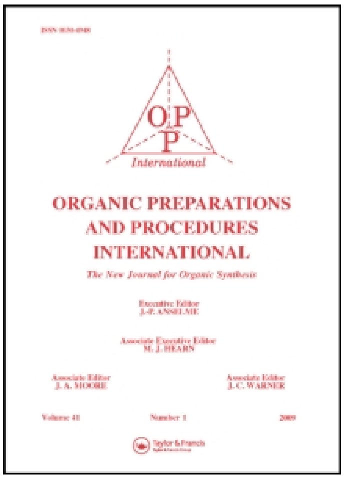

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AN IMPROVED PREPARATION OF QUINUCLIDIN-3-THIOL

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AN IMPROVED PREPARATION OF QUINUCLIDIN-3-THIOL

Submitted by
(12/12/90)

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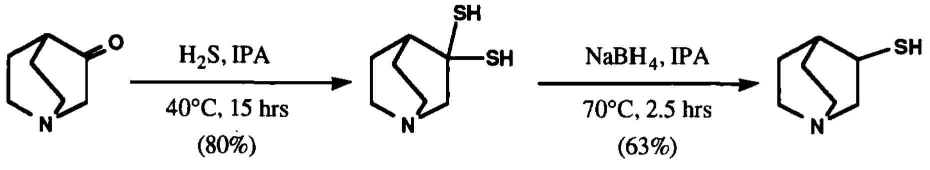
In the course of an ongoing synthesis program, we desired multigram quantities of quinuclidin-3-thiol (**1**). This compound has previously been prepared by Shaw[1] and by Barriere.[2]

Shaw's method involves two successive prolonged saturations of hydrogen sulfide into an isopropanol solution of 3-quinuclidinone followed by borohydride reduction. Alternatively, Barriere produced **1** by Mitsunobu inversion of 3-quinuclidinol with thiolacetic acid followed by hydrolysis. Although both methods work successfully, we now report a modified and more convenient preparation of this quinuclidine in higher yields.



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As a modification of Shaw's procedure, hydrogen sulfide is condensed (-70°) into isopropanol in a glass bomb.[3] The quinuclidinone is added and the sealed reaction mixture stirred at 40° for 15 hrs. Longer reaction times or higher temperatures resulted in less workable reaction mixtures. Our procedure increases the yield of the condensation product (80%) and eliminates the prolonged hydrogen sulfide additions. Reduction with sodium borohydride in isopropanol gives the desired thiol (1) in 63% yield.

EXPERIMENTAL SECTION

CAUTION: Hydrogen sulfide is poisonous and all reactions should be performed in an efficient fume hood.

3,3-Dimercaptoquinuclidine.- Isopropanol (35 mL, distilled from calcium hydride) and a magnetic stirring bar were placed in a 200 mL heavy-walled glass Kjeldahl flask[3] wired with a pressure type porcelain stopper and rubber washer and the contents cooled to -70°. Hydrogen sulfide (ca. 15 mL) was condensed into the bomb and 3-quinuclidinone (17.0 g, 136 mmol) added (HOOD). The bomb was sealed and stirred at 40° for 15 hrs behind a glass shield. The initial suspension cleared after 15 minutes in the 40° bath and the product began to precipitate after 30 minutes. At the end of 15 hrs, the reaction vessel was cooled to -50°, opened, and after slight warming, the thick precipitate was collected, washed with cold isopropanol and dried to give the dithiol as a white solid (19.2 g, 80% yield), mp. 104-108°, lit.[1] 94-99°.

Quinuclidin-3-thiol.- 3,3-Dimercaptoquinuclidine (7.50 g, 42.8 mmol) was added in portions to an efficiently stirred suspension of sodium borohydride (1.62 g, 42.8 mmol) in isopropanol (40 mL) under an argon atmosphere. After gas evolution had subsided, the reaction mixture was stirred at 70° for 2.5 hrs. The mixture was cooled to room temperature and concentrated to a white gum. To decompose the borohydride complex, the residue was dissolved in ice water (25 mL), placed in an ice-bath (argon atmosphere), acidified to pH 1 with conc. hydrochloric acid and then basified to pH 9 with solid potassium carbonate. The solution was extracted with chloroform (5 x 20 mL) and the combined extracts dried ($MgSO_4$) and concentrated. The thick, partially opaque residue was distilled through a short-path Claisen head to give the desired product (3.90 g, 63%) bp. 46-48°/0.05 torr, that solidified as a white solid, mp. 48-50°, lit.[1] bp. 97-98°/8 torr, mp. 48-50°.

Anal. Calcd. for $C_7H_{13}NS$: C, 58.64; H, 9.02; N, 9.64; S, 22.20
Found: C, 58.69; H, 9.15; N, 9.79; S, 22.38

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3. The Kjedahl flask was obtained from an unknown manufacturer but appears to be the same as the Wheaton pressure bottle and stopper assembly (mfr. no. 223077) with rated pressure capability of 150 psi. In a separate experiment, the quinuclidinone and hydrogen sulfide in isopropanol were reacted in the described proportions in a 250 mL glass-lined steel bomb equipped with pressure gauge. Maximum pressure observed after 20 min at 40° was 77 psi. Since the experimental pressures are sufficiently close to the pressure limits of the vessel, increasing the scale of this reaction is not recommended with this flask.

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THE REACTION OF NINHYDRIN WITH ACETIC ACID

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Ninhydrin (**1**) is a versatile chemical that undergoes a large number of reactions that lead to useful chemical intermediates. Indeed the chemistry of **1** is quite extensive having been the subject of three reviews.[1] Compound **1** reacts with many active methylene compounds such as malonic ester,[2] nitromethane,[2] and acetophenone[3] producing aldol products. Many of these condensations are carried out in acetic acid as solvent. It was therefore very surprising to us to discover that **1** will react with acetic acid. For example when **1** is refluxed for 8 days in acetic acid the aldol product **3a** is generated in 41% yield. By this procedure **3a** can be prepared in generous quantities and is easily purified. The reaction of **1** with propionic acid (**2b**) and isobutyric acid (**2c**) proceeds less readily giving only 22% and 5% yields of **3b** and **3c** respectively. It was of interest to determine if **1** would react with ethyl acetate on long refluxing. When this reaction was attempted, no new product could be detected;