# CONDENSATION OF SALICYLNITRILE WITH SOME α-HALO CARBONYL COMPOUNDS

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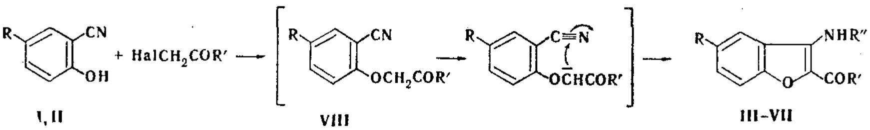
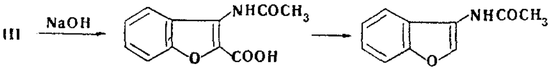
3-Aminobenzofuran derivatives were obtained by condensation of salicylnitrile and 5-bromosalicylnitrile with α-monochloroacetic acid derivatives and α-halo ketones.

In connection with the interest in the synthesis of heterocyclic analogs of anthranilic acid [1], we studied the condensation of salicylnitrile (I) and 5-bromosalicylnitrile (II) with the methyl ester and amide of α-monochloroacetic acid, chloroacetone, and bromoacetophenone. The reaction was carried out by heating the reagents in dimethylformamide (DMFA) or in dioxane–DMFA in the presence of anhydrous potassium carbonate; this procedure gave the previously inacessible 3-aminobenzofuran derivatives (III-VII). Two of them – III and VI – were obtained in the form of their acetyl derivatives.



I R=H; II R=Br; III R=H, R′=$OCH_3$, R″=$COCH_3$; IV R=Br, R′=$OCH_3$, R″=H;
V R=H, R′=$NH_2$, R″=H; VI R=H, R′=$C_6H_5$, R″=$COCH_3$; VII R=H, R′=$CH_3$, R″=H;
VIII R=H, R′=$NH_2$

In one case we were able to isolate intermediate VIII, which makes it possible to consider the process to be a reaction that proceeds through a step involving the formation of a carbanion with subsequent intramolecular cyclization. Intermediate VIII is cyclized to 3-aminobenzofuran derivative V in the presence of sodium alkoxide in absolute alcohol. Hydrolysis of III gave 3-acetamidobenzofuran-2-carboxylic acid (IX), which was converted to 3-acetamidobenzofuran (X) by refluxing in DMFA.



## EXPERIMENTAL

The IR spectra of KBr pellets of the compound were recorded with a UR-10 spectrometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane (HMDS) as the external standard.

Salicylnitrile (I). A 49.2-g (0.4 mole) sample of salicylaldehyde and 47.2 g (0.68 mole) of hydroxylamine hydrochloride were dissolved in 96 ml of dry pyridine. A total of 60 ml (0.6 mole) of acetic anhydride was then added in portions while maintaing the temperature at 80-90°, after which the reaction mixture was heated on a water bath for 5 h, cooled, and poured over ice. The resulting solution was weakly acidified with hydrochloric acid and extracted with ether. The extract was dried with magnesium sulfate,

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TABLE 1. 3-Aminobenzofuran Derivatives

| Compound | R | R′ | R″ | mp, °C | IR spectrum, $cm^{-1}$ |  | PMR spectrum, ppm | Empirical formula | Found, % |  |  | Calc., % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | C=O | N–H |  |  | C | H | N | C | H | N |  |
| III | H | $OCH_3$ | $COCH_3$ | 146—147,5 | 1620, 1680, 1715 | 3320 | 2,7, 3,83s†<br>7,0—7,7 m | $C_{12}H_{11}NO_4$ | 62,2 | 5,0 | 6,04 | 61,8 | 4,7 | 6,0 | 63 |
| IV | Br | $OCH_3$ | H | 149—150 | 1630, 1680 | 3360, 3470, | 4,0c, 7,1—7,8 m | $C_{10}H_8BrNO_3$ | 44,3 | 3,1 | — | 44,4 | 2,9 | — | 40 |
| V | H | $NH_2$ | H | 159* | 1630, 1660 | 3190, 3340, 3465 | — | $C_9H_8N_2O_2$ | 61,5 | 4,6 | — | 61,4 | 4,6 | — | 84 |
| VI | H | $C_6H_5$ | $COCH_3$ | 145 | 1600, 1620, 1690 | — | — | $C_{17}H_{13}NO_3$ | 73,2 | 4,9 | — | 73,1 | 4,7 | — | 20 |
| VII | H | $CH_3$ | H | 153—154 | 1635 | 3190, 3390, 3420 | 2,6c, 7—8 m | $C_{16}H_9NO_2$ | 68,5 | 7,3 | — | 68,6 | 7,5 | — | 42 |

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* From benzene–methanol.

† s is singlet and m is multiplet.

and the ether was removed by distillation to give 23 g (50%) of nitrile I with mp 94-95° (from benzene–hexane) (mp 95° [2]).

5-Bromosalicylnitrile (II). This compound was similarly obtained from 5-bromosalicylaldehyde. The yield of nitrile II with mp 158-159° (from benzene–hexane) (mp 158-159° [3]) was 78%.

3-Aminobenzofuran Derivatives (III, IV, VI, and VII). A mixture of 0.01 mole of nitriles I or II, 0.01 mole of anhydrous potassium carbonate, and 0.01 mole of $\alpha$-halo carbonyl compound in 30 ml of dry DMFA was refluxed for 45 min. The inorganic precipitate was removed by filtration, and the filtrate was vacuum evaporated. The residue was recrystallized from benzene–hexane. Acetyl derivatives III and VI were obtained by treatment of the reaction mixture with acetic anhydride at 20° for 3 h. Data on III, IV, VI, and VII are presented in Table 1.

2-Cyanophenoxyacetamide (VIII). A mixture of 11.9 g (0.1 mole) of nitrile I, 9.4 g (0.1 mole) of monochloroacetamide, and 14 g (0.1 mole) of anhydrous potassium carbonate was refluxed in 150 ml of absolute alcohol for 3 h. The inorganic precipitate was separated, and the solution was evaporated. The yield of VIII with mp 181-182° was 11 g (62%). Found, %: C 61.3; H 4.8. $C_9H_8N_2O_2$. Calculated, %: C 61.4; H 4.6. IR spectrum: 1705 (C=O), 2229 cm$^{-1}$ (C≡N).

3-Aminobenzofuran-2-carboxamide (V). A mixture of 5.7 g (0.037 mole) of amide VIII and 0.2 g of sodium ethoxide in 55 ml of absolute alcohol was refluxed for 1 h, after which the solvent was removed by distillation (Table 1).

3-Acetamidobenzofuran-2-carboxylic Acid (IX). A 2.4-g (0.01 mole) sample of III was added to a solution of 0.8 g (0.02 mole) of sodium hydroxide in 25 ml of 50% aqueous methanol, and the mixture was allowed to stand at 20° for 1.5 h. It was then diluted with water and acidified with hydrochloric acid. The precipitate was removed by filtration and washed with water to give 2 g (90%) of IX with mp 210°C (decomp., from aqueous alcohol). Found, %: C 60.1; H 4.3; N 6.4. $C_{11}H_9NO_4$. Calculated, %: C 60.0; H 4.1; N 6.4.

3-Acetamidobenzofuran (X). A solution of 1 g (0.004 mole) of IX in DMFA was refluxed for 3 h, after which the solvent was removed by distillation, and the residue was worked up to give 0.25 g (31%) of X with mp 175-175.5° (from benzene–heptane). Found, %:C 68.6; H 5.4; N 7.8. $C_{10}H_9NO_2$. Calculated, %: C 68.6; H 5.2; N 8.0.

## LITERATURE CITED

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