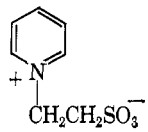
sulfate anion even after boiling with hydrochloric acid, and liberated pyridine on treatment with warm base. Neutralization equivalent and bromine number determinations carried out according to the method of Bordwell and Peterson[3b] gave the expected values for



V

the betaine salt structure.[6] The infrared spectrum exhibited the two absorption bands which are characteristic of the C=C and C=N vibrations of the N-alkylated pyridine ring.[7] The p.m.r. spectrum exhibited the expected chemical shifts for the two pairs of methylenic protons of V. All of the physical and chemical evidence collected in this investigation supported the betaine salt structure (V) for the reaction product of IV and pyridine.

In other experiments, treatment of IV with equimolar or less than equimolar amounts of pyridine gave V in reduced yields. Attempts to utilize alcohols and water as crystallization solvents for the initial oily precipitate failed. However, V was recrystallizable from methanol after crystallization had been effected from N,N-dimethylformamide. Presumably, the oily precipitate formed initially on treatment of IV with pyridine contains the $-SO_2OSO_3^-$ group which is converted to $-SO_3^-$ by removal of sulfur trioxide to yield V. N,N-Dimethylformamide apparently coordinates with sulfur trioxide to form sulfur trioxide–N,N-dimethylformamide and V.

Thus, our investigation shows that carbyl sulfate (IV) undergoes cleavage at bond A on treatment with pyridine under mild conditions. Cyclic sulfonate–sulfate intermediates (III) will probably react in a similar manner with pyridine or other tertiary heterocyclic amines to yield betaine salts identical with the products formed on treatment of intermediates I or II with the same amine.

Experimental[8]

2-(1-Proto-1-pyridyl)-1-ethanesulfonate.–Carbyl sulfate, 10.0 g. (0.0531 mole), prepared according to the method of Breslow and Hough and recrystallized twice from ethylene chloride,[9] was dissolved in 200 ml. of ethylene chloride by gentle warming on the steam bath. The resulting solution was treated with 19.6 g. (0.25 mole) of pyridine in 80 ml. of ethylene chloride. During the addition, the reaction mixture was maintained at room temperature by external cooling with an ice bath. The exothermic reaction produced an oily precipitate which was separated from unreacted pyridine and solvent by decantation of the supernatant liquid and successive washing of the precipitate with two 100-ml. portions of fresh ethylene chloride and two 100-ml. portions of petroleum ether (b.p. 30–60°). The precipitate was crystallized once from boiling N,N-dimethylformamide to yield 3.5 g. (35.3%) of 2-(1-proto-1-pyridyl)-1-ethanesulfonate as white granular crystals, m.p. 250–255° with sintering at 90°. Evaporation of the mother liquor gave an additional 2.5 g. (25.2%) of product melting at 240°. This product was identical with the first crop of crystals by infrared analysis. Elemental analysis of the first crop gave the results indicated below. The salt was soluble in water and methanol, and insoluble in acetone, ether, petroleum ether, and ethylene chloride.

Anal. Calcd. for $C_7H_9NO_3S$ (mol. wt. 187.21): C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 44.97; H, 5.03; N, 7.62; S, 17.10.

Aqueous solutions of the salt were neutral and gave negative tests for sulfate anion after boiling with hydrochloric acid for 5 min. Free pyridine was detected by odor on treatment of an aqueous solution of the salt with 1.0 *N* sodium hydroxide solution and warming on the steam bath for a few minutes. The neutralization equivalent was determined by the method of Bordwell and Peterson.[3b] An aqueous solution of the salt was warmed for 30 min. on the steam bath with excess standard sodium hydroxide solution. Back-titration with standard hydrochloric acid solution gave a neutralization equivalent of 177 (calcd. neut. equiv. 187). Determination of the bromine number with an aliquot of the neutralized solution by the bromide–bromate technique gave a value of 86.4 (calcd. 85.3). Another aliquot of the neutralized solution gave a positive test for sulfate anion after sequential treatment with acidic potassium permanganate solution, a few drops of 30% hydrogen peroxide solution to remove manganese dioxide, and barium chloride solution.[10]

The instrument used to record the infrared spectra was a Perkin-Elmer Model 21 recording spectrophotometer. The spectrum of a potassium bromide pellet of 2-(1-proto-1-pyridyl)-1-ethanesulfonate exhibited sharp peaks at 6.1 (strong) and 6.3 μ (weak) in addition to a considerable amount of fine structure beyond 6.5 μ.[7]

The p.m.r. spectrum was measured in deuterium oxide at 60 Mc./sec. and room temperature with a Varian Associates A-60 spectrometer with an internal standard of Tier's salt.[11] The spectrum showed two triplets with relative intensities of 1:1. The triplet at 5.0 p.p.m. was attributed to the methylenic protons β to the sulfonate group, and the triplet at 4.6 p.p.m. was attributed to the methylenic protons α to the sulfonate group.

(6) This type of neutralization equivalent determination is based upon the quantitative reaction of the betaine salt with sodium hydroxide to afford an aqueous solution of pyridine and sodium vinylsulfonate. The bromine number determination, which is carried out with this aqueous solution, is based upon the reaction of bromine with sodium vinylsulfonate, but the numerical value is calculated as grams of molecular bromine consumed/100 g. of original betaine salt.

(7) Infrared spectra have been measured for several betaine sulfonate and sulfate salts. All spectra exhibit the characteristic absorption bands described in the Experimental section. This work will be published shortly.

(8) Melting points are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Neutralization equivalent and bromine number determinations were performed by the Analytical Research and Services Division of The Pure Oil Co., Crystal Lake, Ill.

(9) D. S. Breslow and R. R. Hough, *J. Am. Chem. Soc.*, **79**, 5000 (1957).

(10) Characteristic of α,β-unsaturated sulfonates.

(11) The p.m.r. determination was kindly carried out by Mr. Stuart Armstrong of Varian Associates. Assignments of the chemical shifts were made after examination of several betaine sulfonate and sulfate salts. The results of this examination will be published in a future paper.

Base-Catalyzed Preparation of Methyl and Ethyl Esters of Carboxylic Acids

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Recently[2] the author described a method of making phenacyl esters of carboxylic acids in which dicyclohexylethylamine (DICE) was used as the proton acceptor. Subsequent work has shown that dimethyl sulfate in the presence of this amine rapidly converts carboxylic acids to methyl esters in high yield. The method is simple and rapid, and is useful when the preparation of diazomethane is not feasible or when strongly acidic conditions must be avoided.

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(2) F. H. Stodola, *Microchem. J.*, **9**, 389 (1963).

In the preparation of methyl esters 1 equiv. of the acid, dissolved in methanol or acetone, is heated in an open flask on a steam bath for 15 min. with 1.1–1.2 moles of dimethyl sulfate and 1.3–2.0 moles of DICE. For microscale work proportionately larger amounts of sulfate and amine can be used to facilitate handling. The following acids were methylated in good yield by this procedure: *m*-nitrobenzoic, *m*-hydroxybenzoic, 2,3,5,6-tetramethylbenzoic, 12-hydroxyoctadecanoic, 9,-10,12-trihydroxyoctadecanoic, triphenylacetic, and 9-anthroic. Tetronic acids behave like carboxylic acids, judging from a single experiment with α-methyltetronic acid.

For the preparation of ethyl esters only 1 mole of diethyl sulfate is used per equivalent of acid since excess reagent cannot be removed readily by hydrolysis as is the case with dimethyl sulfate. In this way, phenaceturic acid was converted to the ethyl ester in over 90% yield when heated with DICE for 15 min. in acetone.

Commercially available tris(2-hydroxypropyl)amine, $[CH_3CH(OH)CH_2]_3N$ (Eastman Kodak[3] 1,1′,1″-nitrilotri-2-propanol), was investigated as a possible substitute for DICE in the esterification of larger amounts of acid (*ca.* 0.15 mole). With *p*-nitrobenzoic acid the Eastman amine gave almost a quantitative yield of methyl ester (20% excess amine, 10% excess sulfate, acetone, 95°, 15 min.); under somewhat different conditions (10% excess amine, 20% excess sulfate, methanol, 95°, 15 min.), a 93% yield was obtained with *p*-bromobenzoic acid and with *erythro*-9,10-dihydroxyoctadecanoic acid. Unlike DICE, which can safely be used in 100% excess, the Eastman amine must be restricted in amount since it appears to remove dimethyl sulfate as a quaternary ammonium salt. For example, *erythro*-9,10-dihydroxyoctadecanoic acid gave only a 79% yield with a 100% excess of amine (20% excess sulfate, methanol, 95°, 15 min.); under the same conditions *p*-bromobenzoic acid yielded 83% methyl ester. When the Eastman amine is used for the preparation of ethyl esters a heating time of 1 hr. is recommended.

Experimental[4]

Methyl 2,3,5,6-Tetramethylbenzoate.—To 2.00 mg. of 2,3,5,6-tetramethylbenzoic acid in a microcentrifuge tube were added 10 μl. of dimethyl sulfate, 20 μl. of DICE, and 2 drops of acetone. After 15 min. heating on a steam bath, 2 *N* HCl was added and the crystals (2.05 mg., 96%) were recovered by filtration, m.p. 59.8–60.8° (lit.[5] m.p. 59°).

Methyl β-9,10,12-Trihydroxyoctadecanoate.—The β-acid[6] (100 mg., 1 equiv.), dimethyl sulfate (47 mg., 1.2 moles), DICE (0.14 ml., 2 moles), and methanol (0.5 ml.) were heated for 15 min. on a steam bath. The crude methyl ester, obtained by addition of 2 *N* HCl and filtration, was dissolved in methanol, and the solution was made alkaline to phenophthalein by addition of dilute alcoholic NaOH. The alkaline solution was diluted with water and the ester was removed by ether extraction (101 mg., 97%), m.p. 113–115° (hot stage). Slow recrystallization from ethyl acetate gave pure methyl ester in the form of aggregates of needles, m.p. 118.4–119.4°. Mihara and Takaoka[7] reported a melting point of 108–109°.

Anal. Calcd. for $C_{19}H_{38}O_5$; C, 65.86; H, 11.05. Found: C, 65.80; H, 11.05.

Ethyl Phenaceturate.—Phenaceturic acid (193 mg., 1 mmole), diethyl sulfate (154 mg., 1 mmole), DICE (0.35 ml., 1.5 mmoles), and acetone (0.5 ml.) were heated for 15 min. on a steam bath. Addition of 2 *N* HCl gave an oil which crystallized on cooling. Filtration yielded 187 mg. (84%) of ethyl ester, m.p. 79.8–81.3°. Another 20 mg. of ester was obtained by ether extraction of the filtrate. Recrystallization from benzene gave pure ethyl phenaceturate, m.p. 81.3–82.3° (lit.[8] m.p. 82°).

Methyl *p*-Nitrobenzoate.—*p*-Nitrobenzoic acid (16.71 g., 0.10 mole), tris(2-hydroxypropyl)amine (22.95 g., 0.12 mole), dimethyl sulfate (13.87 g., 0.11 mole), and 20 ml. of acetone were heated for 15 min. on a steam bath. About 90% of the acetone was removed in this time. The reaction mixture was cooled to room temperature, and 5 ml. of water was added to decompose excess dimethyl sulfate. After addition of 10 ml. of concentrated HCl, the crystals of methyl ester were removed by filtration (17.81 g., 98%), m.p. 94.5–95.5° (hot stage). A portion (17.70 g.) of the ester was dissolved in ether; the ether was then washed with $NaHCO_3$ and water. Evaporation of the ether gave almost pure methyl ester (17.63 g.), m.p. 95.8–96.8° (lit.[9] m.p. 96°).

Ethyl *m*-Hydroxycinnamate.—*m*-Hydroxycinnamic acid (25.00 g., 0.152 mole), tris(2-hydroxypropyl)amine (34.96 g., 0.182 mole), diethyl sulfate (23.47 g., 0.152 mole), and acetone (25 ml.) were heated for 1 hr. on a steam bath. After addition of water, the ethyl ester was removed by ether extraction. The ether was washed with $NaHCO_3$ solution and finally with water. Removal of ether left 26.84 g. (92%) of ethyl ester, m.p. 62–65° (hot stage). Recrystallization from benzene–hexane gave pure ester, m.p. 67.7–68.7° (lit.[10] m.p. 70–71°).

(3) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

(4) Melting points were carried out in melting-point tubes and are corrected, unless otherwise noted. The hot-stage melting points were not corrected.

(5) O. Jacobsen, *Ber.*, **22**, 1223 (1889).

(6) This acid (m.p. 139.6–140.6°) had been prepared and carefully purified by J. P. Kass and S. B. Radlove, *J. Am. Chem. Soc.*, **64**, 2253 (1942).

(7) K. Mihara and K. Takaoka, *Yukagaku*, **7**, 88 (1958); *Chem. Abstr.*, **55**, 4357 (1961).

(8) A. Klages and O. Haack, *Ber.*, **36**, 1648 (1903).

(9) H. Henstock, *J. Chem. Soc.*, 216 (1933).

(10) H. Ley, *Z. physik. Chem.*, **94**, 439 (1920).

On 2,5-Dichloropyrazine[1]

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Recently Klein and associates[2] have reported on the action of phosphoroyl chloride on various pyrazine N-oxides. While the experimental results are on the whole in substantial agreement with the ones we had previously reported,[3,4] there is a question concerning the formation of 2,5-dichloropyrazine by treatment of 3-chloropyrazine 1-oxide with phosphoroyl chloride.

We have repeated this reaction following closely the published[2] procedure and we have obtained a liquid (b.p. 84–88° at 25 mm.) that was analyzed by gas–liquid chromatography.[5] Two peaks were obtained and, upon collection of the peak fractions, the first was shown by infrared spectroscopy to be 2,6-dichloropyrazine (λ_{max} 8.41, 8.69, 8.86, 9.99, and 12.1 μ) and the second 2,3-dichloropyrazine (λ_{max} 8.35, 8.67, 9.52, 11.7, and 12.5 μ). Moreover, careful distillation of the reac-

(1) Paper VIII on pyrazine derivatives; Paper VII: G. Palamidessi and F. Chillemi, *Farmaco*, **18**, 566 (1963).

(2) B. Klein, N. E. Hetman, and M. E. O'Donnel, *J. Org. Chem.*, **28**, 1682 (1963).

(3) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. chim. ital.*, **91**, 1431 (1961).

(4) G. Palamidessi and L. Bernardi, *ibid.*, **93**, 339 (1963).

(5) The analyses were performed with a Perkin-Elmer fractometer, column Q, 2 m., 195°.