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).

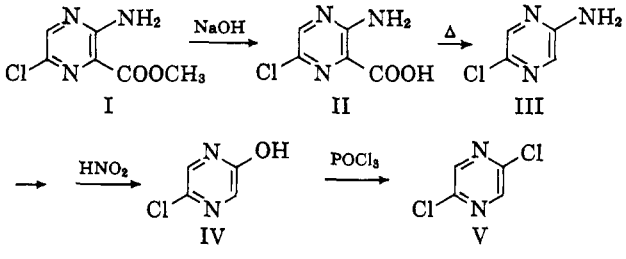
(5) The analyses were performed with a Perkin-Elmer fractometer, column Q, 2 m., 195°.

tion product afforded a first cut that on cooling partly solidified; the crystals were collected and identified as 2,6-dichloropyrazine (melting point, mixture melting point, and infrared spectrum). While the mechanism of formation of this compound is still unclear,[4] its presence in this reaction mixture is definitely proved.

At this point, although our previous results[3] had been, as shown, fully confirmed, it seemed desirable to synthesize a sample of 2,5-dichloropyrazine by a reliable route in order to definitely settle the matter.

Hydrolysis of 3-amino-6-chloromethylpyrazinoate[6] (I) with NaOH gave 3-amino-6-chloropyrazinoic acid (II). Decarboxylation of II in refluxing tetralin afforded, on cooling, an aminochloropyrazine III (m.p. 130–132°) that was definitely different (infrared spectrum and mixture melting point) from both 2-amino-3-chloropyrazine[7] and 2-amino-6-chloropyrazine.[3] It was therefore possible to formulate III as 2-amino-5-chloropyrazine, providing at the same time a rigorous proof of the structure of I, previously reported only in the patent literature.

Treatment of III with sodium nitrite in concentrated sulfuric acid gave 2-hydroxy-5-chloropyrazine (IV) which was converted, by reaction with phosphoroyl chloride, to the required 2,5-dichloropyrazine (V).



Having thus obtained an authentic sample of 2,5-dichloropyrazine, we re-examined the infrared spectrum of the crude mixture of dichloropyrazines formed in the reaction of 3-chloropyrazine 1-oxide and phosphoroyl chloride. All the bands of the spectrum are easily assigned either to 2,3-dichloropyrazine or to 2,6-dichloropyrazine. The conspicuous absorption band at 7.69 μ (which is characteristic of 2,6-dichloropyrazine since it occurs in a region where the two other isomers show no absorption) is completely absent, and we can therefore conclude that no 2,5-dichloropyrazine is formed in the reaction under discussion.

(6) Merck & Co., Inc., Belgian Patent 623,480 (1961).

(7) F. G. McDonald and R. C. Ellingson, *J. Am. Chem. Soc.*, **69**, 1036 (1947).

Experimental

All melting points unless otherwise noted were taken with a Fisher-Johns apparatus and are not corrected. The infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer.

3-Amino-6-chloropyrazinoic Acid (II).—Methyl 3-amino-6-chloropyrazinoate (I, 1 g.) was treated for 1 hr. at reflux temperature with 50 ml. of 2 *N* NaOH. The solution was cooled and acidified with 55 ml. of 2 *N* HCl. The precipitate was collected and dried, giving 0.8 g. of 3-amino-6-chloropyrazinoic acid, m.p. 176–180° dec. A sample was recrystallized from water, m.p. 177–180° dec.

Anal. Calcd. for $C_5H_4ClN_3O_2$: C, 34.59; H, 2.32. Found: C, 34.42; H, 2.47.

2-Amino-5-chloropyrazine (III).—A suspension of 1 g. of 3-amino-6-chloropyrazinoic acid in 10 ml. of tetralin was heated to reflux for 1 hr. On cooling, 0.5 g. of 2-amino-5-chloropyrazine, m.p. 125–126°, separated. A sample was recrystallized from water, m.p. 129–130°.

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.15; H, 3.11. Found: C, 37.08; H, 3.23.

2-Hydroxy-5-chloropyrazine (IV).—Sodium nitrite (0.85 g.) was added, with stirring, at 0° to 4.6 ml. of concentrated sulfuric acid. The cooling bath was withdrawn and the sodium nitrite slowly went into solution. The flask was next cooled again to +5° and a solution of 1.4 g. of 2-amino-5-chloropyrazine in 8 ml. of sulfuric acid was slowly added. After 20 min., the mixture was carefully warmed to 40° and, after an additional 15 min., it was poured onto crushed ice. The solution was repeatedly extracted with ether. The combined organic layers were washed with water and dried over sodium sulfate. After the ether had been removed, the residue was crystallized from cyclohexane; 1 g. of 2-hydroxy-5-chloropyrazine, m.p. 128–129° dec., was collected.

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.78; H, 2.32. Found: C, 37.0; H, 2.74.

2,5-Dichloropyrazine (V).—2-Hydroxy-5-chloropyrazine (2 g.) suspended in 30 ml. of phosphoroyl chloride was heated at reflux temperature for 2 hr. After cooling, the solution was poured carefully onto 300 g. of crushed ice to destroy the excess phosphoroyl chloride. The solution was extracted with methylene chloride and the combined organic extracts were next washed with water and dried over sodium sulfate. After the solvent had been removed, the crude product was distilled under reduced pressure; 1 g. of 2,5-dichloropyrazine, colorless liquid boiling at 72° (12 mm.), was collected, $n^{25}D$ 1.5575. The product solidified on cooling at 0° and melted sharply at 13–14°. The infrared spectrum showed the following strong characteristic bands: λ_{max} 7.68, 8.71, 9.85, and 11.18 μ.

Anal. Calcd. for $C_4H_2Cl_2N_2$: Cl, 47.61. Found: Cl, 47.76