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Synthesis of 2-Acetyl-3-methyl-4*H*-1,4-benzothiazine and its Derivatives

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Summary. 2-Aminothiophenol (**1**) reacts with 3-chloro-2,4-pentanedione (**2**) in the presence of pyridine to form 2-acetyl-3-methyl-4*H*-1,4-benzothiazine (**3**) in high yields. Reaction of **3** with hydrazine gives 4-(2′-aminophenylthio)-3,5-dimethylpyrazole (**5**). Condensation of **3** with 4-nitrobenzaldehyde yields the corresponding Schiff base **7**. Hydroxylamine with benzothiazine **3** affords 3,9a-dimethyl-3a, 9a-dihydro-9*H*-isoxazolo[4,5-b][1,4]benzothiazine (**8**).

Keywords. 4*H*-1,4-Benzothiazines; 3,5-Dimethylpyrazoles; Isoxazolo[4,5-b][1,4]benzothiazines.

Synthese von 2-Acetyl-3-methyl-4*H*-1, 4-benzothiazin und seinen Derivaten

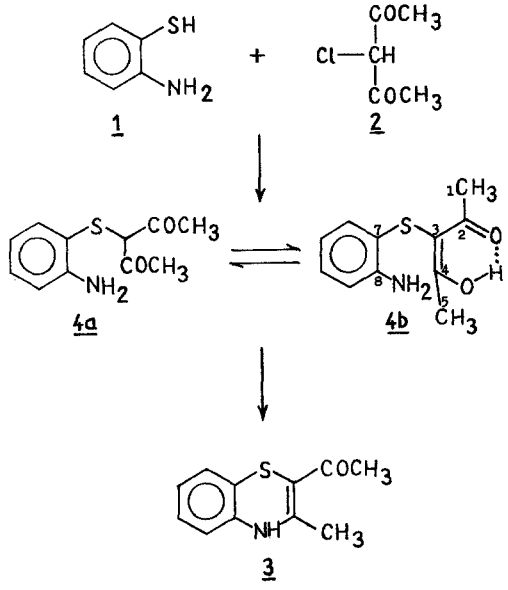
Zusammenfassung. 2-Aminothiophenol (**1**) reagiert mit 3-Chlor-2,4-pentandion (**2**) in Anwesenheit von Pyridin unter Bildung von 2-Acetyl-3-methyl-4*H*-1,4-benzothiazin (**3**) in sehr hoher Ausbeute. Benzothiazin **3** kondensiert mit Hydrazin zu 4-(2′-Aminophenylthio)-3,5-dimethylpyrazol (**5**), dessen Aminogruppe reagiert mit 4-Nitrobenzaldehyd zu einer Schiffschen Base (**7**), die spektroskopisch charakterisiert wurde. Benzothiazin **3** mit Hydroxylamin ergibt 3,9a-Dimethyl-3a,9a-dihydro-9*H*-isoxazolo[4,5-b][1,4]benzothiazin (**8**). Die Stereochemie der letztgenannten Verbindung wurde ermittelt.

Introduction

4*H*-1,4-Benzothiazines gained a significant role with regard to studies on ylides [1] as well as to the preparation of pharmacologically effective analogues of phenothiazines [2–4]. For the preparation of these compounds, substituted 2-aminothiophenol was condensed with a β-diketone in *DMSO* at 120–140 °C. It is assumed that at mentioned temperatures 2-aminothiophenol exists in the form of the disulfide which by the reaction with a β-diketone affords an enamino-ketone. This is then cyclized to the 1,4-benzothiazine [5]. The yield in these syntheses did not exceed 60–70%. Another procedure for the preparation of this skeleton utilizes heating of 2-aminothiophenol with a β-diketone in ethanol in the presence of catalytic amounts of acetic acid [6]. In this paper we have focused our attention on the elaboration of a new, more effective method for synthesis of 2-acetyl-3-methyl-4*H*-1,4-benzothiazine, and we have studied products of its condensation with hydrazine and hydroxylamine.

Results and Discussion

2-Aminothiophenol (**1**) with an equimolar amount of pyridine dissolved in dry benzene reacted with 3-chloro-2,4-pentanedione (**2**) at room temperature, and already after 1 h of stirring, crystals of the product started to separate. By the filtration of the resulting suspension and washing with ethyl acetate, chromatographically pure 2-acetyl-3-methyl-4*H*-1,4-benzothiazine (**3**) was obtained in 96% yield. The identity of compound **3** was proved by comparison of physico-chemical data with those published previously [7]. In the initial stage of the reaction, thin layer chromatography revealed the presence of intermediate **4**. It was not isolated but on the basis of identical chromatographic parameters we assume that compound **4** is identical with 3-(2′-aminophenylthio)-2,4-pentanedione. This compound was prepared from sodium 2-aminothiophenolate by the reaction with diketone **2** in dry ethanol. By preparative TLC of the reaction mixture, benzothiazine **3** and intermediate **4** – which in pyridine almost quantitatively converted into 2-acetyl-3-methyl-4*H*-1,4-benzothiazine (**3**) – were isolated. Spectral data of **4** indicated the existence of the enol tautomer **4b**. The presence of intermediate **4** demonstrates that during the reaction of 2-aminothiophenol (**1**) with β-diketone **2**, the mercapto group is alkylated preferentially and the thiazine ring is formed by subsequent condensation of the amino and carbonyl group (Scheme 1).



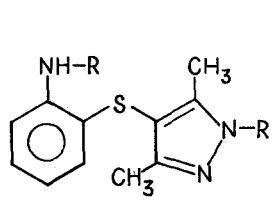
Scheme 1

Owing to the presence of a carbonyl group, benzothiazine **3** easily reacted with hydrazine affording compound **5** under decolourization of the orange-red solution. We have assumed that this is due to an intramolecular cyclization of the formed hydrazone. The ^{1}H-NMR spectrum of compound **5**, in addition to four signals of aromatic protons, exhibited only one singlet of two symmetrically bound methyl groups. By the acetylation of compound **5**, the diacetate **6** was prepared, but in its

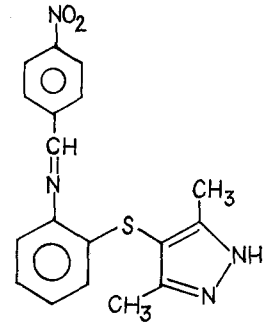
proton spectrum signals of two isolated methyl groups besides signals of two acetyl groups and an unchanged number of signals of aromatic protons were observed.

Condensation of compound **5** with 4-nitrobenzaldehyde gave the Schiff base **7**. Its structure was proved by ^{13}C-NMR (significant signal at $\delta = 167.7$ ppm, CH=N) as well as by MS with characteristic peaks at $m/z = 352$ (M^+), 230 (M–$C_6H_4NO_2$) and 95 ($C_5H_7N_2$). The peak at m/z 95 corresponded to the 3,5-dimethylpyrazole fragment which was also observed in spectra of compounds **5** and **6**. On the basis of these data, the structure of 4-(2′-aminophenylthio)-3,5-dimethylpyrazole was assigned to compound **5**.

Reaction of hydroxylamine with 4*H*-benzothiazine (**3**) afforded compound **8**. The MS of this compound showed a molecular radical ion at $m/z = 220$ and a base peak at $m/z = 163$ (C_9H_9NS) corresponding to the 3-methyl-4*H*-benzothiazine fragment which could be formed from M^+ by retro-Diels-Alder rearrangement. In its ^{1}H-NMR spectrum two singlets of methyl groups, signals of four aromatic protons and a signal of one proton ($\delta = 4.26$ ppm) located at the carbon atom adjacent to the heteroatom, were observed. In its ^{13}C-NMR spectrum, a signal at $\delta = 99.2$ ppm belonged to the unprotonated sp^3 carbon atom connecting the two heteroatoms. Such a case could occur if the oxime formed by the reaction of 4*H*-benzothiazine and hydroxylamine would cyclize intramolecularly. On the basis of spectral data, the structure of 3,9a-dimethyl-3a,9a-dihydro-9*H*-isoxazolo[4,5-b][1,4]benzothiazine was assigned to compound **8**. In its ^{1}H-NMR a signal of the H-3a proton appeared in form of a quartet due to its coupling with C-9a–CH_3 protons. This long-range connectivity proved the *trans* position of H-3a and the C-9a methyl group.



5 R = H
6 R = $COCH_3$



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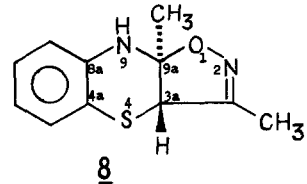

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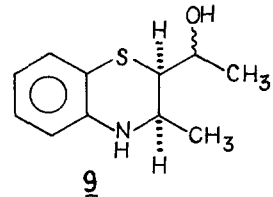

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Upon reaction of 4*H*-1,4-benzothiazine (**3**) with $NaBH_4$, the carbonyl group and C-2–C-3 double bond were reduced simultaneously. The axial position of the H-2 proton was confirmed by a NOE experiment. An increase of the intensity of the H-3 proton only was observed after irradiation of the H-2 proton. Otherwise, a spatial interaction with CH_3 protons should be also observed. The value of the coupling constant $J_{2,3} = 2.6$ Hz confirmed the equatorial position of H-3.

Experimental Part

Melting points were determined on a Kofler hot-stage and are uncorrected. Electron-impact mass spectra (70 eV) were recorded on a Jeol JMS 100D spectrometer at an emission current of 300 μA, applying direct sample-introduction technique. ^{1}H- and ^{13}C-NMR spectra were measured on a Bruker AM-300 spectrometer operating at 300.13 or 75.46 MHz working frequencies with *TMS* as an internal standard. Elemental analyses were performed on a Perkin Elmer 240 analyzer. For HPLC, 150 × 3 mm column packed with Separon SGX C18 7 μm was used with methanol-water (65:35) as mobile phase (flow rate 0.4 ml/min) and a detector wavelength 254 nm. The purity and identity of the compounds were routinely checked by TLC on Silufol UV254 plates (Kavalier, Czechoslovakia). Preparative TLC was carried out using Merck Kieselgel 60 F_{254} plates (20 × 20 cm, 2 mm). In both cases, a mixture of ethyl acetate:*n*-hexane (3:2) was used as an eluent.

2-Acetyl-3-methyl-4H-1,4-benzothiazine (**3**)

To a solution of 2-aminothiophenol (**1**, 2.50 g, 0.02 mol) and pyridine (1.58 g, 0.02 mol) in dry benzene (150 ml), 3-chloro-2,4-pentanedione (**2**, 2.69 g, 0.02 mol) was added dropwise at 25 °C, then the reaction mixture was stirred for additional 1 h. The separated solid was filtered off, washed with a 10% aqueous $NaHCO_3$ solution, then with water and finally with cold ethyl acetate. After drying in vacuum over NaOH, **3** was obtained as orange-red coloured small needles in 96% yield; m.p. 195–196 °C, $R_f = 0.50$. Spectral data were in accordance with Ref. [7].

3-(2'-Aminophenylthio)-2,4-pentanedione (**4**)

To a solution of sodium ethoxide (0.68 g, 0.01 ml) in dry ethanol (30 mol), 2-aminothiophenol (**1**, 1.25 g, 0.01 mol) was added. After 30 min of stirring, **3** (1.34 g, 0.01 mol) was added dropwise. The mixture was left overnight, separated NaCl was filtered off and the solvent was evaporated under reduced pressure. The resulting brownish thick oil was passed through a pad of silica gel and eluted with ethyl acetate. TLC revealed the presence of compounds **3** ($R_f = 0.50$) and **4** ($R_f = 0.38$). Pure **4** (0.47 g, yield 21%) was isolated by preparative TLC, m.p. 71–72 °C. $C_{11}H_{13}NO_2S$ (223.30); calcd. C 59.17, H 5.87, N 6.27%; found C 59.09, H 5.90, N 6.29%. EI-MS (*m/z*, %): 223 (M^+, 42), 181 (24), 180 (11), 138 (60), 124 (40), 93 (61), 43 (100), ^{1}H-NMR (*DMSO-d*$_6$), δ/ppm: 2.40 (s, 6 H, CH_3), 6.65–7.05 (m, 4 H, aromatics). ^{13}C-NMR (*DMSO-d*$_6$), δ/ppm: 24.5 (C-1, C-5), 97.3 (C-3), 114.9 (C-9), 124.4 (C-10), 125.8 (C-11), 126.8 (C-12), 138.7 (C-7), 152.9 (C-8), 197.8 (C-2, C-4).

4-(2'-Aminophenylthio)-3,5-dimethylpyrazole (**5**)

4*H*-Benzothiazine (**3**) (350 mg, 1.7 mmol) was dissolved in ethanol (20 ml) and hydrazine hydrate (80%, 0.2 ml) and heated under reflux. The reaction was checked by HPLC ($t_r = 4.1$ min for compound **5**, $t_r = 6.3$ min for starting material **3**). After 1 h, the solvent was evaporated and the product was crystallized from benzene:*n*-heptane (2:1) giving **5** (320 mg, 86%), m.p. 154–155 °C. $C_{11}H_{13}N_3S$ (219.31); calcd. C 60.24, H 5.98, N 19.16%; found C 60.18, H 6.03, N 19.20%. EI-MS (*m/z*, %): 291 (M^+, 100), 204 (2), 202 (1), 186 (12), 177 (4), 136 (7), 125 (23), 95 (68). ^{1}H-NMR ($CDCl_3$), δ/ppm: 6.98 (1 H,

ddd, $J_{3',4'} = 7.9$ Hz, $J_{4',5'} = 7.3$ Hz, $J_{4',6'} = 1.3$ Hz, H-4'), 6.85 (1 H, dd, $J_{5',6'} = 7.7$ Hz, H-6'), 6.68 (1 H, dd, $J_{3',5'} = 1.2$ Hz, H-3'), 6.62 (1 H, ddd, H-5'), 2.28 (6 H, s, C-3–CH_3, C-5–CH_3). ^{13}C-NMR ($CDCl_3$), δ/ppm: 148.1 (C-3, C-5), 144.5 (C-2'), 129.4 (C-4'), 127.1 (C-6'), 121.0 (C-1'), 119.0 (C-5'), 115.4 (C-3'), 104.2 (C-4), 11.2 (CH_3).

1-Acetyl-4-(2'-acetamidophenylthio)-3,5-dimethylpyrazole (**6**)

To a solution of **5** (200 mg, 0.92 mmol) in pyridine (3 ml), acetic anydride (1 ml) was added and the mixture was heated at 80 °C for 2 h. Then the solvents were evaporated in vacuo and the residue crystallized from acetone:*n*-heptane (1:1) affording **6** (168 mg, 60%), m.p. 134.5–136 °C. $C_{15}H_{17}N_3O_2S$ (303.39); calcd. C 59.38, H 5.65, N 13.85%; found C 59.22, H 5.61, N 13.89%. EI-MS (*m/z*, %): 303 (M^+, 52), 261 (14), 246 (2), 219 (20), 186 (6), 177 (3), 134 (100), 109 (6), 95 (40). ^{1}H-NMR ($CDCl_3$), δ/ppm: 8.07 (1 H, dd, $J_{3',4'} = 8.0$ Hz, $J_{3',5'} = 1.5$ Hz, H-3'), 7.21 (1 H, ddd, $J_{4',5'} = 7.4$ Hz, $J_{4',6'} = 1.6$ Hz, H-4'), 7.00 (1 H, dd, $J_{5',6'} = 7.4$ Hz, H-6'), 6.94 (1 H, ddd, H-5'), 2.69 (3 H, s, CH_3), 2.64 (3 H, s, CH_3), 2.26 (3 H, s, CH_3CO), 2.14 (3 H, s, CH_3CO). ^{13}C-NMR ($CDCl_3$), δ/ppm: 171.3, 168.2 (CO), 154.2 (C-3), 147.3 (C-5), 136.0 (C-2'), 129.4 (C-4'), 127.7 (C-6'), 126.1 (C-1'), 125.1 (C-5'), 122.6 (C-3'), 102.8 (C-4), 24.6, 23.3 (CH_3CO), 13.5, 12.5 (CH_3).

4-(N-(4''-Nitrobenzylidene)-2'-aminophenylthio)-3,5-dimethylpyrazole (**7**).

To a solution of **5** (300 mg, 1.37 mmol) in ethanol (30 ml), 4-nitrobenzaldehyde (207 mg, 1.37 mmol) was added and the mixture was heated under reflux for 3 h. Then ethanol was evaporated under diminished pressure and the product was crystallized from benzene:*n*-hexane (2:1) giving 377 mg (78%) of **7**, m.p. 173 °C (decomp.). $C_{18}H_{16}N_4O_2S$ (352.42); calcd. C 61.35, H 4.58, N 15.90%; found C 61.27, H 4.60, N 15.82%. EI-MS *m/z* (%): 352 (M^+, 80) 306 (6), 280 (14), 257 (10), 230 (100), 221 (16), 167 (37), 149 (56), 136 (23), 95 (66). ^{1}H-NMR ($CDCl_3$), δ/ppm: 8.60 (1 H, s, H-7''), 8.32 (2 H, d, $J_{2'',3''} = J_{5'',3''} =$ 8.0 Hz, H-3'', H-5''), 8.18 (2 H, d, H-2'', H-6''), 7.0–6.8 (3 H, m, H-4', H-5', H-6') 6.62 (1 H, dd, $J_{3',4'} = 8.0$ Hz, $J_{3',5'} = 1.6$ Hz, H-3'), 2.31 (6 H, s, two CH_3). ^{13}C-NMR ($CDCl_3$), δ/ppm: 167.7 (C-7''), 156.6 (C-4''), 149.4 (C-3, C-5), 146.6 (C-1''), 135.4 (C-2'), 129.6 (C-2'', C-6''), 128.7 (C-1'), 128.2 (C-4'), 125.2 (C-6'), 124.3 (C-5'), 124.2 (C-3'', C-5''), 117.0 (C-3'), 102.7 (C-4), 11.1 (C-3, C-5).

3,9a-Dimethyl-3a,9a-dihydro-9H-isoxazolo[4,5-b][1,4]benzothiazine (**8**)

4*H*-1,4-Benzothiazine (**3**) (300 mg, 1.46 mmol) and hydroxylamine hydrochloride (102 mg, 1.46 mmol) in ethanol (20 ml) were heated under reflux in the presence of triethylamine (0.1 ml). After 1 h the ethanol was distilled off in vacuo and the product was crystallized from toluene giving **8** (280 mg, 87%). An analytical sample was obtained by chromatography on silica gel using chloroform:methanol (9:1) as the eluent. Subsequent crystallization of the product from benzene:*n*-heptane (3:1) gave pure **8**, m.p. 168–169 °C. $C_{11}H_{12}N_2OS$ (220.30); calcd. C 59.97, H 5.49, N 12.72%; found C 59.89, H 5.53, N 12.68%. EI-MS *m/z* (%): 220 (M^+, 31), 163 (100), 150 (5), 134 (6), 130 (16), 109 (9), 108 (4), 96 (4), 65 (7). ^{1}H-NMR ($CDCl_3$), δ/ppm: 7.22 (1 H, dd, $J_{5,6} = 7.5$ Hz, $J_{5,7} = 1.2$ Hz, H-5), 7.12 (1 H, ddd, $J_{7,8} = 7.5$ Hz, $J_{6,7} = 7.5$ Hz, H-7), 6.87 (1 H, ddd, $J_{6,8} = 1.2$ Hz, H-6), 6.77 (1 H, dd, H-8), 4.26 (1 H, q, $J_{3a,CH_3} = 1.2$ Hz, H-3a), 1.86 (3 H, s, C-3–CH_3), 1.84 (3 H, s, C-9a–CH_3). ^{13}C-NMR ($CDCl_3$), δ/ppm: 155.0 (C-3), 143.3 (C-8a), 129.1 (C-7), 128.4 (C-5), 121.8 (C-6), 118.9 (C-4a), 117.9 (C-8), 99.2 (C-9a), 59.5 (C-3a), 26.3 (C-3–CH_3), 12.11 (C-9a–CH_3).

2-(1'-Hydroxyethyl)-2,3-dihydro-3-methyl-4H-1,4-benzothiazine (**9**)

To a solution of **3** (600 mg, 2.92 mmol) in methanol (15 ml), $NaBH_4$ (150 mg, 3.97 mmol) was added in the course of 3 h. Then the methanol was distilled off, the residue was dissolved in diluted hydrochloric acid (1%, 30 ml) and the *pH* was adjusted to 9 by the addition of conc. NH_4OH. The resulting emulsion

was exctracted with ethyl acetate (3 × 20 ml) and the combined extracts were dried over $MgSO_4$. After filtration, evaporation of solvent in vacuo, and crystallization from ether, white crystals of **9** (420 mg, 69%) were obtained, m.p. 151–153 °C. $C_{11}H_{15}NOS$ (209.31); calcd. C 63.12, H 7.22, N 6.69%; found C 63.06, H 7.30, N 6.65% EI–MS *m/z* (%): 209 (M^+, 95), 194 (2), 191 (4), 177 (100), 164 (31), 151 (44), 150 (38), 136 (46), 130 (14), 124 (9), 117 (16), 109 (16), 77 (10). ^{1}H-NMR ($CDCl_3$), δ/ppm: 7.09 (1 H, dd, $J_{7,8} = 7.8$ Hz, $J_{6,8} = 1.2$ Hz, H-8), 6.90 (1 H, ddd, $J_{6,7} = 7.5$ Hz, $J_{5,6} = 7.5$ Hz, H-6), 6.76 (1 H, ddd, $J_{5,7} = 1.3$ Hz, H-7), 6.56 (1 H, dd, H-5), 4.37 (1 H, dq, $J_{1',2'} = 6.20$ Hz, $J_{1',2} = 2.6$ Hz, H-1'), 3.82 (1 H, dq, $J_{2,3} = 2.6$ Hz, $J_{3,CH_3} = 6.6$ Hz, H-3), 3.10 (1 H, dd, H-2), 1.46 (3 H, d, C-3–CH_3), 1.32 (3 H, d, H-2').

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