LACTAM AND ACID AMIDE ACETALS.

58.* NEW SYNTHESIS OF 3-NITRO-5-HYDROXYBENZOFURANS

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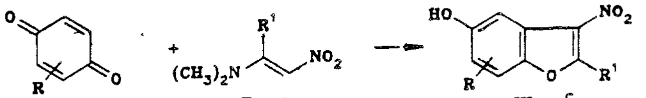
Previously unknown 3-nitro-5-hydroxybenzofuran derivatives were obtained by condensation of p-benzoquinones with nitro enamines.

Information regarding the synthesis and biological activity of 2-nitro-5-hydroxybenzofurans has been presented extensively in the literature (for example, see [2–5]). At the same time, the information on 3-nitro-5-hydroxybenzofurans is limited to a small number of publications [6–8]. The direct nitration of 5-hydroxybenzofuran derivatives in the 3 position is possible under the condition of protection of the hydroxy group and the presence of a substituent (Ar) in the 2 position [6, 7]. 3-Nitro-5-hydroxybenzofurans that have electron-donor substituents (SR and NHR groups) in the 2 position were obtained by the method in [8].

We have developed a new method for the synthesis of previously unknown 3-nitro-5-hydroxybenzofurans IIIa–f, which do not have substituents in the 2 position or have a 2-methyl group.

The method is based on the condensation of p-benzoquinone derivatives II with nitro enamines Ia,b under the conditions of the Nenitzescu reaction and generally ensures stable and satisfactory yields of the desired 3-nitrobenzofurans IIIa–f (Table 1).



II   Ia,b   IIIa-f

Ia, IIIa-d R^1=H; Ib IIIe,f R^1=CH_3; IIIa,e R=H, b,f R= 6,7-Cl_2, c R= 7-SC_6H_5
d R=7-$C_6H_4NO_2$-*p*

The starting nitro enamines Ia,b are readily formed in the reaction of dimethylformamide and dimethylacetamide acetals with nitromethane [9].

In an investigation of the reaction of nitro enamines Ia,b with quinones it was found that the structure of the starting enamines has a significant effect on the process. Thus, when β-dimethylaminonitropropene (Ib) is used, an important condition for carrying out the reaction is the absence of water in acetic acid. If water is not absent, resinification of the reaction mass is not observed, and the desired benzofurans IIIe,f cannot be isolated. At the same time, the presence of water (1–3%) in the acetic acid in carrying out the reaction of quinones with β-dimethylaminonitroethylene (Ia) has virtually no effect on the course of the process.

There is yet another substantial difference in carrying out the process, depending on the presence or absence of a methyl group in the starting enamines: whereas the reaction of enamine Ib with quinones proceeds quite smoothly in acetic acid without any additional reagents, the presence of a strong acid (in our case we used p-toluenesulfonic acid) is required for the successful carrying out of similar reactions of enamine Ia.

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*See [1] for Communication 57.

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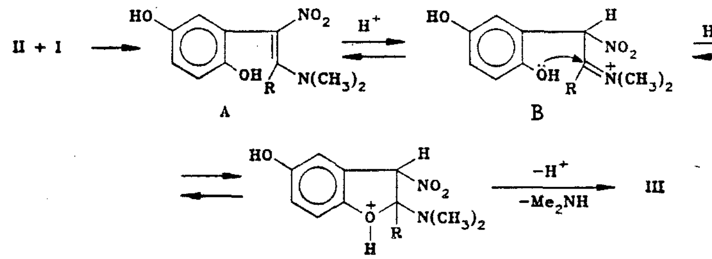
The indicated peculiarities may be a consequence of significant differences in the properties of enamines that have or do not have a methyl group in the α position [10]. It is known that α-methyleneamines are considerably more basic compounds than their 2-demethyl analogs [10]. In addition, in series of enamino ketones with an α-methyl group C protonation, which, according to modern concepts, ensures higher basicity of the enamines and an increase in the rate of their hydrolysis [10], is realized considerably more readily. It might be assumed that both of these facts also determine the differences in the behavior of enamines Ia,b. The substantially greater tendency of Ib to undergo hydrolysis is the reason that water must be absent in the reaction mixture, for otherwise hydrolysis leads to an unstable nitro ketone and dimethylamine; the latter under these conditions can react with the quinone to give readily oxidized aminohydroquinones, which also gives rise to pronounced resinification of the reaction mass. In a preparative respect we found that it was convenient to carry out the process in the presence of the calculated amounts of acetic anhydride necessary for tying up the water in the acetic acid.

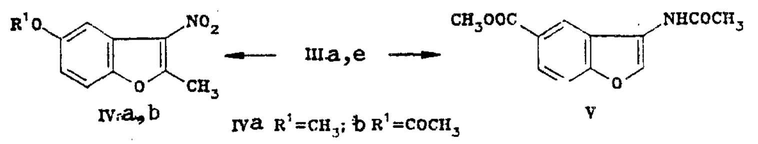
It is a more complicated matter to interpret the need for the presence of p-TsOH in reactions with the participation of enamine Ia.

The formation of benzofurans under the conditions of the Nenitzescu reaction can be represented in the following way:



If it is assumed that the step involving the C protonation of intermediate enamine A is a necessary condition for subsequent intramolecular cyclization (which, in fact, was demonstrated long ago and reliably in many cases for the acidic hydrolysis of enamines, where attack on the immonium salts by water occurs [10]), the formation of immonium salt B for low-basicity enamines (A, R = H) may require a substantial increase in the acidity of the medium as compared with enamines that have higher basicities (A, R = Me). Correspondingly, the A → B process takes place at different rates, depending on the basicities of the starting enamines, and the conditions selected correspond to rather high rates of formation of the benzofuran ring for both types of enamines Ia,b.*

In conclusion, let us note that the 3-nitrobenzofurans obtained have become accessible and promising starting compounds for the synthesis of various new derivatives of the benzofuran series. Within the framework of our research we have shown that they can be alkylated at the 5-hydroxy group to give 5-methoxy (IVa) and 5-acetoxy (IVb) derivatives; we also established the fundamental possibility of reduction of the nitro group with zinc in acetic acid; acylation of the 5-hydroxy group and the resulting 3-amino groups, as a result of which 3-acetamido-5-acetoxybenzofuran (V) was isolated, also occurs here.



The PMR spectra of nitrobenzofurans IIIa–f (Table 1) contain signals of protons of OH groups (9.04–11.07 ppm), as well as signals of protons of the benzene ring: 4-H (7.29–7.62 ppm), 6-H (6.73–7.22 ppm), and 7-H (7.54–7.62 ppm). Singlet signals of protons in the 2 position are observed at 9.26–9.40 ppm in the PMR spectra of 3-nitrobenzofurans that do not contain a 2-methyl group (IIIa–d).

Instead of signals of protons in the 2 position, the PMR spectra of 2-methyl-3-nitrobenzofurans IIIe,f contain singlet signals of protons of methyl groups at 2.88 and 2.93 ppm.

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*A sufficiently high rate of formation of the benzofuran ring is a necessary condition for the successful carrying out of the Nenitzescu reaction, which is known [11] to be accompanied by a large number of faster or slower side reactions.

TABLE 1. Characteristics of IIIa–f, IVa,b, and V

Compound	Empirical formula	Tmp,* °C	PMR spectrum							Yield, %
			solvent	chemical shifts, δ, ppm						
				2-H	2-CH_3	4-H	6-H	7-H	OH	
IIIa	$C_8H_5NO_4$	165 ... 167	d_6-DMSO	9,26, s	—	7,38, d	6,94, qd	7,62, d	9,84, s	68
IIIb	$C_8H_3Cl_2NO_4$	228 ... 230	d_6-DMSO	9,43, s	—	7,53, s	—	—	11,07, s	44
IIIc	$C_{14}H_9NO_4$	160 ... 162	d_6-DMSO	9,32, s	—	7,33, d	6,73, d	—	10,03, s	56
IIId	$C_{14}H_8N_2O_6$	290 dec.	d_6-DMSO	9,4 s	—	7,49, d	7,22 d	—	10,14, s	58
IIIe	$C_9H_7NO_4$	191 ... 193	$CDCl_3$ + d_6-DMSO	—	2,88, s	7,29, d	6,39, qd	7,54, d	9,04, s	62
IIIf	$C_9H_5Cl_2NO_4$	224 ... 225	$CDCl_3$ + d_6-DMSO	—	2,93, s	7,62, s	—	—	—	19
IVa	$C_{10}H_9NO_4$	141 ... 143	—	—	—	—	—	—	—	10
IVb	$C_{11}H_9NO_5$	139 ... 141	—	—	—	—	—	—	—	81
V	$C_{12}H_{11}NO_4$	225 ... 227	—	—	—	—	—	—	—	10

*The compounds were recrystallized: IIIa,b,e from dichloroethane; IIIc,f from benzene; IIId from acetic acid; IVa from petroleum ether; and IVb and V from alcohol.

EXPERIMENTAL

The PMR spectra were obtained with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the individuality of the substances were monitored by chromatography on Silufol UV-254 plates in a benzene–methanol system (9:1) with development with UV light. The results of elementary analysis of C, H, Cl, N, and S were in agreement with the calculated values. The characteristics and yields of the compounds are presented in Table 1.

3-Nitro-5-hydroxybenzofuran (IIIa). A solution of 31.3 g (270 mmole) of Ia in 300 ml of glacial acetic acid was added with stirring at 20°C to a mixture of 25.9 g (240 mmole) of p-benzoquinone and 61.9 g (360 mmole) of p-toluenesulfonic acid, and the mixture was stirred for 1 h. It was then treated with 1 liter of water, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from dichloroethane to give 29.4 g of IIIa.

Compounds (IIIb-d). These compounds were similarly obtained.

2-Methyl-3-nitro-5-hydroxybenzofuran (IIIe). A 3.0-ml sample of acetic anhydride and 19.5 g (150 mmole) of Ib were added with stirring at 20°C to a solution of 10.8 g (100 mmole) of p-benzoquinone in 100 ml of glacial acetic acid, and the mixture was allowed to stand for 20 h at 20°C. The resulting precipitate was removed by filtration, washed with acetic acid and water, and dried to give 8.0 g of IIIe. The acetic acid mother liquor was diluted with 500 ml of water, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from dichloroethane to give an additional 4.0 g of IIIe.

Compound IIf. This compound was similarly obtained.

2-Methyl-3-nitro-5-methoxybenzofuran (IVa). A solution of 0.35 g (15 mmole) of sodium in 50 ml of ethanol was added to a solution of 2.9 g (15 mmole) of IIIe) in 100 ml of ethanol, after which the solvent was removed in vacuo. Dry toluene (50 ml) and 4.3 g (30 mmole) of methyl iodide were added to the residue, and the mixture was refluxed for 8 h. The precipitate was removed by filtration, and the mother liquor was chromatographed with a column packed with silica gel. Workup of the toluene eluate gave 0.31 g of IVa.

2-Methyl-3-nitro-5-acetoxybenzofuran (IVb). A suspension of 1.93 g (10 mmole) of IIIe in 25 ml of acetic anhydride was heated to 70°C, one drop of concentrated H_2SO_4 was added, and the resulting solution was cooled to 20°C and diluted with 100 ml of water. The precipitate was removed by filtration, washed with water, dried, and recrystallized from ethanol to give 1.9 g of IVb.

3-Acetamido-5-acetoxybenzofuran (V). A 6.5-g (100 mmole) sample of zinc dust was added with stirring in portions in the course of 30 min to a refluxing solution of 1.8 g (10 mmole) of IIIa and 2.0 g (20 mmole) of acetic anhydride in 35 ml of acetic acid. The reaction mixture was then filtered hot, the acetic acid was evaporated in vacuo, and the residue was diluted with water and extracted with ether (five 100-ml portions). The ether extract was evaporated to a volume of 50 ml, and the concentrate was cooled to 5°C. The resulting precipitate was removed by filtration to give 0.23 g of V.

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