pyridinium chloride hydrochloride was heated in a sealed tube with aqueous solutions of alkali metal sulfites or bisulfites. It was found that the reaction with sodium sulfite occurred at 100° and sealed tubes were unnecessary. The sodium 4-pyridinesulfonate was extracted from the dehydrated reaction mixture by boiling ethanol; the free sulfonic acid was liberated by passage of a dilute aqueous solution of the sodium salt through a cation-exchange column or by precipitation of the sodium with excess concentrated hydrochloric acid.

The three pyridinesulfonic acids were characterized as the crystalline *S*-benzylisothiuronium salts and *N*-oxide derivatives. The sodium salts, in preference to the free acids, were used to prepare the *N*-oxide derivatives, an acetic acid solution of hydrogen peroxide being used for the oxidation. In the sodium salts (I) the ring nitrogen atom still possessed a pair of unshared electrons which would be ready to coordinate with an electrophilic reagent. In the free acids, this pair of electrons would be unavailable because of the formation of the zwitterion (II).



I II

Marckwald's[6] synthesis of 2,6-lutidine 4-sulfonic acid from 4-chloro-2,6-lutidine via the 4-mercapto derivative is the only method described in the literature.

In this work, we used the same route, but the oxidation of 4-mercapto-2,6-lutidine was carried out with hydrogen peroxide in the presence of barium hydroxide and the barium removed by precipitation with sulfuric acid.

4-Chloro-2,6-lutidine was not obtained by diazotization of 4-amino-2,6-lutidine since the latter was obtained in poor yield from 2,6-lutidine and sodamide in boiling *N*,*N*-dimethylaniline. Instead, it was prepared by conversion of 2,6-lutidine into its *N*-oxide, which reacted with phosphorus oxychloride,[19] tetrachloroethane being used as a diluent to control the reaction.

The bromine atom in 4-bromo-2,6-lutidine was completely replaced by —SO_3Na, with the aid of aqueous alcoholic sodium sulfite at 190°.

The sulfonic acid, a high melting solid, was characterized as its *S*-benzylisothiuronium salt and, in the form of its sodium salt, was oxidized to the *N*-oxide derivative.

The first approach to the synthesis of 2,6-lutidine 3-sulfonic acid, hitherto unknown, was by blocking the 4-position of the 2,6-lutidine nucleus, sulfonating, and then removing the blocking group from the sulfonation product. The two blocking groups used were amino and chloro, respectively.

4-Amino-2,6-lutidine was sulfonated readily under a variety of conditions, but the product proved to be the sulfone. 4-Chloro-2,6-lutidine was sulfonated with difficulty but the product, isolated in very poor yield, was the 4-hydroxy-3-sulfonic acid. It seems likely that the barium hydroxide caused hydrolysis of the chloro group during the isolation of the product.[20]

Direct sulfonation of 2,6-lutidine 1-oxide according to the procedure worked out by McElvain[21] for pyridine was successful. A sulfonic acid was isolated with analysis agreeing with a 2,6-lutidine-

(12) A. M. Comrie and J. B. Stenlake, *J. Chem. Soc.*, 1853 (1958).

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(15) N. L. Drake, *Org. Reactions*, **I**, 106 (1942).

(16) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

(17) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **78**, 593 (1959).

(18) A. E. Tiesler, U. S. Patent **2,330,641**; *Chem. Abstr.*, **38**, 1249 (1944).

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(20) E. Koenigs and O. Jungfer, *Ber.*, **57**, 2080 (1924).

(21) S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.*, **65**, 2233 (1943).

TABLE I

M.P.'S OF THE SULFONIC ACIDS DERIVED FROM PYRIDINE AND 2,6-LUTIDINE

Compound	M.p. This work	M.p. Literature
2-Pyridinesulfonic acid	251–252°	239–240°,[a] 240°,[b] 247–248°[c]
3-Pyridinesulfonic acid	358–360°	338–339°,[d] 339°,[e] 352–356°,[f] 353°,[g] 354°,[h] 357°,[c,i] 365–370°[j]
4-Pyridinesulfonic acid	317–318°	134–135°,[k] 321–322°,[l] 330°,[m] 333–334°[n]
2,6-Lutidine 3-sulfonic acid	>350°	
2,6-Lutidine 4-sulfonic acid	>350°	>300°[a]

[a] Ref. 6. [b] E. Plazek and A. Marcinkow, *Roczniki Chem.*, **14**, 326 (1934); *Chem. Abstr.*, **19**, 2535 (1935). [c] Ref. 7. [d] Ref. 9. [e] Ref. 20. [f] Ref. 21. [g] P. H. Hope and S. Leon, *Ciencia* (Mex.), **8**, 263 (1948); *Chem. Abstr.*, **44**, 7320 (1950). [h] B. F. Duesel and J. V. Scudi, *J. Am. Chem. Soc.*, **71**, 1866 (1949). [i] C. H. Kao, *J. Chem. Eng. China*, **15**, 80 (1948); *Chem. Abstr.*, **44**, 3993 (1950). [j] G. Machek, *Monatsh.*, **72**, 77 (1938). [k] Ref. 11. [l] Ref. 14. [m] Ref. 13. [n] Ref. 12.

sulfonic acid 1-oxide and had a melting point and infrared spectrum different from that of the corresponding 4-acid. This evidence established the identity of this acid as 2,6-lutidine 3-sulfonic acid 1-oxide.

Reduction of the acid with hydrogen and palladized charcoal in acetic anhydride–acetic acid suspension yielded 2,6-lutidine 3-sulfonic acid. Infrared analysis confirmed that reduction had occurred and that the product was not 2,6-lutidine 4-sulfonic acid.

Finally, 2,6-lutidine itself was sulfonated by an adaptation of McElvain's procedure[21] and the product, isolated in good yield, consisted solely of the 3-sulfonic acid, a conclusion based on the examination of the infrared spectra (Table II). Thus 2,6-lutidine 1-oxide behaves exactly like pyridine 1-oxide[9,22] in that sulfonation and nitration occur in different positions in the nucleus.

Table I summarizes the present position with respect to the melting points of the various sulfonic acids.

EXPERIMENTAL[23]

Materials. The 2- and 3-halopyridines used were prepared and purified by Dr. Solomon[24] by standard procedures.

2-Pyridinesulfonic acid. (a) 2-Mercaptopyridine was obtained in 97% yield by heating 2-bromopyridine with aqueous alcoholic potassium hydrogen sulfide[25] in a sealed tube at 160–170° for 20 hr. Recrystallization from benzene and treatment with charcoal afforded yellow plates, m.p. 127.5–129° (lit.[26] m.p. 130–132°).

Oxidation[6] of 11.6 g. of 2-mercaptopyridine with 74 ml. of nitric acid (*d* 1.42) and 222 ml. of water on the steam bath for 30 min. gave a red oil which crystallized from boiling 95% alcohol affording 14.4 g. (86%) of 2-pyridinesulfonic acid m.p. 251–252°.

(b) A mixture of 11.4 g. (0.1 mole) of 2-chloropyridine, 44.7 g. (0.3 mole) of sodium sulfite, 20 ml. of water, and 20 ml. of 95% alcohol was heated in a sealed tube to 185° for 12 hr. The mixture was evaporated to dryness under reduced pressure on the steam bath. Oily drops collected in the distillate receiver and the smell of 2-chloropyridine became evident.

The solid residue, after removal of all unchanged base by repeated solution in water followed by evaporation of the solution, was continuously extracted with alcohol in a Soxhlet extractor. The solid extract, in aqueous solution, was passed through a cation exchange resin (Nalcite HCR) and from the acidic eluate 1.05 g. (7%) of 2-pyridinesulfonic acid m.p. and mixed m.p. 251–252° was obtained.

Anal. Calcd. for $C_5H_5NO_3S$: Equiv. wt. 159.2. Found: equiv. wt. 161. 2-Bromopyridine, under similar conditions, decomposed extensively.

(c) 2-Chloropyridine 1-oxide was prepared by treating 20 g. (0.176 mole) of 2-chloropyridine with 106 ml. of glacial acetic acid and 35.1 ml. of 30% hydrogen peroxide at 70–80° for 12 hr. The solution was then concentrated *in vacuo* to *ca.* 60 ml., water was added, and the concentration process was repeated. After the third such treatment, the cold concentrate was made strongly alkaline with anhydrous sodium carbonate and shaken repeatedly with chloroform. Evaporation of the chloroform extract at 40–50°/20 mm. furnished 14.9 g. (65%) of 2-chloropyridine 1-oxide, which was used for the next stage without further purification. The picrate had m.p. 105–106°.

Anal. Calcd. for $C_{11}H_7ClN_4O_8$: C, 36.83; H, 1.97; N, 15.62. Found: C, 37.12; H, 2.18; N, 15.74.

A mixture of 14.2 g. (0.11 mole) of this 2-chloropyridine 1-oxide, 27.6 g. (0.22 mole) of sodium sulfite, and 50 ml. water was heated in a sealed tube to 150° for 16 hr. The resulting solution was evaporated to dryness and the residue on extraction with ethanol gave 6.6 g. of material, which was dissolved in water and passed through a column of a cation-exchange resin (Nalcite HCR). Evaporation of the acidic eluate yielded 4 g. (23%) of 2-pyridinesulfonic acid, m.p. and mixed m.p. 251–252°.

An aqueous solution of the alcohol-insoluble material was passed over the ion-exchange resin (Nalcite HCR) and the acidic eluate was concentrated to remove sulfur dioxide. The concentrate was then neutralized with barium hydroxide solution, filtered, and the filtrate again passed through Nalcite HCR. Evaporation of this second acidic eluate gave a solid which was recrystallized from aqueous alcohol. It had m.p. 237–239°, which was depressed upon addition of a little 2-pyridinesulfonic acid. However, a mixed m.p. with an authentic sample of 2-pyridinesulfonic acid 1-oxide, prepared by oxidation of sodium 2-pyridinesulfonate, showed no depression.

3-Pyridinesulfonic acid. A solution of 50 g. of sodium 3-pyridinesulfonate in 1 l. of water was slowly passed through Nalcite HCR. The acidic eluate was evaporated to crystallization point and 24.5 g. of white crystals, m.p. 338–342°, were collected. The mother liquor, on complete evaporation, furnished 15.7 g. of impure material, m.p. 220–300°, and made the recovery 92%.

The white crystals, after three recrystallizations from aqueous ethanol, formed thin white needles, m.p. 358–360°.

Anal. Calcd. for $C_5H_5NO_3S$: C, 37.72; H, 3.17; N, 8.80. Found: C, 37.88; H, 3.18; N, 9.16.

Reactions with sodium sulfite. (a) *With 3-chloropyridine.* Only 3-chloropyridine was recovered when 5.7 g. (0.05 mole) of 3-chloropyridine, 14.9 g. (0.12 mole) of sodium sulfite, 0.125 g. (0.0005 mole) of copper sulfate pentahydrate, 20 ml. of water, and 30 ml. of 95% alcohol were heated at 185° in a sealed tube for 16 hr.

(22) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(23) M.p.'s are corrected.

(24) M. M. Solomon, Ph.D. thesis, Purdue University, 1951.

(25) J. R. Thirtle, *J. Am. Chem. Soc.*, **68**, 342 (1946).

(26) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959).

(b) *With 3-chloropyridine 1-oxide.* Eleven and four tenths grams of 3-chloropyridine in 60 ml. of glacial acetic acid was heated with 11.4 ml. of 30% hydrogen peroxide under reflux at 70–80° for 3 hr. The reaction mixture was processed according to Ochiai,[22] yielding 3-chloropyridine 1-oxide (99%) m.p. 59–60° (from ether).

Anal. Calcd. for C_5H_4ClNO: C, 46.35; H, 3.11; N, 10.81. Found: C, 46.07; H, 3.17; N, 10.89.

The picrate had m.p. 137–139°.

Anal. Calcd. for $C_{11}H_7ClN_4O_8$: C, 36.83; H, 1.97; N, 15.62. Found: C, 36.94; H, 1.93; N, 15.48.

A mixture of 7.2 g. (0.0556 mole) of 3-chloropyridine 1-oxide, 14 g. (0.1112 mole) of sodium sulfite, and 42 ml. of water was heated in a sealed tube at 143° for 10 hr. The mixture was evaporated to dryness at 100° under reduced pressure and the solid residue was extracted twice with boiling ether. Evaporation of the ethereal extract furnished 2.4 g. of 3-chloropyridine 1-oxide.

The ether-insoluble material was continuously extracted with ethanol in a Soxhlet apparatus for 30 hr. Evaporation of the ethanolic extract furnished 6.6 g. (90%) of white solid which was dissolved in concd. hydrochloric acid. After filtration of the sodium chloride precipitate, the filtrate was evaporated to dryness and the residue recrystallized twice from methanol. The product had m.p. 238–243°, alone or when mixed with authentic 3-pyridinesulfonic acid 1-oxide, prepared by the direct sulfonation of pyridine 1-oxide.

Sulfonation of pyridine 1-oxide. A mixture of 5 g. (0.053 mole) of redistilled pyridine 1-oxide, 0.5 g. (0.001 mole) of mercuric sulfate, and 50 g. (0.13 mole) of fuming sulfuric acid (21% SO_3) was refluxed at 220° for 22 hr. in an apparatus sealed with a sulfuric acid trap. The cold reaction mixture was poured into ice, neutralized with aqueous barium hydroxide, and filtered. Continuous extraction of the filtrate with chloroform led to the recovery of 1.2 g. of pyridine 1-oxide. The aqueous solution was evaporated to dryness and the solid residue (10.0 g.) was redissolved in 100 ml. of hot water and decomposed with the calculated quantity (2.028 g.) of concd. sulfuric acid in 50 ml. of water. After filtration, the filtrate was evaporated to dryness. The 7 g. of semisolid obtained was stirred with alcohol and filtered, affording 4.4 g. (63%), m.p. 238–243° (lit.[9] m.p. 237–238°). The infrared spectrum of this solid was identical with that of the product from 3-chloropyridine 1-oxide and did not exhibit any features which might be ascribed to the presence of either the 2- or the 4-pyridinesulfonic acid 1-oxides.

N-(4-Pyridyl)pyridinium chloride hydrochloride was prepared from 1190 g. of thionyl chloride and 395 g. of freshly distilled pyridine following the directions of Bowden and Green.[27] The crude product, 328 g. (58%), was used immediately.

A dipicrate, prepared from the complex chloride and picric acid in hot alcoholic solution, formed glistening yellow plates, m.p. 174–175°.

Anal. Calcd. for $C_{22}H_{14}N_8O_{14}$: C, 42.99; H, 2.30; N, 18.25. Found: C, 42.90; H, 2.20; N, 18.29.

4-Hydroxypyridine. A solution of 300 g. (1.31 moles) of crude *N*-(4-pyridyl)pyridinium chloride hydrochloride in 100 ml. of water was distilled until the temperature of the mixture reached 130°. The mixture was then refluxed at this temperature for 24 hr. The solution was made alkaline with aqueous sodium hydroxide and evaporated, under reduced pressure and at 100°, until the smell of pyridine over the reaction mixture had disappeared. The *p*H of the solution was adjusted to 5–6 by the addition of concd. hydrochloric acid and the evaporation process continued until a dry solid residue was obtained. The latter was extracted several times with hot ethanol and the ethanolic extract distilled on the steam bath. Rapid distillation of the residue under reduced pressure gave 86 g. (69%) of material, m.p. 140–146°, b.p. 216–227°/3 mm. The finely divided solid was boiled several times with dry benzene[28] and the residue was recrystallized from ethanol, affording 4-hydroxypyridine, m.p. 147–149° (lit.[29] m.p. 147–151°).

4-Mercaptopyridine prepared from 4-hydroxypyridine and phosphorus pentasulfide[30] in refluxing pyridine, melted with evolution of hydrogen sulfide between 156 and 186° (lit.[26] m.p. 179–189°).

Anal. Calcd. for C_5H_5NS: C, 54.01; H, 4.53; N, 12.6. Found: C, 53.78; H, 4.51; N, 13.05.

Oxidation of 4-mercaptopyridine with hydrogen peroxide. Two and twenty seven one-hundredth grams (0.0203 mole) of 4-mercaptopyridine was neutralized with 45.4 ml. of 0.4487 *N* barium hydroxide (0.0203 equivalent). Seven milliliters of 30% hydrogen peroxide was cautiously added, with external cooling. The mixture was heated on the steam bath under reflux for 90 min., then cooled and the exact quantity of dilute sulfuric acid required to precipitate the barium added. After filtration, the filtrate was evaporated at 20–30°/3 mm. The residue was recrystallized from aqueous ethanol and 2.55 g. (75%) of white needles, m.p. 317–318° dec., of 4-pyridinesulfonic acid were obtained.

Anal. Calcd. for $C_5N_5NO_3S$: C, 37.72; H, 3.17; N, 8.80; equiv. wt. 159.2. Found: C, 37.80; H, 3.03; N, 9.20; equiv. wt. 159.4.

4-Pyridinesulfonic acid. One hundred and fifteen grams (0.5 mole) of *N*-(4-pyridyl)pyridinium chloride hydrochloride was dissolved in 500 ml. of water in a 1 l. flask and 189 g. (1.5 moles) of sodium sulfite was cautiously added. After the evolution of sulfur dioxide had ceased, the solution was refluxed under nitrogen for 12 hr. The solution was diluted to 2 l. with distilled water and refluxed with charcoal for 1 hr. The mixture was filtered and the filtrate distilled on the steam bath under reduced pressure. The moist solid residue was finally air-dried at 100°. This solid was now continuously extracted with ethanol for 24 hr. in a Soxhlet apparatus. Removal of the ethanol from the extract by distillation furnished 83.5 g. of solid which was redissolved in 160 ml. of hot water; 320 ml. of concd. hydrochloric acid was added and the solution was cooled to room temperature. After filtration of the precipitated sodium chloride, the filtrate was evaporated to dryness under reduced pressure on the steam bath and the solid residue was crystallized from aqueous ethanol. There was obtained 40 g. of white crystals, m.p. 310–317° alone or when mixed with the above sample of 4-pyridinesulfonic acid.

Anal. Calcd. for $C_5H_5NSO_3$: equiv. wt. 159.2. Found: equiv. wt. 162.

Concentration of the mother liquors afforded a further 15 g. of material which brought the yield up to 70%.

Reactions involving sodium sulfite and bisulfite. (a) *With 4-hydroxypyridine.* A mixture of 4.5 g. (0.047 mole) of 4-hydroxypyridine, 14.8 g. (0.141 mole) of sodium bisulfite, and 50 ml. of water was heated in a sealed tube to 150° for 9 hr. The tube contents were evaporated to dryness and the residue extracted with ethanol. The cold ethanolic extract deposited 0.33 g. of an infusible white solid which was dissolved in 50 ml. of water and passed through a cation exchange resin column (Nalcite HCR). Evaporation of the acid eluate furnished 0.244 g. (3%) of white solid, identified as 4-pyridinesulfonic acid by m.p. and mixed m.p.

(b) *With 4-chloropyridine.* Pyridine 1-oxide was nitrated according to the general direction of Ochiai[22] and 4-nitropyridine 1-oxide was obtained in 66% yield. Replacement of the nitro group by chlorine to give 4-chloropyridine 1-oxide was best effected by refluxing with concd. hydrochloric acid for 24 hr.,[31] since acetyl chloride, the reagent recom-

(27) K. Bowden and P. N. Green, *J. Chem. Soc.*, 1795 (1954).

(28) F. Arndt and A. Kalischek, *Ber.*, **63**, 587 (1930).

(29) B. Bak and D. Christensen, *Acta Chem. Scand.*, **8**, 390 (1954).

(30) H. King and L. L. Ware, *J. Chem. Soc.*, 873 (1939).

(31) H. J. den Hertog and W. P. Combé, *Rec. trav. chim.*, **70**, 581 (1951).

mended by Ochiai reacted too violently in large scale experiments.

Deoxygenation of 4-chloropyridine 1-oxide was accomplished in 1 hr. by treatment with iron and hot glacial acetic acid. 4-Chloropyridine was an extremely unstable liquid, rapidly polymerizing at room temperature[16,17]; each sample was therefore prepared immediately before use.

A mixture of 5 g. (0.065 mole) of freshly prepared 4-chloropyridine, 15.5 g. (0.123 mole) of sodium sulfite, 30 ml. of 95% alcohol, and 30 ml. of water was heated in a sealed tube to 144° for 12 hr. The mixture was worked up in the usual manner and 3.7 g. of sodium sulfonate was isolated by extraction with ethanol. This salt, after treatment with Nalcite HCR, yielded 2.1 g. of 4-pyridinesulfonic acid. If the reaction were a direct replacement of —Cl by —SO_3Na, 7.98 of sodium salt would have resulted. If dimerization of the 4-chloropyridine had first occurred,[16,17] and then the sodium sulfite had caused fission, the yield would have been halved, *viz.* 3.99 g. If higher polymers were also produced, the yield would have been still lower.

(c) *With 4-chloropyridine 1-oxide.* A mixture of 13 g. (0.1) mole) of 4-chloropyridine 1-oxide and 25.2 g. (0.2 mole) of sodium sulfite in 125 ml. of water was refluxed under nitrogen for 12 hr. The mixture was evaporated to dryness, at 100° and under reduced pressure, and the residue was extracted with three 100-ml. portions of boiling acetone.

The acetone-insoluble solid was dissolved in 110 ml. of hot water, acidified with 220 ml. of concd. hydrochloric acid and cooled to 0°. After filtration, the filtrate was evaporated to dryness on the steam bath and under reduced pressure. The residue was redissolved in the minimum quantity of hot water, acidified with 100 ml. of concd. hydrochloric acid, cooled to 0°, and filtered. The filtrate was evaporated to crystallization point under reduced pressure, cooled in ice, and filtered. There was obtained 9.8 g. (56%) of a white solid, m.p. 306–309° dec. The mother liquor afforded 5.4 g. of impure material. Recrystallization from aqueous alcohol of the white solid furnished 4-pyridinesulfonic acid 1-oxide m.p. 307–309° dec.

Anal. Calcd. for $C_5H_5NO_4S$: C, 34.29; H, 2.88; N, 8.00: equiv. wt. 175.2. Found: C, 34.42; H, 3.16; N, 8.19; equiv. wt. 176.2.

The ultraviolet spectrum measured in 65% sulfuric acid exhibited maxima at 233 and 266 mμ, with ε values of 11,000 and 3,800, respectively. In 0.1 *N* sodium hydroxide, maxima appeared at 214 and 268 mμ, with ε values of 14,000 and 19,400, respectively.

Stability of 4-pyridinesulfonic acid 1-oxide. A mixture of 2 g. (0.011 mole) of 4-pyridinesulfonic acid 1-oxide, 0.2 g. (0.0007 mole) of mercuric sulfate, and 20 g. (0.52 mole of SO_3) of fuming sulfuric acid (21% SO_3) was refluxed at 205° for 20 hr. and then at 250° for a further 4 hr. in the usual apparatus. The cold reaction mixture was poured into ice and neutralized with barium hydroxide solution. After filtration, the filtrate was evaporated to dryness. The residue, weighing 2.0881 g. (75% recovery), was dissolved in the minimum of water and decomposed by the addition of 0.4217 g. of concd. sulfuric acid in 10 ml. of water. The mixture was filtered, the filtrate again evaporated to dryness, and the residue recrystallized from aqueous methanol. There was obtained 0.17 g. of material, m.p. 307–309° dec. alone or when mixed with authentic 4-pyridinesulfonic acid 1-oxide. The mother liquors on evaporation furnished a further 1.1 g. of solid, m.p. 280–295°.

Oxidation of the sodium salts of the sulfonic acids. In a typical experiment, 9.1 g. (0.05 mole) of sodium pyridinesulfonate, 30 ml. of glacial acetic acid, and 7 ml. of 30% hydrogen peroxide were heated under reflux for 1 hr. in a water bath that was carefully maintained at 70–80°. Three milliliters of 30% hydrogen peroxide was now added and heating continued at 70–80° for a further 12 hr. Sixty milliliters of concd. hydrochloric acid was added, the mixture cooled, and then filtered. The filtrate was evaporated to dryness *in vacuo* and digested with 16 ml. of concd. hydrochloric acid on the steam bath for a few minutes. The mixture was again cooled and filtered. The filtrate was evaporated to dryness and the residue recrystallized from methanol.

Sodium 2-pyridinesulfonate gave 3.9 g. (44%) of 2-pyridinesulfonic acid 1-oxide, m.p. 237–239°.

Anal. Calcd. for $C_5H_5NO_4S$: C, 34.29; H, 2.88; N, 8.00; equiv. wt. 175.2. Found: C, 34.30; H, 3.12; N, 8.22; equiv. wt. 176.

With the 3-compound, 3.5 g. (40%) of 3-pyridinesulfonic acid 1-oxide, m.p. and mixed m.p. 238–242°, were recovered.

Finally, with the 4-sulfonate, 3.4 g. (40%) of 4-pyridinesulfonic acid 1-oxide, m.p. and mixed m.p. 307–309° dec., were obtained.

The S-benzylisothiuronium derivatives of pyridinesulfonic acids. In a typical experiment, 1.8 g. (0.01 mole) of sodium 3-pyridinesulfonate and 1.5 g. (0.007 mole) of *S*-benzylisothiuronium chloride were dissolved in 5 ml. of water previously acidified with a few drops of dilute hydrochloric acid. On cooling to 0°, an oil separated which slowly crystallized. Twice recrystallized from isopropyl alcohol the derivative had m.p. 120–122°.

Anal. Calcd. for $C_{13}H_{15}N_3O_3S_2$: C, 47.98; H, 4.65; N, 12.93. Found: C, 48.0; H, 4.59; N, 12.98.

In the case of the 2-sulfonate, the oil crystallized on storage *in vacuo* over phosphorus pentoxide. Two crystallizations from isopropyl alcohol afforded material, m.p. 118.5–119°.

Anal. Calcd. for $C_{13}H_{15}N_3O_3S_2$: C, 47.98; H, 4.65; N, 12.93. Found: C, 48.0; H, 4.59; N, 12.98.

The *S*-benzylisothiuronium salt of 4-pyridinesulfonic acid crystallized from aqueous ethanol as a white solid, m.p. 149–151°.

Anal. Calcd. for $C_{13}H_{15}N_3O_3S_2$: C, 47.98; H, 4.65; N, 12.93. Found: C, 48.26; H, 4.91; N, 12.48.

4-Chloro-2,6-lutidine. 2,6-Lutidine was purified through the boron trifluoride addition compound[32] and then converted, in 88% yield, to 2,6-lutidine 1-oxide following the general directions of Ochiai.[22] It formed a picrate, m.p. 124–125°.

Anal. Calcd. for $C_{13}H_{21}N_4O_8$: C, 44.33; H, 3.44; N, 15.9. Found: C, 44.08; H, 3.77; N, 15.93.

2,6-Lutidine 1-oxide reacted violently with phosphorus oxychloride,[19] but the use of the diluent enabled the reaction to be controlled.

A solution of 120 g. (0.78 mole) of phosphorus oxychloride in 400 ml. of tetrachloroethane was added over 30 min. to 54 g. (0.44 mole) of 2,6-lutidine 1-oxide dissolved in 200 ml. of tetrachloroethane and contained in a 1-l. flask fitted with a reflux condenser. Heat was evolved and a sequence of color changes, green through blue to very deep blue, was observed. The solution was allowed to stand at room temperature for 30 min. and then refluxed for 3 hr. Most of the solvent was removed from the resultant black reaction mixture by distillation at 100°/20 mm. The residue was poured onto ice and the acidic aqueous layer separated. The organic layer was extracted again twice with two 50-ml. portions of 2 *N* hydrochloric acid. The combined extracts were twice extracted with hexane and then combined with the treated extracts from a duplicate experiment run on the same scale. The aqueous solution was made strongly alkaline with aqueous sodium hydroxide and extracted three times with chloroform. After drying with magnesium sulfate, the extract was evaporated on the steam bath and the residue distilled under reduced pressure. There were collected (a) 9.6 g., b.p. up to 109°/84 mm., (b) 53.7 g., b.p. 109–128°/84 mm. and (c) 18.7 g., b.p. 109–130°/34 mm. Fractions (a) + (b) represented a 50% yield. However, all three fractions

(32) H. C. Brown, S. Johnson, and H. Podall, *J. Am. Chem. Soc.*, **76**, 5556 (1954).

were lachrymatory, which suggested that some side chain halogenation had occurred.

Consequently, 53.7 g. of fraction (b) was refluxed with 10 g. of potassium hydroxide in 20 ml. of water and 100 ml. of 95% alcohol for 4 hr. Excess alcohol was removed by distillation, the residue was diluted with water, and then extracted with chloroform. After drying the chloroform extract with magnesium sulfate, the solvent was removed and the residue was fractionally distilled under reduced pressure. There was obtained 11.2 g. of a fraction, b.p. 87.5–88.0°/41 mm., which formed a yellow picrate, m.p. 160.5–162° (lit.[19] m.p. 166–167°).

Anal. Calcd. for $C_{13}H_{11}ClN_4O_7$: C, 42.11; H, 2.99; N, 15.11. Found: C, 41.93; H, 2.89; N, 15.07.

4-Mercapto-2,6-lutidine. A mixture of 11.2 g. (0.08 mole) of 4-chloro-2,6-lutidine, 10 ml. of 95% alcohol, and 17 ml. (0.16 mole) of freshly prepared potassium hydrogen sulfide solution was heated in a sealed tube at 150° for 7 hr. The cold reaction mixture was diluted with water, most of the alcohol was removed under reduced pressure, and the residue was acidified with 12 ml. of glacial acetic acid. The mixture was warmed to dissolve the yellow precipitate, filtered, and the solution allowed to crystallize. There were obtained 9.2 g. of yellow needles, m.p. 221–231° dec. (lit.[6] m.p. 224°). Continuous chloroform extraction of the aqueous mother liquor afforded a further 0.8 g. of solid. The total yield was 91%. Crystallization both from 95% alcohol and from acetone failed to improve the melting behaviour of the compound.

2,6-Lutidine 4-sulfonic acid. (a) One and twenty five-hundredths milliliters of 30% hydrogen peroxide was cautiously added to 0.5 g. (0.036 mole) of 4-mercapto-2,6-lutidine dissolved in 25 ml. of ice-cold water containing 2 g. of potassium hydroxide (0.036 mole). The solution was allowed to warm to room temperature over 1 hr. and then heated under reflux on the steam bath for a further 4 hr. After cooling, the reaction mixture was passed slowly through a cation exchange column (Nalcite HCR) and the acidic eluate was evaporated to dryness. A yellow residue was obtained. After treatment with charcoal and crystallization from aqueous ethanol, 0.37 g. (55%) of 2,6-lutidine 4-sulfonic acid were obtained m.p. > 350°.

Anal. Calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48. Found: C, 44.79; H, 5.00; N, 7.80.

(b) One gram of 4-mercapto-2,6-lutidine, 13 ml. of water, and 6.4 ml. of nitric acid (*d* 1.42) were cautiously heated under reflux on the steam bath. After the vigorous reaction had subsided, heating was continued for a further 30 min. and then the excess nitric acid was removed at 100° under reduced pressure. The residue of 2,6-lutidine 4-sulfonic acid, crystallized from boiling ethanol, amounted to 1.3 g. (97%) m.p. > 350°.

(c) Thirty-seven milliliters (0.33 mole) of 30% hydrogen peroxide was cautiously added with swirling, to the ice-cold solution containing 14.9 g. (0.107 mole) of 4-mercapto-lutidine and 16.0 g. (0.050 mole) of barium hydroxide octahydrate in 270 ml. of water. After standing at room temperature for 30 min., the mixture was heated under reflux at 100° for 4 hr. The white precipitate redissolved and the resultant yellow solution, after filtration, was decomposed with 4.973 g. (0.0507 mole) of concd. sulfuric acid in 20 ml. of water. The mixture was heated on the steam bath for 15 min., filtered, and the filtrate, after a treatment with charcoal, was evaporated to dryness. The residue was repeatedly crystallized from aqueous ethanol and afforded 13.6 g. (68%) of sulfonic acid, m.p. > 350°.

Anal. Calcd. for $C_7H_9NSO_3$: equiv. wt. 187.2. Found: equiv. wt. 186.

Method (b) could not be used on a large scale because of the violence of the oxidation. (c) was preferable to (a), since it eliminated the time-consuming treatment with the ion-exchange resin.

(d) 4-Bromo-2,6-lutidine was first prepared from 4-amino-2,6-lutidine. Twenty grams (0.125 mole) of bromine was added, with stirring, over 1 hr. to an ice-cold mixture of 5 g. (0.041 mole) of the amine and 60 ml. of 48% hydrobromic acid. The orange-red reaction mixture was cooled to −10 to −15° in an ice-salt bath and a solution of 7.1 g. (0.103 mole) of sodium nitrite in 20 ml. of water was added, over 40 min. After standing at −10 to −15° for 1 hr., the mixture was allowed to warm up slowly and was left at room temperature overnight. The reaction mixture was diluted with water, cooled in ice, and made alkaline with concd. aqueous sodium hydroxide. Adter adding concd. aqueous sodium sulfite, the mixture was steam distilled. The distillate was extracted with chloroform, the extract dried over magnesium sulfate and the solvent removed. The residue of 4-bromo-2,6-lutidine (6.8 g., 89%) yielded a picrate crystallizing from ethanol in yellow needles, m.p. 183.5–185°.

Anal. Calcd. for $C_{13}H_{11}BrN_4O_7 \cdot {}^1/_2C_2H_6O$: C, 38.37; H, 3.22; N, 12.78. Found: C, 38.62; H, 2.96; N, 12.83.

A mixture of 2 g. (0.01075 mole) of 4-bromo-2,6-lutidine, 4.1 g. (0.03225 mole) of sodium sulfite, 17 ml. of water, and 17 ml. of 95% alcohol was heated in a sealed tube at 190° for 10 hr. The mixture was diluted to 100 ml. with water and passed through a column of Nalcite HCR. Evaporation of the acidic eluate followed by recrystallization of the residue from aqueous ethanol gave 1.9 g. (94%) of 2,6-lutidine-4-sulfonic acid, m.p. > 350°.

When an almost completely neutralized solution of 1 g. of the acid was mixed with 2 g. of *S*-benzylisothiuronium chloride in 10 ml. of water and cooled to 0°, the *S*-benzylisothiuronium derivative of the sulfonic acid separated as an oil which soon crystallized. Two recrystallizations from isopropyl alcohol afforded a white material, m.p. 150.5–151.5°.

Anal. Calcd. for $C_{15}H_{19}N_3O_3S_2$: C, 51.11; H, 5.40; N, 11.86. Found: C, 51.09; H, 5.49; N, 11.73.

2,6-Lutidine 4-sulfonic acid 1-oxide. Sodium 2,6-lutidine 4-sulfonate, freshly prepared by neutralization of 4.7 g. of the sulfonic acid, was refluxed at 70–80° for 3 hr. with a solution containing 2.9 ml. of 30% hydrogen peroxide and 30 ml. of glacial acetic acid. Two milliliters of 30% hydrogen peroxide was subsequently added and the heating continued for 4 hr. After filtration, the solution was evaporated to dryness at 100° *in vacuo* and the residue dissolved in the minimum of hot water. The solution was decomposed with twice its volume of concd. hydrochloric acid, cooled, and filtered. The filtrate was again evaporated to dryness and the residue on extraction with boiling methanol yielded 0.3 g. of 2,6-lutidine 4-sulfonic acid 1-oxide, m.p. > 350°.

Anal. Calcd. for $C_7H_9NO_4S$: C, 41.37; H, 4.46; N, 6.89; equiv. wt., 203.2. Found: C, 41.60; H, 4.72; N, 7.06; equiv. wt. 203.

4-Amino-2,6-lutidine. A 1-l., three-necked Pyrex round bottom flask was fitted with a stopper, a gas-tight stirrer, and a Y-tube. One arm of the Y-tube merged into a Dry Ice condenser protected by an anhydrite guard tube: The other arm contained an inlet tube. The flask was surrounded with mica chippings in a bath and about 700 ml. of liquid ammonia transferred from a cylinder to the dry apparatus. Twenty three grams (1 g.-atom) of recently prepared sodium shot *ca.* 5 mm. in diameter was gradually added over 2 hr. to the liquid ammonia. Small amounts of freshly crushed ferric nitrate nonahydrate crystals were periodically added to the mixture to speed up the reaction. The ammonia was allowed to evaporate spontaneously. Toward the end of the evaporation, 400 ml. of dry redistilled *N,N*-dimethylaniline was gradually added to the flask via a separating funnel fitted with an equalizing side arm which replaced the stopper. When the contents reached room temperature, 85.6 g. (0.8 mole) of distilled 2,6-lutidine was quickly added and the stirred mixture was refluxed for 7¼ hr. After cooling, the black mass was decomposed by cautious addition of 100 ml. of water. The dimethylaniline layer was extracted four times with water. The combined aqueous extracts of ca. 1 l., after two extractions with hexane, were concentrated by distillation under reduced pressure to crystallization point and gave 12.7 g. (13%) of 4-amino-2,6-lutidine, m.p. 188–

TABLE II

PRINCIPAL ABSORPTION BANDS BETWEEN 7 AND 15 μ IN THE INFRARED SPECTRA OF THE 2,6-LUTIDINE SULFONIC ACID 1-OXIDES[a]

Sulfonation Product of 2,6-Lutidine 1-Oxide (*i.e.*, 2,6-Lutidine 3-Sulfonic Acid 1-Oxide)	2,6-Lutidine 4-Sulfonic Acid 1-Oxide
7.25	7.25 s
7.90 vs	7.82 vs
	8.02 vs
	8.35 vs
8.50 vs	8.50 vs
8.71	8.98 s
9.55 vs	9.64 vs
9.85 vs	9.91
	11.20
11.67 vs	11.78
	13.49
	13.91
14.11 s	
14.37 s	
14.96 s	

[a] Values are wave lengths in μ; s = strong, vs = very strong. Measured in Nujol mull.

TABLE III

PRINCIPAL ABSORPTION BANDS IN THE INFRARED SPECTRA OF THE 2,6-LUTIDINESULFONIC ACIDS IN THE 7–15-μ RANGE[a]

Sulfonation Product of 2,6-Lutidine (*i.e.*, 2,6-Lutidine 3-Sulfonic Acid)	2,6-Lutidine 4-Sulfonic Acid
7.06	7.26
7.18	7.36
7.41	7.94 vs
8.00[b] vs	8.37 vs
8.35[b] vs	
8.70	8.89
9.07	9.60 vs
9.67 vs	10.10
10.15	10.55
	11.14
	11.34
11.72 s	11.74 s
13.88 s	13.93 s
14.71 vs	

[a] Values are wave lengths in μ; s = strong, vs = very strong. Measured in Nujol mull. [b] Twin peaks.

190° (lit.,[33] m.p. 191–192°) after sublimation at 150°/3 mm. pressure and crystallization from acetone.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.47; H, 8.16; N, 23.13.

Sulfonation of 4-amino-2,6-lutidine. Five grams (0.04 mole) of powdered 4-amino-2,6-lutidine, 12 g. of concd. sulfuric acid, and 3 g. (0.008 mole SO_3) of fuming sulfuric acid (21% SO_3) were heated to 162° for 4.5 hr. The cold mixture was then poured into water, neutralized with barium hydroxide solution, and filtered. Since the filtrate did not yield a precipitate with dilute sulfuric acid, it was evaporated to dryness. The solid residue was twice extracted with boiling acetone. The soluble portion (1 g.) proved to be unchanged starting material m.p. 185–190°.

The acetone-insoluble material (5.6 g.) was recrystallized from methanol, affording 3,3′-sulfonylbis(4-amino-2,6-lutidine), m.p. >350°.

Anal. Calcd. for $C_{14}H_{18}N_4O_2S \cdot CH_3OH$: C, 50.27; H, 6.55; N, 16.56. Found: C, 49.57; H, 6.61; N, 16.29.

The infrared spectrum (in Nujol Mull) included a band at 7.30 μ and a broad, intense, diffuse band at 8.75–9.75 μ which suggested the presence of a sulfone grouping.[34]

Sulfonation of 4-chloro-2,6-lutidine. A mixture of 7.6 g. (0.62 mole) of 4-chloro-2,6-lutidine, 0.76 g. of mercuric sulfate (0.0026 mole), and 76 g. (0.20 mole SO_3) of fuming sulfuric acid (21% SO_3) was heated to 190° for 24 hr. under reflux in the usual apparatus. The mixture was poured into ice, neutralized with aqueous barium hydroxide, and filtered. The filtrate smelled strongly of unchanged base but, when evaporated to dryness under reduced pressure, a minute quantity of 4-hydroxy-2,6-lutidine 3-sulfonic acid, m.p. 290–295° dec. (from methanol) was obtained.

Anal. Calcd. for $C_7H_{11}NO_5S$: C, 38.01; H, 5.02; equiv. wt. 221. Found: C, 38.01; H, 5.02; equiv. wt. 229.

2,6-Lutidine 3-sulfonic acid 1-oxide. A mixture of 21.6 g. (0.18 mole) of 2,6-lutidine 1-oxide, 2.16 g. (0.0073 mole) of mercuric sulfate, and 175 g. (0.46 mole SO_3) of fuming sulfuric acid (21% SO_3) was heated to 220 ± 10° for 24 hr. and worked up in the usual way, affording 8.6 g. of unsulfonated material and 13 g. (44%) of barium sulfonate. The sulfonate was dissolved in 300 ml. of hot water and the solution was acidified with 2.3 g. of sulfuric acid diluted with 10 ml. of water. After filtration, the solution was decolorized with charcoal, filtered, and the filtrate evaporated to dryness. Three recrystallizations of the residue from methanol afforded white crystals m.p. 281–283° dec.

Anal. Calcd. for $C_7H_9NO_4S$: C, 41.37; H, 4.46; N, 6.89; equiv. wt. 203.2. Found: C, 41.60; H, 4.64; N, 6.72; equiv. wt. 210.

The infrared spectrum of the solid in Nujol suspension (Table II) differed considerably from that of 2,6-lutidine 4-sulfonic acid 1-oxide and it was therefore concluded that the product was the 3-isomer.

2,6-Lutidine 3-sulfonic acid. (a) Forty three one-hundredths grams of the sulfonation product from 2,6-lutidine 1-oxide was shaken for 5 hr. with hydrogen at 31 lb./in.^{2} in the presence of 0.5 g. of 20% palladized charcoal, 5 ml. of glacial acetic acid, and 7 ml. of acetic anhydride. The mixture was cautiously diluted with water, and after 30 min., when hydrolysis of the acetic anhydride was assumed complete, the mixture was filtered. The filtrate was evaporated to dryness at 100° under reduced pressure and the residual solid was then extracted three times with boiling methanol. When mixed with a little 2,6-lutidine 4-sulfonic acid, the m.p. of the product (>350°) was depressed. Comparison of the infrared spectra, measured in Nujol mull (Table III), confirmed that the product was not the 4-sulfonic acid and hence must be 2,6-lutidine 3-sulfonic acid.

(b) A mixture of 27 g. (0.25 mole) of 2,6-lutidine, 2.7 g. (0.0091 mole) of mercuric sulfate, and 125 g. (0.34 mole SO_3) of fuming sulfuric acid (21% SO_3) was heated under reflux at 215° for 24 hr. in the usual apparatus. The mixture was worked up in a manner analogous to the sulfonation product of pyridine 1-oxide. However, no solvent extraction was necessary, since unsulfonated 2,6-lutidine was removed as its azeotrope with water during the evaporation to dryness of the barium salt solution. A solid residue (40.2 g.) was obtained which was dissolved in water; the solution was decomposed with 7.73 g. of concd. sulfuric acid in 50 ml. of water. After filtration, the filtrate was evaporated to dryness and the residue recrystallized from aqueous methanol yielding 20 g. (43%) of 2,6-lutidine 3-sulfonic acid as white needles m.p. > 350°.

Anal. Calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48; Found: C, 44.69; H, 4.78; N, 7.95.

The infrared spectrum of this solid in Nujol mull was identical with that of the product obtained in (a) and differed from the spectrum of 2,6-lutidine 4-sulfonic acid. It

(33) E. Ochiai and T. Katoh, *J. Pharm. Soc. Japan*, **71**, 156 (1951); *Chem. Abstr.*, **45**, 9543 (1951).

(34) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, 1960, p. 350.

was concluded that sulfonation of 2,6-lutidine occurred in the 3-position.

The *S*-benzylisothiuronium salts was obtained as an oil which could not be induced to crystallize.

Spectra. The infrared spectra of all the materials were obtained using a Perkin Elmer recording instrument, Model 21, Ser. 140.

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Peroxides. IX. New Method for the Direct Preparation of Aromatic and Aliphatic Peroxy Acids[2]

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A new direct, rapid procedure for the preparation of both aromatic and aliphatic peroxy acids is described. This consists in treating 90–95% hydrogen peroxide with a solution or slurry of carboxylic acid in methanesulfonic acid in mole ratios of 5:3:1 of methanesulfonic acid–hydrogen peroxide–carboxylic acid for most of the peroxy acids for one to three hours of reaction time. Optimum temperatures are generally from 30–40°, but higher operating temperatures (up to 60°) and higher mole ratios of methanesulfonic acid–carboxylic acid (up to 20:1) are useful for carboxylic acids having low solubility in the medium. Insoluble acids can be usefully replaced by their more soluble esters. Labile functional groups present in the acids, such as hydroxyl and cyano, are retained unchanged. For the first time, a method is described for the direct preparation of peroxybenzoic acid from benzoic acid in essentially quantitative yield. Peroxy acids of 93–99% purity in yields of 85–97% are obtained with few exceptions. *m*-Methoxy- and *p*-methoxyperoxybenzoic acids cannot be prepared by this procedure. The stability of several of the solid peroxy acids on storage at 25° for two, four, and eight weeks was determined by peroxide oxygen analysis. An attempt has been made to explain the differences in melting point between peroxy acid and corresponding carboxylic acid.

Since publication of the review on organic peroxy acids,[3] several additional procedures for peroxy acid preparations have been reported. Approximately twenty methods and modifications are now available for peroxy acid synthesis. These methods, with possibly one exception, are not general; only a few are of value as synthetic methods for obtaining high purity peroxy acids of specific types in high yields.

Formation of a peroxy acid from the parent acid and hydrogen peroxide is an equilibrium process[4] in accordance with the equation.

$$RCO_2H + H_2O_2 \rightleftharpoons RCO_3H + H_2O$$

In most cases the rate of peroxy acid formation is impractically slow but is increased by acid catalysts. Advantage was taken of the acid-catalyzed equilibrium reaction by removing water at 40–50° by such azeotropic agents as alkyl acetates and chloroform.[5]

Although this method is reported to be useful for peroxyacetic and peroxypropionic acids, it failed to form longer chain peroxy acids, such as peroxy 2-ethylhexanoic acid. No examples were given for the preparation of aromatic peroxy acids by this method.

The most useful procedure for the direct preparation of long chain aliphatic monobasic[6] and dibasic[7] peroxy acids employs concentrated sulfuric acid as reaction medium and catalyst with 50–65% hydrogen peroxide. This procedure, unfortunately, fails with aromatic acids and certain aliphatic acids containing functional groups sensitive to sulfuric acid. Also, it is limited to monobasic acids up to palmitic acid and dibasic acids up to about 1,10-decanedicarboxylic acid owing to solubility problems. Benzoic, *p*-methoxybenzoic and *p*-*tert*-butylbenzoic acids violently decompose or carbonize in the presence of concentrated sulfuric acid and concentrated hydrogen peroxide (see Experimental) while *p*-nitrobenzoic[8] and *o*-nitrobenzoic acids give yellow-orange colored compounds containing no active oxygen. Failure of the sulfuric acid method may be attributed to its strong oxidation-sulfonation properties and low solvation capacity for most of the aromatic acids and long chain aliphatic acids above palmitic.

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(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Presented in part at the Spring Meeting of the American Chemical Society, St. Louis, Mo., March 27, 1961. Paper VIII is *J. Am. Chem. Soc.*, **81**, 3244 (1959).

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(8) M. Vilkas, *Bull. soc. chim. France*, **1959**, 1401, attempted to prepare *p*-nitroperoxybenzoic acid by this direct method and also failed.