New Compounds

New Thio Derivatives of Carcinogenic Arylamines. IV.[1] 4-Acetamido-3-methylthiodiphenyl

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In earlier papers in this series,[1b] we described the synthesis of some new thiofluorenes related to the metabolism of the carcinogen 2-acetamidofluorene. Since we have just received word that the compound named in the title is identical with the compound isolated from a reaction of methionine and 4-acetamidodiphenyl *N*-sulfate[2] (carried out to elucidate the path of carcinogenesis of *N*-hydroxy-4-acetamidodiphenyl), we wish to report our synthesis.

Experimental Section[3]

4-Amino-3-bromodiphenyl.—To a stirred solution of 4-aminodiphenyl (1.69 g, 0.01 mol) in DMSO (8 ml) was added, dropwise, 48% HBr (1.2 ml, 0.01 mol).[4] The solution was stirred overnight at room temperature, and then heated to 95–100° for 1 hr, poured into H_2O (100 ml), and basified with NH_4OH. The brown product (1.85 g, 74%) was collected and recrystallized from EtOH, mp 64–65° (lit.[5] mp 66°).

3-Bromo-4-nitrodiphenyl.—A mixture of 4-amino-3-bromodiphenyl (2.49 g), 40% AcO_2H (35 ml), and AcOH (25 ml) was refluxed for 15 min, cooled, and then poured into H_2O (500 ml). After the light yellow emulsion was allowed to stand overnight, the yellow solid [1.6 g, a mixture of low-melting (35–40°) product and high-melting (*ca.* 140°) by-product] was collected and purified by chromatography on alumina (C_6H_6). Fractional crystallization from EtOH allowed separation of the more soluble yellow needles (1.25 g, 45%), mp 41–42° [lit.[6] bp 252–254° (7 mm)]. *Anal.* ($C_{12}H_8BrNO_2$) C, H, N.

3-Methylthio-4-nitrodiphenyl.—3-Bromo-4-nitrodiphenyl (14 g, 0.05 mol), DMSO (346 ml), and a freshly made[7] solution of $NaSCH_3$ in abs EtOH (36 ml), containing 1 equiv of the sulfide, were stirred together ($CaCl_2$ tube) for 48 hr, heated on a steam bath for 0.5 hr, then diluted with water containing a few milliliters of HCl. The yellow precipitate was filtered off, washed (H_2O), and dried giving 12.1 g (96%), mp 88–98°. Chromatography on alumina (C_6H_6) and recrystallization from EtOH gave shiny yellow plates, mp 99–100°. *Anal.* ($C_{13}H_{11}NO_2S$) C, H, N.

4-Amino-3-methylthiodiphenyl.—A mixture of 3-methylthio-4-nitrodiphenyl (4 g), 2,2′-oxydiethanol (50 ml), and 99–100% hydrazine hydrate (62 ml) was refluxed for 1.5 hr. The condenser was removed and boiling continued until the internal temperature reached 205°. Refluxing was then resumed for 2.5 hr. The mixture was cooled and diluted with H_2O. The white precipitate (3 g, 86%) was isolated and recrystallized from EtOH–H_2O to give an analytical sample, mp 55.5–56.5°. *Anal.* ($C_{13}H_{13}NS$) C, H, N.

4-Acetamido-3-methylthiodiphenyl.—4-Amino-3-methylthiodiphenyl (1 g) dissolved in C_6H_6 (5 ml) was mixed with Ac_2O (0.5 ml), boiled gently for 3 min, and evaporated to dryness to yield a white product (1.2 g, 100%). Recrystallization from EtOH gave an analytical sample, mp 120.5–121.5°. *Anal.* ($C_{15}H_{15}NOS$) C, H, N, S.

(1) (a) Supported in part by a grant (CA-01744) from the National Cancer Institute, National Institutes of Health, and in part by Research Career Development Award 5-K3-CA-14,991 (T. L. F.); (b) H.-L. Pan, M. J. Namkung, and T. L. Fletcher, *J. Med. Chem.*, **11**, 1236 (1968).

(2) We thank Dr. J. A. Miller and Dr. E. C. Miller, McArdle Laboratory for Cancer Research, University of Wisconsin, for sending us this information from a paper by J. R. Deltaan, E. C. Miller, and J. A. Miller, *Cancer Res.*, in press.

(3) All melting points were taken on a Fisher–Johns block and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analyses were performed by A. Bernhardt, Elbach über Engelskirchen, West Germany, and by Schwarzkopf Laboratories, Woodside, N. Y.

(4) T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *Chem. Ind. (London)*, 660 (1957).

(5) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," Vol. 1, 4th ed, Oxford University Press, New York, N. Y., 1965, p 93.

(6) F. H. Case and H. A. Sloviter, *J. Amer. Chem. Soc.*, **59**, 2382 (1937).

(7) T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *J. Med. Chem.*, **10**, 936 (1967); a solution containing 0.1 g of $NaSCH_3$/ml was prepared by mixing a solution (337 ml) of NaOH (20.8 g), at < 5°, in abs EtOH with 25 g of MeSH.

New Benzimidazoles

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Since a variety of pharmacological and chemotherapeutic activities have been reported[1] for benzimidazole derivatives, a number of previously unreported compounds containing the benzimidazole nucleus were prepared for biological screening. The substances and associated data are listed in Tables I and II. The methods of preparation are adaptations of known procedures.

Experimental Section[2]

Method A.—Equimolar amounts of the appropriate 2-methylbenzimidazole and aromatic aldehyde[3] were dissolved in Ac_2O and the solution refluxed for 24 hr during 3 working days. The Ac_2O was decomposed with ice–H_2O and the solution neutralized with NH_4OH. In the case of **2**, the acetoxy intermediate could not be isolated in a pure state so it was saponified with NaOH to the free phenol which was purified as the hydrochloride. Compound **3** was prepared by NaOH hydrolysis of **5** and **4** was obtained by heating **7** with pyridine·HCl; yields are based on the starting materials **5** and **7**.

Method B.—Equimolar amounts (usually about 0.03 mol or approximately 5 g) of the appropriate 2-methylbenzimidazole and aromatic aldehyde were mixed in a large test tube and heated in a wax bath at 200° for 2 hr during which the H_2O which formed distilled out of the reaction mixture. The residual mass

(1) Illustrative examples include (a) cholesterol-lowering: M. L. Black, G. Rodney, and D. B. Capps, *Biochem. Pharmacol.*, **17**, 1803 (1968); (b) analgetic: A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Experientia*, **13**, 400 (1957); (c) antifungal: S. Herrling, H. Sous, W. Krüpe, G. Osterloh, and H. Mückter, *Arzneim.-Forsch.*, **9**, 489 (1959); (d) antiviral: I. Tamm, H. J. Eggers, R. Bablanian, A. F. Wagner, and K. Folkers, *Nature*, **223**, 785 (1969); (e) anthelmintic: H. D. Brown, A. R. Matzuk, I. R. Ilves, L. H. Peterson, S. A. Harris, L. H. Sarett, J. R. Egerton, J. J. Yakstis, W. C. Campbell, and A. C. Cuckler, *J. Amer. Chem. Soc.*, **83**, 1764 (1961).

(2) Melting points are corrected. With the exceptions noted in the tables, analytical results were within ±0.4% of the theoretical values.

(3) Except for 4-(2-dimethylaminoethoxy)benzaldehyde, which was prepared by the procedure of M. W. Goldberg, and S. Teitel, U. S. Patent 2,879,293 (1959), the starting aldehydes were obtained from commercial sources.