Improved Synthesis of 2-Hydroxy-*p*-phenetidine and Derivatives

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In view of the biologically interesting nature of 2-hydroxy-*p*-acetophenetidine reported by Klutch, *et al.*,[2] who devised an unequivocal synthesis of this compound, and our interest in making certain derivatives for biological testing, we developed a more reliable and simple synthesis of the title compound in higher yield than is available in the literature,[3,4] starting with resorcinol.

Experimental Section[5]

3-Ethoxyphenol.—A mixture of resorcinol (550 g), EtOH (500 ml), KOH (320 g), and EtBr (540 g) was heated under reflux for 8 hr and then cooled to room temperature, and the KBr was filtered off. EtOH and unreacted EtBr were distilled from the filtrate. The remainder was treated with 600 ml of 20% aqueous KOH and an oily layer separated, giving 130 g of crude diethylresorcinol. Upon acidification of the aqueous portion with HCl, an oil separated out which was dried and distilled at atmospheric pressure at 250–260° giving 310 g of 3-ethoxyphenol. Redistillation at atmospheric pressure gave 257 g (37%), bp 254–256°, n^{25}D 1.5428 (lit.[6a] bp 246–247°).

4-Ethoxy-2-hydroxynitrosobenzene.—To a solution of 138 g of 3-ethoxyphenol in a mixture of 100 ml of EtOH and 100 ml of AcOH, a saturated aqueous solution of 72 g of $NaNO_2$ was added with stirring and cooling. An exothermic reaction took place and a greenish yellow precipitate formed. The temperature of the mixture was held under 45°. The yield was 135 g (81%), mp 144–147° (lit.[6b] mp 130° and 146–147°).

2-Hydroxy-*p*-phenetidine.—The nitroso compound was reduced, adapting a literature procedure[6] as follows. A solution of 42 g of the foregoing compound in 500 ml of 0.05 *N* KOH (16.5 g of KOH in 500 ml of H_2O) was added dropwise to a stirred mixture of 15 g of $NaBH_4$ in 100 ml of H_2O and 2.5 g of 5% Pd–C with N_2 bubbling through the mixture. The addition was regulated to hold the temperature under 45°. After the addition stirring was continued for 1 hr and the mixture was filtered. The filtrate was made acidic with 100 ml of HCl and then neutralized with NH_4OH. A brown precipitate came out which, after cooling in an ice bath was filtered off giving 26 g (68%) of the product, mp 140–145°. Two recrystallizations from EtOH–$CHCl_3$ (1:1) raised the melting point to 147–149° (lit.[3] mp 148°).

2-Hydroxy-*p*-acetophenetidine.—A suspension of 7.6 g of the above amine in 50 ml of PhH was acetylated with 6 g of Ac_2O, with brief warming, giving 7 g (72%), mp 166–169°. One recrystallization from EtOH raised the melting point to 170–171° (lit.[2] mp 169.3–171.7°).

2-Acetoxy-*p*-acetophenetidine.—To a solution of 7.6 g of 2-hydroxy-*p*-phenetidine in 20 ml of EtOH and 10 ml of 20% aqueous NaOH, 9.5 g of Ac_2O was added. The precipitate was filtered off and dried giving 8.3 g (90%), mp 126–127°. Recrystallization from EtOH raised the melting point to 131–132° (lit.[2] mp 131.7–132.3°).

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(2) A. Klutch, M. Harfensit, and A. H. Conney, *J. Med. Chem.*, **9**, 63 (1966).

(3) W. Will and W. Pukall, *Ber.*, **20**, 1135 (1887).

(4) (a) C. Kietaibl, *Monatsh.*, **19**, 536 (1898); (b) F. Henrich and F. Selderenberg, *J. Prakt. Chem.*, [2] **70**, 325 (1906). These authors reported 2-hydroxy-*p*-phenetidine as the HCl salt with yield unspecified.

(5) Boiling points are not corrected. Melting points were determined on a Fisher-Johns block and are corrected to standards.

(6) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

Book Reviews

Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. By ERNEST L. WYNDER and DIETRICH HOFFMAN. Academic Press, New York and London. 1968. xiii + 730 pp. 23 × 16.4 cm. $29.00

There is no *direct* evidence for stating that tobacco or tobacco smoke is carcinogenic in man, but the indirect evidence is overwhelmingly positive. Public discussion of the indirect evidence has been so frequent and so agitated that every teen-ager who starts on a career of smoking may be regarded as amply warned: indeed they can read a general health warning on every pack of cigarettes. In laboratory animals, tobacco smoke and its condensates have been established as tumorigenic by topical, parenteral, and inhalation methods of application beyond a doubt. A detached and comprehensive book on experimental carcinogenesis by tobacco is therefore to be welcomed, especially if presented by Dr. Wynder and his associates who, even in the eyes of the most doubting Thomases, speak with the authority of years of unprejudiced and exact study.

The authors have enlisted the aid of six experts in dealing with technical aspects of tobacco manufacture and smoke filtration. F. A. Wolf writes on tobacco production, curing, aging, and fermenting and on manufactured products of tobacco. R. J. Mosby has contributed a chapter on reconstituted tobacco sheet and the smoke from this material. J. E. Kiefer, G. P. Toney, T. W. George, and C. H. Keith present two chapters on the filtration of tobacco smoke, of particulate matter, and of the gaseous phase, and they describe in detail experiments on cigarette filters and their effectivenes in removing noxious constituents selectively. The physical state of tobacco smoke is summarized well, smoking machines and experimental smoking techniques are discussed, and an excellent chapter surveys the many constituents of tobacco smoke. This section gives much food for thought, because nobody in his right mind would inhale any of these constituents separately, inorganic or organic.

Reduction of tumorigenic and cilia-toxic activity opens vistas for the future of the tobacco industry and for the health of the smoker. In an excellent final chapter, Wynder interprets his own experimental studies, and those of others, in a dispassionate and factual way. This book, regarded by some as a "hot potato," will remain a classic of unbiased presentation, of amply documented and well-indexed review, and of wisdom looking toward future experimentation.

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Pharmaceutical Chemistry. Part I: Principles. By M. L. SCHROFF. Foreword by U. P. BASU. National Book Centre, Calcutta 14, India. 1968. xxxvi + 628 pp. 15.5 × 22 cm.

This is an introduction to college chemistry for pharmacy students, starting from high school level concepts and advancing to chemical thermodynamics. It corresponds roughly to the contents of freshman chemistry courses at average American colleges. There is no special application to or leaning toward biological problems. Diction, spelling, and nomenclature are British; the print, small index, and binding are nice. There are no references.

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