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SYNTHESIS OF 5-NITRO-2-SUBSTITUTED FURANS ON THE BASIS OF 5-NITROFURFURYL NITRATE

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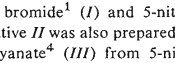
The authors describe the preparation of 5-nitrofuran-2-CH_2-X-substituted derivatives, where X = Br, NH_2, SCN, NCS, SO_2R (R = CH_3, *p*-CH_3CONH, C_4H_3S), and 5-nitropyromucic acid methyl ester from 5-nitrofurfuryl nitrate. The possibility of the substitution of the ONO_2 group in 5-nitrofurfuryl nitrate by various nucleophilic reagents has been investigated.

The synthesis of 5-nitrofuran derivatives becomes important in connection with their antimicrobial activity. From the point of view of the synthesis of more complex 5-nitrofuran derivatives the search for new suitable methods of preparation of starting materials is of basic importance. Some of the substances described in this paper have been synthetised by other methods, from less accessible material; 5-nitrofurfuryl bromide[1] (*I*) and 5-nitrofurfurylamine hydrochloride[2] (*II*) from 5-nitrofurfuryl alcohol. Derivative *II* was also prepared by hydrolysis of N-(5-nitrofurfuryl)-phthalimide[3]; 5-nitrofurfuryl thiocyanate[4] (*III*) from 5-nitrofurfuryl nitrate[5-7] and recently also from 5-nitrofurfuryl iodide[8,9] under the effect of thiocyanates.



I, R = Br
II, R = NH_2.HCl
III, R = SCN
IV, R = NCS
V, R = SO_2CH_3
VI, R = $SO_2C_6H_4NHCOCH_3$-*p*
VII, R = α-SO_2 thienyl
VIII, R = $COOCH_3$
IX, R = ONO_2

For the synthesis of all the substances described in this paper, *i.e.* *I* (ref.[10]), *II* (ref.[11]), *III*, 5-nitrofurfuryl isothiocyanate[12] (*IV*), 5-nitrofurfuryl methyl sulfone[13] (*V*), 5-nitrofurfuryl *p*-acetamidophenyl sulfone (*VI*), 5-nitrofurfurylthienyl sulfone (*VII*), and 5-nitropyromucic acid methyl ester (*VIII*), the easily accessible 5-nitrofurfuryl nitrate (*IX*) was made use of, which can be prepared by one-step synthesis by nitration of furfuryl alcohol with fuming nitric acid in acetic anhydride, under simultaneous esterification[6]. The two-step method of preparation of *I* consists in the

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substitution of the nitrate group in *IX* by the Br^- anion under the effect of alkali bromides; the yield of *I* is 73·5%. Among the investigated bromides, NaBr, KBr, and NH_4Br were found best. As solvents, ketones and alcohols may be used, of which methanol is most suitable. During the study of the conditions of preparation of substance *II* it was shown that the complex salt can be prepared directly from *IX* by reaction with hexamethylenetetramine, and the salt decomposed with dry hydrogen chloride. The yields in this case are low, however. It is more advantageous to transform *IX* to *I* in alcohol and condense this without isolation with hexamethylenetetramine and then decompose to *II*. This method of preparation of *II* gives better yields in comparison with other method[2,3], and it can be carried out by a single operation. The nitrate group in *IX* is easily substituted by the SCN^- anion with alkali thiocyanates; *III* is formed in 70% yield. When alkali thiocyanates react with 5-nitrofurfuryl halogenides the yields are 30–60%. The reaction takes place already in the cold, best in ethanol or acetone.

The attempts at the substitution of the nitrate group in *IX* by CN^- anion were unsuccessful in all solvents tested (alcohols, ketones, dimethylformamide, dimethyl sulfoxide, xylene). In all instances a rapid polymerisation took place and we were unable to isolate well defined products. The attempts at the substitution of the nitrate group in IX by $CH_3O^{(-)}$ anion under the effect of sodium methoxide in methanol were also unsuccessful. The methyl ester of 5-nitro-2-furancarboxylic acid was isolated from the resinous product in 10–15% yield instead of the expected 5-nitrofurfuryl methyl ether. It was identified by elemental analysis, comparison of the IR spectra with a standard, and thin-layer chromatography (silica gel, tetrahydrofuran–benzene–heptane (0·5 : 2 : 2). We have not investigated the mechanism of this reaction so far.

The nitrate group in *IX* may also be substituted by sulfonyl residue on reaction with alkali salts of alkyl or arylsulfinic acids. The reaction requires an elevated temperature and it is advantageous if it is carried out in lower alcohols or ketones. Better yields of sulfones can be achieved after the addition of one equivalent of inorganic bromide which substitutes the nitrate group under formation of *I*; the latter reacts more willingly with the salts of sulfinic acids. During the preparation of *IV* with the thiophosgene method *II* may be used, from which the free amine is liberated in the reaction mixture on addition of basic reagents, best calcium carbonate. If alkali hydroxides are used, an appreciable part of amine polymerises, the isolation procedure is more difficult, and the yields are lower.

EXPERIMENTAL

5-Nitrofurfuryl Bromide (*I*)

To substance *IX* (9·4 g; 0·05 mol) in acetone (25 ml) sodium bromide (10·3 g; 0·1 mol) in 90% acetone (100 ml) was added and the mixture refluxed for 3 h. Acetone was distilled off and the residue extracted with ether (4 × 10 ml). The extract was dried over anhydrous sodium sulfate, ether was distilled off and the residue crystallised from light petroleum. Yield. 7·6 g (73·5%); light yellow needles, m.p. 46·5–47·5°C; lit.[1] gives 46–47°C.

5-Nitrofurfurylamine Hydrochloride (*II*)

To a solution of *IX* (18·8 g; 0·1 mol) in 99% acetone (120 ml) sodium bromide (11·3 g; 0·11 mol) was added and the mixture refluxed for 1·5 h. The precipitated product was filtered off under suction and the filtrate was additioned with hexamethylenetetramine (14·1 g; 0·1 mol). After short boiling or standing for several hours a complex salt separated. A strong stream of hydrogen chloride was introduced into this mixture which warmed up spontanesously. The salt passed into solution under separation of ammonium chloride. After the end of the spontaneous heating of the reaction mixture (2·5 h) the saturation with hydrogen chloride was continued for another hour. The reaction mixture was filtered while hot and the crystals separated from the filtrate were filtered off and dried. By concentration of the mother liquor another crop of crystals was obtained. Total yield 11 g (61·7%), m.p. 182—183°C (decomp.); lit.[2] gives 180—182°C (with decomposition, the substance darkens at 140°C).

5-Nitrofurfuryl Thiocyanate (*III*)

A mixture of *IX* (70 g; 0·37 mol) and potassium thiocyanate (48·5 g; 0·5 mol) in acetone or ethanol (400 ml) was stirred at room temperature for 3 h, or boiled for 40—50 min. After approximately 10 min a precipitate was formed. The mixture was allowed to stand for 48 h and the separated salt filtered off while hot. The solution was boiled with charcoal, filtered, and the solvent evaporated. After crystallisation from 80% ethanol 49 g (71·5%) of the product was obtained, m.p. 93·5°C, lit.[8] m.p. 92—94°C.

5-Nitrofurfuryl Isothiocyanate (*IV*)

To a mixture of thiophosgene (12·6 g; 0·11 mol) in chloroform (150 ml) and calcium carbonate (30 g; 0·3 mol) substance *II* dissolved in water (75 ml) was added at room temperature over 4 h. The unreacted carbonate was filtered off, the chloroform layer was separated, and the aqueous layer was extracted with chloroform (2 × 50 ml). The combined chloroform extracts were dried over sodium sulfate and, after decolorizing with charcoal, evaporated under reduced pressure. After crystallisation from ether 8·5 g (46%) of yellow needles were obtained, m.p. 55—56°C. For $C_6H_4N_2O_3S$ (184·2) calculated: 39·12% C, 2·18% H, 15·21% N; found: 39·70% C, 2·37% H, 15·24% N.

5-Nitrofurfuryl Methyl Sulfone (*V*)

To a solution of *IX* (19·8 g; 0·1 mol) in acetone or ethanol sodium bromide was added (10·7 g; 0·1 mol) and the mixture refluxed for 1·5 h. Sodium methansulfinate (13·6 g; 0·1 mol) was then added and the mixture heated for another 2·5 h. After dilution with boiling water (20 ml) and cooling the separated crystals were filtered, washed with water and then with ether. Yield 12·5 g (61%), m.p. 123°C. For $C_6H_7NO_5S$ (205·2) calculated: 35·12% C, 6·82% N, 15·61% S; found: 35·18% C, 6·99% N, 15·57% S. *5-Nitrofurfuryl p-acetaminophenyl sulfone* (VI): This was prepared in a manner analogous to that used for the preparation of *V*, yield 21 g (65%), m.p. 214—215°C. For $C_{13}H_{12}N_2O_6S$ (324·3) calculated: 48·18% C, 8·65% N, 9·88% S; found: 48·11% C, 8·78% N, 9·92% S. *5-Nitrofurfuryl thienyl sulfone* (VII). It was prepared similarly as *V*, yield 17·9 g (65·7%), m.p. 172—174°C. For $C_9H_7NO_5S_2$ (273·3) calculated: 33·00% C, 5·15% N, 23·48% S; found: 33·17% C, 5·40% N, 23·48% S.

5-Nitropyromucic Acid Methyl Ester (*VIII*)

To a solution of *IX* (18.8 g; 0.1 mol) in methanol (50 ml) sodium methylate (5.4 g; 0.1 mol) in methanol (20 ml) was added at room temperature. The mixture was stirred for 2 h, concentrated *in vacuo*, and diluted with water (50 ml). The product was extracted with ether and the extract dried over sodium sulfate. Ether was distilled off and the residue crystallised from ethanol. Yield 1·7—2·5 g (10—15%), m.p. 80°C. Lit.[14] gives 81°C.

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