These often require tedious synthesis. By comparison, an unusually large variety of ring-substituted anilines are commercially available for use in our procedure. For the synthesis of 1-substituted indoles the Fischer method requires the availability of the appropriate 1,1-disubstituted hydrazine. These are difficult to prepare. Our method requires the appropriate N-substituted aniline. Again, many such secondary anilines are common catalog chemicals. The keto sulfides are also easily obtained. Many are commercially available. Those which cannot be purchased are easily synthesized from the appropriate halo ketone and methyl mercaptide.

Another advantage of our process is the unusually mild conditions involved in the formation of the indole nucleus. All of the steps involved can be run below 0°. No acid or strong base is involved. Hence, our method is applicable to the preparation of indole derivatives with functionality which would be sensitive to elevated temperatures, acids, or strong base.

Finally, the yields obtained in our synthesis of the indole nucleus appear superior to the average yields obtained by the Fischer method.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for a grant which partially supported this investigation.

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

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Use of Methylthioacetaldehyde in the Synthesis of Indole and Its Derivatives

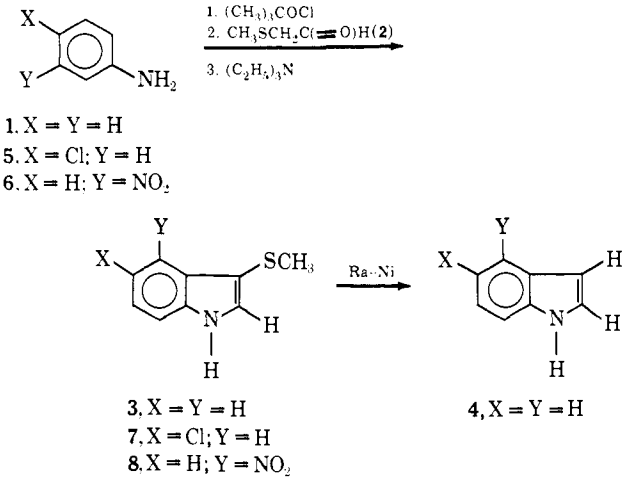
Sir:

In the preceding communication, we have described a general method for the synthesis of 2-alkyl- and 2-arylindoles from anilines and keto sulfides.[1] We now wish to report a modification of this synthetic method, which permits the synthesis of a variety of indoles unsubstituted in the 2 position. We also wish to present what we believe to be the mechanism of this very useful and versatile method for the synthesis of indoles.

When aniline (**1**) was treated with 1 equiv of *tert*-butyl hypochlorite in methylene chloride solution at −65°, followed by addition of methylthioacetaldehyde (**2**)[2] at −65° and treatment with triethylamine, we obtained **3** in 30% yield (Scheme I). Raney nickel reduction of **3** at room temperature gave an 82% yield of indole (**4**). Similar treatment of *p*-chloroaniline (**5**) and *m*-nitroaniline (**6**) gave the indoles **7** and **8**, in 35 and 38% yields, respectively. In the case of **7**, the yield was 50% when unreacted *p*-chloroaniline was taken into consideration.

From mechanistic considerations (*vide post*), we felt that the use of **9**,[2] the dimethyl ketal of **2**, might provide some advantages over the use of **2**. When **1** was treated

Scheme I



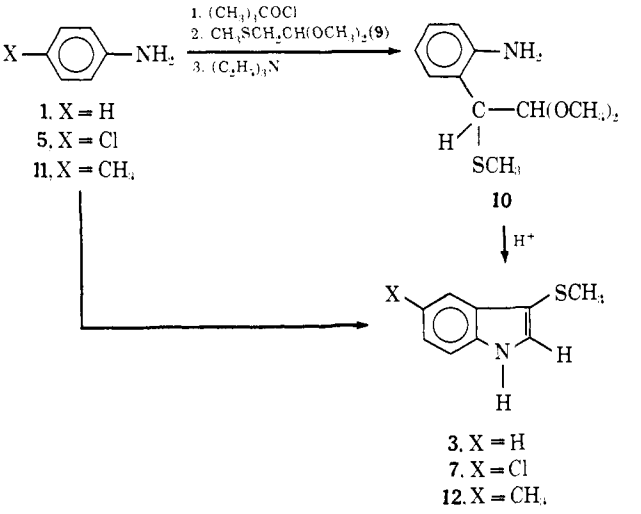
1. X = Y = H
5. X = Cl; Y = H
6. X = H; Y = NO_2

3. X = Y = H
7. X = Cl; Y = H
8. X = H; Y = NO_2

4. X = Y = H

with *tert*-butyl hypochlorite under the standard conditions, followed by the addition of 1 equiv of **9**, and subsequent addition of triethylamine, we were able to isolate **10** in 57% yield (Scheme II). The structure of

Scheme II



1. X = H
5. X = Cl
11. X = CH_3

10

3. X = H
7. X = Cl
12. X = CH_3

10 was established on the basis of elemental analysis,[3] ir spectroscopy, and its nmr spectrum, which showed peaks at τ (CCl_4) 2.82–3.67 (4 H, aromatic protons), 5.39 (1 H, d, J = 7 Hz), 6.02 (1 H, d, J = 7 Hz), 6.17 (2 H, br s, NH_2), 6.65 and 6.88 (3 H, s, diastereomeric OCH_3), and 8.22 (3 H, s, SCH_3). Treatment of an ethereal solution of **10** with a 0.5 *N* aqueous solution of hydrochloric acid gave a 97% yield of **3** for an overall yield of 55% of **3** from **1**. If, instead of isolating **10**, the crude reaction mixture was treated with acid, we obtained an overall yield of 45% of **3**. Utilizing this procedure (no isolation of the intermediate ketal) with *p*-toluidine (**11**) and *p*-chloroaniline (**5**) gave **12** and **7** in 39 and 23% yields, respectively.

The general mechanism for the formation of indoles from anilines is depicted in Scheme III. As we have previously shown,[4,5] anilines (**13**) react readily with

(1) P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **95**, 590 (1973).

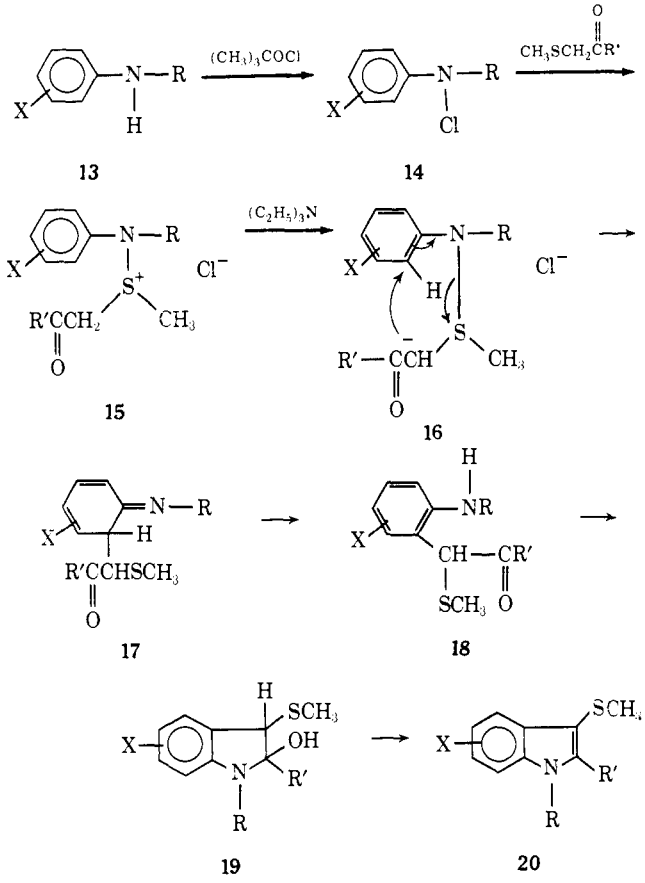
(2) For the preparation of **2** and **9** see E. H. Wick, T. Yamanishi, H. C. Wertheimer, Y. E. Hoff, B. E. Proctor, and S. A. Goldblith, *J. Agr. Food Chem.*, **9**, 289 (1961). A slight modification of the literature procedure allowed us to improve the yield of **2** from the 21% reported to 67%.

(3) Satisfactory elemental analyses have been obtained on all new compounds. Infrared and nmr spectra of all new compounds have also been consistent with the assigned structures. The structure of **4** was authenticated by comparison with a known sample.

(4) P. G. Gassman, G. A. Campbell, and R. C. Frederick, *J. Amer. Chem. Soc.*, **94**, 3884 (1972); P. G. Gassman and G. A. Campbell, *ibid.*, **94**, 3891 (1972); see also P. Haberfield and D. Paul, *ibid.*, **87**, 5502 (1965).

(5) P. G. Gassman and G. Gruetzmacher, *ibid.*, **95**, 588 (1973).

Scheme III



tert-butyl hypochlorite, or with a variety of other hypohalites, to produce *N*-chloroanilines (**14**). *N*-Chloroanilines react readily with sulfides to yield azasulfonium salts (**15**).[6] The azasulfonium salts have fairly acidic hydrogens on the carbons adjacent to the sulfur due to the inductive effect of the positive sulfur. Thus, triethylamine is a strong enough base to abstract a proton from the activated adjacent methylenes.[7] Since the one methylene is also activated by the carbonyl function, it is more acidic and gives up a proton to yield the ylide **16**. Intramolecular attack of the nucleophilic end of the ylide in a Sommelet–Hauser type[5,6,8,9] rearrangement then produces **17**. Proton transfer and rearomatization leads to **18**. In the case where the ketal, **9**, was used instead of a ketone or an aldehyde, the intermediate at this stage was the isolable ketal as illustrated by the characterization of **10**. Intramolecular addition of the free amine to the carbonyl function would be expected to yield the α-amino alcohol **19** after proton transfer. Dehydration would then give the observed polysubstituted indole **20**.

An indication of the scope of the synthesis of indoles by our method can be obtained with reference to the mechanistic scheme presented above (Scheme III). For the substituent on the aromatic ring, X has varied in electronic character from methyl to nitro. Anilines where R has been either hydrogen or methyl[1] have been used successfully. In relation to the sulfide, the indole synthesis has been shown to work well when R′ was hydrogen, methyl,[1] and phenyl.[1] In principle, X, R, and R′ should be able to vary greatly. We are continuing to investigate the various applications of our reaction scheme.

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C_8 Epimerizations of Erythromycin B and 10,11-Anhydroerythromycin B[1]

Sir:

The lactone rings of the macrolide antibiotics provide important and interesting substrates for fundamental studies of the chemistry of large ring alicyclic compounds.[2] Knowledge of their chemistry is of practical significance with respect to the goal of preparing chemically modified macrolides with improved antibacterial activities, and should prove useful for contemplated total syntheses of these complex molecules.

The extreme sensitivity of the macrolides to both acidic and basic conditions presents a challenge with regard to effecting both chemical and stereochemical modifications. It is hoped that the studies initiated in these laboratories on the chemistry of the erythromycin lactone rings[3] may have some general applicability to other macrolide antibiotics.

Our approach to the selective chemical modification of the erythromycin lactone rings is based on the introduction of functionalizable sites of unsaturation. Our interest in 8-*epi*-erythromycins derives from the postulate of Celmer concerning the importance of the stereochemistry at C_8 to antibacterial activity.[2a,4]

A detailed study of the chemistry of the erythromycin B aglycone was carried out by Perun,[5] who isolated

(1) The configurational notation of macrolides used in this and the accompanying communication is different from that used previously at positions 3, 6, 10, and 13. This change at the inward directed bonds has been made to conform to the notation used by Celmer.[2a]

(2) For recent reviews of the macrolide antibiotics see: (a) W. D. Celmer in "Symposium on Antibiotics, March 1–3, 1971, St. Marguerite, Quebec, Canada," Butterworths, London, 1971, pp 413–453; *Pure Appl. Chem.*, **28**, No. 4 (1971); (b) R. S. Egan, Ph.D. Thesis, University of Illinois Medical Center, 1971; (c) T. J. Perun in "Drug Action and Drug Resistance in Bacteria. I. Macrolide Antibiotics and Lincomycin," S. Mitsuhashi, Ed., University of Tokyo Press, Tokyo, Japan, 1971, pp 123–152.

(3) P. Kurath, P. H. Jones, R. S. Egan, and T. J. Perun, *Experientia*, 27, 362 (1971).

(4) W. D. Celmer in "Biogenesis of Antibiotic Substances," Z. Vanek and Z. Hošťalek, Ed., Academic Press, New York, N. Y., 1965, Chapter 10.

(5) T. J. Perun, *J. Org. Chem.*, 32, 2324 (1967).

(6) P. G. Gassman, G. Gruetzmacher, and R. H. Smith, *Tetrahedron Lett.*, 497 (1972); see also R. Appel and W. Büchner, *Chem. Ber.*, **95**, 849, 855 (1962).

(7) When R was hydrogen, the possibility existed that the proton might be removed from nitrogen to give a sulfilimine. If a sulfilimine was formed, it must have been equilibrated with **16** by the triethylamine.

(8) M. Sommelet, *C. R. Acad. Sci.*, **205**, 56 (1937); G. C. Jones and C. R. Hauser, *J. Org. Chem.*, 27, 3572 (1962); G. C. Jones, W. Q. Beard, and C. R. Hauser, *ibid.*, 28, 199 (1963).

(9) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); **89**, 4725 (1967); P. Claus, *Monatsh. Chem.*, **102**, 913 (1971); P. Claus, N. Vavra, and P. Schilling, *ibid.*, **102**, 1072 (1971); P. Claus and W. Vycudilik, *ibid.*, **101**, 396, 405, (1970); P. Claus and W. Vycudilik, *Tetrahedron Lett.*, 3607 (1968); U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3861 (1971).