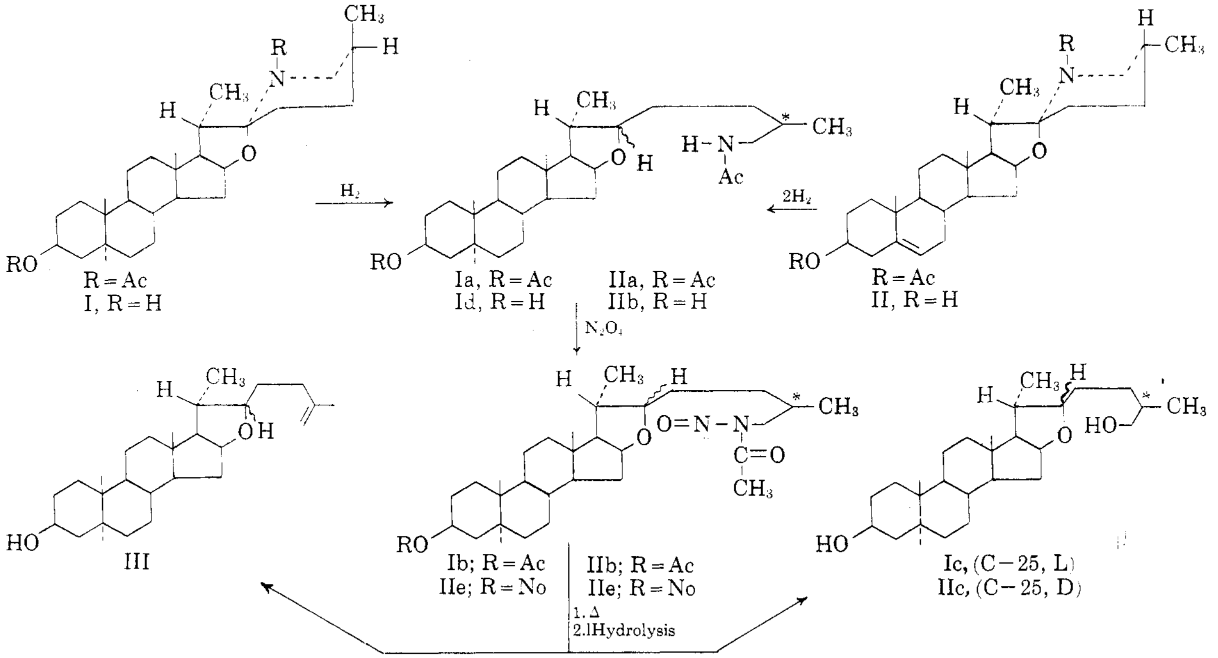

Acknowledgment. The authors are deeply indebted to Dr. Erich Mosettig of this Institute for his interest and kind guidance.

National Institute of Arthritis
and Metabolic Diseases
National Institutes of Health,
Public Health Service
U. S. Department of Health,
Education, and Welfare
Bethesda 14, Md.

A Convenient Method for Preparation of Quaternary Ammonium Salts

Meyer M. Markowitz

Received January 4, 1957

Three laboratory procedures are generally available for the synthesis of quaternary ammonium salts.[1,2] These methods are: (*a*) neutralization of the free quaternary ammonium base with the acid of the desired anion, *viz.*, $R_4NOH + HX \rightarrow R_4NX + H_2O$, (*b*) metathetical reactions involving the formation of an insoluble compound and the quaternary ammonium salt, *viz.*, $R_4NY + AX \rightarrow AY + R_4NX$, and (*c*) alkylation of amines (the Hofmann reaction), *viz.*, $R_3N + RX \rightarrow R_4NX$.[2-4] The work reported here presents a fourth approach based upon the reaction of equivalent quantities of the free quaternary ammonium base and the ammonium salt of an anion.

The kinship of the quaternary ammonium bases to the alkali metal hydroxides is well known.[5, 6] Accordingly, the quaternary ammonium hydroxides will tend to displace the more weakly basic ammonia from aqueous solutions of ammonium salts as per the equation: $R_4NOH + NH_4X \rightarrow R_4NX + H_2O + NH_3$. Because this latter reaction may be driven quantitatively to the right without destruction of the quaternary ammonium ion, a simple, direct means for the preparation of the quaternary ammonium salts of many of the less stable, less familiar acids is made possible. Though the ensuing examples utilize tetraalkylammonium bases, there should be no restrictions preventing the use of other quaternary ammonium bases under suitable experimental conditions.

EXPERIMENTAL

Aqueous solutions (2–3 wt. %) of tetramethyl- and tetraethylammonium hydroxide were prepared from the commercially available 10 wt. % solutions (Eastman Kodak "White Label" grade). The exact titers of the dilute solutions were obtained by titration with standard 0.1*N* acid to the phenolphthalein end-point. All ammonium salts used were of "Reagent" grade.

Tetramethylammonium thiocyanate. To 2.831 g. (0.03106 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.364 g. (0.03106 mole) of ammonium thiocyanate. The solution was boiled down to a volume of 50 ml. three times, the water being replaced after each volume decrease. The mixture was then carefully heated to dryness and placed in an oven for 2 hr. at 100°. Yield: 100% (4.1 g.).

---

(1) Beilstein, *Handbuch der Organischen Chemie*, Vol. 4, pp. 52–54, J. Springer, Berlin, 1922.

(2) R. S. Shelton, M. G. Van Campen, C. H. Tilford, H. C. Lang, L. Nisonger, F. J. Bandelin, and H. L. Rubenkoenig, *J. Am. Chem. Soc.*, **68**, 753, 755, 757 (1946).

(3) P. Walden, *Z. Elektrochem.*, **27**, 36 (1921).

(4) C. R. McCrosky, F. W. Bergstrom, and G. Waitkins, *J. Am. Chem. Soc.*, **62**, 2031 (1940).

(5) P. Karrer, *Organic Chemistry*, pp. 112, 118, Elsevier, Amsterdam, 1938.

(6) N. V. Sidgwick, *The Organic Chemistry of Nitrogen*, pp. 28, 30–32, Oxford, 1937.

Anal. Calcd. for $(CH_3)_4NSCN$: SCN, 43.90. Found: 43.45, 43.50, 43.62 (by precipitation as silver thiocyanate).

Tetramethylammonium sulfate. To 2.754 g. (0.03022 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.997 g. (0.01511 mole) of ammonium sulfate. The solution was boiled and brought to dryness as in preparation (I), whereupon the residue was heated in an oven for 12 hr. at 120° and 6 hr. at 130°. Yield: 92% (3.4 g.).

Anal. Calcd. for $[(CH_3)_4N]_2SO_4$: SO_4, 39.30. Found: 39.44, 39.47 (by precipitation as barium sulfate).

Tetramethylammonium bromide. To 2.661 g. (0.02925 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.865 g. (0.02925 mole) of ammonium bromide. The resulting solution was treated as in preparation (II). Yield: 100% (4.5 g.).

Anal. Calcd. for $(CH_3)_4NBr$: Br, 51.88. Found: 51.19, 51.27, 51.28 (by precipitation as silver bromide).

Tetramethylammonium iodide. To 2.9651 g. (0.03253 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 4.7157 g. (0.03252 mole) of ammonium iodide which had been previously washed with carbon tetrachloride to remove all traces of free iodine formed as a result of decomposition during prolonged storage. The resulting solution was treated as in preparation (II); yield: 100% (6.5 g.).

Anal. Calcd. for $(CH_3)_4NI$: I, 63.12. Found: 62.42, 62.54, 62.64 (by precipitation as silver iodide).

Tetramethylammonium chromate. To 3.518 g. (0.03860 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.5 ml. of aqueous 28% ammonia and 2.433 g. (0.00965 mole) of ammonium dichromate. The additional ammonia was needed to bring about conversion of the dichromate ion to the chromate ion. The resulting solution was treated as in preparation (II).

Anal. Calcd. for $[(CH_3)_4N]_2CrO_4$: CrO_4, 43.89. Found: 43.14, 43.20, 43.41 (by precipitation as barium chromate).

Tetramethylammonium oxalate. To 3.170 g. (0.03478 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.471 g. (0.01739 mole) of ammonium oxalate monohydrate. The resulting solution was treated as in preparation (II).

Anal. Calcd. for $[(CH_3)_4N]_2C_2O_4$: C_2O_4, 26.85. Found: 26.40, 26.45, 26.46 (by precipitation as calcium oxalate monohydrate).

Tetramethylammonium thiosulfate. To 2.265 g. (0.02484 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.841 g. (0.01242 mole) of ammonium thiosulfate. The solution was boiled down twice to 25 ml. with replacement of water, evaporated, and dried for 12 hr. at 105°, and for 4 hr. at 130°; yield 97% (3.1 g.).

Anal. Calcd. for $[(CH_3)_4N]_2S_2O_3$: S_2O_3, 43.03. Found: 41.97, 42.10, 42.13 (by conversion to sulfate and precipitation as barium sulfate).

Tetraethylammonium iodide. To 2.221 g. (0.01508 mole) of tetraethylammonium hydroxide in 125 ml. of water was added 2.186 g. (0.01508 mole) of ammonium iodide. The solution was boiled down twice to 10 ml. with replacement of water, evaporated, and dried for 20 hr. at 85°; yield 100% (3.9 g.).

Anal. Calcd. for $(C_2H_5)_4NI$: I, 49.35. Found: 48.84, 48.87, 48.92.

Tetraethylammonium thiocyanate. To 2.468 g. (0.01676 mole) of tetraethylammonium hydroxide in 125 ml. of water was added 1.276 g. (0.01676 mole) of ammonium thiocyanate. The resulting solution was treated as in preparation (VII); yield 94% (3.0 g.).

Anal. Calcd. for $(C_2H_5)_4NSCN$· SCN, 30.84. Found: 29.83, 29.84, 29.87.

DEPARTMENT OF CHEMICAL ENGINEERING
NEW YORK UNIVERSITY
NEW YORK 53, N. Y.

Synthesis of Compounds for Chemotherapy of Tuberculosis. VII. Pyridine *N*-Oxides with Sulfur-Containing Groups[1]

THOMAS S. GARDNER, EDWARD WENIS, AND JOHN LEE

Received January 21, 1957

In view of the high activity of thioisonicotinamide in the chemotherapy of experimental tuberculosis in mice,[2] a number of pyridine derivatives containing a —CSNH— moeity were prepared.

Reduction of the pyridine ring eliminated activity; *N*-oxidation reduced activity, and separation from the ring of the —CSNH— group (thioureas and pseudothioureas) eliminated activity as did also the conversion of the group into a ring system (thiazole and thiazolone).

The previously known *N*-oxides of picolinamide,[3,9] thiopicolinamide,[4] nicotinamide,[3] and isonicotinamide,[3] as well as 4-pyridylthiourea,[5] also showed no activity in the same test in which nicotinamide is active.[6] All other compounds prepared were either inactive or less active than thioisonicotinamide.[2]

EXPERIMENTAL[7]

Isonicotinonitrile-1-oxide. Isonicotinamide-1-oxide (147 g.) was heated at reflux for 0.5 hr. with 1500 g. of phosphorus oxychloride. The solution was concentrated to a small volume under vacuum and poured onto cracked ice. The solution was made alkaline with concentrated ammonia and the separated nitrile filtered off. The solution was extracted five times with chloroform using a total of 800 ml. for the extractions. The previously separated solid was extracted at the boiling point with the chloroform extractants and filtered. On cooling, almost pure nitrile separated which could be recrystallized from chloroform or methanol; yield, 85 g., m.p. 229–230°.

Anal. Calcd. for $C_6H_4N_2O$: N, 23.3. Found. *N*: 22.9.

This compound has been previously reported,[8] with a melting point of 220–221° by preparation from 4-aminopyridine-1-oxide using the Sandmeyer reaction.

Thioisonicotinamide-1-oxide. Isonicotinonitrile-1-oxide (30 g.) was dissolved in 300 ml. of a methanol solution containing 30% ammonia by weight. The solution was saturated with hydrogen sulfide gas and on standing 2 days the thioamide separated. The recovered yellow-orange product was recrystallized from hot water; yield, 12 g., m.p. 205–206°.

---

(1) Contribution No. 453 from this Laboratory.

(2) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, **19**, 753 (1954).

(3) M. Shimizu, T. Naito, G. Ohta, T. Yoshikawa, and R. Dohmori, *J. Pharm. Soc. Japan*, **72**, 1474 (1952); *Chem. Abstr.*, **47**, 8077 (1953).

(4) F. Leonard and A. Wajngurt, *J. Org. Chem.*, **21**, 1077 (1956).

(5) D. Libermann, N. Rist, and F. Grumbach, *Bull. soc. chim. biol.*, **38**, 231 (1956).

(6) V. Chorine, *Compt. rend.*, **220**, 150 (1945).

(7) All melting points are corrected.

(8) E. Ochaiai, T. Teshigawara, K. Oda, and T. Naito, *J. Pharm. Soc. Japan*, **65**, 5/6A, 1 (1945); *Chem. Abstr.*, **45**, 8527 (1951).