Anal. Calcd. for $C_{11}H_{25}N_3O_2Cl_2$: Cl^-, 23.41. Found: Cl^-, 23.50.

2-(4'-Carbethoxypiperazino)-ethyldimethyldodecylammonium Bromide (I).—The hydrochloride of the dimethyl tertiary base (above) was converted to the base by excess of aqueous potassium carbonate and subsequent ether extraction and treated with a 100% excess of *n*-dodecyl bromide in acetone at 40° for 19 days. The *extremely hygroscopic* solid produced by dilution with ether was recrystallized twice from ethyl acetate, m.p. 67°.

Anal. Calcd. for $C_{23}H_{48}N_3O_2Br$: Br^-, 16.71. Found: Br^-, 16.58.

The picrate had m.p. 124° (mixed m.p. depression with picric acid).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Protecting Groups in the Synthesis of Unsymmetrical Piperazines[1]

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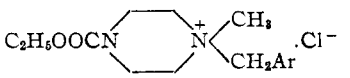
RECEIVED NOVEMBER 17, 1956

Methods for removing various groups useful in protecting one of the two nitrogens of substituted piperazines were studied using piperazine quaternaries with the following N-substituting protective groups: carbethoxyl (removal by aqueous barium hydroxide), acetyl (removal by acid), nitroso (removal by hydrogenolysis catalyzed by Raney nickel) and nitroso with an equivalent of carbamyl (removal of nitroso as nitrous acid, destroyed by the carbamyl function). The relative utility of these methods is briefly considered.

Syntheses in the field of unsymmetrical piperazines are based to a considerable extent on the mono-carbethoxylation of piperazine[2] to protect one nitrogen, although the direct preparations of other mono-amides, and even of alkyl and aralkyl piperazines,[3] have been reported.

The carbethoxy group may be removed either by heating the carbethoxypiperazines with constant-boiling (approx. 6 *N*) aqueous hydrochloric acid at its boiling point (approx. 110°) for two to three days or much more rapidly, as would be anticipated on theoretical grounds, by heating them with alkali.[2,4]

The requirement of protective groups other than carbethoxy became urgent when attempts to hydrolyze the unsymmetrical 1-carbethoxy-4-methyl-4-benzylpiperazinium chlorides (I)[1] by the hydrochloric acid method led to loss, not only of the carbethoxyl, but also of the benzyl group.[5] Further,



I, Ar = C_6H_5, *p*-Cl-C_6H_4, *p*-$CH_3OC_6H_4$-

the acid-catalyzed decarbethoxylation of 1-carbethoxy-4-methyl-4-propargylpiperazinium chloride gave a product containing an impurity of lower halide content, which could not be removed by repeated crystallization.

Although it was felt that the basicity required for saponification of the carbethoxyl group might lead to decomposition of the quaternaries, the rate of the saponification of the propargyl quaternary (I for Ar put C≡CH) by aqueous barium hydroxide was studied. At about 50°, an excess of 0.4 *N* aqueous barium hydroxide gave 85% hydrolysis of the carbethoxyl function (by acidimetric titration of aliquots) in 1 hr. The decarbethoxylated 1-methyl-1-propargylpiperazinium chloride isolated in fair yield after 140 min. under reflux or remaining overnight at 50° was moderately pure and readily gave analytically pure product on recrystallization, although each recrystallization was accompanied by great loss of material.

Theoretical considerations indicated that acid hydrolysis of a 1-acylpiperazine should be rapid, especially under conditions in which the 4-nitrogen, if not quaternized, would be protonated. As anticipated, the de-acetylations of the test substances 1-acetyl-4,4-dimethylpiperazinium chloride and 1-acetyl-4-methyl-4-benzylpiperazinium chloride had been completed (titration) after 30–40 minutes at 95° in the presence of two equivalents of 2 *N* hydrochloric acid and, indeed, were about half completed after four days at room temperature. Hydrolysis of the carbethoxy group of the 1-carbethoxy-4,4-dimethyl quaternary, in contrast, was undetectable after 24 hr. at 95°, in the presence of the same excess of acid. Although the hydrolysis mixture of the acetylmethylbenzyl quaternary had a faint odor resembling benzyl chloride (or alcohol), the appropriate de-acetylated quaternary was isolated in excellent yield from it as well as from the dimethyl analog.

The Raney nickel-catalyzed hydrogenolysis of the nitroso group[6] from 1-nitroso quaternaries was studied with 1-nitroso-4-methyl-4-dodecylpiperazinium iodide which readily gave an 86% yield of analytically pure de-nitrosated quaternary. The corresponding 1-nitroso-4-methyl-4-benzylpiperazinium chloride absorbed the theoretical amount of hydrogen rapidly, and then absorption nearly stopped. Yields averaging 75% were obtained, but the product was contaminated by nickel ion. This was removed by treatment of the reduction filtrate

(1) This is paper No. 11 in a series on unsymmetrical piperazines from these laboratories. For the preceding paper, see M. Harfenist, THIS JOURNAL, **79**, 2211 (1957).

(2) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(3) *Cf.* R. Baltzly, THIS JOURNAL, **76**, 1164 (1954), and references given there.

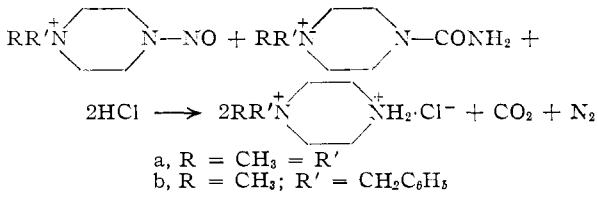
(4) M. Harfenist, *ibid.*, **76**, 4991 (1954).

(5) A related reaction, the spontaneous loss of the 4-methoxybenzhydryl group from 1-(4'-methoxybenzhydryl)-4-methylpiperazine dihydrochloride has been reported by R. Baltzly, S. DuBreuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, **14**, 775 (1942). However, the *p*-methoxy group appeared to be necessary for decomposition under these mild conditions, even though a benzhydryl group should be lost more readily than the benzyl group present in the compounds reported here.

(6) E. Lorz and R. Baltzly, THIS JOURNAL, **73**, 93 (1951).

with dimethylglyoxime, as outlined in the Experimental section. However, since no source of anion for the nickel other than the quaternary chloride is evident, it is likely that slight hydrogenolysis had occurred at the quaternary nitrogen in this case. This point was not investigated further.

Another route used successfully for pilot preparations of both dimethyl- and methylbenzylpiperazinium chlorides also utilized the 1-nitrosopiperazinium compounds. It was anticipated on the basis of extension of the known intermolecular nature of rearrangements of N-nitrosamines ("Fisher–Hepp Rearrangement") that N-nitrosamines exist in equilibrium with the free amine and nitrous acid. Indeed, acidification of a solution of 1-nitroso-4,4-dimethylpiperazinium chloride led to a pronounced odor of nitrogen oxides, and the acidified solution would diazotize sulfanilamide (tested by coupling to β-naphthol).[7] However, as would be anticipated from the fact that amines are usually nitrosated in acid solution, the equilibrium strongly favors the nitrosamine, and no appreciable hydrolysis of this one could be found after several days in 2 *N* hydrochloric acid at 95°. A nitrous acid acceptor would therefore be required to make acidic de-nitrosation practical. To avoid introducing extraneous substances, the nitrous acid acceptor selected was the 1-carbamyl derivative of the same piperazine quaternary whose nitroso-derivative was used. The reaction



a, R = CH_3 = R′
b, R = CH_3; R′ = $CH_2C_6H_5$

was complete, as determined by the drop in acid titer, after 30–40 minutes at 95° in the presence of 4 equivalents (100% excess) of 2 *N* hydrochloric acid. Nearly quantitative yields of the expected quaternaries were isolated from these reactions. The rate of hydrolysis of the carbamyl compound under these conditions was separately determined and was found to be negligible by comparison. The product of such hydrolysis, ammonium chloride, would of course also react with nitrous acid rapidly.[8]

Conclusions.—Use of the N-acetyl function as a protective group, and its hydrolytic removal in the presence of mineral acid, is probably the mildest and most convenient of the protective methods discussed here. The use of a mixture of equivalent amounts of N-nitroso- and N-carbamylpiperazine requires the preparation of both, but is otherwise very satisfactory except, presumably, for compounds which might react with nitrous acid irreversibly at a rate comparable to that of the carbamyl group. The barium hydroxide method is best suited to compounds soluble in the basic aqueous solution and stable to alkali for several hours at a temperature somewhat over room temperature. The limits of the Raney nickel-catalyzed hydrogenolytic de-nitrosation have not been determined. The potential utility of this method is great, since reduction of the very readily reduced nitroso function probably would be more rapid than that of most other functional groups.

Acknowledgment.—We thank Dr. R. Baltzly for many helpful discussions during the course of the work.

(7) The application of a similar reaction as a spot test has been published since completion of this work; F. Feigl and C. C. Neto, *Anal. Chem.*, **28**, 1311 (1956).

(8) It should be remembered that iodides react with nitrites in acid solution. Iodides can be converted to chlorides, bromides or methanesulfonates under neutral conditions by use of the appropriate silver salt.

Experimental

1-Propargyl-1-methylpiperazinium Bromide (Barium Hydroxide Method).—A filtered solution of 295 ml. of 0.4 *N* barium hydroxide in water at 50° was treated with 10 g. of 1-carbethoxy-4-methyl-4-propargylpiperazinium bromide.[1] Aliquots removed after 1 hr. and 5 hr. at 50° revealed an uptake of base corresponding to 86 and 100%, respectively, of the ultimate total base uptake (after 17 hr.). Analogously, 0.35 *N* aqueous barium hydroxide under reflux gave about 70% of the ultimate base uptake after 27 minutes and a base titer after 80 minutes not changed by an additional hour of heating.

This latter alkaline solution was treated with an excess of carbon dioxide and then heated on a steam-bath while nitrogen was bubbled through it to reprecipitate the barium as carbonate. It was then filtered and evaporated on the steam-bath *in vacuo*. The remaining dark oil was dissolved in absolute ethanol, an equal volume of acetone was added and the solution was cooled and filtered from inorganic solids. The hydrobromide of the quaternary was precipitated by addition of 9 g. of 30% hydrobromic acid in acetic acid followed by ether. The resulting 6.5 g. of tan solid had m.p. 160°, after much preliminary sintering. It was recrystallized with difficulty from ethanol (95%)–acetone–ether, yielding 1.5 g., melting with decomposition about 177–180°. The workup of batches decarbethoxylated at 50° was the same in all essentials.

Anal. Calcd. for $C_8H_{16}N_2Br_2$: Br^-, 53.35. Found: Br^-, 53.10.

The compound, in contrast with acetylenic piperazine amines and quaternaries with the other nitrogen present as part of an amide function, gave no usable end-point on titration for acetylenic hydrogen,[1] although qualitative tests were positive for that function.

Conversion to the chloride by the use of silver chloride suspended in methanol containing hydrochloric acid gave a product of m.p. 171–172°.

Anal. Calcd. for $C_8H_{16}N_2Cl_2$: Cl^-, 33.57. Found: Cl^-, 32.70.

1-Methyl-1-benzylpiperazinium Chloride (Nitroso-compound with Hydrogen and Raney Nickel).—A solution of 12.5 g. (0.05 mole) of 1-nitroso-4-methyl-4-benzylpiperazinium chloride[1] dissolved in 50 ml. of methanol was treated with approximately 4 g. (dry weight) of Raney nickel, and hydrogen initially at 40 pounds over-pressure in a Parr hydrogenator at room temperature (28°). The initial rapid reduction slowed markedly when very nearly the theoretical amount of hydrogen had been absorbed, but reduction was continued until the rate fell below 1% of the initial value (3.5 hr.). The green solution was filtered from catalyst and treated with a bit over the theoretical amount of solid dimethylglyoxime (determined by portionwise addition to an aliquot), refiltered and concentrated on the steam-bath *in vacuo*. The resulting pink solid was recrystallized from ethanol–ether, converted to the hydrochloride and that recrystallized from absolute ethanol–benzene–ether. Another recrystallization gave 7.2 g., m.p. 116°, apparently a monohydrate.

Anal. Calcd. for $C_{12}H_{20}N_2Cl_2 \cdot H_2O$: Cl^-, 25.20. Found: Cl^-, 25.10.

Drying for 2 hr. at room temperature and 0.01 mm. gave a product of m.p. 172–175°.

Anal. Calcd. for $C_{12}H_{20}N_2Cl_2$: Cl^-, 26.92. Found: Cl^-, 27.12.

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