SYNTHESIS OF 3-N-BUTYLPYRIDINE — A TOXIC METABOLITE OF THE FUNGUS *Fusarium oxysporum* AND ITS HOMOLOGUES

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The interaction of the tri-n-butylphosphine complex of lithium di(3-pyridyl) copper (I) with 1-iodobutane and with other alkyl halides in ether at room temperature has given 3-n-butylpyridine and its homologues with yields of 82-89%.

The fungus *Fusarium oxysporum* and its forms, which are the causative agents of fusarial wilt of the cotton plant, tomatoes, and other agricultural crops, produce fusaric (3-n-butylpicolinic) acid (I) both in the plants damaged by them and also on cultivation [1]. In the damaged plants, the acid (I) taken up in the transpiration points exerts its pathological action in different ways. It is assumed, for example, that, on its decarboxylation in a plant affected by wilt, 3-n-butylpyridine (II) is formed, the toxic action of which is 100 times greater than that of the unchanged acid [2-4]. This hypothesis has been confirmed by a study of its action on the cotton plant [5, 6]. The capacity for causing the symptoms of wilt is 22 times greater for compound (II) than for the acid (I).

It must be mentioned that the performance of large-scale investigations of the properties of compounds (I) and (II) is hindered by the absence of rational methods for obtaining them, which is connected with the difficulty of introducing alkyl substituents into position 3 of the pyridine ring. Several methods of synthesizing acid (I) are known [7-13], among which the most acceptable are methods based on the condensation of the corresponding 1,5-dicarbonyl compounds with ammonia or hydroxylamine [11] and on transformations of 2-methyl-5-vinylpyridine [12, 13], while there is only one method for the directed synthesis of compound (II), in which the starting material is 3-pyridyl propyl ketone, obtained by the interaction of 3-pyridyllithium with butyronitrile [14].

The existing methods of synthesizing compounds (I) and (II) are laborious and involve many stages. To develop a preparative method of obtaining toxin (II) and its homologs we decided to start from 3-iodopyridine (III) and to confirm the synthetic possibilities of a complex of lithium di-n-butylcuprate with tri-n-butylphosphine (IV) obtained by a known method [15], since the interaction of such complexes with organohalogen compounds has given various alkyl- and aryl-substituted products with good yields [16]. In the present work we have shown the interaction of the complex $(n\text{-}C_4H_9)_2CuLi\cdot P(n\text{-}C_4H_9)_3$ (IV) with (III) leads to the formation of compound (II). But the yield of the latter in these experiments was only 18% in the best case. Such a result cannot, of course, satisfy the demand of research workers for toxin (II). In the following series of experiments we therefore used for its synthesis a complex of lithium di(3-pyridyl) cuprate with tri-n-butylphosphine (V) which we had obtained for the first time [17] by the reaction of 3-pyridyllithium with tetrakis[iodo(tri-n-butylphosphine)copper(I)]. On the interaction of this complex with 1-bromobutane [17] or 1-iodobutane (VIII) in ether at room temperature for 8 h, compound (II) was formed with yields of 86 and 84%, respectively. We confirmed this unexpected result by the reaction of complex (V) with other alkyl halides (VI-IX) and obtained good yields of 3-ethyl-, 3-n-propyl-, and 3-n-pentylpyridines (X-XII) — 82, 86, and 89%, respectively. The reaction takes place in accordance with the scheme given on next page.

Thus, it has been established that it is possible to use the reaction of complex (V) with the appropriate alkyl iodides for the preparative synthesis of compound (II) and its homologs.

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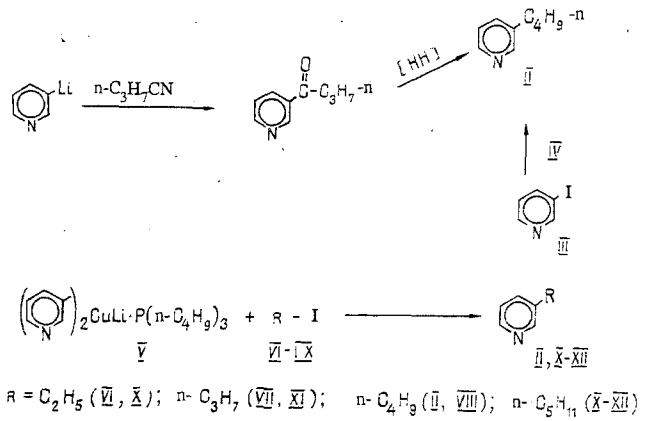

EXPERIMENTAL

The refractive indices of the compounds synthesized were measured on a IRF-22 instrument at 20°C. The reaction products were analyzed on a Chrom-5 chromatograph with 3 × 2100 mm glass columns containing as the stationary phase 5% of SE-30 on the support Chromaton N-AW-Super, 5% ON-17. The detector was a katharometer, and the carrier gas helium. P_{init} = 0.5 atm. T = 100-260°C (4°C/min), fr. 0.125-0.16. $T_{intro.}$ = 260°C, $T_{detect.}$ = 270°C.

Synthesis of 3-Butylpyridine (II) from 3-Iokopyridine (III) and the Complex (IV). A one-liter three-necked flask fitted with a tube for the introduction of nitrogen and a mechanical stirrer was charged with 100 g (0.255 mole) of tetrakis[iodo(tri-n-butylphosphine)copper(I)], and then 500 ml of ether was added and nitrogen was passed through for 10-15 min to eliminate air. After this, the solution was cooled to −78°C and, with stirring, 0.5 mole of n-butyllithium in 280 ml of n-hexane was added over 20 min. Then 10.3 g (0.05 mole) of (III) dissolved in 15 ml of ether was added dropwise over 30 min to the stirred reaction mixture at −78°C. The temperature of the mixture was brought to that of the room, and stirring at this temperature was continued for 8 h. Then the reaction mixture was cooled to −20°C and was carefully hydrolyzed with 100 ml of 20% HCL solution. The two layers that formed were separated, and the aqueous layer was washed with n-hexane (2 × 100 ml). After drying and distillation, the combined portions of the solvent yielded 45 g of tri-n-butylphosphine.

The residual aqueous layer was made strongly alkaline (pH 14) with potassium hydroxide solution and was distilled with steam until the reaction with the Dragendorff reagent was negative. Compound (II) was extracted from the aqueous distillate with ether, and the ethereal extract was dried with potassium carbonate and distilled, giving a product with bp 98-100°C (20 mm Hg); yield 1.2 g (18%); n_D^{20} 1.4976; picrate, mp 88-89°C (from alcohol) [18].

Synthesis of 3-n-Butylpyridine (II) by the Reaction of Complex (V) with Compound (VIII). A solution of 0.05 mole of (VIII) in 15 ml of ether was added dropwise over 30 min at −78°C to an ethereal solution of complex (V) obtained by Goshav's method. The temperature of the mixture was raised to that of the room, and stirring was continued for 8 h. The reaction mixture was worked up and the products were isolated in the same way as in the preceding experiment: the yield of compound (II) was 5.7 g (84%).

The following were synthesized analogously: 3-ethylpyridine (X) with a yield of 82%, 3-n-propylpyridine (XI) with a yield of 86%, and 3-n-pentylpyridine (XII) with a yield of 89%, their characteristics corresponding to those given in the literature [18].

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