Communications TO THE EDITOR

A New Synthesis of 3,6-Dibromopyridazine

Sir:

A new method for the preparation of 3,6-dibromopyridazine makes it possible to employ this substance in the synthesis of 3-sulfanilamido-6-methoxypyridazine which has recently shown great promise as a drug. 3,6-Dibromopyridazine is much more reactive than the corresponding dichloropyridazine and may be used to advantage in the following reactions.

Phosphorus oxybromide (3 parts) reacted vigorously with 3,6-dioxohexahydropyridazine (1 part) at 70–80° for 2 hours; the OH groups were substituted by Br and the partially unsaturated ring became fully aromatized. The excess $POBr_3$ was removed *in vacuo* and the residue treated with water and made basic with ammonia. The product, 3,6-dibromopyridazine, separates on cooling; recrystallization from cyclohexane yields soft white needles, m.p. 118–119,° which is identical with material prepared from maleic hydrazide.[1] Yields higher than 50% may be obtained by operating in the presence of bromine (1.5 parts). In this case the reaction is violent at the beginning and requires cooling; short heating is then sufficient to complete the reaction. Phosphorus trichloride–bromine reacts similarly although with inferior yields.

An intimate mixture of 3,6-dibromopyridazine (1 part), potassium carbonate (1.1 parts) and sulfanilamide (1.4 parts) was heated in an oil bath (bath temp. 150–160°) until it began to melt and evolve carbon dioxide. Upon completion of gas evolution the mixture was extracted with hot water. Insoluble sulfanilamide was removed after cooling by filtration. Acidification of the filtrate with acetic acid yielded 3-sulfanilamido-6-bromopyridazine in yields exceeding 75%. A sample recrystallized from alcohol (yellow needles) became brown at 210° and melted at 243–244° (dec.).

Anal.: Calcd. for: $C_{10}H_9BrN_4O_2S$: Br, 24.31. Found: Br, 24.29; 24.60.

The replacement of bromine by alkoxyl may be accomplished easily by the Williamson reaction. A methanolic solution of 3-sulfanilamido-6-bromopyridazine (1 mole) was heated for 10 hours at 100–110° with 2.5 moles of sodium methoxide. The product, 3-sulfanilamido-6-methoxypyridazine, resulted in yields exceeding 85%.

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(1) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, **76**, 3225 (1954).

Trialkyl Phosphites as Reagents in a Novel Reductive *O*-Alkylation of Quinones[1]

Sir:

We have shown[2] that in the reaction of chloranil with either triphenylphosphine or triethyl phosphite, phosphorus-oxygen bonds are exclusively established, as in I and II. With triethyl phosphite, a subsequent group translocation takes place and yields an ether-phosphate V as the final product. The reaction of *p*-benzoquinone with triphenylphosphine, however, takes an entirely different course and yields a product in which a phosphorus-carbon bond has been established (VIII).[2a]

The purpose of this communication is to describe the interesting behavior of the *p*-benzoquinone-triethyl phosphite system. In this system, over 90% of diethyl(4-ethoxyphenyl)phosphate (VII) was formed, presumably *via* intermediate IV. The ether-phosphates V, VI (obtained from chloranil and trimethyl phosphite), and VII, were readily hydrolyzed to the corresponding quinol-monoalkyl-ethers, namely, tetrachlorohydroquinone-monoethylether (IX), tetrachlorohydroquinone-monomethylether (X)[3] and hydroquinone-monoethyl-ether (XI). Likewise, 2,5-dimethylhydroquinone-monomethylether was obtained from 2,5-dimethyl-*p*-benzoquinone and trimethyl phosphite. These reactions proceed in high yields under mild conditions. Thus, trialkyl phosphites become reagents in a facile method for the reductive *O*-alkylation of quinones and for the synthesis of monoalkylethers of hydroquinones.

The quinone and the trialkyl phosphite were allowed to react for several hours at room temperature in anhydrous benzene (or for shorter periods at reflux temperature). The products were isolated (after alkaline extraction of small amounts of acidic by-products) by distillation or recrystallization. Hydrolysis to the quinol-monoalkylethers (such as IX, X, and XI) was effected with 5% aqueous-alcoholic alkali (15–20 hours reflux).

If the trialkyl phosphite is slowly added to a solution of the quinone in benzene containing aqueous ethanol, the only products isolated are the

(1) The Structure of Quinone-Donor Adducts. III. Carried out under Public Health Service Grant CY-3250; we are also grateful to the Eli Lilly Research Grants Committee for initial financial support.

(2) (a) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, **78**, 5614 (1956); (b) *J. Org. Chem.*, **22**, 856 (1957).

(3) The naturally occurring antibiotic Drosophilin A has been identified as tetrachlorohydroquinone-monomethylether (X) [M. Anchel, *J. Am. Chem. Soc.*, **74**, 2943 (1952)].