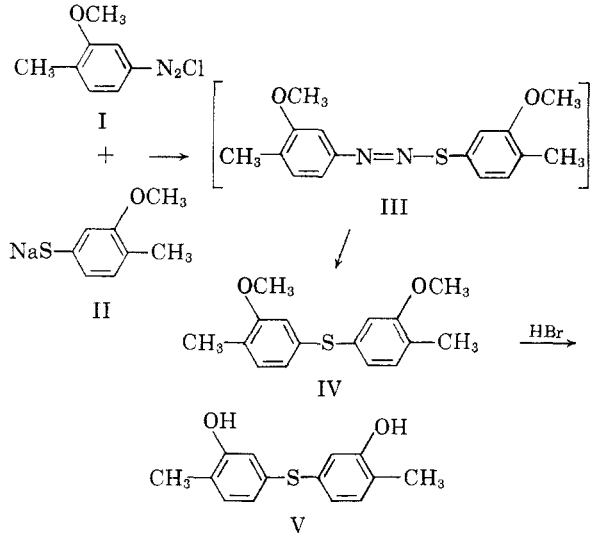
the sulfur bridge. Because suitable synthetic methods are not available, we have utilized an approach based on the diazotization and coupling of substituted anisidines rather than phenols.[1] The product is an ether which must be hydrolyzed to the desired *meta*-dihydroxydiaryl sulfide.

The outline of the experimental procedure for the preparation of 3,3′-thiobis(6-methylphenol) follows below:



The diazotized 4-methyl-*m*-anisidine (I) was prepared from 5-nitro-*o*-toluidine,[2] and the sodium salt of 3-methoxy 4-methylbenzenethiol (II) from 4-methyl-*m*-anisidine *via* the ethyl xanthate reaction.[3]

EXPERIMENTAL

3-Methoxy-4-methylbenzenethiol. The procedure was essentially the same as that reported for *m*-toluenethiol.[3] The product, obtained in 43.3% yield, was a colorless oil boiling at 145° at 1 mm. Its infrared spectrum showed the characteristic −SH group.

Anal. Calcd. for $C_8H_{10}OS$: C, 62.26; H, 6.55; S, 20.79. Found: C, 62.10; H, 6.07; S, 21.19.

3,3′-Thiobis(6-methylanisole) (IV). Diazotized 4-methyl-*m*-anisidine (11.2 g.) was slowly added to a warm (70°) alkaline solution of 10.0 g. of 3-methoxy-4-methylbenzenethiol. A yellow precipitate (III) formed which rapidly decomposed with the evolution of nitrogen (Caution!) and the formation of a brown oil. After the mixture had been kept at 70° for about 1 hr. it was steam distilled (to remove 4.2 g. of unchanged 3-methoxy-4-methylbenzenethiol), and then extracted with ether. The brown ether extract was washed with dilute sodium hydroxide, followed by water, and distilled *in vacuo*. The product (5.0 g.) came over at 165–205° at 0.2 mm.

Anal. Calcd. for $C_{16}H_{18}O_2S$: C, 70.00; H, 6.60; S, 11.67. Found: C, 70.51; H, 6.18; S, 11.25.

3,3′Thiobis(6-methylphenol) (V). To 22.5 g. of acetic anhydride was added, cautiously and with cooling, 9.0 g. of 48% hydrobromic acid, followed by 5.0 g. of 3,3′-thiobis(6-methoxyanisole). The mixture was then permitted to reflux for 6 hr.

After removing the excess hydrobromic and acetic acids *in vacuo*, the residual oil was stirred with 30 ml. of 10% sodium hydroxide solution for an hour at 95°. An ether extraction removed any unhydrolyzed methoxy compound; the alkaline residue was then acidified with 10 ml. of concd. hydrochloric acid and extracted with ether. The product (1.0 g.) distilled at 210–235° and 0.3 mm. in the atmosphere of nitrogen, and came over as a very viscous light amber oil. It solidified on standing and crystallized from petroleum ether (b.p. 30–60°) as white odorless solid, m.p. 85–87°.

Anal. Calcd. for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02. Found: C, 68.19; H, 5.89, S, 12.79.

WASHINGTON RESEARCH CENTER
W. R. GRACE & CO.
CLARKSVILLE, MD.

(1) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1526 (1929).

(2) R. A. Benkeser and W. E. Buting, *J. Am. Chem. Soc.*, **74**, 3013 (1952).

(3) *Org. Syntheses*, **Coll. Vol. III**, 809 (1955).

Homopiperazine and Its Derivatives. II.[1] A Convenient Synthesis of 1-Methylhomopiperazine

F. POPPELSDORF, R. C. MYERLY, AND R. B. CONROW

Received February 23, 1961

1-Methylhomopiperazine is a pharmaceutical intermediate of interest inasmuch as several of its derivatives have recently been reported to have useful physiological activity.[2–4] It has been made by lithium aluminum hydride reduction of 1-methyl 5-homopiperazinone[2,5,6]; by the catalytic cyclodehydration of *N*-(2′-hydroxyethyl)-*N*-methyl-1,3-propanediamine[7]; and by the catalytic reductive cyclization of *N*- (or *N*′-) (2-cyanoethyl)-*N*-methylethylenediamine.[1] These preparative methods suffer from the disadvantage of mediocre yields or of being based on relatively inaccessible starting materials.

We present a simple and convenient synthesis of 1-methylhomopiperazine involving the reductive methylation of homopiperazine. Homopiperazine is now readily available by catalytic reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine,[1] the addition product of ethylenediamine and acrylonitrile.

Treatment under pressure of a methanolic solution of homopiperazine with aqueous formaldehyde (1.11 molecular proportions), hydrogen, and Raney

(1) Part I, F. Poppelsdorf and R. C. Myerly, *J. Org. Chem.*, **26**, 131 (1961).

(2) A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *J. Am. Chem. Soc.*, **76**, 5805 (1954).

(3) J. W. Reinertson and P. E. Thompson, *Antibiotics and Chemotherapy*, **5**, 566 (1955).

(4) P. Brookes, R. J. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).

(5) J. G. Scruggs, Ph.D. dissertation, University of Michigan, 1956.

(6) P. S. Wadia and N. Anand, *J. Sci. Ind. Research (India)*, **17B**, 31 (1958); *Chem. Abstr.*, **52**, 15549 (1958).

(7) Takeo Ishiguro and Masaaki Matsumura, *Yakugaku Zasshi*, **78**, 153 (1959); *Chem. Abstr.*, **53**, 13163 (1959).

nickel catalyst gave 1-methylhomopiperazine in a yield of 59.5%. 1,4-Dimethylhomopiperazine was co-produced in a yield of 24.2% and 11.2% of the homopiperazine remained unchanged. Separation of the reaction products could not be effected satisfactorily by simple distillation because their boiling points lie too closely together (see Table I).

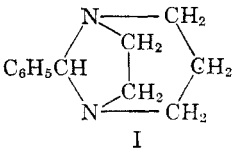
TABLE I

BOILING POINTS OF HOMOPIPERAZINE AND ITS *N*-METHYL DERIVATIVES

Pressure Mm.	B.P. Homopiperazine	1-Methylhomopiperazine	1,4-Dimethylhomopiperazine
750	168	164	161
50	92	83	
10	60	50	

Removal of 1,4-dimethylhomopiperazine proved to be easy, however, because it was found to form a minimum boiling azeotrope (b.p. 97.5°/750 mm.) with water.

Efficient separation of 1-methylhomopiperazine and homopiperazine was made possible by the somewhat surprising discovery that benzaldehyde would combine preferentially and almost exclusively with the homopiperazine in a mixture of these two cyclic amines.[8] A stable bicyclic derivative, 8-phenyl-1,5-diazabicyclo[3.2.1]octane, (I) was produced; its structure[9] followed from elemental analyses, its molecular weight, and from its hydrolysis to homopiperazine and benzaldehyde by aqueous hydrochloric acid. As the compound (I) has a boiling point considerably higher than that of 1-



I

methylhomopiperazine, benzaldehyde treatment of the mixture enabled the monosubstituted homopiperazine to be distilled in a high degree of purity.

EXPERIMENTAL

1-Methylhomopiperazine. A solution of homopiperazine (200.4 g., 2.0 moles) in methanol (602 g.) and commercial Raney nickel catalyst (aqueous sludge, 29.6 g.) were added to a 3-l. stainless-steel autoclave fitted with a stirrer. The free space was purged of air with hydrogen, the mixture heated to 100°, and the pressure increased to 500 p.s.i.g. by the addition of hydrogen. Aqueous 36% formaldehyde (185.4 g., 1.11 × 2.0 moles) was then introduced continuously into the autoclave over a period of 3.0 hr. by means of a proportioning pump. Absorption of hydrogen took place smoothly and regularly and was almost complete at the conclusion of the feed. During the reaction the temperature was kept at 100° and the hydrogenating pressure at 500 p.s.i.g.

The reaction product was filtered through a kieselguhr-coated filter, the catalyst washed with methanol (2 × 50 g.), and the washings were combined with the filtrate.

Water (387 cc.) was added to the methanolic solution and the mixture distilled at atmospheric pressure at a reflux ratio of 3 to 1 through a column having an efficiency of about ten theoretical plates. After the methanol, there distilled a 1,4-dimethylhomopiperazine-water azeotrope, b.p. 97.5°/750 mm., which contained 19.7% by weight of the dimethyl compound. Distillation was continued until the azeotrope and excess of water had been removed. Analyses of the residue for total alkalinity[10] and for tertiary amines[11] showed 1-methylhomopiperazine (136.0 g.) and homopiperazine (22.5 g., 0.225 mole) to be present.

Benzaldehyde (23.9 g., 0.225 mole) was added with stirring to the residue whereupon a moderate exothermic reaction ensued. Distillation of the mixture at reduced pressure at a reflux ratio of 5 to 1 through the column previously used gave substantially pure 1-methylhomopiperazine (136.0 g., 59.5% yield) as a fraction of b.p. 60.5–62.5°/20 mm., n_D^{20} 1.4770.

Anal. Calcd. for $C_6H_{14}N_2$: Tertiary N, 12.3. Found: Tertiary N (by the method of Critchfield, Funk, and Johnson[11]), 12.3.

Crystallization first from triethylamine then from hexane of the residue after removal of the 1-methylhomopiperazine afforded 8-phenyl-1,5-diazabicyclo[3.2.1]octane as colorless prisms, m.p. 82–84°.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.5; H, 8.6; N, 15.0; mol. wt., 188; neut. equiv., 94.1. Found: C, 76.4; H, 8.8; N, 14.7; mol. wt., 188; neut. equiv., 94.3.

1,4-Dimethylhomopiperazine. The aqueous fractions containing 1,4-dimethylhomopiperazine (from the foregoing preparation) were dehydrated by azeotropic distillation with benzene. Distillation of the dry solution gave the 1,4-dimethyl compound (62.0 g., 24.2% yield), b.p. 161°/750 mm., n_D^{20} 1.4615 (lit. b.p. 158–161°/738 mm.,[12] 162–164°/745 mm.[5]; n_D^{25} 1.4582[12]).

Anal. Calcd. for $C_7H_{16}N_2$: Tertiary N, 21.9; neut. equiv., 64.1. Found: Tertiary N (by the method of Critchfield, Funk, and Johnson[11]), 21.6; neut. equiv., 64.8.

Hydrolysis of 8-phenyl-1,5-diazabicyclo[3.2.1]octane. Aqueous 37% hydrochloric acid (186 cc., 2.2 moles) and water (150 cc.) were added with cooling to 8-phenyl-1,5-diazabicyclo[3.2.1]octane (188.3 g., 1 mole). The mixture was refluxed with stirring for 2.25 hr. and then steam-distilled. Benzaldehyde (104.3 g., 0.98 mole) was recovered from the distillate.

The acid solution remaining was made basic with aqueous 50% sodium hydroxide (176 g., 2.2 moles) and distilled with stirring at reduced pressure. Mineral oil (b.p. 300°) (200 g.) was added to the residue after most of the water had been removed and the distillation continued to give homopiperazine (62.7 g., 62.7% yield) as a fraction of b.p. 87–92°/50 mm.; after being cooled it formed platelets, m.p. 41°.

Anal. Calcd. for $C_5H_{12}N_2$: Neut. equiv., 50.1. Found: Neut. equiv., 50.8.

DEVELOPMENT DEPARTMENT
UNION CARBIDE CHEMICALS CO.
SOUTH CHARLESTON, W. VA.

(8) French Pat. 691,614 (1930) and British Pat. 350,539 (1931) state that aliphatic secondary amines and aromatic aldehydes do not interact.

(9) Two geometric isomers of derivative (I) are possible. No attempt has yet been made to ascertain whether one or both of the possible isomers are formed when benzaldehyde and homopiperazine react.

(10) G. F. Nadeau and L. E. Branchen, *J. Am. Chem. Soc.*, **57**, 1363 (1935).

(11) F. E. Critchfield, G. L. Funk, and J. B. Johnson, *Anal. Chem.*, **28**, 76 (1956).

(12) S. M. McElvain and L. W. Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).