## Experimental

**Aldehydes.**—*m*-Chloro- and *m*-bromobenzaldehydes were prepared as described in "Organic Syntheses."[14] The crude aldehydes obtained on steam distillation were used without further purification. 2-Chloro-, 4-chloro-, 2,4-dichloro- and 3,4-dichlorobenzaldehydes were obtained from the Heyden Chemical Corp., the remainder from the Eastman Kodak Co.

**Cinnamic Acids.**—*m*-Nitrocinnamic acid was obtained from Eastman Kodak Co. The remainder of the acids were prepared by the Doebner reaction. The aldehyde (1.0 mole), malonic acid (1.1 mole), 200 cc. ethanol (either 95% or absolute) and 25 cc. pyridine were heated overnight on the steam bath. In the morning the alcohol which had evaporated was replaced, the mixture cooled and the cinnamic acid filtered off and washed. Recrystallization was generally unnecessary, but additional acid could usually be recovered by concentration of the filtrate. Yields are given in column two of Table II, and at no time was the necessity for anhydrous reagents noted which is mentioned in connection with this reaction when carried out in pyridine as solvent,[3] and observation that hardly seems surprising since the condensation itself liberates a mole of water.

In the case of *p*-dimethylaminocinnamic acid no product was obtained by the above procedure. However, when the reaction mixture was merely warmed to solution (50–60°) and then allowed to stand at room temperature for a week the acid crystallized from the mixture in 50% yield.

The two dichlorocinnamic acids have not previously been reported. Melting points and analytical data on samples recrystallized five times from ethanol are given below.

2,4-Dichlorocinnamic acid: m. p. 228.5–229.5° (uncor.). *Anal.* Calcd. for $C_9H_6O_2Cl_2$: C, 49.8; H, 2.79; Cl, 32.7. Found: C, 49.87; H, 2.89; Cl, 32.60.

3,4-Dichlorocinnamic acid: m. p. 217.2–218.2° (uncor.). *Anal.* Found: C, 49.69; H, 2.94; Cl, 32.65.

**Decarboxylations** were carried out in ordinary Claisen or distilling flasks heated either with a Glass-Col heater or a free flame, the former giving easier control and requiring less attention. From 25 to 200 g. of the cinnamic acids was decarboxylated at a time, usually in the presence of two parts of base and one tenth part of catalyst, both by weight. The size of the run seemed to have no effect on yields and, for the smaller experiments, it was sometimes convenient to use four parts of base. In experiments in quinoline, distillation was carried out at such a rate that during the bulk of the reaction the temperature of the vapors remained below 220°, and one third to two thirds of the reaction mixture distilled within an hour. The completion of the reaction required usually forty to fifty minutes and was signalled by a rise in the temperature of the vapors to the boiling point of quinoline. In the higher-boiling bases the acid was added in a number of small portions, the heat being adjusted so that, after each addition, the temperature of the vapors rose to 235–240° in two to five minutes, at which point a fresh portion of acid was introduced.

**Purification of Products.**—The halostyrenes were separated from base by steam distilling from at least a 50% excess of 2.4 *N* hydrochloric acid in the presence of 0.02–0.05 mole per cent. trinitrobenzene as a polymerization inhibitor, and employing a Dean and Stark trap so that the water was continuously recycled. Only traces of polymer remained in the pot and the cloudy steam distillate was dried and clarified with a small amount of drierite, calcium chloride or sodium carbonate. Since the alkoxystyrenes were found to be unstable toward hot acid, yielding chiefly gummy polymers, they were separated from quinoline by taking up the distillates in ether, washing twice with cold 2.4 *N* hydrochloric acid and water, drying, and removing ether, the last traces under vacuum at room temperature. Subsequent distillations were carried out through short, helices-packed columns at the pressures indicated in Table II. In general, only very small foreruns and high-boiling fractions were obtained, and the yield of purified styrene from crude material was in general more sensitive to the quantity of material available for distillation than to any other variable. Accordingly, in Table II the crude yields probably furnish the best basis for comparing experiments, and many runs, carried out to determine the effect of experimental conditions on yield, were not carried beyond this point.

**Acknowledgment.**—The authors wish to thank Mr. Edward Phillips for carrying out most of the fractional distillations of styrenes described in this paper.

## Summary

1. A number of halo- and alkoxycinnamic acids are converted to the corresponding styrenes in good yield by slow distillation from quinoline in the presence of copper powder.

2. The reaction fails or gives poor yields with 3-nitro-, 4-dimethylamino-, 2,4-dichloro-, 3,4-dichloro- and 3,4-dimethoxycinnamic acids.

PASSAIC, NEW JERSEY RECEIVED NOVEMBER 21, 1946

(14) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, 1943, p. 130.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

# Derivatives of Piperazine. XXI. Synthesis of Piperazine and C-Substituted Piperazines

BY LELAND J. KITCHEN[1] AND C. B. POLLARD

Piperazine, known as long ago as 1853,[2] has not been readily available, although numerous processes for its synthesis have been described.

A method now is described by which piperazine itself and numerous of its C-substituted homologs readily are derivable by the catalytic cyclodehydration of N-(2-hydroxyethyl)-ethenediamine and its C-substituted derivatives. The dehydration is carried out at atmospheric pressure by refluxing the hydroxyethylethenediamine, alone or with suitable diluent, with catalyst under a fractionating column and collecting water and the piperazine as formed or, better, by carrying out the reaction in an autoclave.

## Experimental

**Equipment.**—Purifications by distillation were carried out with a 15 in. × 19 mm. column packed with glass Raschig rings and having an efficiency of 6-theoretical plates. The column was provided with a head designed for distillation of solids; it had a Hopkins-type condenser made removable by a standard taper connection, enabling

(1) Present address: Firestone Tire and Rubber Co., Akron, Ohio.

(2) Cloëz, *Jahresber. fortschr. Chem.*, 468 (1853).

some control of reflux by rotation of the condenser and allowing recovery of condensate solidified on the walls of the condenser. The same apparatus was used for continuous removal of piperazine–water mixture in the dehydrations carried out at atmospheric pressure.

Autoclave reactions were carried out in an American Instrument Co. hydrogenation bomb of 750-ml. capacity, electrically heated and provided with a rocker for agitation.

**Materials.**—Dioxane was purified by long (ten to twenty hours) reflux of commercial dioxane with aniline and metallic sodium, followed by fractional distillation. N-(2-Hydroxyethyl)-ethenediamine from Carbide and Carbon Chemicals Corp. was distilled; other intermediates were prepared.[3]

**Preparation of Piperazine at Atmospheric Pressure.**—One hundred and fifty grams of N-(2-hydroxyethyl)-ethenediamine containing 5 g. of Raney nickel catalyst were heated under a distillation column for two and one-half hours. Distillate of b. p. about 120° slowly was collected; 75 g. of tarry resin remained in the still-pot. The distillate, 57 g. of aqueous piperazine, contained piperazine in amount equivalent to a 32% yield, determined by titration with 0.1 *N* acid (brom phenol blue indicator): benzoyl deriv., m. p. 191.7–192.8° (from alc.); dibenzoylpiperazine, m. p. 192.1–193.0°; mixed m. p. 191.7–193.0°. With diethylcarbitol as diluent, twelve hours were required for reaction, giving 34% yield.

TABLE I

SYNTHESIS OF PIPERAZINE FROM N-(2-HYDROXYETHYL)-ETHENEDIAMINE, AUTOCLAVE METHOD

| g. | Catalyst | Reactant, g. | Dioxane, ml. | Reaction time, hr. | Reaction temp., °C. | Yield, % | Recovered amino-alc., g. |
|---|---|---|---|---|---|---|---|
| 60 | Copper–chromium oxide | 156[a] | 1050 | 3 | 275 | 45 | [b] |
| 30 | Raney nickel | 156[a] | 1050 | 3 | 200 | 50 | [b] |
| 10 | Raney nickel | 85 | 400 | 3 | 200 | 51 | 0 |
| 15 | Act. alumina | 150 | 200 | 3 | 300 | 20 | 82 |
| 30 | Silica gel | 279 | None | 3 | 300 | 17.4 | 150 |
| 30 | Cupric oxide | 150 | 200 | 3 | 275 | 43 | [b] |
| 30 | Iron ($H_2$ red.) | 150 | 200 | 3 | 300 | 26 | 0 |

[a] Composites of three runs, 52 g. reactant per run. [b] Not determined.

(3) Kitchen and Pollard, *J. Org. Chem.*, **8**, 342 (1943).

**Autoclave Method for Piperazine Preparation.**—The autoclave was charged with 150 g. of N-(2-hydroxyethyl)-ethenediamine in 200 ml. of dioxane, 5–30 g. of catalyst was added, and reaction was carried out for three hours at a temperature in the range 200–300° (Table I). The reaction mixture, filtered from catalyst, was distilled; dioxane-water azeotrope distilled at 87°, then dioxane at 100–103°, and finally piperazine at 140–150°.

Raney nickel appeared the catalyst of choice; copper-chromium oxide, activated alumina, silica gel, cupric oxide and iron (hydrogen reduced) were intermediate in effectiveness. Low yields were obtained with palladium/Norit (225–246°, 13%) and fuller's earth (300°, 5%); and little or no piperazine was obtained when the catalyst was platinum/Norit (180–230°), vermiculite (300°), barium oxide (300°), chromic oxide (280°), stannous oxide (300°) or Norit (300°).

**Preparation of 2-Methylpiperazine.**—Two hundred and twenty-five grams of N-(2-hydroxypropyl)-ethenediamine in 350 ml. of dioxane was autoclaved with 10 g. of Raney nickel under 200 p. s. i. (cold) of hydrogen for five hours at 185–203°. Yield of 2-methylpiperazine was 121 g. (52% yield; 70%, based upon unrecovered starting material).

2-Methylpiperazino-bis-(phenylthiourea), from benzene–absolute alcohol; gave a m. p. 189.0–189.9° (cor.).

**Preparation of 2-Phenylpiperazine.**—One hundred and eight grams of N-(2-hydroxy-2-phenylethyl)-ethenediamine in 300 ml. of dioxane, agitated with 20 g. of Raney nickel at 220° for three and one-half hours, yielded 32 g. (32% yield) of crude 2-phenylpiperazine, a yellow oil of $n^{30}D$ 1.5766 and b. p. 124–146° (10 mm.) which crystallized to a mush on standing. Redistilled, it boiled mainly at 138° (10 mm.). Purified by three recrystallizations from hexane, it had m. p. 87.5–87.8° (cor.). Dihydrochloride, from aqueous alcohol, gave a m. p. *ca* 335° (dec.). *Anal.* Calcd. for $C_{10}H_{16}N_2Cl_2$: Cl, 30.15. Found: 29.35. Dinitroso deriv., m. p. 69.9–70.2° (cor.) (from methanol); diacetyl deriv., m. p. 70.1–71.2° (cor.) (hexane); picrate (prepared in alcohol), m. p. *ca.* 276° (dec.) (cor.).

## Summary

Preparation of piperazine, 2-methylpiperazine and 2-phenylpiperazine, a new compound, by catalytic cyclodehydration of hydroxyethylethenediamines is described.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Synthesis of 4-Hydroxyquinolines. X. Quinoline Derivatives with Sulfur-Containing Substituents[1]

BY CHARLES C. PRICE,[2] NELSON J. LEONARD AND GARDNER W. STACY[3]

In continuation of studies in the 4-hydroxyquinoline series[4] it appeared of interest to prepare some quinolines with sulfur-containing substituents. The 6-substituted quinoline derivatives are the most convenient examples of this type of compound since the possibility of ambiguity of structure on ring closure is eliminated.

The application of the ethoxymethylenemalonic ester synthesis[4] to *p*-aminophenyl sulfide (I) proceeded successfully to produce 6,6′-bis-[4-(4-diethylamino-1-methylbutylamino)-quinolyl] sulfide (VII). One unusual and interesting feature was the apparent oxidation of the sulfide to sulfoxide during replacement of the 4-hydroxyl group by chlorine (V → VI), and the subsequent reduction of the sulfoxide during treatment with 1-amino-4-diethylaminopentane (VI → VII).

Application of this synthesis to *p*-aminophenyl

(1) The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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(4) Price and co-workers, THIS JOURNAL, **68**, 1204, 1251, 1253, 1255, 1256, 1279, 1282 (1946); **69**, 371, 374 (1947).