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° (987 mg., 73%). After three recrystallizations from cyclohexane-pentane the material melted as before; $[\alpha]_D^{20}$ +208.1° in acetone (*c* 2.94).

Anal. Calcd. for $C_8H_{10}O_4Br_4$: Br, 65.26. Found: Br, 65.07.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE, U. S. DEPT. OF HEALTH, EDUCATION, AND WELFARE
BETHESDA 14, MD.

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

WILLIAM O. FOYE,[1] LESTER CHAFETZ,[2] AND EDWARD G. FELDMANN[3]

Received January 21, 1957

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 hemorrhagic[4] and heat shock[5] 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 decarbethoxylation of piperazine monourethans 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 decarbethoxylation 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 monosubstituted 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-carbobenzyloxypiperazines appeared more suitable and is presently being investigated for the preparation of 1-acylpiperazines.

No cleavages were observed at room tempera-

(1) Present address: Massachusetts College of Pharmacy, Boston, Mass., to which any requests should be directed.

(2) Wisconsin Alumni Research Foundation Fellow, 1953–1955.

(3) Fellow of the American Foundation for Pharmaceutical Education, 1953–1955.

(4) D. Bovet, S. Courvoisier, R. Ducrot, and R. Jacob, *Compt. rend.*, **227**, 1423 (1948).

(5) S. E. Jordan, A. G. Wheeler, W. O. Foye, and O. S. Orth, *Federation Proc.*, **13**, 371 (1954).

(6) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(7) G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5309 (1952).

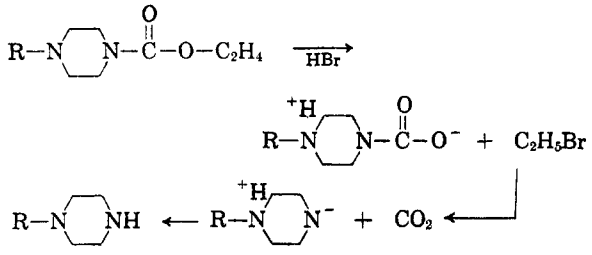
TABLE I

N-ALKYL AND *N*-ACYL PIPERAZINES FROM HBr CLEAVAGE R—N⟨⟩NH • 2HBr

R	M.P., °C.	Recrystallization solvent	Yield, %	Formula	Analyses, % Calcd.	Found[a]
CH_3	202–204	Absolute ethanol	85	$C_5H_{14}N_2Br_2$	N: 10.69	N: 10.44
C_2H_5	200–202	Absolute ethanol	89	$C_6H_{16}N_2Br_2$	C: 26.10	C: 26.36
					H: 5.84	H: 6.08
n-C_3H_7	224–230	Absolute ethanol	98	$C_7H_{18}N_2Br_2$	C: 28.98	C: 29.40
					H: 6.26	H: 6.15
$C_2H_5SO_2$[b]	216–217	Ethanol-ether	39	$C_6H_{15}N_2O_2SBr$	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 Berger[6] 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.

EXPERIMENTAL[8]

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 recrystallization. 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 $C_{14}H_{18}N_2O_3$: 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 $C_4H_{12}N_2Br_2$: C, 19.37; H, 4.88. Found: C, 19.27; H, 5.14.

1-Carbethoxy-4-ethylsulfonylpiperazine hydrochloride. The ethylsulfonation procedure of Jacob[12] 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%.

SCHOOL OF PHARMACY
UNIVERSITY OF WISCONSIN
MADISON, WIS.

MASSACHUSETTS COLLEGE OF PHARMACY
BOSTON, MASS.

(8) All melting points were obtained on a Fisher-Johns block and are uncorrected.

(9) R. Baltzly, J. S. Buck, E. Lorz, and W. Schön, *J. Am. Chem. Soc.*, **66**, 263 (1944).

(10) W. S. Ide, E. Lorz, and R. Baltzly, *J. Am. Chem. Soc.*, **77**, 3142 (1955).

(11) A. W. Hofmann, *Ber.*, **23**, 3297 (1890).

(12) R. M. Jacob, U. S. Patent **2,507,408** (1950).