

mass. Recrystallized from carbon tetrachloride the product (130 mg., 55%) melted at 208–210° either alone or in admixture with an authentic sample of 1,6-dideoxy-2,4,3,5-di-O-methylene-L-iditol.³

9,10-D-threo-4,8-Dibromo-4,8-di(bromomethyl)-1,3,5,7-naphthodioxane hexane. A solution of 470 mg. of the diene, II, in 5 ml. of carbon tetrachloride was treated at 0° with 7 ml. of a 4% (v/v) solution of bromine in the same solvent. The slight excess of bromine, together with the solvent was immediately removed *in vacuo* and the crystalline residue dissolved in hot cyclohexane. The resulting solution was treated with a trace of solid sodium bicarbonate and of alumina, filtered and diluted with pentane. At 0° the substance crystallized as elongated plates melting (after darkening at ca. 120°) at 135–150° and showing in acetone (*c* 3.35) $[\alpha]_D^{20} +210.0^\circ$ (987 mg., 73%). After three recrystallizations from cyclohexane-pentane the material melted as before; $[\alpha]_D^{20} +208.1^\circ$ in acetone (*c* 2.94).

Anal. Calcd. for $C_{18}H_{10}O_4Br_4$: Br, 65.26. Found: Br, 65.07.

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Preparation of Mono-*N*-alkyl and -*N*-Acyl Piperazines by Non-Hydrolytic Cleavage of 1-Carbethoxypiperazines

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Recent discoveries have made piperazine derivatives important as medicinal agents, and a large number of 1,4-unsymmetrically substituted piperazines has been prepared for various purposes. Among them, a promising agent for the treatment and prophylaxis of both hemorrhagic⁴ and heat shock⁵ is the relatively simple structure, 1-ethyl-4-ethylsulfonylpiperazine. Because of the tedious method of synthesis available for this compound, an improved procedure was sought. Specifically, the use of a nonhydrolytic cleavage of 1-carbethoxy-4-substituted piperazines which would permit the preparation of both 1-alkyl and 1-acyl piperazines was investigated.

The hydrolytic procedures which have been described for decarboxylation of piperazine mono-urethans require conditions too drastic for use in the presence of other hydrolyzable functions such

as amides or esters. Use of the benzyl group as a blocking agent for piperazines is also undesirable in cases where other groups may be reduced or may poison the catalyst during catalytic debenzylation. A mild, nonhydrolytic, nonreductive decarboxylation was therefore attempted with dry hydrogen bromide in glacial acetic acid. This reagent has previously been used for the removal of carbobenzoxy groups in peptides^{6,7} and was found suitable for the preparation of mono-*N*-alkyl piperazines. For example, 1-carbethoxy-4-ethylpiperazine was cleaved to 1-ethylpiperazine dihydrobromide in 3 hr. with an 89% yield. The mono-substituted piperazines prepared by this method are shown in Table I. 1-Isopropylpiperazine dihydrobromide was also obtained but could not be satisfactorily purified.

To investigate the suitability of the hydrogen bromide cleavage method for 1-acylpiperazines, 1-benzoyl-4-carbethoxypiperazine was first selected. When a basic aqueous solution of 1-carbethoxypiperazine was treated with an excess of benzoyl chloride at room temperature, however, a good yield of 1,4-dibenzoylpiperazine resulted. This result is in contrast to the relatively slow hydrolysis of the carbethoxy group observed in either acid or alkali. The 1-benzoyl-4-carbethoxypiperazine was obtained by treatment with benzoyl chloride in pyridine, and the cleavage with hydrogen bromide was carried out at a temperature of 60–70° for 30 min. The product was found to be piperazine dihydrobromide, however.

Similar results were obtained using 1-carbethoxy-4-acetylpiperazine and 1-carbethoxy-4-benzenesulfonylpiperazine; both the carbethoxy and acyl groups were cleaved in each instance. No indication of cleavage was apparent, from the liberation of ethyl bromide and carbon dioxide gases, until a temperature of 60–70° was reached, which prevented the use of lower temperatures for this reaction. Reduction of the reaction time to a period of 5 to 10 min. (using quantities of 0.005 mole of substituted piperazine) also resulted in the formation of piperazine dihydrobromide, either pure or admixed with starting material.

A fair yield of a monoacyl piperazine was secured, however, from the cleavage of 1-carbethoxy-4-ethylsulfonylpiperazine. After removal of the piperazine dihydrobromide and several recrystallizations, a 39% yield of 1-ethylsulfonylpiperazine hydrobromide was obtained. Further search for optimum conditions for this cleavage has not been made, since the use of 1-carbobenzoyloxypiperazines appeared more suitable and is presently being investigated for the preparation of 1-acylpiperazines.

No cleavages were observed at room tempera-

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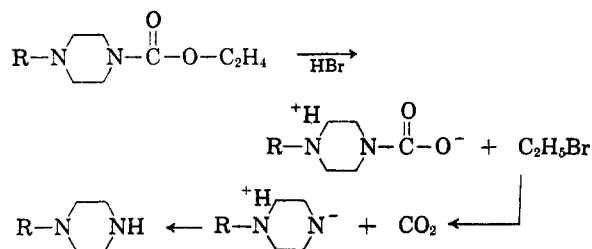
TABLE I

N-ALKYL AND N-ACYL PIPERAZINES FROM HBr CLEAVAGE $R-N \begin{array}{c} \diagup \diagdown \\ \text{ } \end{array} NH \cdot 2HBr$

R	M.P., °C.	Recrystallization solvent	Yield, %	Formula	Analyses, %	
					Calcd.	Found ^a
CH ₃	202–204	Absolute ethanol	85	C ₈ H ₁₄ N ₂ Br ₂	N: 10.69	N: 10.44
C ₂ H ₅	200–202	Absolute ethanol	89	C ₈ H ₁₆ N ₂ Br ₂	C: 26.10	C: 26.36
					H: 5.84	H: 6.08
n-C ₃ H ₇	224–230	Absolute ethanol	98	C ₇ H ₁₈ N ₂ Br ₂	C: 28.98	C: 29.40
					H: 6.26	H: 6.15
C ₂ H ₅ SO ₂ ^b	216–217	Ethanol-ether	39	C ₈ H ₁₈ N ₂ O ₂ SBr	C: 27.81	C: 27.43
					H: 5.83	H: 5.95

^a Analyses were obtained from the Clark Microanalytical Laboratory, Urbana, Ill., and the Weiler and Strauss Microanalytical Laboratory, Oxford, England. ^b The mono-hydrobromide was isolated.

ture, which is consistent with the observations of Ben-Ishai and Berger⁶ that hydrogen bromide-acetic acid cleaves benzyl carbamates at room temperature to the amine hydrobromide, benzyl bromide, and carbon dioxide, while hydrogen chloride in acetic acid acts analogously at 75°. In the case of the ethyl carbamates, less tendency for nucleophilic attack by bromide would be expected to occur than with the benzyl carbamates, and bromide ion is a better nucleophile than chloride ion. This reaction may therefore be represented by equation I.



Equation I. Hydrogen bromide cleavage of carbethoxypiperazines.

EXPERIMENTAL⁸

Cleavage of 1-carbethoxy-4-alkylpiperazines by hydrogen bromide. In a 500-ml. flask fitted with a gas absorption trap was placed 37 g. (0.2 mole) of 1-carbethoxy-4-ethylpiperazine^{9,10} and 250 ml. of a 1*N* solution of hydrogen bromide in glacial acetic acid, prepared by adding glacial acetic acid to 30–32% hydrogen bromide in glacial acetic acid (Eastman Organic Chemicals). The mixture was warmed on a steam bath, and after an induction period of 25 min., carbon dioxide and ethyl bromide were evolved. After the reaction had proceeded 3 hr. at 60°, it was cooled and filtered, yielding 12.5 g. of crystals. Additional product was obtained by pouring the filtrate into 950 g. of dry ether and chilling the resulting oil. A total yield of 49.0 g. (89%) of 1-ethylpiperazine dihydrobromide was obtained after re-

crystallization. The methyl, propyl, and isopropyl derivatives were obtained in the same manner.

1,4-Dibenzoylpiperazine. A chilled aqueous solution of 3.9 g. (0.02 mole) of 1-carbethoxypiperazine hydrochloride was treated with 5.6 g. (0.04 mole) of benzoyl chloride and 10% sodium hydroxide solution in the usual manner. A yield of 5.2 g. (88%) of 1,4-dibenzoylpiperazine resulted, m.p. 188–189° (lit.¹¹ m.p. 191°).

1-Benzoyl-4-carbethoxypiperazine. A solution of 4.8 g. (0.03 mole) of 1-carbethoxypiperazine hydrochloride in 100 ml. of dry pyridine was treated at 0° with 4.2 g. (0.03 mole) of benzoyl chloride. After being stirred for 2.5 hr., the mixture was poured into cold 5*N* sulfuric acid, and the resulting oil was extracted with ether. The extract was dried, evaporated, and crystallized from Skellysolve B, giving 5.5 g. of product melting at 96–98°. The yield was 70% of slightly impure compound.

Anal. Calcd. for C₁₄H₁₈N₂O₃: C, 64.10; H, 6.91. Found: C, 64.92; H, 6.56.

Cleavage of 1-benzoyl-4-carbethoxypiperazine by hydrogen bromide. A solution of 0.23 g. (0.001 mole) of 1-benzoyl-4-carbethoxypiperazine in 10 ml. of 15% hydrogen bromide in glacial acetic acid was heated at 70° for 30 min. and allowed to cool. The white, crystalline product was filtered, washed with ether and acetone, and dried. A yield of 0.07 g. of piperazine dihydrobromide was obtained which sublimed at 238°.

Anal. Calcd. for C₁₄H₁₂N₂Br₂: C, 19.37; H, 4.88. Found: C, 19.27; H, 5.14.

1-Carbethoxy-4-ethylsulfonylpiperazine hydrochloride. The ethylsulfonation procedure of Jacob¹² was used, and a 59% yield of product melting at 177–179° was obtained.

1-Ethylsulfonylpiperazine hydrobromide. A solution of 5.0 g. (0.02 mole) of 1-carbethoxy-4-ethylsulfonylpiperazine in 50 ml. of 1*N* hydrogen bromide in glacial acetic acid was warmed on a steam-bath for 0.5 hr. After cooling, the mixture was treated with 300 ml. of anhydrous ether, and the product was filtered. It was purified by digestion with 2 l. of hot absolute ethanol, filtration of the piperazine dihydrobromide, concentration to one-half volume, and addition of 2 l. of anhydrous ether. The product was twice recrystallized from ethanol-ether and once from absolute ethanol to give 2.0 g. of prisms melting at 216–217.5°. The yield was 39%.

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