These arguments suggest strongly that $[(CH_3)_2N]_3P$ does not have C_{3v} symmetry and that its structure should be reinvestigated.

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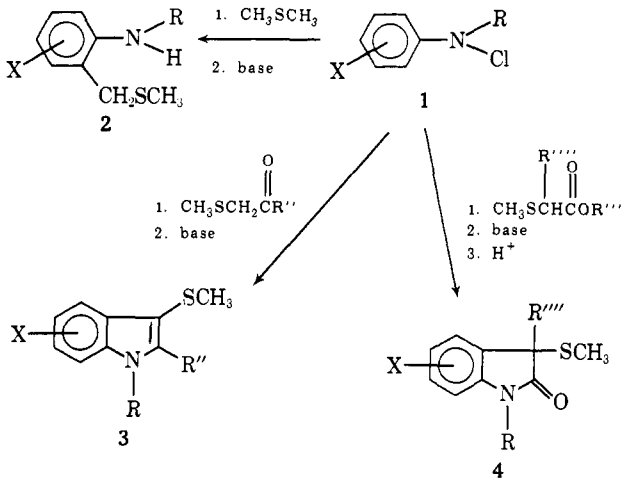
Use of Halogen–Sulfide Complexes in the Synthesis of Indoles, Oxindoles, and Alkylated Aromatic Amines

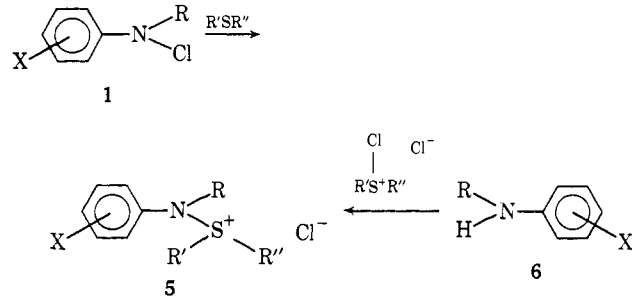
Sir:

Recently, we reported on the reactions of *N*-chloroanilines (**1**) with dialkyl sulfides, β-keto sulfides, and



α-carboalkoxy sulfides to yield intermediate azasulfonium salts, which on treatment with base produced methylthiomethylanilines (**2**),[1] 3-methylthioindoles (**3**),[2] and 3-methylthiooxindoles (**4**)[3] in good to excellent yields. Raney-nickel desulfurization of these products gave *o*-alkylanilines, indoles, and oxindoles, respectively. A major limitation of this surprisingly general synthetic process was associated with the instability of the *N*-chloroaniline when X was a cation stabilizing group such as *p*-methoxy. As we have previously shown, *N*-chloro-*p*-anisidines are extremely reactive,[4] even at temperatures as low as −78°. Thus, our original procedures[1-3] were not readily applicable to the synthesis of 4-methoxyanilines, 5-methoxyindoles, or 5-methoxyoxindoles. In view of the importance of methoxylated natural products related to the desulfurized versions of **2**, **3**, and **4**, we now wish to report a major modification of our original synthetic concept which permits the preparation of the desired methoxylated compounds.

Mechanistically, the reaction of *N*-chloroanilines (**1**) with a disubstituted sulfide initially produces the azasulfonium salt **5**. Base reacts with **5**, removing an



α-proton to give a sulfur ylide, which undergoes an intramolecular Sommelet–Hauser type rearrangement with exclusive attack on the aromatic ring ortho to the amino function.[1] Since the instability of methoxylated derivatives of **1** precluded their use in the formation of the key intermediate **5**, we have developed an alternate route to **5** which involves the nucleophilic attack of anilines (**6**) on the long-known[5] complexes, formed from the reaction of halogens with sulfides.

In a typical procedure, 0.044–0.050 mol of sulfide in 10 ml of methylene chloride at −70° was added to a solution of 0.044 mol of chlorine in 120 ml of methylene chloride at *ca.* −70°. On addition, a slight exotherm (*ca.* 5°) was noted. The solution was stirred for 5 min and a solution of 1 equiv of the aniline (**6**) and 1 equiv of triethylamine[6] in 10 ml of methylene chloride at *ca.* −70° was added dropwise. The solution was stirred for 2–4 hr at *ca.* −70° and 0.06 mol of sodium methoxide[7] in 15 ml of absolute methanol was added. The cooling bath was removed and the reaction was allowed to warm to room temperature with stirring over a 12-hr period.[7] Work-up by dilution with water and extraction with methylene chloride gave the crude ortho-substituted aniline. When the sulfide contained a β-keto function, spontaneous cyclization to produce indoles occurred. When the sulfur was β to a carboalkoxy group, acid was added to catalyze cyclization to an oxindole.

Through the general procedure described above, *p*-anisidine (**7**, X = OCH_3) could be converted into 4-methoxy-2-(methylthiomethyl)aniline (**8**, X = OCH_3) in 62% yield. The procedure was quite general. For a series of anilines (**7**, X = CH_3, H, Cl, $CO_2C_2H_5$, and NO_2), reaction with chlorodimethylsulfonium chloride gave the corresponding 2-(methylthiomethyl)anilines in 54, 67, 45, 35, and 31% yields, respectively. The reaction was not restricted to chlorodialkylsulfonium chlorides. When bromodimethylsulfonium bromide was used with aniline, a 69% yield of **8** (X = H) was obtained. Treatment of aniline with halotetramethylenesulfonium halide (**10**, Y = Cl or Br) gave **9** (X = H) in *ca.* 20% yield.

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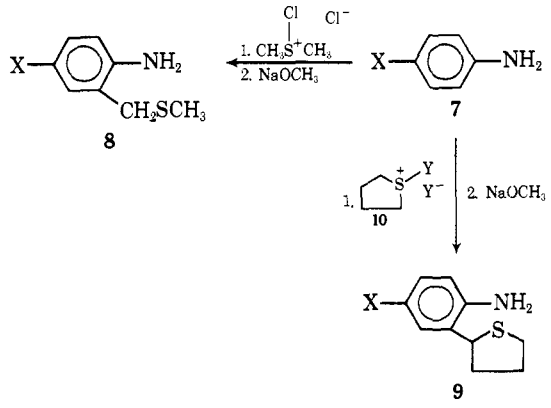
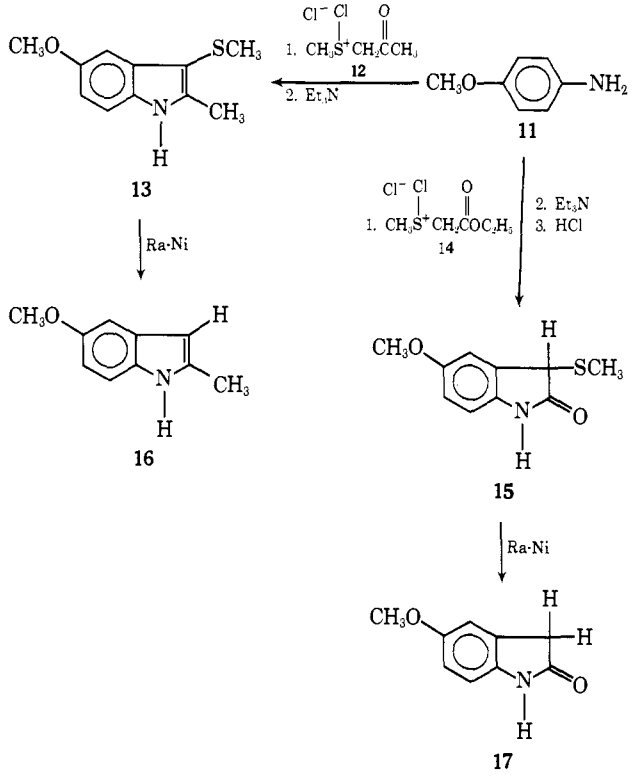
(6) The triethylamine was used to neutralize the hydrochloric acid which was generated. In place of the aniline–triethylamine mixture, 2 equiv of the aniline was used in some cases.
(7) In the indole and oxindole syntheses, triethylamine (neat) was used as the base in the ylide generation step, and the reaction mixture was stirred for 15 min at −70° and allowed to warm to room temperature.



The use of β-keto sulfides and α-carboalkoxy sulfides in this reaction provided a simple route to indoles and oxindoles. Treatment of *p*-anisidine (**11**) with **12** followed by triethylamine, according to the general procedure, gave **13** in 38% yield.[8] The reaction of **11** with **14**, followed by treatment of the intermediate azasulfonium salt with triethylamine and then with hydrochloric acid, gave the oxindole **15** in 53% yield.[9] Raney-nickel desulfurization of **13** and **15** gave **16** and **17** in 72 and 71% yields, respectively.



In summary, the use of halosulfonium halides with substituted anilines provides a simple process for the preparation of ortho-alkylated anilines, indoles, and oxindoles. The process is of particular importance in the synthesis of methoxylated indoles, which constitute a portion of numerous indole alkaloids, and in the synthesis of methoxylated oxindoles. Variation of the substitution patterns of the β-keto sulfides and α-carboalkoxy sulfides used in our prototype studies should provide a ready access to a wide variety of methoxylated indoles of value as key intermediates in the synthesis of certain natural products.

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(8) The reaction was not restricted to *p*-anisidine. With aniline, *p*-chloroaniline, and benzocaine, we obtained the corresponding 2-methyl-3-methylthioindoles in 68, 45, and 33% yields, respectively.

(9) Other substituted oxindoles can be prepared *via* this procedure. With aniline, *o*-toluidine, and 4-nitroaniline, we obtained the corresponding 3-methylthiooxindoles in 65, 62, and 12% yields, respectively.

(10) Fellow of the Netherlands Organization for the Advancement of Pure Research (Z. W. O., 1972–1973).

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A Stereoselective Approach to Eremophilane Sesquiterpenes. A Synthesis of (±)-Nootkatone

Sir:

The sesquiterpene nootkatone (**6**) is a principal flavor component of grapefruit peel oil.[1] Syntheses to date[2–4] have relied on the Robinson annelation reaction, with subsequent establishment of the cis (*C*)-4,5-dimethyl structure.

The present approach to construction of the ring system and steric control in this important area depends on the Diels–Alder reaction. The catalyzed production of Diels–Alder adducts directly from available 1-methoxycyclohexa-1,4-dienes[5] and acid catalyzed conversion of derived tertiary carbinols into 4-substituted cyclohexenones[6] have been noted.

Synthesis of the adduct **2a** from diene **1** and methyl acrylate is the initial requirement for the present route to **6**. The indicated stereochemistry of the bridge methyl group would be expected to predominate owing to the steric interactions arising in the transition state between **1** and the dienophile in the Diels–Alder reaction. Acid catalyzed ring opening[6] of the carbinol **3** derived from **2a** would be expected to lead to the trienone **4**, in which a cis relationship exists between the adjacent methyl groups (Scheme I). It was conceived, however, that in formic acid this compound would directly undergo further cyclization[7] to the eremophilane derivative **5a**.

The diene **1** was obtained from the aromatic precursor by Birch reduction[8] (NH_3, THF, *t*-BuOH, 90%). Subsequent *in situ* Diels–Alder reaction with methyl acrylate in the presence of dichloromaleic anhydride[5] gave the adduct **2a** (85% based on 33% recovered **1**). Selective functionalization of the vinylic methyl group of **2a** to give **2b** was accomplished by selenium dioxide in refluxing dioxane[9] (70%), due to the absence of any other

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(7) For a somewhat analogous process see J. A. Marshall, N. Cohen, and A. R. Hochstetter, *J. Amer. Chem. Soc.*, 88, 3408 (1966).
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