Aldol condensation of 2-methylbenzothiazole and 2-cyanomethylbenzothiazole with dicarboxylic acids anhydrides

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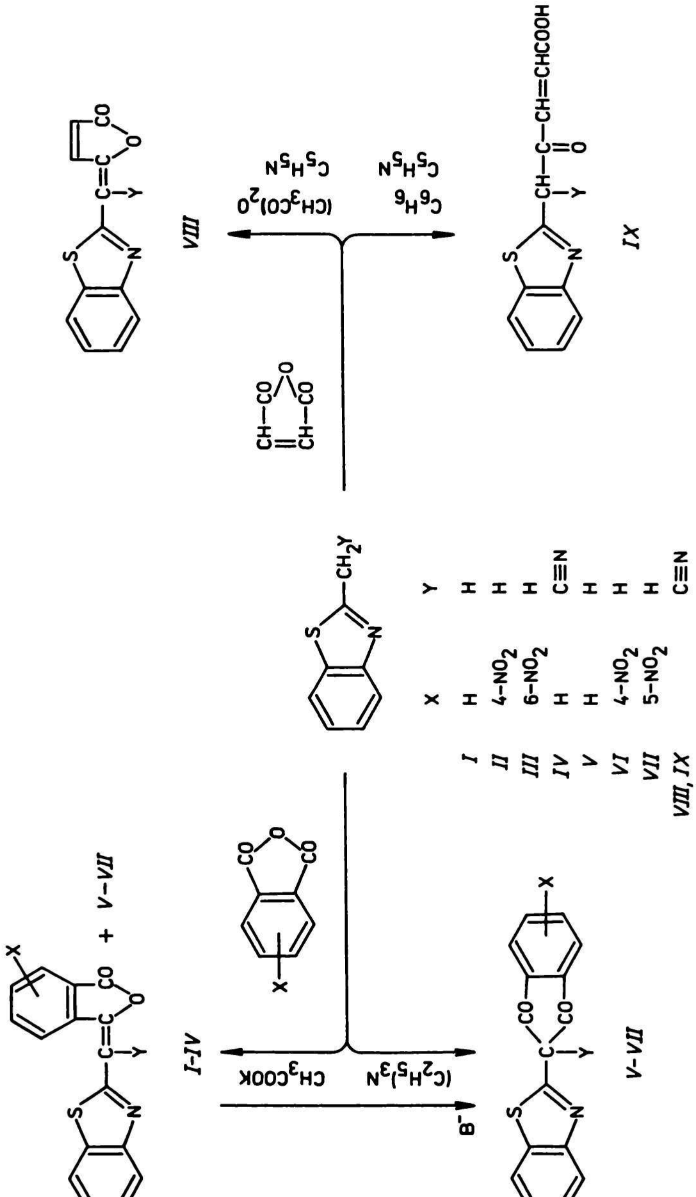
By the Perkin synthesis of 2-methyl- and 2-cyanomethylbenzothiazole with phthalic anhydride or its 3- or 4-nitro derivatives the corresponding phthalides or 1,3-indandiones were prepared. 2-Cyanomethylbenzothiazole reacts with maleic anhydride in acetic anhydride to yield 4-[2-benzothiazolyl(cyano)methylene]-4-butenolide; in benzene these reactants afforded 5-(2-benzothiazolyl)-5-cyano-4-oxo-2-pentenoic acid. Treatment of the phthalides with hydrazine or phenylhydrazine led to 1-oxo-2-R-4-(2-benzothiazolylmethyl)-1,2-dihydrophthalazines.

Путем синтеза Перкина, исходя из 2-метил- и 2-цианометилбензотиазола и фталевого ангидрида или его 3- или 4-нитропроизводных, были получены соответствующие фталиды или 1,3-индандионы. 2-Цианометилбензотиазол взаимодействует с малеиновым ангидридом в уксусном ангидриде с образованием 4-[2-бензотиазолил(циано)метилен]-4-бутенолида; в бензоле из этих реагентов образовалась 5-(2-бензотиазолил)-5-циано-4-оксо-2-пентеновая кислота. Воздействие на фталиды гидразином или фенилгидразином вело к образованию 1-оксо-2-R-4-(2-бензотиазолилметил)-1,2-дигидрофталазинов.

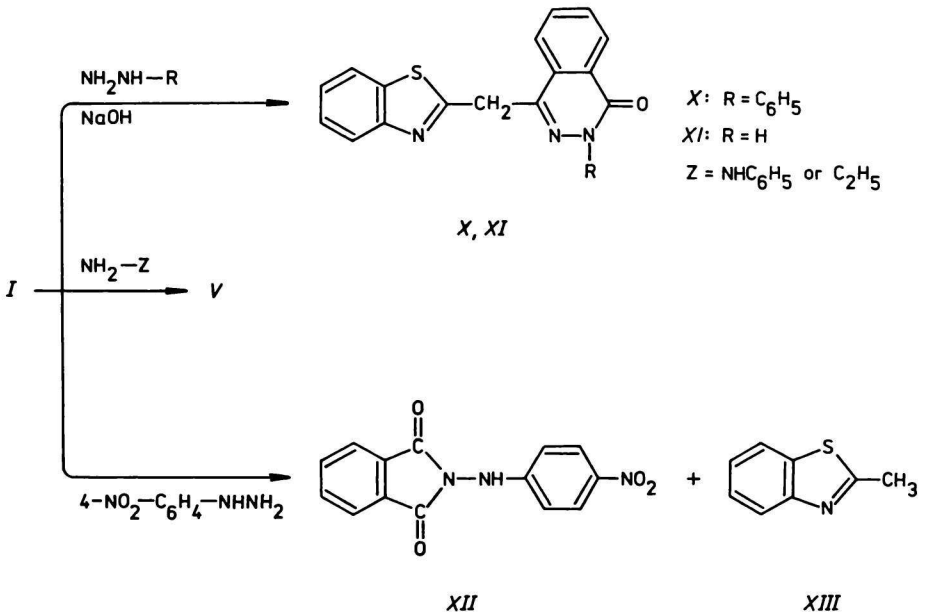
The methyl group of 2-methylbenzothiazole can react as a *C*-acid and affords with aldehydes under catalysis of NaOH or $LiNH_2$ products of either aldol reaction [1] or aldol condensation [2, 3] depending on temperature applied. Similarly, the methylene group of 2-cyanomethylbenzothiazole reacts under catalysis of tertiary amines to give 2-benzylidenecyanomethylbenzothiazoles [4].

As found, 2-methylbenzothiazole and phthalic, 3-nitrophthalic or 4-nitrophthalic anhydrides furnished either derivatives of phthalide (*I—III*), or 1,3-indandione (*V—VII*) depending on the type of catalyst and reaction time. With potassium acetate as a catalyst, the main product was phthalide *I* or its nitro analogues and the yield reached 60—70 %. An excess of triethylamine and pyridine and extension of the reaction time to 3 h resulted in formation of 1,3-indandione (*V*) or its nitro analogues (*VI*, *VII*) in 75—85 % yields


VIII
IX
$(CH_3CO)_2O$ C_5H_5N
C_6H_6 C_5H_5N
CH—C—CH=CHCOOH
CH_2Y
X Y
I H H
II 4-NO_2 H
III 6-NO_2 H
IV H C≡N
V H H
VI 4-NO_2 H
VII 5-NO_2 H
VIII, IX C≡N
I-IV
V-VII
+ V-VII
CH_3COOK
$(C_2H_5)_3N$
B^-

Scheme 1

(Scheme 1) due to rearrangement of phthalides *I*—*III* in the presence of sodium methoxide in methanol.



Scheme 2

Derivatives of 1,3-indandione were reported to originate *via* aldol condensation of 2-methyl- or 4-methylpyridine and phthalic anhydride [5, 6] similarly as with quinaldine, the condensation product of which with phthalic anhydride is utilized as a dyestuff [7].

Since neither positional, nor spatial isomers of phthalides *I*—*IV* were so far published, we suppose that only the more stable *Z*-isomers and positional isomers of nitro derivatives were prepared, which resulted from condensation of the more reactive carbonyl group of 3- or 4-nitrophthalic anhydride.

Aiming to prepare the benzothiazole derivatives of phthalimidine, phthalide *I* was reacted with formamide, ethylamine, hydrazine, phenylhydrazine, and 4-nitrophenylhydrazine. Depending on the medium and reagent, the condensations offered various products. The anticipated derivatives of phthalimidine were, however, not detected. 3-(2-Benzothiazolyl)phthalimidine could not even be obtained by such a general method of preparation as is the reaction of phthalides with formamide at 110—150 °C [8, 9].

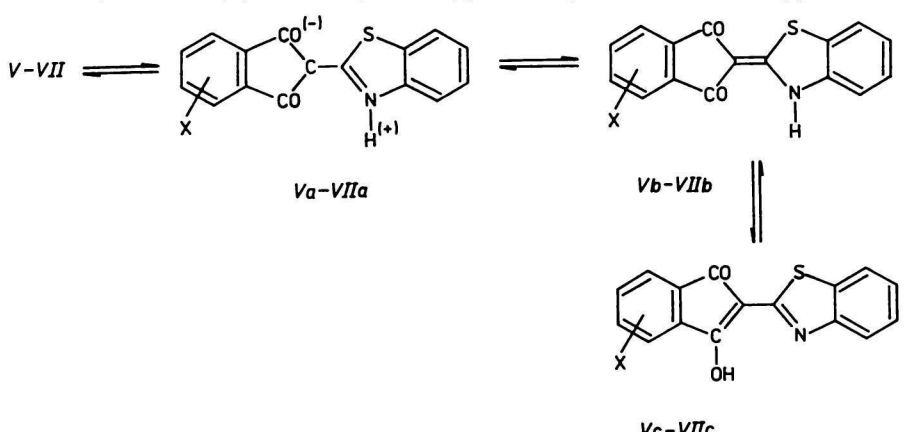
We reported that ethylamine and phenylhydrazine in tetrahydrofuran or

toluene catalyze the rearrangement of phthalide *I* to 2-(2-benzothiazolyl)-1,3--indandione (*V*) and therefore, no derivatives of phthalimidine were formed like other derivatives of methylenephthalide.

Phenylhydrazine and hydrazine react with phthalide *I* in tetrahydrofuran and aqueous NaOH to furnish derivatives of 1-oxo-2-R-4-(2-benzothiazolylmethyl)--1,2-dihydrophthalazine (*X*, *XI*). Both *X* and *XI* show in their ^{1}H NMR spectra the signal belonging to the methylene group, and in their infrared spectra the band of a ν(CO) stretching vibration at relatively low values characteristic of amides. These data indicate that this reaction is accompanied with both reduction of methine to methylene and a shift of the exocyclic double bond to the phthalazine ring. Compound *X* revealed absorption bands of the ν(NH) stretching vibration as a complex broader band at $\tilde{\nu} = 3040$—$3175\ \mathrm{cm}^{-1}$.

Phenylhydrazine does not react with phthalide *I* in acetic acid, but under reflux acetylation takes place. 4-Nitrophenylhydrazine does react under reflux with phthalide *I* in acetic acid or toluene to give *N*-(4-nitrophenyl)aminophthalimide and 2-methylbenzothiazole. These results make it possible to outline the mechanism of nucleophilic attack to the phthalide system of compound *I*. To get compounds *X*, *XI*, and *XII*, the NH group of the hydrazines employed has to enter position 3 and not position 1 of the phthalide skeleton (Scheme 2).

Compounds *V*—*VII* are yellow to red substances, sparingly soluble in little polar and low-boiling solvents; they could be crystallized from dimethylformamide, dimethyl sulfoxide or nitrobenzene. They could possess four tautomeric structures [10]. Tautomers isolated from neutral or weakly basic medium ($NaHCO_3$) displayed stretching vibration of a secondary NH group in the range $\tilde{\nu} = 3145$—$3278\ \mathrm{cm}^{-1}$, and two bands of a ν(CO) stretching vibration at low wavenumber values. These findings indicate a tautomer with bipolar structure (*Va*—*VIIa*) (Scheme 3). Like types of bipolar structure of pyridine and



Scheme 3

quinoline derivatives of 1,3-indandione were reported [7, 11—15] to be the more stable tautomers.

2-Cyanomethylbenzothiazole was shown to be a very reactive and suitable component for condensations with phthalic or maleic anhydrides, since it reacts at 50 °C in acetic anhydride and affords high yields (80—90 %) of condensation products *IV* and *VIII*. With maleic anhydride in benzene 5-(2-benzothiazolyl)-5--cyano-4-oxo-pentenoic acid (*IX*) was the product. It is obvious that the molecule of water formed by the reaction was involved in opening the oxolene ring.

The infrared spectra of compounds *I*—*IV* and *VIII* disclose ν(CO) absorption bands at high wavenumber values 1790—1830 cm^{-1}, this being in line with the data reported [16, 17] for carbonyl groups of cyclic unsaturated five--membered lactones.

Experimental

The infrared spectra of nujol suspension were recorded with a Specord 75 IR (Zeiss, Jena) spectrophotometer in the range $\tilde{\nu} = 400$—4000 cm^{-1}. The ^{1}H NMR spectra of saturated deuteriodimethyl sulfoxide solutions were measured with a Tesla BS 487 A apparatus operating at 80 MHz; the internal reference was hexamethyldisiloxane.

3-(2-Benzothiazolylmethylene)phthalide (I) and 2-(2-benzothiazolyl)--1,3-indandione (V)

Method A

A mixture consisting of fused phthalic anhydride (30 mmol) 2-methylbenzothiazole (20 mmol), and fused potassium acetate (0.1 g) was heated at 170—180 °C for 2 h till the reaction water was distilled off. The residue was poured into water (100 cm^3) to which $NaHCO_3$ was added (3 g) and the mixture was stirred for 1 h. The undissolved part was filtered off, washed with water, ethanol, dried and crystallized from ethanol or acetic acid. Yield of *I* was 3.3 g (59 %), m.p. = 212—213 °C. For $C_{16}H_9NO_2S$ (M_r = 279.3) w_i(calc.): 68.80 % C, 3.25 % H, 5.01 % N, 11.48 % S; w_i(found): 68.57 % C, 3.44 % H, 5.32 % N, 11.50 % S.

The acetic acid insoluble portion was crystallized from dimethyl sulfoxide. Yield of *V* was 1 g (18 %), m.p. = 352—354 °C. For $C_{16}H_9NO_2S$ (M_r = 279.3) w_i(calc.): 68.80 % C, 3.25 % H, 5.01 % N, 11.48 % S; w_i(found): 68.91 % C, 3.22 % H, 5.08 % N, 11.56 % S.

Method B

Fused phthalic anhydride (30 mmol), 2-methylbenzothiazole (20 mmol), anhydrous triethylamine (10 cm^3), and pyridine (10 cm^3) were stirred at 150 °C for 3 h, the mixture

was poured into water (200 cm^3) and $NaHCO_3$ (3 g) was added with stirring. After 1 h the undissolved precipitate was filtered off, washed with water, ethanol, and finally heated in ethanol (100 cm^3). The ethanol insoluble portion was crystallized from dimethyl sulfoxide. Yield of *V* was 70 %, m.p. = 352—354 °C. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1625, 1670 (ν(CO)), 3145—3155 (ν(NH)).

The ethanol soluble portion was concentrated to 10 cm^3 and cooled, crystals of *I* were filtered off. Yield = 0.5 g (9 %), m.p. = 211—213 °C. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1790 (ν(CO)), 1660 (ν(C=C)). ^{1}H NMR spectrum, δ/ppm: 7.38—8.37 (9H, m).

4-Nitro-3-(2-benzothiazolylmethylene)phthalide (II) and 4-nitro-2-(2-benzothiazolyl)-1,3-indandione (VI)

Method C

A freshly prepared 3-nitrophthalic anhydride (30 mmol), 2-methylbenzothiazole (30 mmol), and fused potassium acetate (0.4 g) were stirred at 150 °C for 90 min and poured into water (150 cm^3). The products were isolated according to the method *A*.

Yield of *II* — 3.3 g (50 %), m.p. = 278—280 °C. For $C_{16}H_8N_2O_4S$ (M_r = 324.3) w_i(calc.): 59.26 % C, 2.49 % H, 8.64 % N, 9.89 % S; w_i(found): 59.39 % C, 2.63 % H, 8.47 % N, 10.04 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1810 (ν(CO)), 1340 ($\nu_s(NO_2)$), 1530 ($\nu_{as}(NO_2)$), 1660 (ν(C=C)).

Yield of *VI* — 1.7 g (25 %), m.p. = 293—295 °C. For $C_{16}H_8N_2O_4S$ (M_r = 324.3) w_i(calc.): 59.26 % C, 2.49 % H, 8.64 % N, 9.84 % S; w_i(found): 58.95 % C, 2.41 % H, 8.86 % N, 9.80 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1630, 1680 (ν(CO)), 3270 (ν(NH)), 1330 ($\nu_s(NO_2)$), 1518 ($\nu_{as}(NO_2)$). Compound *VI* could be obtained in 90 % yield employing the method *B*.

6-Nitro-3-(2-benzothiazolylmethylene)phthalide (III) and 5-nitro-2-(2-benzothiazolyl)-1,3-indandione (VII)

Compound *III* was prepared according to the method *C*. Yield = 3 g (45 %), m.p.(acetic acid) = 272—274 °C. For $C_{16}H_8N_2O_4S$ (M_r = 324.3) w_i(calc.): 59.26 % C, 2.49 % H, 8.64 % N, 9.89 % S; w_i(found): 59.33 % C, 2.14 % H, 8.38 % N, 9.63 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1828 (ν(CO)), 1640 (ν(C=C)), 1545 ($\nu_{as}(NO_2)$), 1340 ($\nu_s(NO_2)$).

Yield of *VII* according to the method *C* — 2 g (30 %), m.p. = 360—367 °C. For $C_{16}H_8N_2O_4S$ (M_r = 324.3) w_i(calc.): 59.26 % C, 2.49 % H, 8.64 % N, 9.89 % S; w_i(found): 59.40 % C, 2.19 % H, 8.38 % N, 10.20 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1635, 1682 (ν(CO)), 1520 ($\nu_{as}(NO_2)$), 1340 ($\nu_s(NO_2)$), 3278 (ν(NH)).

Compound *VII* was obtained in 85 % yield employing the method *B*.

2-(2-Benzothiazolyl)-1,3-indandione (V), 4-nitro-2-(2-benzothiazolyl)-1,3-indandione (VI), and 5-nitro-2-(2-benzothiazolyl)-1,3-indandione (VII)

The respective phthalide *I*, *II* or *III* (3 mmol) was stirred in a 2 % sodium methoxide

in methanol (50 cm^3) at 50 °C for 1 h. Methanol was removed under diminished pressure, the residue was diluted with water (50 cm^3), acidified with HCl to pH = 1, stirred at an ambient temperature, the separated product was filtered off, washed with water and crystallized from dimethyl sulfoxide or acetic acid. Yield = approx. 90 %; the melting point for compound *V* is 352—354 °C, for compound *VI* 293—295 °C, for compound *VII* 360—367 °C. Analyses and IR spectrum coincided with those for compounds *V*, *VI*, and *VII* as determined in previous experiments.

3-(2-Benzothiazolyl)cyanomethylphthalide (IV)

Fused phthalic anhydride (13.5 mmol), 2-cyanomethylbenzothiazole (5.7 mmol), pyridine (2 cm^3), and benzene (30 cm^3) were refluxed for 1 h, during which little soluble yellow compound precipitated. The mixture was cooled, diluted with ether (30 cm^3) and allowed to stand in a refrigerator for 2 h. The separated precipitate was filtered off and crystallized from acetic acid. Yield = 1.6 g (96 %), m.p. = 298—300 °C. For $C_{17}H_8N_2O_2S$ (M_r = 304.3) w_i(calc.): 67.09 % C, 2.65 % H, 9.21 % N, 10.54 % S; w_i(found): 66.87 % C, 2.37 % H, 9.36 % N, 10.64 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2208 (ν(C≡N)), 1800 (ν(CO)), 1610 (ν(C=N)), 1278, 1040 (ν(C—O—C)).

4-(2-Benzothiazolylcyano)methylene-4-butenolide (VIII)

Maleic anhydride (20 mmol), 2-cyanomethylbenzothiazole (5.7 mmol), fused potassium acetate and acetic anhydride (20 cm^3) were reacted with stirring at 60 °C for 1 h. The mixture was cooled, ice (50 g) was added and stirring was continued at room temperature for 1 h. The precipitate was filtered off and crystallized from ethanol. Yield = 1 g (71 %), m.p. = 198—199 °C (decomp.). For $C_{13}H_6N_2O_2S$ (M_r = 254.2) w_i(calc.): 61.41 % C, 2.39 % H, 11.02 % N, 12.61 % S; w_i(found): 61.15 % C, 2.71 % H, 10.80 % N, 12.32 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2224 (ν(C≡N)), 1800 (ν(CO)), 1730 (ν(V=C)). ^{1}H NMR spectrum, δ/ppm: 6.20 (1H, d, *J* = 12 Hz), 6.80 (1H, d, *J* = 12 Hz), 7.12—8.25 (4H, m).

5-Cyano-5-(2-benzothiazolyl)-4-oxo-2-pentanoic acid (IX)

Maleic anhydride (10 mmol), 2-cyanomethylbenzothiazole (5.7 mmol), fused potassium acetate (2 mmol), pyridine (2 cm^3), and benzene (30 cm^3) were refluxed for 1 h, benzene was distilled off, the residue was diluted with 2 % aqueous $NaHCO_3$ (100 cm^3) and stirred at room temperature for 3 h. The insoluble portion was separated and the filtrate was acidified to pH = 1. The precipitated yellow compound was crystallized from ethanol. Yield = 0.8 g (52 %), m.p. = 217 °C. For $C_{13}H_8N_2O_3S$ (M_r = 272.3) w_i(calc.): 57.15 % C, 2.96 % H, 10.29 % N, 11.78 % S; w_i(found): 57.38 % C, 3.01 % H, 10.15 % N, 11.64 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2208 (ν(C≡N)), 1710 (ν(CO)), 1650, 1645 (ν(C=C)), 3180 (ν(OH)). For sodium salt of *IX* $C_{13}H_7N_2O_3SNa$ (M_r = 293.4) w_i(calc.): 53.17 % C, 2.38 % H, 9.54 % N, 10.90 % S; w_i(found): 53.30 % C, 2.72 % H, 9.46 % N, 10.98 % S.

1-Oxo-2-phenyl-4-(2-benzothiazolylmethyl)-1,2-dihydrophthalazine (X) and 1-oxo-4-(2-benzothiazolylmethyl)-1,2-dihydrophthalazine (XI)

A 2 % aqueous NaOH (12 cm^3) was successively added to a cooled (0 °C) mixture of *I* (5 mmol) and phenylhydrazine (6 mmol) in tetrahydrofuran (40 cm^3); after a 3 h stirring at an ambient temperature water (50 cm^3) was added and the mixture was left to stand in a refrigerator overnight. The separated precipitate was filtered off and crystallized from ethanol. Yield of *X* — 2.6 g (72 %), m.p. = 155—157 °C. For $C_{22}H_{15}N_3OS$ (M_r = 369.4) w_i(calc.): 71.52 % C, 4.09 % H, 12.37 % N, 8.68 % S; w_i(found): 71.47 % C, 4.16 %H, 11.62 % N, 8.37 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1673 (ν(CO)). ^{1}H NMR spectrum, δ/ppm: 4.87 (2H, s), 7.12—7.47 (13H, m).

The same procedure was applied for preparation of *XI*. Yield = 1.2 g (82 %), m.p. = 287 °C. For $C_{16}H_{11}N_3OS$ (M_r = 253.3) w_i(calc.): 65.46 % C, 3.75 % H, 14.31 % N, 10.91 % S; w_i(found): 65.52 % C, 3.65 % H, 14.21 % N, 10.60 % S. ^{1}H NMR spectrum, δ/ppm: 4.77 (2H, s), 7.25—8.30 (9H, s).

N-(4-Nitrophenylamino)phthalamide (XII)

Compound *I* (5 mmol), 4-dinitrophenylhydrazine (6 mmol), and acetic acid or toluene (30 cm^3) were refluxed for 3 h, the solvent was distilled off under reduced pressure, the residue was extracted with ether and the insoluble portion was crystallized from ethanol. Yield = 1.1 g (78 %), m.p. = 254 °C. For $C_{14}H_9N_3O_4$ (M_r = 283.2) w_i(calc.): 59.36 % C, 3.18 % H, 14.84 % N; w_i(found): 59.40 % C, 3.13 % H, 14.84 % N. ^{1}H NMR spectrum, δ/ppm: 6.85 (2H, d, J = 10 Hz), 8.02 (2H, d, J = 10 Hz), 7.07 (4H, s), 9.52 (1H, s).

The ethereal extract showed the presence of 2-methylbenzothiazole (*XIII*), b.p. = 238 °C.

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