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2,3-DIHYDROBENZOFURAN-3-ONE IN THE SYNTHESIS OF 3-CYANO-2-IMINO-1-*p*-NITROPHENYL-1,2-DIHYDROPYRIDO[3,2-*b*]BENZOFURAN

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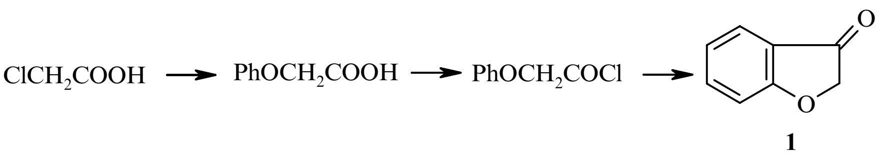
3-p-Nitrophenylaminobenzofuran was obtained by the reaction of 2,3-dihydrobenzofuran-3-one with p-nitroaniline and was used in the Vilsmeier reaction for the synthesis of 2-formyl-3-p-nitrophenylaminobenzofuran. Treatment of the latter with malononitrile led to 1-p-nitrophenyl-2-imino-3-cyano-1,2-dihydropyrido[3,2-b]benzofuran.

Keywords: aminobenzofuran, benzofuran, malononitrile, pyridobenzofuran.

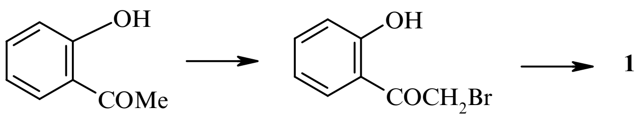
Indoxyl derivatives are extremely promising and accessible starting compounds in the synthesis of various indole-containing heterocycles [1]. Recently it was shown that 1-acetylindoxyl can be converted smoothly through the formation of derivatives of 3-arylaminoindole [2], 3-arylamino-2-formylindole, and 3-arylamino-2-(dicyanovinyl)indole into 1-substituted δ-carboline, which exists in the form of a structure with a nonbenzenoid condensed indole fragment [3, 4]. We note that the immonium salt formed during the synthesis of 2-formylindole by the Vilsmeier reaction undergoes cyclization to a derivative of indolo[3,2-*b*]quinoline. Here it was shown specially that it is the immonium derivative that undergoes cyclization, whereas aldehyde is not transformed into a tetracycle under these conditions [2].

The oxa analog of indoxyl – 2,3-dihydrobenzofuran-3-one (**1**) – has been studied much less, and it seemed interesting to examine the possibility of similar heterocyclizations based on this compound.

The synthesis of the bicyclic ketone **1** was realized by the usual methods [5, 6]. Initially an attempt was made to obtain compound **1** from phenoxyacetic ester according to the following scheme [5]:



However, this method proved unsuitable for preparative purposes on account of the low yield at the Friedel–Crafts cyclization stage. The method [6], based on *o*-hydroxyacetophenone, was much more suitable:



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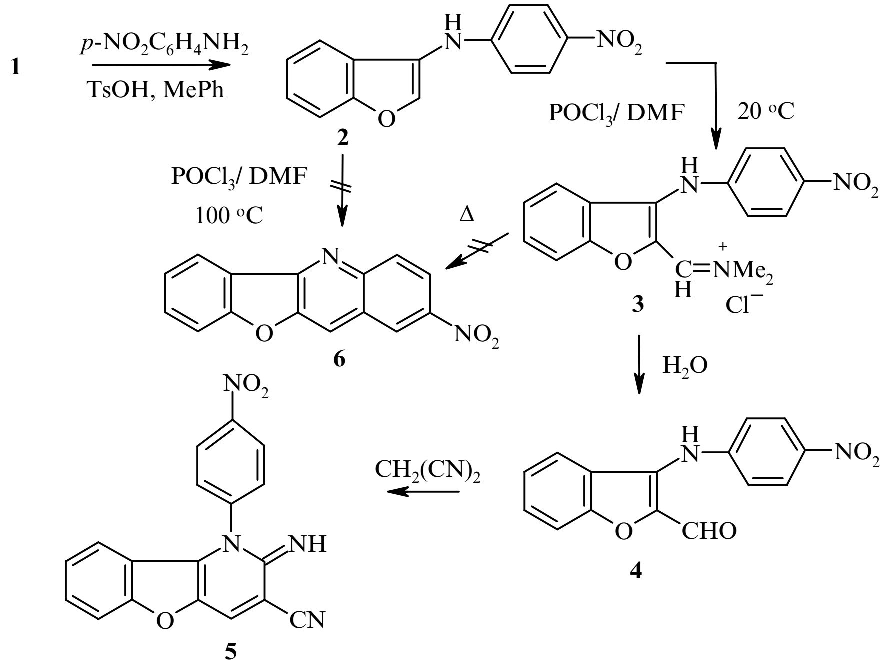
The reaction of benzofuranone **1** with *p*-nitroaniline in glacial acetic acid led to the desired 3-*p*-nitrophenylaminobenzofuran **2** extremely contaminated with the initial compounds and resinification products, and it was only possible to isolate the pure compound **2** during twofold purification by column chromatography on silica gel. Compound **2** was obtained here with a low yield. The reaction is much more successful when the components are heated in toluene in the presence of *p*-toluenesulfonic acid and the water formed in the process is distilled off. Under these conditions compound **2** was obtained with a yield of 80%. The presence of the "enamine-like" fragment in the derivative **2**, as in the corresponding indole analog, secures the possibility of electrophilic attack at position 2 of the furan ring, and the Vilsmeier reaction takes place under mild conditions. Here immonium salt **3** is isolated from the reaction mixture, and this is converted smoothly into the formyl derivative **4** when treated with water. In the reaction of this compound with malononitrile the condensation is accompanied by cyclization with the formation of 3-cyano-2-imino-1-*p*-nitrophenyl-1,2-dihydropyrido[3,2-*b*]benzofuran (**5**). In the ^{1}H NMR spectrum in DMSO-d$_6$ there are signals at 6.10 (1H, m, 9-H), 7.10 (1H, m), 7.51 (1H, m), and 7.70 (1H, m) for the protons of the condensed benzene ring, 6.92 (1H, strongly broadened signal, NH), 7.93 and 8.56 (4H, A_2B_2 system, 1',5'- and 2',4'-H), and 8.57 ppm (1H, s, 4-H). The signal of the proton at position 9 is shifted upfield on account of rotation of the nitrophenyl substituent, as was observed for the corresponding δ-carboline [3, 4]. Comparison of the ^{1}H NMR spectra of analogous compounds of the indole and benzofuran series shows that an appreciable upfield shift of all the proton signals is observed for the former. This is due to the lower electronegativity of the nitrogen atom of the indole ring compared with the oxygen atom of the benzofuran ring.

An attempt at the synthesis of benzofuro[3,2-*b*]quinoline **6** by analogy with the synthesis of indolo[3,2-*b*]-quinoline under the conditions of the Vilsmeier reaction, was unsuccessful even with prolonged heating of the reaction mass.



Such a difference between the structurally similar compounds is not easy to interpret. It must be considered, however, that indolo[3,2-*b*]quinolines are formed much more readily in the presence of an acetyl group at position 1 of 3-arylaminoindoles (**7** → **8**).

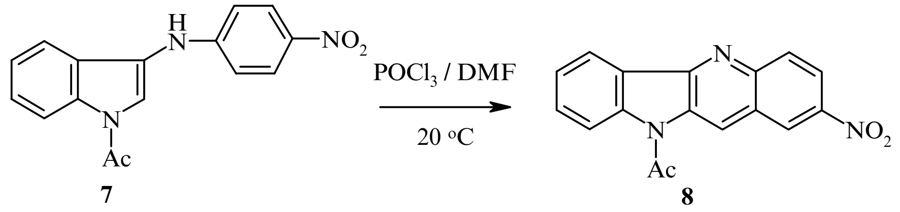


TABLE 1. Comparative Characteristics of the ^{1}H NMR Spectra of 3-*p*-Nitrophenylaminoindole and 3-*p*-Nitrophenylaminobenzofuran and their 2-Formyl Derivatives

Compound	2-H s	CHO s	NHAr s	NH-ind. br. s	$C_6H_4NO_2$ A_2B_2-system	Aromatic protons, m
9	7.42	—	8.93	11.14	8.01; 6.76	6.99; 7.13; 7.32; 7.41
2	8.25	—	9.21	—	8.10; 7.02	7.30; 7.38; 7.62
12*	—	9.88	9.41	11.85	8.08; 6.88	6.95-7.59
3	—	9.94	10.2	—	8.17; 8.13	7.35; 7.58; 7.63; 7.75

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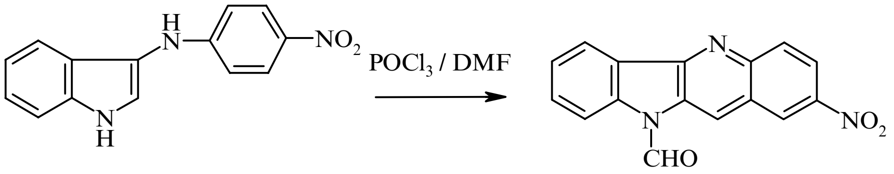
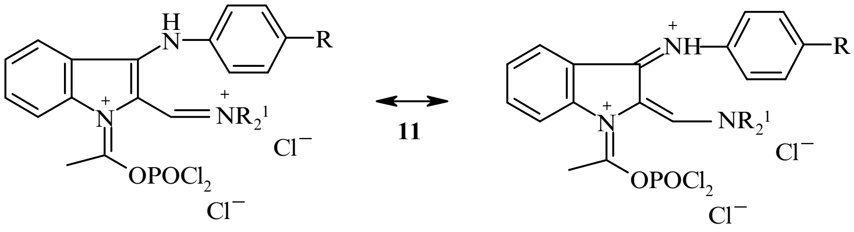
*2-Formyl-3-*p*-nitrophenylaminoindole.

The reaction with the N-unsubstituted 3-*p*-nitrophenylaminoindole (**9**) takes place with considerably greater difficulty. The 10-formyl derivative **10** was only isolated after heating with the Vilsmeier reagent.



9 **10**

Thus, it can be supposed that the first stage in the reaction of compound **9** with the Vilsmeier complex is 1-N-formylation and that only the 1-acyl derivatives undergo cyclization, while the isolation of the N-unsubstituted indoloquinoline is due to the easy elimination of the formyl substituent in the aqueous acidic solution. It can be supposed that the reacting particle for the N-acylindole derivatives is a dication of the **11** type, in which the immonium fragment is activated by an additional strong electron acceptor – it is this that gives rise to the readily occurring cyclization to indoloquinolines.



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Such a situation is of course impossible for the benzofuran derivative **3**, and this probably gives rise to its stability in cyclization.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 457 instrument in vaseline oil. The mass spectra were obtained on a Finnigan SSQ 700 spectrometer with direct injection of the sample into the ion source. The ^{1}H NMR spectra were recorded on a Varian Uniti 400 Plus instrument with TMS as internal standard and DMSO-d_6 as solvent. The reactions and the individuality of the substances were monitored by TLC on Silufol UV-254 plates in the methanol–toluene system (1:10).

3-*p*-Nitrophenylaminobenzofuran (2). A mixture of benzofuranone **1** (0.73 g, 5.6 mmol), *p*-nitroaniline (0.75 g, 5.6 mmol), and *p*-toluenesulfonic acid (10 mg) was boiled for 2 h in toluene (100 ml) with simultaneous distillation of azeotropes of toluene with water (50 ml). After cooling the reaction mass was filtered from *p*-toluenesulfonic acid, and toluene was distilled off under vacuum. The residue (15 ml) was cooled, the precipitate was filtered off, and 1.14 g (80%) of the pure compound **2** was obtained; mp 168-170°C. Found, %: C 66.13; H 3.91; N 11.12. $C_{14}H_{10}N_2O_3$. Calculated, %: C 66.13; H 3.96; N 11.02. Mass spectrum (M^+): 254. IR spectrum, cm^{-1}: 3320, 1590, 1500.

2-Formyl-3-*p*-nitrophenylaminobenzofuran (4). Phosphorus oxychloride (0.7 ml) and DMF (1.4 ml) were mixed at 5°C. After 10 min a solution of compound **2** (0.64 g, 2.5 mmol) in DMF (8 ml) was added, and the mixture was kept at 20°C for 15 h. The precipitated ammonium salt **3** was filtered off and washed with DMF (8 ml). The mixture was boiled for 1 h with water (20 ml), and the precipitate was filtered off, washed with water, and dried. Yield of 2-formylbenzofuran **4** 0.36 g (50%); mp 184-185°C. Found, %: C 63.80; H 3.40; N 9.70. $C_{15}H_{10}N_2O_4$. Calculated, %: C 63.83; H 3.57; N 9.93. Mass spectrum (M^+): 282. IR spectrum, cm^{-1}: 3290, 3240, 1635, 1580, 1555, 1495.

3-Cyano-2-imino-1-*p*-nitrophenyl-1,2-dihydropyrido[3,2-*b*]benzofuran (5). Triethylamine (1 ml) was added to a suspension of 2-formylbenzofuran **4** (1.54 g, 5.4 mmol) and malononitrile (0.36 g, 5.5 mmol) in isopropyl alcohol (25 ml). A red solution was formed at once, and a new precipitate separated. After 3 h the precipitate was filtered off and washed with methanol (20 ml). Yield of pyridobenzofuran **5** 0.7 g (40%); mp 281-283°C. Found, %: C 65.62; H 3.01; N 16.86. $C_{18}H_{10}N_4O_3$. Calculated, %: C 65.45; H 3.05; N 16.96. Mass spectrum (M^+-1): 329. IR spectrum, cm^{-1}: 3280, 3040, 2200, 1610, 1540, 1515.

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