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SYNTHESIS OF 2-CARBETHOXYBENZOFURAN DERIVATIVES

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A mixture of 3-formyl and 3-acetoxymethyl derivatives is formed in the oxidation of 2-carbethoxy-3-methyl-7-ethylbenzofuran with selenium dioxide. Reduction with lithium aluminum hydride gives 2,3-dihydroxymethyl derivatives, which are converted to 2,3-diformyl derivatives by successive oxidation. A number of derivatives of 3-methyl-7-ethylbenzofurancarboxylic acid were obtained.

Continuing our investigation of benzofuran derivatives [1-3], we studied the synthesis of previously undescribed 2-carbethoxybenzofuran derivatives. The starting 2-carbethoxy-3-methyl-7-ethylbenzofuran was obtained from o-ethylphenol by the Boheme method [4]. Its oxidation with selenium dioxide in glacial acetic acid led to 2-carbethoxy-3-formyl- and 2-carbethoxy-3-acetoxymethyl-7-ethylbenzofuran (II, III). 2,3-Dihydroxymethyl-7-ethylbenzofuran (IV) was obtained by the action of lithium aluminum hydride on II and III. Compound IV was oxidize by means of Ag_2CO_3 [5] to 2-hydroxymethyl-3-formyl-7-ethylbenzofuran (V), oxidation of which with pyridine chlorochromate led to 2,3-diformyl-7-ethylbenzofuran (VI). The reaction of dialdehyde VI with hydrazine hydrate leads to 6-ethylbenzofuro[2,3-d]pyridazine (VII). Similarly obtained from II was 3,4-dihydro-6-ethyl-4-oxobenzofuro[2,3-d]pyridazine (VIII), the reaction of which with benzyl chloride gives the corresponding N-benzyl derivative IX, while the addition to it of formaldehyde leads to 3,4-dihydro-3-hydroxymethyl-6-ethyl-4-oxabenzofuro[2,3-d]pyridazine (X). The hydrolysis of III gave 2-carbethoxy-3-hydroxymethyl-7-ethylbenzofuran (XI), which was converted to 2-carbethoxy-3-chloromethyl-7-ethylbenzofuran (XII) (see Scheme I below).

In addition, hydrolysis of starting ester I by the usual method [6] gave 3-methyl-7-ethyl benzofuran-2-carboxylic acid (XIII), which was converted to acid chloride XIV. The reaction of XIV with morpholine and phenothiazine leads to derivatives XVa,b. 2-(2-Benzothiazolyl)-7-ethylbenzofuran XVI was obtained in the reaction of acid chloride XIV with o-aminothiophenol, while N-(2-nitrophenyl)-3-methyl-7-ethylbenzofuran-2-carboxamide (XVII) was obtained in the reaction with o-nitroaniline. Reduction of the nitro group of XVII by means of $SnCl_2$ led to N-(2-aminophenyl)-3-methyl-7-ethyl-benzofuran-2-carboxamide (XVIII), cyclization of which under the influence of 4 H HCl gave 2-(2-benzimidazolyl)-7-ethylbenzofuran XIX (see Scheme II)

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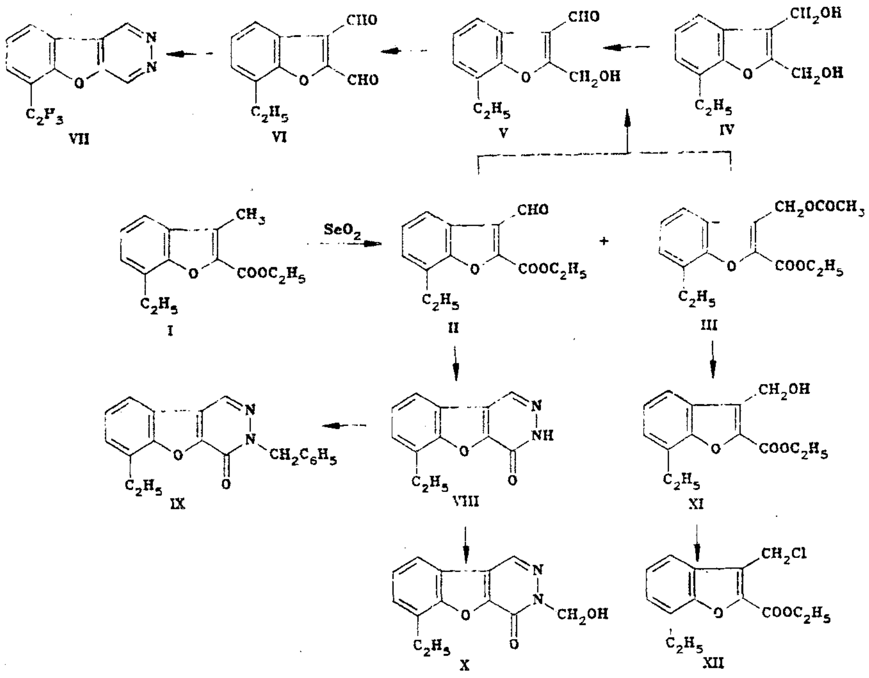
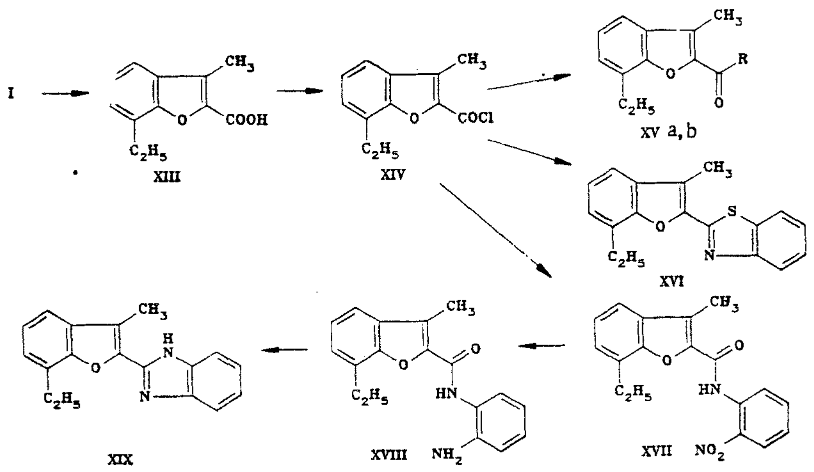


Scheme I



XV a R= morpholinyl ; b R= phenothiazinyl

Scheme II

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla B-487 spectrometer (80 Hz) with hexamethyldisiloxane (HMDS) as the internal standard. The IR spectra of KBr pellets of the compounds were obtained with a UR-10 spectrometer.

2-Carbethoxy-3-formyl-7-ethylbenzofuran (II) and 2-Carbethoxy-3-acetoxymethyl-7-ethylbenzofuran (III). A solution of 23.2 g (0.1 mole) of I in 300 ml of glacial acetic acid and 13.1 g (0.1 mole) of selenium dioxide were refluxed with stirring for 75 h, after which the precipitated selenium was removed by filtration, and the solvent was evaporated in vacuo. The resulting II was separated by converting it to an adduct with bisulfite. For this, 50 ml of methanol and a solution of 35 g (0.3 mole) of $NaHSO_3$ in 10 ml of water were added to the reaction product, and the adduct was dried at 20°C. The dry adduct was washed with ether (five 50-ml portions) to separate III, after which it was decomposed with saturated Na_2CO_3 solution, and the mixture was extracted with ether (four 75-ml portions). The ether was evaporated, and the reaction product was crystallized from alcohol to give 5 g (20.2%) of II with mp 58-59°C. PMR spectrum: 10.70 (1H, s, CHO), 7.30-7.90 (3H, m, aromatic), 4.30 (2H, q,

OCH_2), 2.80 (2H, q, CH_2), 1.30 (3H, t, CH_3), and 1.15 ppm (3H, t, CH_3). Found, %: C 68.2, H 5.6. $C_{14}H_{14}O_4$. Calculated, %: C 68.3, H 5.7. The semicarbazide had mp 210-211°C. Compound III was distilled in vacuo [bp 152°C (3 mm)] and crystallized from alcohol to give 16.9 (58%) of a product with mp 47-48°C. PMR spectrum (d_6-acetone): 7.30-7.90 (3H, m, aromatic), 5.45 (2H, s, CH_2), 4.30 (2H, q, CH_2), 2.85 (2H, q, CH_2), 1.95 (3H, t, CH_3), 1.35 (3H, t, CH_3), and 1.15 ppm (3H, t, CH_3). Found, %: C 66.3, H 6.3. $C_{16}H_{18}O_5$. Calculated, %: C 66.2, H 6.

2,3-Dihydroxymethyl-7-ethylbenzofuran (IV). A solution of 9.6 g (34 mmole) of III in 100 ml of ether was added to a solution of 3.1 g (34 mmole) of lithium aluminum hydride in 200 ml of ether, after which the mixture was stirred for 4 h. The excess $LiAlH_4$ was decompose with 10 ml of water, and the reaction product was extracted with ether (four 50-ml portions). The ether was removed by distillation, and the residue was crystallized from chloroform to give 6.7 g (86%) of a product with mp 114-115°C. PMR spectrum (d_6-acetone): 7.10-7.70 (3H, m, aromatic), 4.80 (2H, s, CH_2), 4.74 (2H, s, CH_2), 2.80 (2H, q, CH_2), and 1.35 ppm (3H, t, CH_3). Found, %: C 69.8, H 6.8. $C_{12}H_{14}O_3$. Calculated, %: C 69.9, H 6.7. Di-α-naphtylurethane, mp 123-124°C.

2-Hydroxymethyl-3-formyl-7-ethylbenzofuran (V). A mixture of 1.5 g (7 mmole) of IV, 150 ml of ethyl acetate, and 23 g of Ag_2CO_3 [5] was refluxed with stirring for 24 h, after which the precipitate was removed by filtration, and the solvent was evaporated in vacuo. The residue was crystallized from chloroform to give 1.2 g (82%) of a product with mp 72-73°C. PMR spectrum: 7.10-7.60 (3H, m, aromatic), 4.85 (2H, s, CH_2), 2.80 (2H, q, CH_2), and 1.30 (3H, t, CH_3). Found, %: C 70.6, H 5.9. $C_{12}H_{12}O_3$. Calculated, %: C 70.5, H 5.8. The semicarbazide had mp 227-228°C.

2,3-Diformyl-7-ethylbenzofuran (VI). A mixture of 1 g (5 mmole) of V and 2.9 g (7 mmole) of pyridine dichromate in 10 ml of dichloroethane was stirred at 20°C for 24 h, after which it was filtered, and the filtrate was evaporated. The residue was crystallized from chloroform to give 0.4 g (47%) of a product with mp 90-92°C. PMR spectrum: 10.60 (1H, s, CHO), 10.50 (1H, s, CHO), 7.15-7.70 (3H, m, aromatic), 2.45 (2H, q, CH_2), and 1.35 ppm (3H, t, CH_3). Found, %: C 71.3, H 4.9. $C_{12}H_{10}O_3$. Calculated, %: C 71.4, H 5.0.

6-Ethylbenzofuro[2,3-d]pyridazine (VII). A mixture of 0.18 g (1 mmole) of VI and 0.05 g (1 mmole) of hydrazine hydrate in 10 ml of methanol was refluxed for 1 h, after which the solvent was evaporated, and the residue was crystallized from propanol to give 0.16 g (82%) of a product with mp 132-134°C. Found, %: C 73.5, H 4.0, N 14.4. $C_{12}H_{18}N_2O$. Calculated, %: C 73.4, H 4.1, N 14.3.

3,4-Dihydro-6-ethyl-4-oxobenzofuro[2,3-d]pyridazine (VIII). A solution of 1.5 g (6 mmole of II and 5.7 g (69 mmole) of hydrazine hydrate in 100 ml of absolute ethanol was refluxed with stirring for 2 h, after which the solvent was evaporated, and 15 ml of 10% NaOH solution was added to the residue. The solution was filtered and neutralized to pH 7 with concentrated HCl. The resulting precipitate was removed by filtration, washed with water (three 10-ml portions), and crystallized from ethanol to give 1 g (76.8%) of a product with mp 237-239°C. PMR spectrum (DMSO): 11.5 (1H, s, NH), 7.50-8.80 (4H, m, aromatic), 2.90 (2H, q, CH_2), and 1.30 ppm (3H, t, CH_3). Found, %: C 67.2, H 4.6, N 13.2. $C_{12}H_{10}N_2O_2$. Calculated, %: C 67.3, H 4.7, N 13.1.

3-Benzyl-3,4-dihydro-6-ethyl-4-oxobenzofuro[2,3-d]-pyridazine (IX). A mixture of 0.3 g (1 mmole) of VIII and 0.32 g (4 mmole) of sodium ethoxide in 100 ml of absolute ethanol was refluxed for 1 h, after which 0.9 g (7 mmole) of benzyl chloride was added, and the mixture was refluxed for another 5 h. The solution was concentrated to a volume of 3 ml, and the resulting precipitate was separated and crystallized from acetone to give 0.27 g (64.9%) of a product with mp 260-262°C. Found, %: C 75.1, H 5.3, N 9.3. $C_{19}H_{16}N_2O_2$. Calculated, %: C 75.0, H 5.3 N 9.2.

3,4-Dihydro-3-hydroxymethyl-6-ethyl-4-oxobenzofuro[2,3-d]pyridazine (X). A solution of 0.5 g (2 mmole) of VIII in 30 ml of ethanol and 15 ml of 15% formaldehyde solution were refluxed for 2 h, after which the mixture was concentrated to a volume of 2 ml, and the precipitate was separated and crystallized from acetone to give 0.25 g (50%) of a product with mp 161-162°C. PMR spectrum: 7.40-8.50 (4H, m, aromatic), 5.60 (2H, s, CH_2), 2.85 (2H, q, CH_2), and 1.35 ppm (3H, t, CH_3). Found, %: C 64.0, H 4.8, N 11.4. $C_{13}H_{12}N_2O_3$. Calculated, %: C 63.9, H 4.9, N 11.5.

2-Carbethoxy-3-hydroxymethyl-7-ethylbenzofuran (XI). A solution of 5.5 g (20 mmole) of III in 100 ml of absolute ethanol and 2 ml of concentrated H_2SO_4 were allowed to stand at

20°C for 24 h, after which the solution was concentrated to a volume of 10 ml, and the resulting precipitate was extracted with ether (five 25-ml portions). The ether was removed by distillation, and the product was crystallized from chloroform to give 4.5 g (92%) of a substance with mp 117-118°C. PMR spectrum (d_6-acetone): 7.20-7.90 (3H, m, aromatic), 4.80 (2H, s, CH_2), 4.50 (2H, q, CH_2), 2.90 (2H, q, CH_2), and 1.35 ppm (3H, t, CH_3). Found, %: C 67.8, H 6.3. $C_{14}H_{16}O_4$. Calculated, %: C 67.8, H 6.4.

2-Carbethoxy-3-chloromethyl-7-ethylbenzofuran (XII). A mixture of 2.5 g (10 mmole) of XI, 150 ml of ether, and 4 ml of thionyl chloride was allowed to stand at 20°C for 24 h, after which the solution was concentrated to a volume of 5 ml, and the resulting precipitate was separated and crystallized from chloroform to give 2.1 g (80%) of a product with mp 61-62°C. PMR spectrum: 7.20-7.80 (3H, m, aromatic), 4.85 (2H, s, CH_2), 4.50 (2H, q, CH_2), 2.85 (2H, q, CH_2), and 1.30 ppm (3H, t, CH_3). Found, %: C 62.6, H 5.7, Cl 13.6. $C_{14}H_{15}ClO_3$. Calculated, %: C 62.5, H 5.7, Cl 13.5.

2-(N-Morpholinylcarbonyl)-3-methyl-7-ethylbenzofuran (XVa) and 2-(N-Phenothiazinylcarbonyl)-3-methyl-7-ethylbenzofuran (XVb). A mixture of 2.2 g (10 mmole) of XIV, 0.9 g (10 mmole) of morpholine, and 1 g of triethylamine in 30 ml of benzene was refluxed for 2 h, after which the solvent was evaporated, and 50 ml of water was added to the residue. The resulting precipitate was separated and crystallized from chloroform to give 2.1 g (77%) of a product with mp 41-42°C. PMR spectrum: 7.10-7.80 (3H, m, aromatic), 3.75 (8H, s, morpholine), 2,80 (2H, q, CH_2), 2.40 (3H, s, CH_3), and 1.40 ppm (3H, t, CH_3). Found, %: C 70.4, H 7.0, N 5.2. $C_{16}H_{19}NO_3$. Calculated, %: C 70.3, H 6.9, N 5.1.

Compound XVb [2.3 g (60%)], with mp 153-154°C, was similarly obtained.

2-(2-Benzothiazolyl)-3-methyl-7-ethylbenzofuran (XVI). A mixture of 2.2 g (10 mmole) of acid chloride XIV and 1.3 g (10 mmole) of o-aminothiophenol in 50 ml of anhydrous dimethylformamide was refluxed, after which 50 ml of water was added to the reaction product, and the mixture was filtered. The precipitate was washed with ether (three 25-ml portions) and crystallized from methanol to give 2.4 g (82%) of a product with mp 130-132°C. PMR spectrum: 7.60-8.20 (3H, m, aromatic), 7.25-7.50 (4H, m, aromatic), 2.85 (2H, q, CH_2), 2.60 (3H, s, CH_3) and 1.35 ppm (3H, t, CH_3). Found, %: N 4.9. $C_{17}H_{15}NOS$. Calculated, %: N 5.0.

N-(2-Nitrophenyl)-3-methyl-7-ethylbenzofuran-2-carboxamide (XVII). A mixture of 4.4 g (20 mmole) of acid chloride XIV and 2.8 g (20 mmole) of o-nitroaniline in 70 ml of dimethylforamide was refluxed for 8 h, after which it was poured into 50 ml of water, and the precipitate was removed by filtration and crystallized from methanol to give 5.6 g (86%) of a product with mp 151-152°C. IR spectrum: 3310 (NH), 1690 cm^{-1} (CONH). PMR spectrum: 11.75 (1H, s, NH), 7.30-8.60 (7H, m, aromatic), 2.85 (2H, q, CH_2), 2.60 (3H, s, CH_3), and 1.40 ppm (3H, t, CH_3). Found, %: 66.7, H 5.0, N 8.5. $C_{18}H_{16}N_2O_4$. Calculated, %: C 66.6, H 4.9, N 8.6.

N-(2-Aminophenyl)-3-methyl-7-ethylbenzofuran-2-carboxamide (XVIII). A 3.2 g (10 mmole) sample of XVII was heated in 40 ml of methanol to 60°C, after which 8 g (45 mmole) of $SnCl_2$ and 5 ml of concentrated HCl were added in the course of 15 min, and the mixture was refluxed for 1 h. It was then poured into 50 ml of water, and the aqueous mixture was neutralized to pH 12 with 5% NaOH solution. The resulting precipitate was removed by filtration. The solution was extracted with chloroform (five 30-ml portions), the solvent was evaporated, and the residue was crystallized from alcohol to give 1.8 g (61%) of a product with mp 116-117°C. IR spectrum: 3360 (NH_2), 3280 (NH), and 1675 cm^{-1} (CONH). Found, %: C 73.5, H 6.2, N 9.6. $C_{18}H_{18}N_2O_2$. Calculated, %: C 73.4, H 6.1, N 9.5.

2-(2-Benzimidazolyl)-3-methyl-7-ethylbenzofuran (XIX). A solution of 1.5 g (5 mmole) of XVIII in 40 ml of 4 N HCl was refluxed for 8 h, after which it was cooled and neutralized to pH 7 with concentrated ammonium hydroxide. The precipitate was removed by filtration and crystallized from chloroform to give 1.1 g (80%) of a product with mp 179-180°C. PMR spectrum 7.20-7.85 (7H, m, aromatic), 2.80 (2H, q, CH_2), 2.60 (3H, s, CH_3), and 1.40 ppm (3H, t, CH_3). Found, %: C 78.3, H 5.8, N 10.2. $C_{18}H_{16}N_2O$. Calculated, %: C 78.2, H 5.8, N 10.1.

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