

# Reaction of 2-benzothiazolythioethanoic acid with phthalic anhydride under conditions of Gabriel modification of Perkin synthesis

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In addition to the anticipated 3-(2-benzothiazolythiomethylene)phthalide four more compounds resulted from the reaction of 2-benzothiazolythioethanoic acid with phthalic anhydride under conditions of Gabriel modification of Perkin synthesis. These four compounds were identified as (*Z,Z*)-, (*E,Z*)-3,3'-thio-bis(methylenephthalide), 1-(2-benzothiazolyloxy)-1-inden-3-one, and dibenzothiazolyl disulfide. The starting compounds did not react in the presence of acetic anhydride, since 2-benzothiazolythioethanoic acid was preferentially acetylated to yield 4-methylthiazol[2,3-*b*]benzothiazolium 5-carboxylate by an intramolecular condensation.

2-Бензотиазолилтиоэтановая кислота с фталевым ангидридом в условиях Габриэлевой модификации синтеза Перкина дает кроме ожидаемого 3-(2-бензотиазолилтиометилен)фталида еще четыре соединения, не отвечающие обычному протеканию альдольной конденсации. Были выделены *Z,Z*- и *E,Z*-изомеры 3,3'-тио-бис(метиленфталида), 1-(2-бензотиазолил-окси)-1-инден-3-он и дибензотиазолилдисульфид. В присутствии уксусного ангидрида исходные соединения не реагируют между собой, поскольку 2-бензотиазолилтиоэтановая кислота предпочтительно подвергается ацетилированию и в результате внутренней конденсации дает 4-метилтиазо[2,3-*b*]бензотиазолий-5-карбоксилат.

This paper is a continuation of our study [1—4] on aldol condensation with heterocyclic acids as e.g. 2-furylethanoic, 2-thienylethanoic, 3-indolylethanoic, and 4-cumarinylethanoic acids. These, similarly as arylthioethanoic acid [5] afforded the corresponding 3-substituted phthalides by aldol condensation.

2-Benzothiazolythioethanoic acid (*I*, Scheme 1) was found to react atypically with phthalic anhydride (*II*) under conditions of Gabriel modification of Perkin synthesis. Totally five products were isolated from the reaction medium of which

only (*Z*)-3-(2-benzothiazolylthiomethylene)phthalide (*III*) corresponded to a normal course of aldol synthesis. The remaining products were identified as (*Z,Z*)- and (*E,Z*)-3,3'-thio-di(methylenephthalides) (*IV*) and (*V*), respectively, 1-(2-benzothiazolyloxy)-1-inden-3-one (*VI*) and dibenzothiazolyl disulfide (*VII*). Tarry products present in the mixture complicate the isolation of the above-mentioned products. We assumed, therefore, that formation of the unwanted by-products might be due to the high temperature (180–200 °C) causing also decomposition of 2-benzothiazolyloxyethanoic acid. Some dehydration reagents, as e.g. acetic anhydride make it possible to lower the reaction temperature, nonetheless, 2-benzothiazolyloxyethanoic acid preferentially reacts with this anhydride to give the darkblue 4-methylthiazo[2,3-*b*]benzothiazolium 5-carboxylate by an intramolecular condensation. This reaction is quite fast and exothermic.

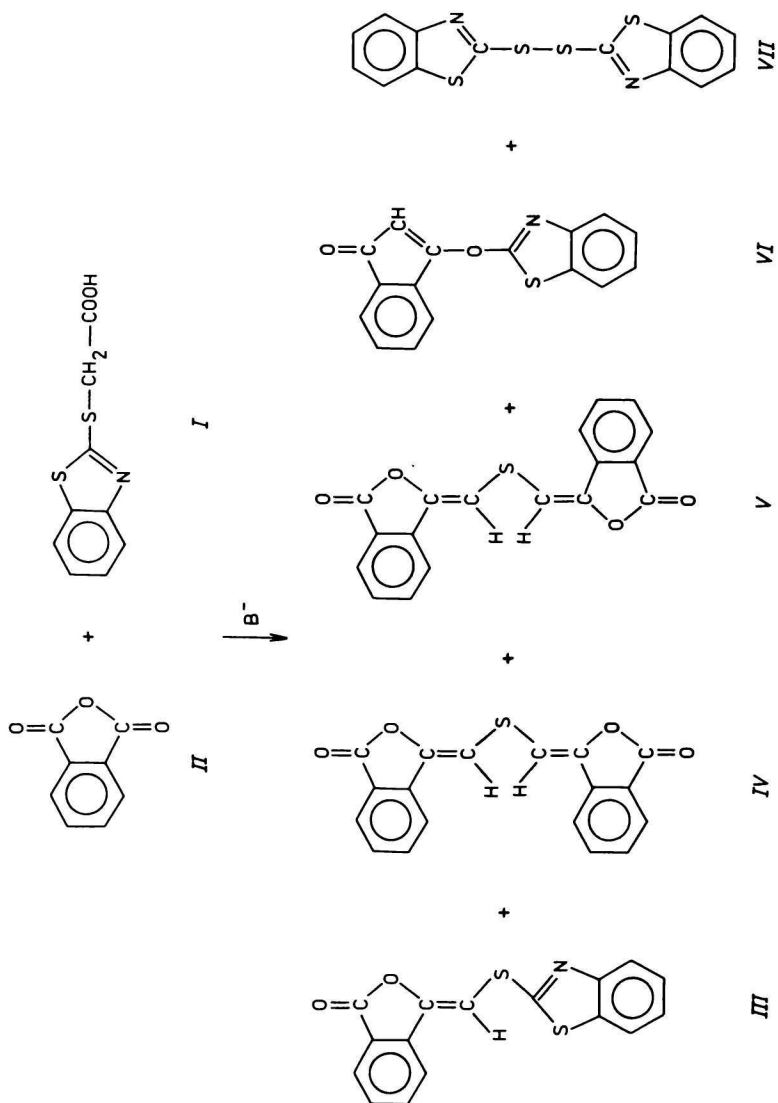
*III* was oxidized at 25 °C with an equimolecular amount of H<sub>2</sub>O<sub>2</sub> to the substituted sulfoxide *VIII* and with an excess of H<sub>2</sub>O<sub>2</sub> at 60 °C to the substituted sulfone *IX*. The degree of oxidation of the bridgehead sulfur can be seen in the IR spectrum by the wavenumber shift towards higher values. Thus, 1771 cm<sup>-1</sup>, 1784 cm<sup>-1</sup>, and 1790 cm<sup>-1</sup> were the respective  $\bar{\nu}$  values found for compounds *III*, *VIII* and *IX*, evidencing the influence of the electron-accepting group on the position of the phthalide absorption band.

Compounds *IV* and *V* were proved isomeric by reaction with ethanol in the presence of H<sub>2</sub>SO<sub>4</sub> as a catalyst, both giving ethyl 2,2'-thio-di(acetylbenzoate) (*X*).

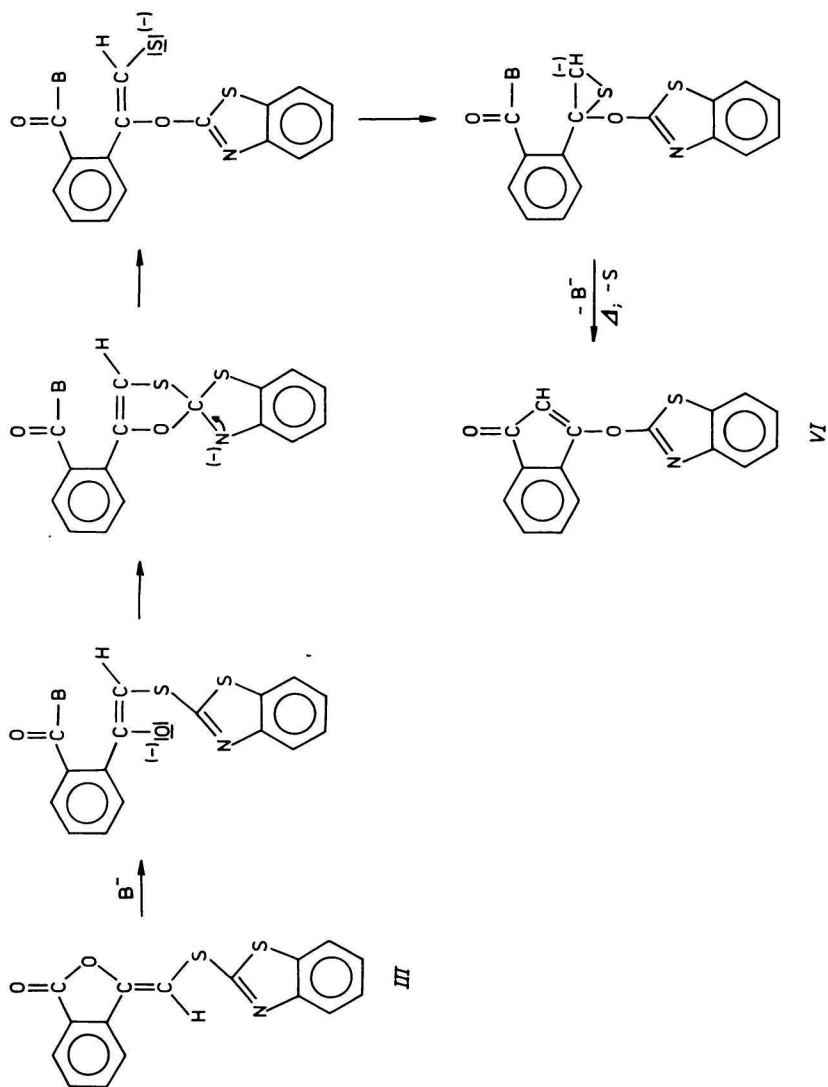
3,3'-Thio-di(methylenephthalide) can exist in three isomeric forms as (*Z,Z*)-, (*E,Z*)-, and (*E,E*)-. Two of them, the (*Z,Z*)- (*IV*) and (*E,Z*)- (*V*) were isolated from the reaction mixture and their constitution was deduced from <sup>1</sup>H NMR spectra. Singlet for hydrogens of methine groups of compound *IV* appeared at  $\delta = 7.23$  ppm (2H) corresponding to a (*Z,Z*)- arrangement, compound *V* had two singlets at  $\delta = 7.17$  ppm (1H) and  $\delta = 7.22$  ppm (1H) indicative of an (*E,Z*)- arrangement. Models of 3,3'-thio-di(methylenephthalide) showed that the (*Z,Z*)-isomer of *IV* can occupy a plane structure in two conformations, compound (*E,Z*)- *V* in one conformation, whilst the (*E,E*)- isomer cannot occupy a plane structure without being strained. Compound *IV* absorbed in the higher wavelength region of the electronic spectrum ( $\lambda_{\max} = 378.5$  nm,  $\log(\epsilon/(m^2 \text{ mol}^{-1})) = 5.59$ ) than compound *V* ( $\lambda_{\max} = 374.5$  nm,  $\log(\epsilon/(m^2 \text{ mol}^{-1})) = 5.52$ ), and also the intensity of the former was higher; the (*E,E*)- isomer was not succeeded to isolate.

Oxidation of phthalides *IV* and *V* with an equimolecular amount of H<sub>2</sub>O<sub>2</sub> at 25 °C led to (*Z,Z*)- (*XI*) and (*E,Z*)- (*XII*) 3,3'-sulfinyldi(methylenephthalides).

Structure of 1-(2-benzothiazolyloxy)-1-inden-3-one (*VI*) was adduced from spectral data (IR, <sup>1</sup>H NMR, and mass spectrometric), by formation of a derivative



Scheme I



Scheme 2

with benzylamine and by considering the presumed reaction mechanism. We found that compound **VI** is identical with the product of phthalide **III** rearrangement in alkoxide medium [6, 7]. Rearrangement of arylmethylenephthalides to 1-aryl-1-inden-3-ones has not been described as yet. We suppose that compound **VI** was formed in the reaction medium from compound **III** via an alkaline catalysis as shown in Scheme 2.

The starting compounds were also reacted without any catalyst at 200 °C. The only product isolated was **VII**, in addition to the reactants and brown tarry products.

## Experimental

The IR spectra were measured in mineral oil suspension with a Specord 75 IR (Zeiss, Jena) spectrophotometer in the 400—4000  $\text{cm}^{-1}$   $\tilde{\nu}$  range. The  $^1\text{H}$  NMR spectra of compounds **IV** and **V** were recorded in DMSO at 70 °C with a Jeol FX-100 apparatus operating at 99.54 MHz, the remaining compounds were run with Tesla BS 487 A (80 MHz) instrument as saturated dimethyl sulfoxide solutions. The mass spectrum was measured with an AEI-MS 902 S spectrometer (Manchester) at 170 °C and 70 eV.

### Reaction of phthalic anhydride (**II**) with 2-benzothiazolythioethanoic acid (**I**)

Fused **II** (29 g; 0.2 mol), **I** (22 g; 0.1 mol), fused potassium acetate (2.5 g) and pyridine (0.08 mol) were heated at 185—195 °C for 3 h with stirring and recovering the reaction water. When no more water separated, the hot mixture was poured into water (800  $\text{cm}^3$ ), free acids were neutralized with  $\text{NaHCO}_3$ , and the undissolved portion was filtered off and washed with water. The dried product was stirred with ethanol (50  $\text{cm}^3$ ), the undissolved portion was filtered off after 30 min, the filtrate was purified with charcoal, concentrated to one third of its original volume and the product **VII** was filtered off. Yield = 2.5 g (15 %), m.p. = 181—182 °C. For  $\text{C}_{14}\text{H}_8\text{N}_2\text{S}_4$  ( $M_r = 332$ )  $w_i(\text{calc.})$ : 50.56 % C, 2.24 % H, 8.42 % N, 38.56 % S;  $w_i(\text{found})$ : 50.24 % C, 2.45 % H, 8.40 % N, 38.22 % S.

Portion, which was insoluble in ethanol at room temperature was refluxed in ethanol (50  $\text{cm}^3$ ) for 30 min, hot-filtered, the filtrate was purified with charcoal, concentrated to one half and the white crystalline precipitate **III** was filtered off. Yield = 3 g (10 %), m.p. = 174 °C. For  $\text{C}_{16}\text{H}_9\text{O}_2\text{NS}_2$  ( $M_r = 311$ )  $w_i(\text{calc.})$ : 61.71 % C, 2.91 % H, 4.49 % N, 20.59 % S;  $w_i(\text{found})$ : 61.75 % C, 2.94 % H, 4.49 % N, 20.39 % S. IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1771 ( $\nu(\text{CO})$ ), 1628 ( $\nu(\text{C}=\text{C})$ ), 972 ( $\nu(\text{C}-\text{O}-\text{C})$ ), 1443 ( $\delta(\text{CH})$ ).  $^1\text{H}$  NMR spectrum;  $\delta/\text{ppm}$ : 7.00—7.62 (m).

The precipitate, which was insoluble in hot ethanol was refluxed in acetic acid (70  $\text{cm}^3$ ), filtered while hot and cooled. The yellow precipitate separated **V** was crystallized from acetic acid. Yield = 1.5 g (5 %), m. p. = 306 °C. For  $\text{C}_{18}\text{H}_{10}\text{O}_4\text{S}$  ( $M_r = 322$ )  $w_i(\text{calc.})$ : 67.07 % C, 3.12 % H, 9.94 % S;  $w_i(\text{found})$ : 67.29 % C, 3.13 % H, 9.73 % S. IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1757, 1720 sh, 1787 sh ( $\nu(\text{CO})$ ), 1440 ( $\nu(\text{CH})_{\text{arom}}$ ), 960 ( $\nu(\text{C}-\text{O}-\text{C})$ ).

$^1\text{H}$  NMR spectrum;  $\delta/\text{ppm}$ : 7.17 (s, 1H), 7.22 (s, 1H), 7.64—8.21 (m, 8H). UV spectrum;  $\lambda_{\text{max}}/\text{nm}$  ( $\log(\epsilon/(\text{m}^2 \text{mol}^{-1}))$ ): 374.5 (5.52).

The filtrate concentrated to 2/3 of its original volume afforded after cooling approximately 0.5 g of the former substance. Further concentration to 1/4 of the original volume furnished 1 g (7 %) of the yellow substance VI, m.p. = 359—360 °C. For  $\text{C}_{16}\text{H}_9\text{O}_2\text{NS}$  ( $M_r = 279$ )  $w_i(\text{calc.})$ : 68.80 % C, 3.24 % H, 5.01 % N, 11.47 % S;  $w_i(\text{found})$ : 68.73 % C, 3.18 % H, 5.02 % N, 11.66 % S. IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1628, 1625 sh ( $\nu(\text{CO})$ ), 1510, 1584 ( $\nu(\text{C}=\text{C})$ ).  $^1\text{H}$  NMR spectrum;  $\delta/\text{ppm}$ : 7.27 (s, 1H), 7.06—8.02 (m, 8H). Mass spectrum;  $m/z$ : 279 ( $M^{+*}$ ), 251, 235, 223, 190, 146, 138, 126, 121, 111, 108, 105, 81, 77, 76, 69, 44.

The acetic acid insoluble precipitate was crystallized from dimethyl sulfoxide to give yellow crystals IV. Yield = 2.5 g (8 %), m.p. = 311—312 °C. For  $\text{C}_{18}\text{H}_{10}\text{O}_4\text{S}$  ( $M_r = 322$ )  $w_i(\text{calc.})$ : 67.07 % C, 3.12 % H, 9.94 % S;  $w_i(\text{found})$ : 67.11 % C, 3.11 % H, 9.97 % S. IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1750, 1772 sh, 1715 sh ( $\nu(\text{CO})$ ), 1628 ( $\nu(\text{C}=\text{C})$ ), 1445 ( $\delta(\text{CH})_{\text{arom}}$ ), 975 ( $\nu(\text{C}-\text{O}-\text{C})$ ).  $^1\text{H}$  NMR spectrum;  $\delta/\text{ppm}$ : 7.24 (s, 2H), 7.56—7.97 (m, 8H). UV spectrum;  $\lambda_{\text{max}}/\text{nm}$ , ( $\log(\epsilon/(\text{m}^2 \text{mol}^{-1}))$ ): 378.5 (5.59).

### 3-(2-Benzothiazolylsulfinylmethylene)phthalide (VIII)

30 % Hydrogen peroxide (12 mmol) was added to III (10 mmol) dissolved in acetic acid (20  $\text{cm}^3$ ) at room temperature with stirring. After 3 h stirring the mixture was left to stand for 24 h, diluted with ice-cold water (50  $\text{cm}^3$ ) and the precipitate was filtered off and crystallized from ethanol. Yield = 2.7 g (81 %), m.p. = 222—224 °C. For  $\text{C}_{16}\text{H}_9\text{O}_3\text{NS}_2$  ( $M_r = 327$ )  $w_i(\text{calc.})$ : 58.69 % C, 2.77 % H, 4.28 % N, 19.59 % S;  $w_i(\text{found})$ : 58.88 % C, 2.74 % H, 4.38 % N, 19.38 % S. IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1784 ( $\nu(\text{CO})$ ), 1638, 1490 ( $\nu(\text{C}=\text{C})$ ), 966, 1060 ( $\nu(\text{C}-\text{O}-\text{C})$ ).

### 3-(2-Benzothiazolylsulfonylmethylene)phthalide (IX)

The title compound was prepared from 21 mmol  $\text{H}_2\text{O}_2$  at 60 °C by the same procedure as given for VIII. Yield = 2.4 g (70 %), m.p. = 211 °C. For  $\text{C}_{16}\text{H}_9\text{O}_3\text{NS}_2$  ( $M_r = 343$ )  $w_i(\text{calc.})$ : 55.97 % C, 2.64 % H, 4.08 % N, 18.71 % S;  $w_i(\text{found})$ : 55.68 % C, 2.39 % H, 4.24 % N, 18.54 % S. IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1790 ( $\nu(\text{CO})$ ), 1652, 1490 ( $\nu(\text{C}=\text{C})$ ).

### Diethyl 2,2'-thio-di(acetylbenzoate) (X)

IV or V (5 mmol) was refluxed in ethanol (30  $\text{cm}^3$ ) for 10 h with  $\text{H}_2\text{SO}_4$  (2 mmol). The insoluble portion was filtered off, the filtrate was concentrated to 1/3 of its volume, diluted with water (40  $\text{cm}^3$ ), neutralized with  $\text{NaHCO}_3$  and extracted into ether. The ethereal extract

was dried and the solvent removed under diminished pressure afforded the product as colourless oil. Yield = 1 g (48 %),  $n_D(20^\circ\text{C}) = 1.5778$ . For  $\text{C}_{22}\text{H}_{22}\text{O}_6\text{S}$  ( $M_r = 414$ )  $w_i(\text{calc.}): 63.75\% \text{ C}, 5.34\% \text{ H}, 7.73\% \text{ S}$ ;  $w_i(\text{found}): 63.61\% \text{ C}, 5.48\% \text{ H}, 7.75\% \text{ S}$ . IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1742, 1754 sh ( $\nu(\text{CO})$ ), 1480 ( $\nu(\text{C}=\text{C})_{\text{arom}}$ ), 1096 ( $\nu(\text{C}-\text{O}-\text{C})$ ).  $^1\text{H NMR}$  spectrum;  $\delta/\text{ppm}$ : 0.87—1.25 (m, 6H), 3.87 (s, 4H), 4.05—4.37 (q, 4H), 7.37—7.95 (m, 8H).

*(Z,Z)*-3,3'-Sulfinyl-di(methylenephthalide) (XI)

3,3'-Thio-di(methylenephthalide) (IV) (5 mmol) was stirred with  $\text{H}_2\text{O}_2$  (5 mmol) and acetic acid (20  $\text{cm}^3$ ) at  $25^\circ\text{C}$  till it dissolved. Water (50  $\text{cm}^3$ ) was added and the precipitate was crystallized from acetic acid. Yield = 1.2 g, (74 %), m.p. =  $254\text{--}255^\circ\text{C}$ . For  $\text{C}_{18}\text{H}_{10}\text{O}_5\text{S}$  ( $M_r = 338$ )  $w_i(\text{calc.}): 63.90\% \text{ C}, 2.97\% \text{ H}, 9.48\% \text{ S}$ ;  $w_i(\text{found}): 64.18\% \text{ C}, 2.82\% \text{ H}, 9.43\% \text{ S}$ . IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1784 ( $\nu(\text{CO})$ ), 1628, 1650 sh ( $\nu(\text{C}=\text{C})$ ), 1115, 970 ( $\nu(\text{C}-\text{O}-\text{C})$ ).  $^1\text{H NMR}$  spectrum;  $\delta/\text{ppm}$ : 7.28 (s, 2H), 7.62—8.25 (m, 8H).

*(E,Z)*-3,3'-Sulfinyl-di(methylenephthalide) (XII)

The same procedure as given for XI was applied for preparation of the *(E,Z)*- isomer from V. For  $\text{C}_{18}\text{H}_{10}\text{O}_5\text{S}$  ( $M_r = 338$ )  $w_i(\text{calc.}): 63.90\% \text{ C}, 2.97\% \text{ H}, 9.48\% \text{ S}$ ;  $w_i(\text{found}): 63.78\% \text{ C}, 2.83\% \text{ H}, 9.65\% \text{ S}$ . M.p. =  $188\text{--}191^\circ\text{C}$ .

3,3'-Sulfonyl-di(methylenephthalide) (XIII)

Compound V (5 mmol) was oxidized with  $\text{H}_2\text{O}_2$  (10 mmol) at  $90^\circ\text{C}$  in the same way as described with XII. For  $\text{C}_{18}\text{H}_{10}\text{O}_6\text{S}$  ( $M_r = 354$ )  $w_i(\text{calc.}): 61.01\% \text{ C}, 2.82\% \text{ H}, 9.03\% \text{ S}$ ;  $w_i(\text{found}): 61.28\% \text{ C}, 2.58\% \text{ H}, 9.03\% \text{ S}$ . IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1795, 1814 sh ( $\nu(\text{CO})$ ), 1622, 1476 ( $\nu(\text{C}=\text{C})$ ).

3-Benzylimino-1-(2-benzothiazoloxo)-1-indene (XIV)

VI (5 mmol) and benzylamine (6 mmol) were heated in xylene (30  $\text{cm}^3$ ) at  $110^\circ\text{C}$  for 3 h, the unreacted benzylamine and xylene were distilled off, the residue was diluted with ether (10  $\text{cm}^3$ ), the precipitate was filtered off and crystallized from benzene. Yield = 1.4 g ( $\approx 80\%$ ), m.p. =  $214\text{--}216^\circ\text{C}$ . For  $\text{C}_{23}\text{H}_{16}\text{N}_2\text{OS}$  ( $M_r = 368$ )  $w_i(\text{calc.}): 74.95\% \text{ C}, 4.37\% \text{ H}, 7.59\% \text{ N}, 8.69\% \text{ S}$ ;  $w_i(\text{found}): 75.18\% \text{ C}, 4.21\% \text{ H}, 7.85\% \text{ N}, 8.34\% \text{ S}$ . IR spectrum;  $\tilde{\nu}/\text{cm}^{-1}$ : 1610 ( $\nu(\text{C}=\text{N})$ ), 1506, 1515 ( $\nu(\text{C}=\text{C})$ ), 1439, 1363.

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