moved *in vacuo* at room temperature and the residue dissolved in water (3 ml.). The resulting solution was adjusted to *p*H 2–3 with 4 *N* sulfuric acid and cooled in ice for 1 hour. The crystalline 2,4-dimethoxy-5-pyrimidinecarboxylic acid which separated was removed and washed with ice-water (1 ml.) and cold ether (3 ml.) (213–290 mg., 55–75% yield). The analytical sample, m.p. 167–168°, was recrystallized from ethyl acetate.

*Anal.* Calcd. for $C_7H_8N_2O_4$: N, 15.22. Found: N, 15.1, 15.3.

The 2,4-dialkoxy-5-pyrimidyllithium intermediate in this reaction is somewhat more thermostable than the 6-substituted analog. Longer reaction times (up to 15 minutes) and higher working temperatures (up to −50°) do not noticeably affect the yield in the above reaction, nor is it necessary to cool the alkyllithium solution before addition to the halide.

**Hydrolysis of 2,4-Dimethoxy-5-pyrimidinecarboxylic Acid to 5-Uracilcarboxylic Acid.**—A solution of this dimethoxy acid (188 mg.) in 8 *N* hydrochloric acid (2 ml.) was heated in a steam-bath for 30 minutes and then diluted with water (2 ml.). The crude 5-uracilcarboxylic acid monohydrate (130 mg., 73% yield) which crystallized from this solution was removed, washed with water (2 ml.) and recrystallized from hot water. The product, when dried at 140° (0.01 mm.) for 24 hours, gave an analytical sample of anhydrous 5-uracilcarboxylic acid.

*Anal.* Calcd. for $C_5H_4N_2O_4$: C, 38.46; H, 2.56; N, 17.94. Found: C, 38.8; H, 2.7; N, 17.8.

The ultraviolet absorption of this acid was identical with that shown by 5-uracilcarboxylic acid[12b]: $\lambda_{max}$ 272–274 mμ, $\epsilon_{max}$ 10,800 (in 0.1 *N* HCl); $\lambda_{max}$ 291 mμ, $\epsilon_{max}$ 13,300 (in 0.1 *N* NaOH) for which Stimson[35] quotes $\lambda_{max}$ 270 mμ, $\epsilon_{max}$ 11,200 (at *p*H 3.0); $\lambda_{max}$ 290 mμ, $\epsilon_{max}$ 12,800 (at *p*H 11.0). A paper chromatogram made with this acid using *n*-propyl alcohol–water as the solvent[26] showed only one spot, $R_f$ 0.37, identical with that shown by 5-uracilcarboxylic acid.

(35) M. M. Stimson, THIS JOURNAL, **71**, 1470 (1949).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

# 2-Bromopyrazines, 2-Cyanopyrazines and their Derivatives

BY GEORGE KARMAS[1] AND PAUL E. SPOERRI

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A variety of 2-bromopyrazines has been synthesized by reaction of hydroxypyrazines with phosphorus tribromide or phosphorus oxybromide. The corresponding 2-cyanopyrazines are formed on heating the bromides with cuprous cyanide in γ-picoline. A few nitrile derivatives, such as carboxamides, methyl ketones and amidines have been prepared.

After 2-hydroxypyrazines had become readily accessible,[2,3] our interest in this field centered on the conversion of these compounds to useful derivatives. A previous publication[3] discussed the synthesis of 2-chloropyrazines by reaction of hydroxypyrazines with phosphorus oxychloride. When it was found that displacement of chlorine by the cyano group could not be satisfactorily accomplished the conversion of hydroxypyrazines to bromopyrazines was studied in anticipation of a greater reactivity for the latter class of compounds.

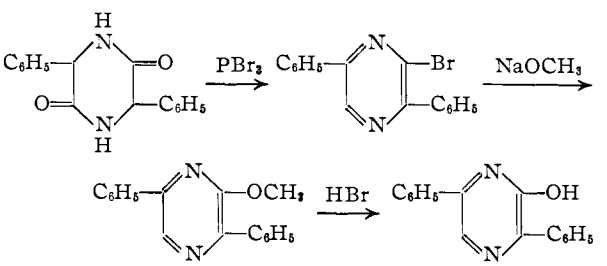
The only known example of such a reaction was the finding of Erickson and Spoerri[4] that a mixture of phosphorus oxybromide and phosphorus pentabromide converted 2-hydroxypyrazine to a mixture of 2-bromopyrazine and 2,6-dibromopyrazine.

In this investigation such displacements were first attempted using phosphorus tribromide alone. It was found that all phenylsubstituted 2-hydroxypyrazines were transformed to the corresponding 2-bromopyrazines in good yield by refluxing with this reagent. This simple procedure was not satisfactory when applied to alkylhydroxypyrazines; the latter formed complexes insoluble in phosphorus tribromide and the yields of bromopyrazines were poor.

Phosphorus oxybromide alone, or with tribromide as diluent, proved to be a useful reagent for the synthesis of alkylated 2-bromopyrazines. However, it complicated the reaction by yielding polybromides as by-products, presumably as a result of free radical bromination of alkyl substituents and of the pyrazine nucleus. This behavior prohibited forcing conditions as a means of improving the yields of monobromopyrazines.

The displacement of chlorine by bromine was considered as an obvious synthesis of 2-bromopyrazines, and it was observed that such a reaction occurred readily when 2-chloro-5,6-diphenylpyrazine and 2-chloro-3-ethyl-5,6-diphenylpyrazine were refluxed in phosphorus tribromide. However, this offered no advantage over direct synthesis from the phenylhydroxypyrazines. Very little displacement occurred when *alkyl*monochloropyrazines were heated in phosphorus tribomide, and so the general synthesis of 2-bromopyrazines started with hydroxypyrazines and is summarized in Table I.

In connection with the work on bromopyrazines, a decided improvement was effected in the synthesis of 2-hydroxy-3,6-diphenylpyrazine. The report[5] that *dl*-phenylglycine anhydride reacts with phosphorus oxychloride to give small amounts of this hydroxypyrazine and its 2-chloro analog in addition to 2,5-dichloro-3,6-diphenylpyrazine suggested an investigation of the reaction of the anhydride with phosphorus tribromide. This was found to yield




(1) Ortho Pharmaceutical Corporation, Raritan, New Jersey.

(2) R. G. Jones, THIS JOURNAL, **71**, 78 (1949); R. G. Jones, U. S. Patent 2,520,088 (1950).

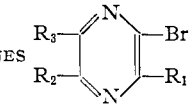
(3) G. Karmas and P. E. Spoerri, THIS JOURNAL, **74**, 1580 (1952).

(4) A. E. Erickson and P. E. Spoerri, *ibid.*, **68**, 400 (1946).

(5) J. J. Gallagher, G. T. Newbold, F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 910 (1949).

TABLE I

BROMOPYRAZINES

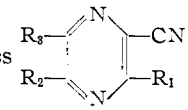


| Cpd. | $R_1$ | $R_2$ | $R_3$ | Conditions[a] | Yield, % | B.p. °C. | Mm. | M.p.,[b] °C. | $n^{20}D$ | Br, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | H | H | H[c] | A: 10 min. at 50° | 58 | 57–58 | 9 | L | 1.5814 | ... | ... |
| II | $CH_3$ | H | H | B: 1 hr. at 120° | 61 | 105–107 | 50 | L | 1.5667 | 46.18 | 45.97 |
| III | $C_2H_5$ | H | H | B: 1 hr. at 125° | 22 | 85–87 | 14 | L | 1.5553 | 42.65 | 42.84 |
| IV | $C_3H_7$ | H | H | A: ½ hr. at 125° | 38 | 101–102 | 14 | L | 1.5456 | 39.69 | 39.92 |
| V | $C_6H_5$ | H | H | C: refl. 4 hr. | 42 | 110–115 | 0.5 | 90–91 | .... | 33.96 | 33.60 |
| VI | $CH_3$ | $CH_3$ | H | B: 10 min. at 145° | 53 | 91–92 | 14 | L | 1.5594 | 42.65 | 42.92 |
| VII | H | $CH_3$ | $CH_3$ | C: refl. 20 min. | 14 | 94–96 | 14 | L | 1.5606 | 42.65 | 43.10 |
| VIII | $CH_3$ | $CH_3$ | $CH_3$ | C: refl. 15 min. | 41 | 105–110 | 20 | 53–54 | .... | 39.69 | 39.56 |
| IX | H | $C_6H_5$ | $C_6H_5$ | C: refl. 20 min. | 63 | ..... | .. | 149–150 | .... | 25.68 | 25.87 |
| X | $CH_3$ | $C_6H_5$ | $C_6H_5$ | C: refl. 30 min. | 48 | ..... | .. | 155–156 | .... | 24.55 | 24.91 |
| XI | $C_2H_5$ | $C_6H_5$ | $C_6H_5$ | C: refl. 1 hr. | 48 | ..... | .. | 99–100 | .... | 23.53 | 23.39 |
| XII | $C_3H_7$ | $C_6H_5$ | $C_6H_5$ | C: refl. 3 hr. | 82 | 135–140 | $10^{-3}$ | L | .... | 22.62 | 22.89 |
| XIII | $i$-$C_3H_7$ | $C_6H_5$ | $C_6H_5$ | C: refl. 3 hr. | 62 | ..... | .. | 118–119 | .... | 22.62 | 22.76 |
| XIV | $C_6H_5$ | H | $C_6H_5$ | C: refl. 16 hr. | 52 | ..... | .. | 119–120 | .... | 25.68 | 25.29 |
| XV | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | C: refl. 30 hr. | 50 | ..... | .. | 178–180 | .... | 20.62 | 20.75 |

[a] A means $POBr_3 + PBr_3$; B means $POBr_3$ alone; C means $PBr_3$ alone. [b] L means liquid at 25°. [c] Previously prepared by Erickson and Spoerri (ref. 4).

TABLE II

CYANOPYRAZINES



| Cpd. | $R_1$ | $R_2$ | $R_3$ | Yield, % | B.p. °C. | Mm. | M.p.,[b] °C. | $n^{20}D$ | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XVI | H | H | H[a] | 29 | 116–117 | 50 | L | 1.5343 | ... | ... | .. | .. | ... | ... |
| XVII | $CH_3$ | H | H | 78 | 125–126 | 50 | L | 1.5278 | 60.48 | 60.42 | 4.23 | 4.34 | ... | ... |
| XVIII | $C_2H_5$ | H | H | 82 | 102–103 | 15 | L | 1.5206 | 63.20 | 63.20 | 5.30 | 5.38 | ... | ... |
| XIX | $C_3H_7$ | H | H | 82 | 112–113 | 15 | L | 1.5136 | 65.29 | 65.49 | 6.16 | 6.20 | ... | ... |
| XX | $CH_3$ | $CH_3$ | H | 75 | 113–115 | 20 | L | 1.5273 | 63.20 | 63.28 | 5.30 | 5.41 | ... | ... |
| XXI | H | $CH_3$ | $CH_3$ | 80 | 119–120 | 17 | 29–30 | .... | 63.20 | 63.13 | 5.30 | 5.63 | ... | ... |
| XXII | $CH_3$ | $CH_3$ | $CH_3$ | 90 | 120–121 | 17 | 68–69 | .... | ... | ... | .. | .. | 28.53 | 28.51 |
| XXIII | $C_6H_5$ | H | H | 90 | 117–118 | 0.2 | 77–78 | .... | ... | ... | .. | .. | 23.19 | 23.20 |
| XXIV | H | $C_6H_5$ | $C_6H_5$ | 96 | ..... | .. | 153–154 | .... | ... | ... | .. | .. | 16.34 | 16.29 |
| XXV | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 97 | ..... | .. | 173–174 | .... | ... | ... | .. | .. | 15.51 | 15.60 |
| XXVI | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 97 | ..... | .. | 255–256 | .... | ... | ... | .. | .. | 12.61 | 12.29 |

[a] Previously prepared from the amide (ref. 5, 6). [b] L means liquid at 25°.

60–65% of 2-bromo-3,6-diphenylpyrazine which was easily converted to the hydroxypyrazine through its methyl ether in an over-all yield of 55% from the anhydride.

2-Hydroxy-3,5,6-triphenylpyrazine has been synthesized in 75% yield by a reaction new to the pyrazines, direct arylation of 2-hydroxy-5,6-diphenylpyrazine following the addition of phenyldiazonium chloride to a cold, strongly alkaline solution of the pyrazine. This is a general reaction and will be discussed in the next publication, which will deal with nuclear substitutions on hydroxypyrazines.

It was found that 2-bromopyrazines could very conveniently be converted to the corresponding nitriles on refluxing with cuprous cyanide in dry γ-picoline. The variety of 2-cyanopyrazines prepared in this manner is indicated in Table II. The only monobromide for which this procedure was not suitable was bromopyrazine itself. Apparently cyanopyrazine was unstable in boiling γ-picoline and was completely polymerized. However, when the reaction was performed in pyridine, a 29% yield of 2-cyanopyrazine was obtained.

TABLE III

2-CARBOXAMIDOPYRAZINES

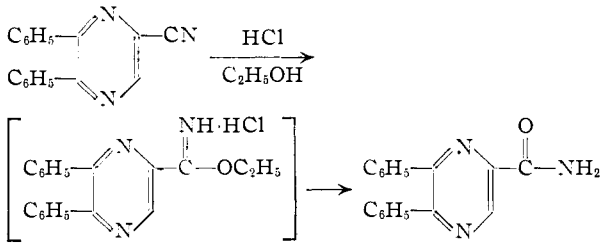
| Substituents | Yield, % | Cryst. solvent | M.p., °C. | N, % Calcd. | Found |
|---|---|---|---|---|---|
| 3-$CH_3$ | 17 | Acet. | 164–165 | 30.68 | 30.74 |
| 3-$C_2H_5$ | 35 | Acet. | 119–120 | 27.80 | 27.60 |
| 3-$C_3H_7$ | 60 | Ether | 98–99 | 25.42 | 25.30 |
| 3-$C_6H_5$ | 70 | Chloroform | 171–172 | 21.10 | 20.86 |
| 3,5,6-$(CH_3)_3$ | 44 | Acet. | 165–166 | 25.42 | 25.31 |

A few conventional reactions of representative cyanopyrazines indicated that the normal behavior of nitriles could be anticipated. Hydrolysis with sulfuric acid yielded the 2-carboxamides of 3-methyl-, 3-ethyl-, 3-propyl-, 3-phenyl-, and 3,5,6-trimethylpyrazine, as summarized in Table III.

In normal Grignard syntheses with methylmagnesium iodide, 45% of 2-acetyl-3,5,6-trimethylpyrazine and 76% of 2-acetyl-5,6-diphenylpyrazine were obtained from the corresponding nitriles. The synthesis of 2-acetylpyrazine in this manner has previously been reported by other workers.[6]

(6) S. Kushner, *et al.*, THIS JOURNAL, **74**, 3617 (1952).

Pyrazinamidine hydrochloride has been prepared from 2-cyanopyrazine through the iminoether in the conventional Pinner synthesis.[7] We have found that 2-cyano-3,5,6-trimethylpyrazine also reacts normally to yield the amidine. However, 2-cyano-5,6-diphenylpyrazine could not be converted to the amidine in this manner because the intermediate iminoether hydrochloride spontaneously lost ethyl chloride and formed the 2-carboxamide



5,6-Diphenylpyrazinamidine was eventually prepared in 2% yield by heating the nitrile with ammonium thiocyanate at 180°, a method developed by Partridge and Short.[8]

## Experimental

I. **Reagents. A. 2-Hydroxy-3,6-diphenylpyrazine.**—A mixture of 41.5 g. (0.156 mole) of *dl*-phenylglycine anhydride[5] and 120 ml. of phosphorus tribromide was refluxed gently for five hours, cooled to 25°, and filtered on a sintered glass funnel with crushing of the insoluble red lumps and washing with 20 ml. of phosphorus tribromide. The filtrate was cautiously poured onto 2 kg. of well-stirred chopped ice and then this hydrolysis mixture was made strongly alkaline with 50% aqueous sodium hydroxide and extracted while still warm (35–40°) with two 400-ml. portions of chloroform. Acidification of the aqueous phase caused precipitation of 6.0 g. of the hydroxypyrazine which was filtered off and later added to the major portion. Evaporation of the chloroform extracts left a residue of crude 2-bromo-3,6-diphenylpyrazine which was added to a solution of 10.0 g. (an excess) of sodium in 350 ml. of methanol and the mixture was refluxed for four hours and then boiled down to 200 ml. and poured into 2 l. of water. After the brown methyl ether had solidified it was filtered off, dried in air, and then cleaved by stirring and refluxing for ten hours in 300 ml. of 48% hydrobromic acid plus 100 ml. of acetic acid. The mixture was poured into 2 l. of water and the 2-hydroxy-3,6-diphenylpyrazine was filtered off, washing with 5% aqueous sodium bicarbonate and then water. After it had dried in air this product, plus the earlier six-gram portion, was dissolved in 350 ml. of hot pyridine, filtered while hot with Super-Cel as a filter aid, and cooled slowly to 0°. The small yellow granules melted at 292–293° and the yield was 21.3 g. (55%).

*Anal.* Calcd. for $C_{16}H_{12}N_2O$: C, 77.39; H, 4.87. Found: C, 77.14; H, 4.87.

B. **2-Hydroxy-3,5,6-triphenylpyrazine.**—A solution of 10.0 g. (0.043 mole) of 2-hydroxy-5,6-diphenylpyrazine[2,3] in one liter of warm (65°) 1% aqueous sodium hydroxide was cooled to 0° and stirred while a solution of phenyldiazonium chloride, prepared in the usual manner fron 6.0 g. of aniline plus 12 ml. of 12 *N* hydrochloric acid in 70 ml. of water and 4.6 g. of sodium nitrite in 10 ml. of water, was added in one portion. The resulting gel was kept at 0° for 30 minutes and at 20° for one hour, and then it was stirred very vigorously while 40 ml. of 12 *N* hydrochloric acid was added. The orange 2-hydroxy-3,5,6-triphenylpyrazine was filtered off, dried in air and then recrystallized from acetic acid to give (in two crops) 10.5 g. (75%) of small yellow prisms of m.p. 279–281°.

*Anal.* Calcd. for $C_{22}H_{16}N_2O$: N, 8.64. Found: N, 8.60.

C. **Phosphorus Oxybromide.**—One pound of this reagent was generously supplied by the Dow Chemical Company. Larger amounts were prepared by the method of Booth and Seegmiller,[9] with a variation that eliminated occasional difficulties due to the sublimation of phosphorus pentabromide and to poor quality phosphorus pentoxide. A cautiously prepared mixture of 12.0 ml. (32.4 g., 0.12 mole) of phosphorus tribromide, 6.2 ml. (19.2 g., 0.12 mole) of bromine and 5.7 g. (0.04 mole) of phosphoric anhydride was refluxed in 30 ml. of phosphorus oxychloride. The latter serves as a solvent to assure easy starting of the reaction and washes back sublimed pentabromide from the flask and condenser. After most of the phosphoric anhydride had dissolved, more of the first three reagents, in the same quantities as originally, was added and the refluxing was continued until most of the anhydride had again reacted. This process of portionwise addition of stoichiometric amounts of the reagents (no more oxychloride was needed) was continued until the final reaction mixture totalled roughly 1200 g. and then the mixture was distilled at atmospheric pressure through a 12-inch Vigreux column. The forerun was discarded and phosphorus oxybromide (a low-melting solid) was collected at 185–193° in a yield of 70–80%. It was used without further purification in the reaction with hydroxypyrazines.

II. **2-Bromopyrazines.**—Three general procedures were used and are referred to as A, B and C in Table I.

A. **Compounds I and IV.**—To a warm (50°) solution of 20 ml. (0.20 mole) of phosphorus tribromide in 40 ml. (0.36 mole) of phosphorus oxybromide was added with stirring 0.20 mole of the appropriate 2-hydroxypyrazine, and the mixture was heated with slow stirring under the conditions specified in Table I. The pasty reaction mixture was cooled to 25° and was cautiously poured onto 750 g. of ice layered with 200 ml. of ether. This hydrolysis mixture was made alkaline with 28% aqueous ammonia and was then filtered, using 10 g. of Super-Cel as a filter aid. The filtrate layers were separated and the aqueous phase was extracted with 100 ml. more ether. After drying over magnesium sulfate the (combined) ether solution was concentrated through a 15-inch packed column and the residue was twice fractionated through a 12-inch Vigreux column to purify the bromopyrazine.

B. **Compounds II, III and VI.**—To 45 ml. (0.40 mole) of molten phosphorus oxybromide at 50° was added with slow stirring 0.20 mole of the hydroxypyrazine. The dark pasty mass was slowly stirred while it was heated under the conditions specified in Table I, and then it was cooled and cautiously hydrolyzed exactly as described in Procedure A. The bromopyrazine was isolated and purified by fractional distillation as in A.

C. **Compounds VII and VIII.**—A mixture of 0.10 mole of the hydroxypyrazine and 35 ml. of phosphorus tribromide was vigorously stirred and refluxed for the period of time specified in Table I, and then it was cooled to 25° and cautiously hydrolyzed as described in procedure A. The bromopyrazine was isolated and purified as in A.

C′. **Compounds V and IX–XV.**—A mixture of 0.10 mole of the hydroxypyrazine and 35 ml. of phosphorus tribromide was refluxed for the specified period and was cooled and cautiously poured onto 500 g. of ice. After hydrolysis was complete the bromide was extracted with two 150-ml. portions of chloroform and the (combined) extract was washed with 100 ml. of 2% aqueous sodium hydroxide, dried over magnesium sulfate and evaporated to dryness. The crude solid bromopyrazines were recrystallized from ethanol. 2-Bromo-3-propyl-5,6-diphenylpyrazine was a viscous liquid and was purified by distillation.

III. **2-Cyanopyrazines of Table II. A. Compound XVI.**—A mixture of 14.0 g. (0.088 mole) of 2-bromopyrazine and 14.0 g. (0.157 mole) of cuprous cyanide in 40 ml. of anhydrous pyridine was refluxed for three hours and then poured with stirring into 300 ml. of ice-cold 6 *N* hydrochloric acid layered with 150 ml. of ether. After ten minutes of stirring this was diluted to one liter with cold water and filtered to remove the brown solid, washing with 150 ml. more ether. The aqueous portion of the filtrate was further extracted with three 100-ml. portions of ether and the combined, dried (magnesium sulfate) ether solution was concentrated through a 15-inch packed column. After fractional distillation throgh a semimicro Vigreux column the yield of 2-

(7) H. W. Del Vecchio, Thesis, Polytechnic Institute of Brooklyn, 1944.

(8) M. W. Partridge and W. F. Short, *J. Chem. Soc.*, 390 (1947).

(9) H. S. Booth and C. G. Seegmiller, "Inorganic Syntheses," Coll. Vol. II, McGraw-Hill Book Co., New York City, N. Y., 1946, p. 151.

cyanopyrazine was 2.7 g. (29%); b.p. 116–117° (100 mm.), $n^{20}D$ 1.5343.

B. **Compounds XVII–XXVI.**—A mixture of 0.05 mole of the appropriate 2-bromopyrazine and 15 g. (0.168 mole) of cuprous cyanide in 40 ml. of anhydrous γ-picoline was refluxed for three hours (ten hours for cpd. XXVI) and poured while hot into a vigorously stirred mixture of 400 ml. of ice-cold 4 *N* hydrochloric acid and 100 ml. of chloroform. After one-half hour of stirring this was filtered and the solid was washed with 50 ml. of chloroform. The aqueous portion of the filtrate was further extracted with 100 ml. more chloroform and the combined, dried (magnesium sulfate) extracts were concentrated through a 15-inch packed column. Cyanopyrazines XVII–XXII were purified by distillation through a 10-inch Vigreux column. The phenylcyanopyrazines were dried under vacuum to remove chloroform and then XXIII was distilled (b.p. 117–118° at 0.2 mm.; m.p. 77–78°), XXVI was recrystallized from 500 ml. of toluene, and XXIV and XXV were recrystallized from 350 ml. of heptane.

**IV. 2-Carboxamidopyrazines of Table III.**—A solution of 0.05 mole of the appropriate 2-cyanopyrazine in 25 ml. of concentrated sulfuric acid was heated at 120–125° for three hours and then poured onto 400 g. of ice. This solution was made alkaline with 50% aqueous sodium hydroxide and the amide was extracted with three 150-ml. portions of chloroform, filtering with Super-Cel when necessary to assist in separation of layers. After evaporation of the chloroform solutions, the crude amides were recrystallized from the solvents specified in Table III.

**V. 2-Acetyl-5,6-diphenylpyrazine.**—A solution of 4.3 g. (0.0167 mole) of 2-cyano-5,6-diphenylpyrazine in 200 ml. of dry benzene was stirred at 25° while 7.0 ml. of 4.0 *molar* ethereal methylmagnesium bromide was added and then the mixture was refluxed for one hour and cooled to 10°. After addition of 50 ml. of 6 *N* hydrochloric acid, the hydrolysis mixture was refluxed with stirring for one hour and then diluted with 200 ml. of water. The solid residue from evaporation of the benzene solution was recrystallized from 20 ml. of acetone to give 3.5 g. (76%) of the ketone, small golden flakes, m.p. 152–153°.

*Anal.* Calcd. for $C_{18}H_{14}N_4O$: N, 10.22. Found: N, 10.16.

**VI. 2-Acetyl-3,5,6-trimethylpyrazine.**—The reaction of 5.0 g. (0.034 mole) of 2-cyano-3,5,6-trimethylpyrazine with 13.0 ml. (0.052 mole) of 4.0 *molar* methylmagnesium bromide was performed as described in V for the diphenyl analog, except that the final reflux period (with 25 ml. of 6 *N* hydrochloric acid) was one-half hour. The benzene solution was then washed with water and with 2% aqueous sodium hydroxide, dried over magnesium sulfate and concentrated through a Vigreux column. Distillation of the residue gave 2.5 g. (45%) of the solid ketone, b.p. 113–114° (14 mm.). After recrystallization from pentane the analytical sample of soft white flakes melted at 61–62°.

*Anal.* Calcd. for $C_9H_{12}N_2O$: N, 17.07. Found: N, 17.28.

**VII. 2-Amidino-3,5,6-trimethylpyrazine Hydrochloride.**—A cold (0°) solution of 2.0 g. (0.0136 mole) of 2-cyano-3,5,6-trimethylpyrazine in 5 ml. of anhydrous ethanol plus 15 ml. of pure dioxane was saturated with hydrogen chloride and stored at 25° for three days. The iminoether hydrochloride was filtered off, washed with dry ether and added with stirring to 100 ml. of cold (0°) saturated ammoniacal ethanol (anhydrous), and then this mixture was stored at 25° for three days. Ammonium chloride was filtered off and the filtrate was evaporated to dryness under vacuum. The solid was dissolved in 10 ml. of warm anhydrous ethanol and the solution was diluted with 20 ml. of acetone. After ten minutes, more ammonium chloride was filtered off and the filtrate was evaporated to a volume of 6 ml., diluted with 25 ml. of acetone and stored at 0° to give 2.0 g. (73%) of hard, cream-colored granules of the amidine hydrochloride, m.p. 170–171°.

*Anal.* Calcd. for $C_8H_{13}N_4Cl$: N, 27.92. Found: N, 27.98.

**VIII. 2-Amidino-5,6-diphenylpyrazine Hydrochloride.**—A mixture of 2.0 g. (0.0078 mole) of 2-cyano-5,6-diphenylpyrazine and 2.4 g. (0.0316 mole) of dry ammonium thiocyanate was stirred at 180° for 45 minutes. After cooling the tarry mass was leached with 100 ml. of boiling water, decanting from the tar which was then leached with two 80-ml. portions of boiling 1% hydrochloric acid. The combined acid extracts were made alkaline with sodium hydroxide and chilled to precipitate the crude amidine which was filtered off. This was boiled with 70 ml. of 1% hydrochloric acid and the mixture was filtered. Buff granules of the amidine hydrochloride crystallized from the filtrate on cooling. The yield was 50 mg. (2%), m.p. 260–265° with decomposition.

*Anal.* Calcd. for $C_{17}H_{15}N_4Cl$: N, 18.02. Found: N, 17.90.

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# The Japp–Klingemann Reaction with γ,δ-Unsaturated β-Ketoesters. Synthesis of Pyridazinones[1]

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Ethyl 2,3-dioxo-octadec-4-enoate-2-phenylhydrazone (Ia) is found to isomerize in alcohol to ethyl 1,2,3,4-tetrahydro-1-phenyl-6-tridecylpyridazin-4-one-3-carboxylate (IIIa) which, on reduction with zinc and acetic acid, suffers ring-opening with loss of ammonia to give ethyl 3-hydroxy-5-anilino-octadec-2,4-dienoate (IVa). These structures are confirmed by infrared measurements. The isomerization to pyridazinones is of potentially general applicability with products of the Japp–Klingemann reaction of γ,δ-unsaturated β-ketoesters and constitutes an original route to this heterocyclic system.

The key intermediate in the total synthesis of sphingosine[2a] is ethyl 2,3-dioxo-octadec-4-enoate-2-phenylhydrazone (Ia), which is prepared by the Japp–Klingemann reaction[3] of benzenediazonium chloride with ethyl α-hexadec-2-enoylacetoacetate. Occasionally, instead of the required product Ia there was obtained an isomeric product A, tentatively formulated as IIa,[2b] which differed from Ia in melting point and was lighter in color. Molecular weight determinations eliminated the possibility that A was a polymeric form of Ia. Zinc and

(1) Part of this work was embodied in a lecture by D. Shapiro at the International Congress on Pure and Applied Chemistry, Zürich, 1955.

(2) (a) D. Shapiro and K. Segal, THIS JOURNAL, **76**, 5849 (1954); (b) D. Shapiro and R. A. Abramovitch, Congress Handbook, XIVth International Congress of Pure and Applied Chemistry, Zürich, 1955, p. 340.

(3) R. Japp and F. Klingemann, *Ber.*, **20**, 2942, 3284, 3398 (1887).