7. Ya. P. Stradyn', V. P. Kadysh, and S. A. Giller, Khim. Geterotsikl. Soedin., No. 12, 1587 (1973).
8. V. G. Mairanovskii and G. I. Samokhvalov, Elektrokhimiya, 2, No. 6, 717 (1966).
9. V. P. Ippolitova and G. A. Domrachev, Zh. Obshch. Khim., 39, 826 (1969).
10. P. A. Ten Thije and M. J. Janssen, Rec. Trav. Chim., 84, 1169 (1965).
11. I. N. Zatsepina, Yu. L. Kaminskii, and I. F. Tupitsyn, Reakts. Sposobn. Org. Soedin., No. 6, 778 (1969).
12. The Chemist's Handbook [in Russian], Vol. 4, Khimiya, Moscow–Leningrad (1964), p. 998.
13. Ya. P. Stradyn', V. P. Kadysh, and S. A. Giller, Khim. Geterotsikl. Soedin., No. 2, 157 (1974).

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# SYNTHESIS OF 2,3-DIFORMYL-5-ETHYLBENZOFURAN AND ITS DERIVATIVES

A. Prewysz-Kwinto

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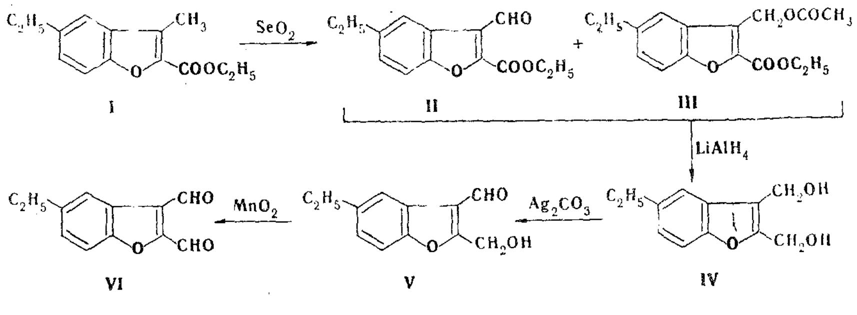
A mixture of 3-formyl and 3-acetoxymethyl derivatives is formed in the oxidation of 2-carbethoxy-3-methyl-5-ethylbenzofuran with selenium dioxide. Reduction of the products with lithium aluminum hydride gives the corresponding 2,3-dihydroxymethyl derivatives, which are converted to 2,3-diformyl derivatives by successive oxidation by the Fetizon method and with manganese dioxide. The corresponding benzofuro[2,3-d]pyridazines were synthesized by reaction of 2-carbethoxy-3-formyl-5-ethylbenzofuran with hydrazine hydrate.

The biological activity of many benzofuran derivatives has been the subject of intensive investigation [1-3]. In a continuation of previous research on benzofuran derivatives [4, 5], the present study is devoted to the synthesis of previously undescribed diformyl derivatives of 2-carbethoxybenzofuran.

The starting 2-carbethoxy-3-methyl-5-ethylbenzofuran (I) was obtained from p-ethylphenol by the Boheme method [6]. Oxidation of this compound with selenium dioxide in glacial acetic acid led to 2-carbethoxy-3-formyl-5-ethylbenzofuran (II) and 2-carbethoxy-3-acetoxymethyl-5-ethylbenzofuran (III). 2,3-Dihydroxymethyl-5-ethylbenzofuran (IV) was obtained by the action of lithium aluminum hydride on II and III. We then carried out the direct oxidation of IV by means of $SeO_2$, $MnO_2$, and $CrO_3$ in order to obtain 2,3-diformyl-5-ethylbenzofuran. However, numerous attempts did not give positive results. Only the unchanged starting compound and a small amount of resinous substances were obtained each time. The reaction was then carried out in two steps. Compound IV was initially subjected to oxidation with $Ag_2CO_3$ by the method of Fetizon and Goldfier [7], and the resulting 2-hydroxymethyl-3-formyl-5-ethylbenzofuran (V) was oxidized with active $MnO_2$ to give 2,3-diformyl-5-ethylbenzofuran (VI). The results of analysis of the compounds thus obtained by PMR spectroscopy confirmed the indicated course of the reaction.



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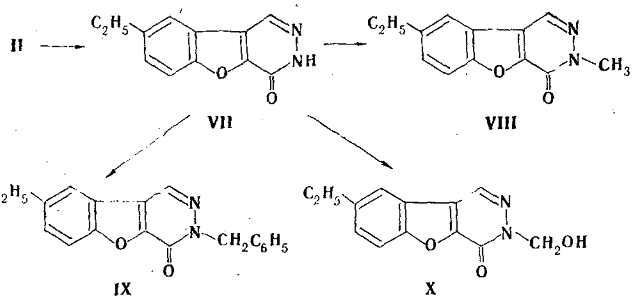
Institute of Chemistry, N. Copernicus University, Torun 87-100, Poland. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 893-895, July, 1982. Original article submitted December 14, 1981.

The 2-carbethoxy-3-formyl-5-ethylbenzofuran (II) was subjected to reaction with hydrazine hydrate, and 3,4-dihydro-8-ethyl-4-oxobenzofuro[2,3-d]pyridazine (VII) was obtained. This compound undergoes electrophilic substitution with reagents such as dimethyl sulfate and benzyl chloride to give the corresponding derivatives VIII and IX, which have a lactam structure, as confirmed by the IR and PMR spectra. The addition of formaldehyde gives the corresponding 3,4-dihydro-3-hydroxymethyl-8-ethyl-4-oxabenzofuro[2,3-d]pyridazine (X).



## EXPERIMENTAL

The PMR spectra were recorded with a Tesla B-487C spectrometer (80 Hz); the chemical shifts are given on the δ scale with hexamethyldisiloxane as the internal standard. The IR spectra were recorded with a UR-10 spectrometer.

2-Carbethoxy-3-formyl-5-ethylbenzofuran (II) and 2-Carbethoxy-3-acetoxymethyl-5-ethylbenzofuran (III). A solution of 23.2 g (0.1 mole) of I in 250 ml of glacial acetic acid was refluxed with stirring with 13.1 g (0.1 mole) of selenium dioxide for 72 h, after which the precipitated selenium was removed by filtration, and the solvent was evaporated in vacuo. The II was separated by conversion to an adduct with bisulfite. Decomposition of the bisulfite adduct gave 4 g (16.2%) of II with mp 60°C. PMR spectrum ($CDCl_3$): 10.60 (1H, s, CHO), 7.10-7.80 (3H, m, aromatic), 4.35 (2H, q, $OCH_2$), 2.60 (2H, q, $CH_2$), 1.40 (3H, t, $CH_3$), and 1.15 ppm (3H, t, $CH_3$). Found: C 68.3; H 5.7%. $C_{14}H_{14}O_4$. Calculated: C 68.2; H 5.6%. The semicarbazone had mp 170-171°C.

The residue was distilled in vacuo to give 16.7 g (57.3%) of III with mp 49-50°C. PMR spectrum ($CDCl_3$): 7.10-7.40 (3H, m, aromatic), 5.60 (2H, s, $CH_2O$), 4.30 (2H, q, $CH_2$), 2.60 (2H, q, $CH_2$), 1.90 (3H, s, $CH_3$), 1.35 (3H, t, $CH_3$), and 1.10 ppm (3H, t, $CH_3$). Found: C 66.2; H 6.2%. $C_{16}H_{18}O_5$. Calculated: C 66.3; H 6.1%.

2,3-Dihydroxymethyl-5-ethylbenzofuran (IV). A solution of 3.1 g (13 mmole) of II in 50 ml of ether was added to a solution of 1 g (26 mmole) of lithium aluminum hydride in 150 ml of dry ether, and the mixture was stirred for 4 h. The excess $LiAlH_4$ was decomposed with water, and the reaction product was extracted with ether. The ether was removed by distillation, and the precipitate was crystallized from chloroform to give 2.1 g (83%) of a product with mp 113-114°C. PMR spectrum ($d_6$-acetone): 7.10-7.50 (3H, m, aromatic), 4.75 (2H, s, $CH_2$), 4.60 (2H, s, $CH_2$), 2.60 (2H, q, $CH_2$), and 1.20 ppm (3H, t, $CH_3$). Found: C 69.6; H 6.7%. $C_{12}H_{14}O_3$. Calculated: C 69.8; H 6.8%. The same product was obtained by reduction of III. The diphenylurethane had mp 227-228°C.

2-Hydroxymethyl-3-formyl-5-ethylbenzofuran (V). A mixture of 1.5 g (7 mmole) of IV, 150 ml of ethyl acetate, and 23 g of $Ag_2CO_3$ [7] was refluxed with stirring for 24 h, after which the precipitate was removed by filtration, and the filtrate was evaporated in vacuo. The precipitated product was crystallized from chloroform to give 1.3 g (89%) of a product with mp 108-109°C. PMR spectrum ($CDCl_3$): 10.25 (1H, s, CHO), 7.10-7.40 (3H, m, aromatic), 4.80 (2H, s, $CH_2$), 2.60 (2H, q, $CH_2$), and 1.20 ppm (3H, t, $CH_3$). Found: C 70.5; H 5.8%. $C_{12}H_{12}O_3$. Calculated: C 70.4; H 5.9%. The semicarbazone had mp 231-232°C, and the α-naphthylurethane had mp 273°C.

2,3-Diformyl-5-ethylbenzofuran (VI). A mixture of 1.1 g (5 mmole), 40 ml of chloroform, and 4 g (46 mmole) of $MnO_2$ was stirred at 20°C for 4 h, after which the precipitate was removed by filtration, and the filtrate was concentrated. The precipitated product was crystallized from $CCl_4$–$CHCl_3$ (1:5) to give 0.5 g (46%) of a product with mp 82-83°C. PMR spectrum ($CDCl_3$): 10.55 (1H, s, CHO), 10.45 (1H, s, CHO), 7.20-7.80 (3H, m, aromatic), 2.50 (2H, q, $CH_2$), and 1.20 ppm (3H, t, $CH_3$). Found: C 71.4; H 5.0%. $C_{12}H_{10}O_3$. Calculated: C 71.3; H 4.9%.

3,4-Dihydro-8-ethyl-4-oxobenzofuro[2,3-d]pyridazine (VII). A solution of 1 g (4 mmole) of II, and 3.8 g (76 mmole) of hydrazine hydrate in 50 ml of absolute ethanol was refluxed with stirring for 1 h, after which the solvent was evaporated, and 10 ml of 10% NaOH was added to the product. The solution was filtered and neutralized with concentrated HCl, and the precipitate was removed by filtration, washed with water, and crystallized from ethanol to give 0.55 g (63.2%) of a product with mp 224-225°C. PMR spectrum (DMSO): 13.40 (1H, s, NH), 7.60-8.80 (4H, m, aromatic), 2.70 (2H, q, $CH_2$), and 1.30 ppm (3H, t, $CH_3$). IR spectrum (KBr) 3160 (NH) and 1665 $cm^{-1}$ (CO). Found: C 67.3; H 4.7; N 13.1%. $C_{12}H_{10}N_2O_2$. Calculated: C 67.2; H 4.6; N 13.2%.

3,4-Dihydro-3-methyl-8-ethyl-4-oxobenzofuro[2,3-d]pyridazine (VIII). A mixture of 0.22 g (1 mmole) of VII, 0.2 g (3 mmole) of sodium ethoxide, and 80 ml of absolute ethanol was refluxed for 1 h, after which 0.7 g (5 mmole) of dimethyl sulfate was added, and the mixture was refluxed for 6 h. The solution was concentrated, and the reaction product was crystallized from acetone to give 0.14 g (60%) of a product with mp 134-135°C. PMR spectrum ($d_6$-acetone): 7.60-8.75 (4H, m, aromatic), 2.90 (3H, s, $CH_3$), 2.60 (2H, q, $CH_2$), and 1.30 ppm (3H, t, $CH_3$). Found: C 69.0; H 5.3; N 12.4%. $C_{13}H_{12}N_2O_2$. Calculated: C 68.9; H 5.3; N 12.3%.

3-Benzyl-3,4-dihydro-8-ethyl-4-oxobenzofuro[2,3-d]pyridazine (IX). The reaction was carried out as in the case of VIII starting from 0.22 g (1 mmole) of pyridazine VII, 0.2 g (3 mmole) of sodium ethoxide, and 0.7 g (5 mmole) of benzyl chloride. The reaction product was crystallized from acetone to give 0.18 g (59%) of a product with mp 158-159°C. Found: C 75.0; H 5.3; N 9.2%. $C_{19}H_{16}N_2O_2$. Calculated: C 75.1; H 5.2; N 9.2%.

3,4-Dihydro-3-hydroxymethyl-8-ethyl-4-oxobenzofuro[2,3-d]pyridazine (X). A solution of 0.5 g (2 mmole) of VII, 30 ml of ethanol, and 10 ml of a 10% solution of formaldehyde was heated for 1 h, after which it was concentrated, and the reaction product was crystallized from acetone to give 0.2 g (40%) of a product with mp 151-152°C. PMR spectrum ($CDCl_3$): 7.30-8.50 (4H, m, aromatic), 5.65 (2H, s, $CH_2$), 2.70 (2H, q, $CH_2$), and 1.30 ppm (3H, t, $CH_3$). Found: C 63.9; H 4.9; N 11.5%. $C_{13}H_{12}N_2O_3$. Calculated: C 63.8; H 4.9; N 11.4%.

## LITERATURE CITED

1. P. Nore and E. Hankanen, J. Heterocycl. Chem., 17, 985 (1980).
2. M. Rooba, M. Cugnon de Sevricourt, and A. Godard, J. Heterocycl. Chem., 15, 1387 (1978).
3. A. N. Grinev, S. A. Zotova, A. A. Smolyarchuk, V. P. Gaevoi, and V. V. Matsak, Khim.-farm. Zh., No. 1, 51 (1979).
4. A. Prewysz-Kwinto, J. Prakt. Chem., 322, 487 (1980).
5. A. Prewysz-Kwinto and I. G. Tishchenko, Dokl. Akad. Nauk SSSR, 24, 442 (1980).
6. W. R. Boheme, Organic Synthesis, Vol. 33 (1953), p. 43.
7. N. Fetizon and M. Goldfier, Compt. Rend., C267, 900 (1973).