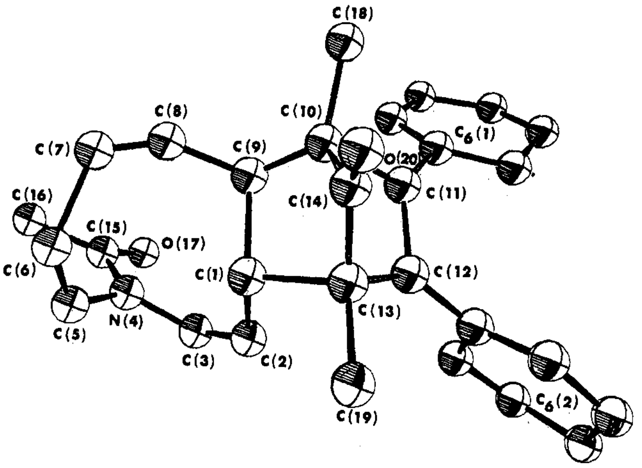
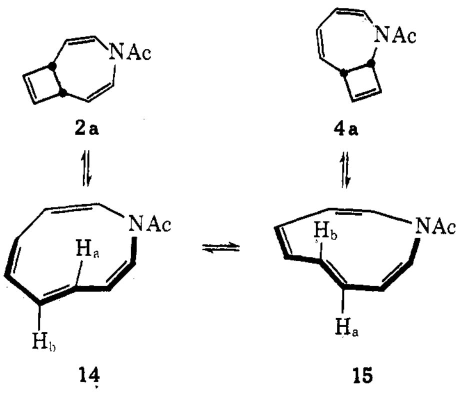


Figure 1.—A structural view of 10 as determined by X-ray analysis depicting conformation.

5.0 Hz, J_{19} = 10.0 Hz, H_1), 7.25 (2 H, m, $H_7 + H_9$), 7.60 (1 H, dd, J_{87} = 10.0 Hz, J_{89} = 4.5 Hz, H_8), 7.90 (3 H, s), 8.79 (3 H, s), 8.82 (3 H, s)],[4] *i.e.*, the product of symmetry-controlled $[_\pi 2_s + _\pi 4_s]$ cycloaddition of **8** onto the cyclobutene double bond of **4a** as a major constituent. It follows that the mono-*trans*-azonine responsible for the formation of cycloadducts **9** and **10** in the trapping of thermally activated **2a** with **8** is derived directly from **2a**, *i.e.*, without prior isomerization of this substance to **4a**. The question of whether the initially generated *trans*-azonine is trapped prior to its rotational conversion to **15** cannot be answered at present. Nonetheless, the absence of **13** among the cycloadducts of thermally activated **1a** could be interpreted to mean that any participation of **15** in the formation of **9** and/or **10** is minor.

The thermal rearrangement of **2a** can be dissected into symmetry-allowed (k_a) and forbidden (k_f) components; it is instructive to contrast the thermal reactions of **2a** in the presence and absence of **8** in terms of the ratio of k_a/k_f. Comparison of past[1] and present findings reveals that this ratio increases from (**4a**)/(**3a**) $\sim$ 0.8 in the absence of trapping agent to (**9** + **10**)/(**11** or **12**) $\sim$ 13 in the presence of **8**. Clearly then, the use of isomer product ratios grossly underestimates the control imposed on the various steps by orbital symmetry. Undoubtedly, this misrepresentation is chiefly due to the reversibility of various symmetry-allowed steps that generate fleeting intermediates, *e.g.*, Scheme III, providing for eventual drain through less accessible but irreversible symmetry-disallowed channels. This rationale also accounts for the thermolytic behavior of the carbocyclic members of the family. It is readily seen for example that the k_a/k_f ratio associated with the thermal response of *cis*-bicyclo[6.1.0]nona-2,4,6-triene at 80° increases in magnitude from $\sim$0.1 in the absence of trapping agent[16] to $\sim$3 in the presence of **8**.[17]

SCHEME III



Acknowledgment—The Syracuse University group thanks the National Science Foundation (GP-26347) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial assistance. The Iowa State University group thanks the Ames Laboratory of the U. S. Atomic Energy Commission for support.

[16] E. Vogel, *Angew. Chem.*, **73**, 548 (1961); **74**, 829 (1962).

[17] A. G. Anastassiou and R. C. Griffith, *J. Amer. Chem. Soc.*, **93**, 3083 (1971).

[18] NDEA Graduate Fellow, 1971–1974.

[19] Camille and Henry Dreyfus Foundation Teacher–Scholar Grant Awards, 1972–1977.

DEPARTMENT OF CHEMISTRY A. G. ANASTASSIOU*
SYRACUSE UNIVERSITY R. L. ELLIOTT[18]
SYRACUSE, NEW YORK 13210

AMES LABORATORY—USAEC AND H. W. WRIGHT
IOWA STATE UNIVERSITY J. CLARDY[19]
AMES, IOWA 50010

RECEIVED FEBRUARY 9, 1973

Selective Demethylation of Quaternary Salts with Lithium *n*-Propylpercaptide in Hexamethylphosphoramide[1]

Summary: Lithium *n*-propylmercaptide in hexamethylphosphoramide provides a mild, rapid, and convenient system for dealkylation of quaternary ammonium salts in excellent yield with high propensity for methyl group removal.

Sir: The perennial problem of dealkylating quaternary ammonium salts has received considerable attention and led to the development of several reagent systems for effecting such transformations. The most successful of these include alkyl displacement using lithium aluminum hydride,[2a] sodium in ammonia,[2b] ethanolamine,[2c] thiophenoxide anion,[2d] lithium iodide,[2e] or acetate anion.[2f]

The recent disclosure of the exceptional nucleophilic displacement ability of lithium *n*-propylmercaptide in hexamethylphosphoramide (HMPA)[3] prompts this report of the utility of this reagent system as an effective, mild, and rapid method for dealkylation of aromatic and aliphatic quaternary ammonium salts with superior selectivity for displacement of methyl

---

[1] Presented in part of the 7th Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1972.

[2] (a) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. Meisinger, *J. Amer. Chem. Soc.*, **82**, 4651 (1962); (b) E. Grovenstein, Jr., S. Chandra, C. Collum, and W. Davis, Jr., *ibid.*, **88**, 1275 (1966); (c) S. Hunig and W. Baron, *Chem. Ber.*, **90**, 395 (1957); (d) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966); (e) H. O. House, H. Muller, C. Pitt, and P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); (f) N. D. V. Wilson and J. A. Joule, *Tetrahedron*, **24**, 5493 (1968). In addition, 1,4-diazabicyclo-[2.2.2]octane in DMF or HMPA has recently been shown to effectively dealkylate quaternary salts; see T. L. Ho, *Synthesis*, 702 (1972).

[3] P. A. Bartlet and W. S. Johnson, *Tetrahedron Lett.*, 4659 (1970).

groups. The procedure for the selective demethylation of phenyldimethylethylammonium iodide is illustrative. A solution of the ammonium salt (376 mg, 2.5 mmol) and *n*-tridecane (235 mg, 1.25 mmol, internal standard) in 5 ml of HMPA (distilled from CaH_2) was cooled to 0–5° and lithium hydride (159 mg, 20 mmol) was added, followed by freshly distilled *n*-propylmercaptan (630 mg, 8.3 mmol, 0.75 ml). The solution was stirred under nitrogen at 0° for 30 min, then diluted with water, and extracted with cyclohexane. Analysis of the cyclohexane solution by glpc indicated a 97% yield of phenylmethylethylamine (**1**) and <0.5% deethylated product, phenyldimethylamine (**2**). A similar reaction conducted at 85° gave a 94% yield of **1** and 4% **2**. With completely aliphatic salts, slightly more vigorous conditions (50°, 2–3 hr) were required to effect demethylation as expected since the departing amines are stronger bases. The results for a variety of quaternary salts are presented in Table I. As evident from the table, the reagent system offers several advantages including excellent yields of tertiary amines (93–99%), relatively short reaction times, and mild conditions. Furthermore, the method shows exceptional selectivity for methyl group removal, especially at lower temperatures, and appears to surpass other procedures[2,4] in this regard. Coupled with recent improved procedures for quaternary salt formation,[5] the method offers a convenient method for preparing unsymmetrical tertiary amines *via* alkylation of methylamines and demethylation with *n*-propylmercaptide.

$$C_6H_5\overset{+}{N}(CH_3)_2(C_2H_5)I^- \xrightarrow[\text{HMPA, 0°, 30 min}]{C_3H_7S^-Li^+} \underset{\mathbf{1},\ 97\%}{C_6H_5NCH_3(C_2H_5)} + \underset{\mathbf{2},\ \sim 0}{C_6H_5N(CH_3)_2}$$

$$C_6H_5\overset{+}{N}(CH_3)_2(C_2H_5)I^- \xrightarrow[\text{85°, 5 min}]{} \quad 94\% \qquad\qquad 4\%$$

The high nucleophilicity of the reagent system limits the procedure to compounds devoid of ester groups, which are readily cleaved, at least at higher temperatures.[3] In addition, primary and secondary alkyl halides afford substitution and/or elimination products and aromatic nitro groups may be displaced[6] or give undefined, highly colored products. Most other functional groups such as cyano, amido, carboxylic acid, and carbonyls should be tolerable. We are currently further exploring the scope and limitations of the reagent system.

TABLE I

DEALKYLATIONS OF QUATERNARY AMMONIUM SALTS WITH LITHIUM *n*-PROPYLMERCAPTIDE IN HEXAMETHYLPHOSPHORAMIDE

			% yields[a]		
Quaternary salts	Temp, °C	Time, min	Demethylated product	Dealkylated product	Selectivity ratio
$C_6H_5N(CH_3)_3I$	25	15	96		
	85	5	95		
$C_6H_4N(CH_3)_2C_2H_5I$	0	30	97	~0	
	85	5	94	4	24:1
$C_6H_5N(CH_3)_2CH(CH_3)_2I$	0	30	93	~0	
$CH_3(CH_2)_{11}N(CH_3)_2C_2H_5I$	50	120	94	<3	>31:1
	85	15	92	4	23:1
$CH_3(CH_2)_{11}N(CH_3)_2CH(CH_3)_2I$	50	180	99	~0	~100:1
	85	15	94	4	24:1
$CH_3(CH_2)_{11}N(CH_3)_2(CH_2)_3CH_3I$	50	180	99	~0	~100:1

[a] Yields were determined by glpc using internal standards and predetermined detector response factors. The percentages are averages of four–six samples.

DEPARTMENT OF CHEMISTRY
DREXEL UNIVERSITY
PHILADELPHIA, PENNSYLVANIA 19104

ROBERT O. HUTCHINS*
FRANK J. DUX

RECEIVED FEBRUARY 23, 1973

---

[4] For instance, the most selective reagent system previously developed appears to be thiophenoxide anion in refluxing (80°) 2-butanone which afforded a 3.5:1 ratio of demethylated to deethylated product with methyltriethylammonium halides in 19 hr[2d] while ethanolamine gave only a 1.6:1 ratio of the same products at 172° for 5 hr.[2c]

[5] H. Z. Sommer, H. I. Lipp, and L. J. Jackson, *J. Org. Chem.*, **36**, 824 (1971).

[6] J. B. Bauman, *ibid.*, **36**, 396 (1971).