A Facile Synthesis of Substituted 1,4-Benzothiazepin-5(4*H*)-ones and Pyrido[3,2-*f*][1,4]thiazepin-5(4*H*)-ones − Crystal and Molecular Structure of 2-Ethylthio-4-methyl-5(4*H*)-oxopyrido[3,2-*f*][1,4]thiazepine-3-carbonitrile

Wolfgang Dölling*[a], Matthias Biedermann[b], and Helmut Hartung[b]

Martin Luther University Halle-Wittenberg, Institute of Organic Chemistry[a],
Kurt-Mothes-Straße 2, D-06120 Halle (Saale), Germany

Martin Luther University Halle-Wittenberg, Institute of Physical Chemistry[b],
Mühlpforte 1, D-06108 Halle (Saale), Germany

Received September 1, 1997

Keywords: Pyrido[3,2-*f*][1,4]thiazepine / Carbon disulfide / 1,4-Benzothiazepin-5(4*H*)-ones / 2-Chloro-*N*-cyanomethyl-*N*-methylnicotinamide / Aromatic nucleophilic substitution

A new synthesis of pyrido[3,2-*f*][1,4]thiazepine derivatives **3** starting with 2-chloronicotinic acid (**1**), methylaminoacetonitrile hydrochloride and carbon disulfide is described. As proved by a crystal structure determination, a boat conformation with approximated mirror symmetry can be assigned to the 1,4-thiazepine ring in **3b**. 2-Chloro-*N*-cyanomethyl-*N*-methyl-5-nitrobenzamide (**5**) reacts with carbon disulfide in presence of a strong base in DMF or DMSO depending on the temperature to either the benzothiopyran compound **6** or by intramolecular aromatic nucleophilic substitution to a seven-membered ring system as thiolate anion which can be alkylated to give the 1,4-benzothiazepine derivative **7**, or to an open-chain amido ketene dithioacetal **8**.

Introduction

Calcium channel blockers are important cardiovascular drugs in the treatment of angina pectoris, cardial arrhythmies and hypertension. Most of these agents belong either to the 1,4-dihydropyridines or to the phenylalkylamines or to the 1,5-benzothiazepine-2-ones, represented by Diltiazem[1]. Benzo- and pyridothiazepines have attracted considerable attention because of their remarkable diversity of biological activities[2]. As structural analogues of benzazepines- and -diazepines they show a wide range of pharmacological properties including not only neurological agents[3] (antidepressiva, tranquilizers, neuroleptica), but also antiarrhythmics[4], antihyperlipidemics[5][6][7], antihistaminics[8], etc.

The extensive use of ketene dithioacetals in organic synthesis clearly demonstrates their power as synthetic tools. Among the various possible reactions available for their preparation the dithiocarboxylation of carbanions or heterocarbanions with subsequent alkylation is often preferred. However, it was recently demonstrated in our laboratory that the use of 2-chloro-substituted benzamides can favour formation of 1,4-thiazepines through internal nucleophilic aromatic substitution by the intermediate enedithiolate[9][10]. In order to extend the scope of this method we investigated the reaction of 2-chloronicotinamide and 2-chloro-5-nitro-benzamide with regard to their reactions as α-heteroatom substituted C-nucleophiles with carbon disulfide.

Results and Discussion

In this paper we describe a conceptually and experimentally simple access to the pyrido[3,2-*f*][1,4]thiazepine skeleton. This new general way represents the formation of the seven membered heterocycle by the two fragments C−C−C−N−C and C−S hitherto not reported in the review literature[11][12][13][14]. The synthesis of anellated 1,5-benzothiazepines has been surveyed[15].

Cyclocondensation of 3-(*N*-methylacetamido)-2-chloropyridine or 3-acetamido-2-chloropyridine gives 2-arylpyrido[2,3-*b*][1,5]thiazepin-4(5*H*)-ones[16] and the reaction of aromatic and heteroaromatic *O*-ethyl thiocarboxylates with the anions of *N*-arylmethyl(2-chloropyridyl)methylide amines represents a convenient route to the barely accessible 2,3-di(hetero)arylpyrido[3,2-*f*][1,4]thiazepines[17]. 5-Phenyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine was synthesized by a nucleophilic aromatic fluoride displacement-cyclization procedure in 25% yield[18] and the preparation of 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine[19] is also described by the same authors.

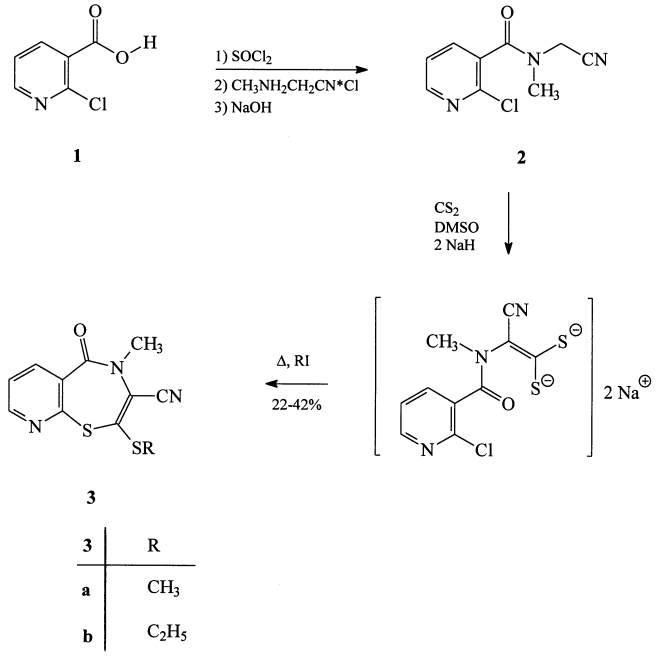
The *N*-cyanomethyl-*N*-methyl amides of nicotinic acid or substituted benzoic acids are obtained in a conventional manner by treating the acids with thionyl chloride and reacting the intermediate acid chloride (2-chloronicotinoyl chloride[20][21][22][23]) with methylaminoacetonitrile hydrochloride in a two phase system of aqueous (10%) sodium hydroxide/toluene. The new compounds are obtained in good to excellent yields with the exception of the new derivative **2** of 2-chloro nicotinic acid which was isolated only in 19% yield (89% yield is obtained in dichloromethane/triethylamine at room temperature for 22h). The 2-chloro-*N*-cyanomethyl-*N*-methyl-4-pyridinecarboxamide[24][25] and the 4-chloro-*N*-cyanomethyl-*N*-methyl-benzamide[26] are already described in literature.

 © WILEY-VCH Verlag GmbH, D-69451 Weinheim, 1998 1434−193X/98/0606−1237 $ 17.50+.50/0

Amides are known to exist as *syn*- and *anti*-rotamers. Therefore, NMR spectra of these unsymmetrically substituted amides **2** and **5** show a double set of signals (see experimental section).

Compound **2** reacts in dry DMSO with carbon disulfide in presence of sodium hydride at 50−60°C giving a cyclised intermediate which may be alkylated to the pyridothiazepines **3** with acceptable yield. This reactivity can be explained by the intermediacy of the enedithiolate and the intramolecular aromatic nucleophilic substitution of the 2-chloro-substituent by thiolate anion. The constitution of the new compounds **3a** and **3b** is supported by analytical and spectroscopical findings. Moreover, **3b** has been structurally characterized in detail by X-ray analysis.

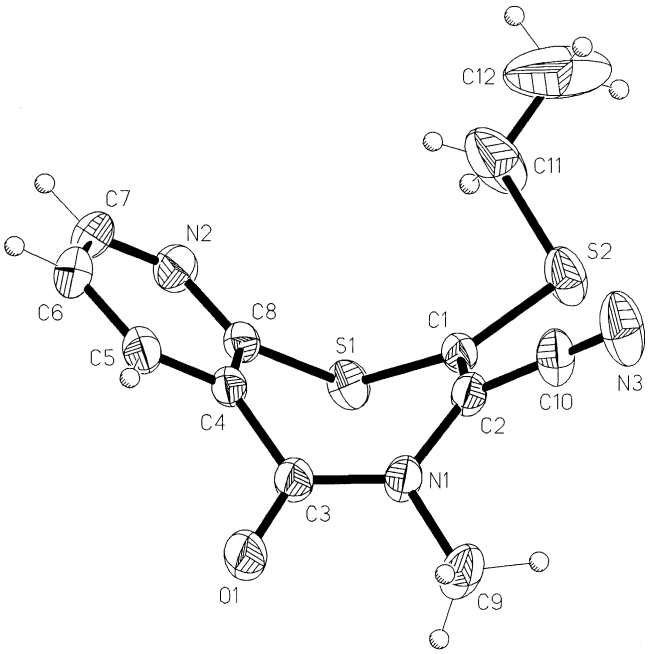
Scheme 1



3	R
a	CH_3
b	C_2H_5

The molecular structure and crystallographic atom numbering of **3b** used in this section are displayed in Figure 1. The conformation of the 1,4-thiazepine ring is characterized by the endocyclic torsion angles (enumerated clockwise and starting with S1−C1−C2−N1) 10.5(4), −55.0(4), 1.1(4), 49.8(5), −5.9(4), −58.6(3), 56.2(3)°. The thiazepine ring assumes a boat conformation with approximated mirror symmetry; the mirror plane is defined by S1 atom and the median perpendicular to the C3−N1 bond. The April 1997 version of the Cambridge Structural Database[27] was searched for pyrido[3.2-*f*][1,4]thiazepines (and other related 1,4-thiazepines, too) but only 5-(4-methyl-piperazinylpyrido[3,2-*f*][1,4]benzothiazepine[28] as a compound with a suitable comparative structure was found. Its seven-membered ring conformation is close to that of **3b**, the maximum difference of corresponding torsion angles in the two structures is less than 10°. The N1 atom in **3b** is sp^2 hybridized (bond angles sum to 359.8°). Due to their different environments the two endocyclic bond lengths N1−C2 [1.420(5) Å] and N1−C3 [1.352(5) Å] are significantly unequal. The standard values for a C(sp^2)−N(sp^2) single and double bond are given in the literature[29] with 1.40 and 1.29 Å, respectively. Compared with these values, N1−C2 is slightly longer than a usual normal single bond and N1−C3 length is the average between a single and double bond. The two bond lengths C1−S1 [1.750(4) Å] and C8−S1 [1.785(4) Å] deviate only slightly from each other having the standard value of 1.76 Å for a C(sp^2)−S single bond[29] in between. Anomalously high values of the displacement parameters (see Figure 1) and unusual geometric parameters indicate a certain degree of disorder of the ethylthio substituent. The pyridine ring is exactly planar with no atom deviating by more than 0.008 Å from the l.s. plane.

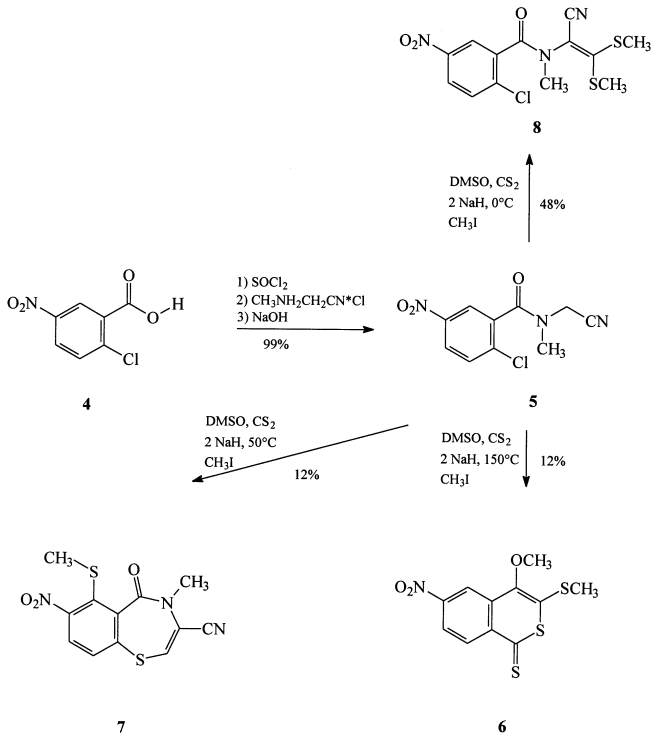
Figure 1. Molecular structure and atom numbering of **3b**. Displacement ellipsoids are drawn at the 30% probability level and H atoms as small circles of arbitrary radii.



Thus, deprotonation of the α-aza methylene group of these especially designed 2-chloro substituted aromatic amides with sodium hydride or potassium *tert*-butoxide yields the corresponding α-aza carbanions which are stable and react with carbon disulfide. Heating the reaction mixture for 6 hours at 130−150°C ensures the completion of the nucleophilic aromatic substitution[30−38], clearly demonstrating the versatility of this synthetic strategy for the formation of arene or hetarene anellated 1,4-thiazepines (Scheme 1).

To our surprise another reaction pathway was found in the case of the treatment of 2-chloro-*N*-cyanomethyl-*N*-methyl-5-nitrobenzamide (**5**) with sodium hydride in DMSO or DMF and carbon disulfide. In contrast to the expected formation of a compound analogous to **3** a halogen metal exchange in *ortho* position occured[39][40][41] followed by attack of carbon disulfide and cyclization to 4-methoxy-3-methylthio-6-nitro-2-benzothiopyran-1-thione (isothiocumarin-thione) (**6**).

Scheme 2



The structure assigned to product **6** is supported by spectral and analytical data as follows: The mass spectrum contains peaks at *m/z* 255 (M − CS) and 135 ($MeOC_6H_4CO$, 85%) and the ^{1}H-NMR spectral properties are characteristic for a nitrophenyl, methoxy (but not for a methylamino) and methylthio group. There is no CN-absorption in the IR spectrum. In the ^{13}C-NMR a relatively low field signal for the thiocarbonyl group was observed (see experimental section).

There is some evidence for the existence of compounds like **6** in literature[42][43].

Furthermore, we were able to isolate the ketene dithioacetal **8** by reaction of **5** with carbon disulfide. The NMR spectrum obtained at 30°C shows a double set of all expected signals in the ratio of 1 to 5 (see experimental section).

Another result should be mentioned in this connection. In the case of 4-nitro derivative instead of **5** at 130−150°C the formation of 4-methyl-2-methylthio-8-nitro-5(4*H*)-oxo-1,4-benzothiazepine-3-carbonitrile (yield 19%) in analogy to that of **3** is observed whereas at lower temperatures no reaction took place.[50] This behaviour is quite different from that of the benzamide **5** bearing the nitro group in 5-position. For **5** already at 50°C cyclization and ring transformation to **7** occurs whereas at 0°C the appropriate ketene dithioacetal **8** is formed (cf. Scheme 2).

Apparently, reaction pathway is influenced by the presence of the nitro group in 4- or 5-position.

The structure of compound **7** was confirmed by ^{1}H- and ^{13}C-NMR-investigations, IR spectroscopy as well as mass spectrometry. In ^{1}H-NMR spectrum only two signals (δ 7.47 and 8.38) were observed in the aromatic region. At δ 5.78 there is a singlett corresponding to an olefinic proton. At δ 2.61 and 3.30 there are singletts of the protons of the *S*-methyl or *N*-methyl group, respectively. A ^4J coupling of the two hydrogen atoms in *ortho* position to the nitro group indicating the initially postulated 2-methylthio-compound is not observed and the signal at δ 52 in the ^{13}C-NMR gives a C−H coupling of 158 Hz. That means that H and SCH_3 have changed their positions. The conversion presumably proceeds *via* ring transformation. In a first step the enedithiolate cyclises and its H atom in 6-position is converted into a hydride ion. The latter then opens the ring formed in the first step to an enthiolate which for its part substitutes the chlorine atom in 2-position. As the result of the described sequence after reaction with iodomethane compound **7** is formed.

Comparable difficulties concerning the presence of a nitro group were reported in literature. 2-Chloro-5-nitro-2′-mercaptobenzanilide fails to undergo cyclization to a dibenzothiazepinone by hot aq. alkali[44]. It readily changes to the benzothiazole derivative, whereas 2-chloro- and 2,5-dichloro-2′-mercaptobenzanilides can be readily converted into the expected anellated heterocycles.

The support by the *Fonds der Chemischen Industrie* is gratefully acknowledged. The authors thank Mr. *Frédéric Géraud* (ENSCR, Rennes, France) and Mr. *Jan Procházka* (University of Pardubice, Czech Republic) for experimental work during a practical trainee course.

Experimental Section

General: All dithiocarboxylation reactions were carried out under argon atmosphere. Melting points were determined with a Kofler hot stage microscope and are uncorrected. Infrared spectra were measured with an IR-spectrophotometer "Specord" Carl Zeiss Jena or FTIR-spectrometer 1000 of Perkin-Elmer. ^{1}H- and ^{13}C-NMR spectra were recorded with either a Bruker WP 200 or AC 80 or a Varian Gemini 200 or Unity 500 spectrometer in $CDCl_3$. Mass spectra (70 eV) were measured with an AMD 402 of the AMD Intectra GmbH. Reactions were monitored by TLC using DC Alufolien, Kieselgel 60 F_{254} (Merck) plates and were visualized under UV irradiation. Column chromatography was performed with Kieselgel 60 (Merck; particle size 0.063−0.2 mm). The elemental analyses were performed with an elementary analyser Vario EL Foss Heraeus of Elementar-Analysen-Systeme GmbH.

2-Chloro-N-cyanomethyl-N-methylnicotinamide (**2**): Methylaminoacetonitrile hydrochloride (10.56 g, 0.1 mol) was dissolved in water (60 ml). 2-Chloronicotinoyl chloride, [prepared by reacting 2-chloronicotinic acid (**1**) (15.76 g, 0.1 mol) in thionyl chloride (70 ml) and distillation of the excess $SOCl_2$] dissolved in toluene (60 ml) was added. Under cooling and vigorous stirring a sodium hydroxide solution was added until the reaction mixture was alkaline. After one hour stirring the layers were separated. The organic one was washed three times with water, dried with anhydrous sodium sulfate and concentrated to give 4.0 g (yield: 19%) of a colourless solid which may be purified by recrystallisation from water, m.p. 78−81 °C. − IR (KBr): $\tilde{\nu}$ = 3064, 3026, 2994, 2965, 2935, 2253, 1642, 1605, 1580, 1561, 1499, 1491, 1449, 1437, 1405, 1397, 1339, 1296, 1263, 1237, 1205, 1134, 1107, 1061, 1047, 985, 961, 927, 889, 825, 774, 761, 736, 682, 638, 617 cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 3.02 (s, 2.57 H, NCH_3), 3.25 (s, 0.43 H, NCH_3), 4.07 (s, 0.3 H, NCH_2), 4.53 (s, 1.7 H, NCH_2), 7.36 (dd, H, H-4, ^3J = 7.62 Hz,

^4J = 4.88 Hz), 7.69 (dd, H, H-5, ^3J = 7.62 Hz, ^4J = 1.95 Hz), 8.48 (dd, H, H-6, ^3J = 4.88 Hz, ^4J = 1.95 Hz) . – MS; *m/z* (%): 209 (M^+, 7), 174 (16), 140 (100), 112 (46), 85 (7), 76 (29). – $C_9H_8ClN_3O$ (209.6): calcd. C 51.55, H 3.85, N 20.04, Cl 16.91; found C 51.53, H 3.90, N 20.22, C 16.89.

2-Chloro-N-cyanomethyl-N-methyl-5-nitrobenzamide (**5**): Methylaminoacetonitrile-HCl (10.56 g, 0.1 mol) was dissolved in water (40 ml). 2-Chloro-5-nitro benzoyl chloride (prepared by refluxing of 20.16 g, 0.1 mol 2-chloro-5-nitro benzoic acid (**4**) and thionyl chloride) in toluene (40 ml) was added. Under cooling and vigorous stirring a sodium hydroxide solution was added until the reaction mixture was alkaline. After one hour stirring the product precipitated was separated by filtration to give 25.21 g (yield: 99%) of a colourless solid, m.p. 121 °C. – IR (KBr): $\tilde{\nu}$ = 3099, 3075, 3036, 2995, 2951, 2864, 2403, 2347, 2245, 1920, 1641, 1593, 1527, 1497, 1467, 1404, 1349, 1299, 1261, 1221, 1185, 1142, 1121, 1088, 1043, 989, 961, 924, 911, 876, 839, 773, 750, 727, 697, 655, 608, 540, 486, 417 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.99 (s, 2.6 H) and 3.26 (s, 0.4 H, CH_3), 4.03 (s, 0.28 H) and 4.54 (s, 1.72 H, NCH_2), 7.52 (d, H, ^3J = 8.4 Hz, aromatic H-3), 8.211 (dd, H, ^3J = 8.4 Hz, ^4J = 2.15 Hz, aromatic H-4), 8.307 (d, H, ^3J = 2.15 Hz, aromatic, H-6) . – MS; *m/z* (%): 253 (11), 218 (13), 184 (100), 168 (5), 154 (8), 138 (32), 126 (15), 110 (15), 75 (19). – $C_{10}H_8ClN_3O_3$ (253.7): calcd. C 47.35, H 3.18, N 16.57; found C 47.44, H 3.17, N 16.36.

4-Methyl-2-methylthio-5(4H)-oxopyrido[3,2-f][1,4]thiazepine-3-carbonitrile (**3a**): Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-*N*-cyanomethyl-*N*-methylnicotinamide (**2**) (1.05 g, 5 mmol) and carbon disulfide (0.38 g, 0.3 ml, 5 mmol) in dry DMSO (20 ml) at 10 °C. After the addition, the mixture was warmed up to 50–60 °C and stirred for 6 h. After this time iodo methane (1.53 g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 3 h at room temp. Then the solution was poured into ice water. The precipitate was filtered off and dried. This yellow solid material (1.76 g) obtained was heated with methanol and filtered off. The filtrate was cooled and a pale yellow substance precipitated. Recrystallization from methanol gave the pure sample (0.55 g, yield: 42%) as colourless needles, m.p. 176–177.5 °C. – IR (KBr): $\tilde{\nu}$ = 2928, 2210, 1649, 1575, 1557, 1471, 1452, 1403, 1365, 1297, 1232, 1173, 1116, 1079, 1029, 962, 926, 894, 820, 793, 757, 716, 642, 582, 523 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.62 (s, 3 H, SCH_3), 3.37 (s, 3 H, NCH_3), 7.41 (dd, H, ^3J = 7.82 Hz and 4.85 Hz, pyrid. H-7), 8.12 (dd, H, ^3J = 7.82 Hz, ^4J = 1.95 Hz, pyrid. H-6) , 8.52 (dd, H, ^3J = 4.75 Hz, ^4J = 1.95 Hz, pyrid. H-8) . – ^{13}C-NMR ($CDCl_3$): δ = 166.4 (C=O), 156.6 (C-9a), 153.2 (C-2), 151.5 (C-8), 140.7 (C-6), 133.5 (C-5a), 124.5 (C-7), 113.4 (CN), 113.3 (C-3), 35.6 (N-CH_3), 18.3 (SCH_3) . – MS; *m/z* (%): 263 (M^+, 35), 217 (100), 196 (47), 189 (16), 152 (69), 109 (8), 91 (53), 77 (17), 67 (56). – $C_{11}H_9N_3OS_2$ (263.3): calcd. C 50.17, H 3.44, N 15.96; found C 50.01, H 3.46, N 15.48.

2-Ethylthio-4-methyl-5(4H)-oxopyrido[3,2-f][1,4]thiazepine-3-carbonitrile (**3b**): Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-*N*-cyanomethyl-*N*-methylnicotinamide (**2**) (1.05 g, 5 mmol) and carbon disulfide (0.38 g, 0.3 ml, 5 mmol) in dry DMSO (20 ml) at 10 °C. After the addition, the mixture was warmed up to 50–60 °C and stirred for 6 h. After this time iodoethane (1.53 g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 3 h at room temp. Then the solution was poured into ice water. The oily precipitate was extracted several times with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. The residue was filtered off and dried. This material (2.12 g) obtained was dissolved in dichloromethane and purified by column chromatography on silica gel (Merck 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 0.39 g of a green white solid. Recrystallization from methanol gave the pure sample (0.30 g, yield: 22%) as a colourless solid, m.p. 135–136.5 °C. – IR (KBr): $\tilde{\nu}$ = 3050, 2927, 2212, 1652, 1575, 1557, 1450, 1421, 1402, 1373, 1295, 1253, 1170, 1112, 1077, 1060, 1028, 974, 930, 894, 825, 795, 759, 734, 716, 643, 582, 524, 478, 427 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.18 (t, 3 H, CH_3), 3.17 (br s, 2 H, SCH_2), 3.40 (s, 3 H, NCH_3), 7.44 (dd, H, ^3J = 7.81 Hz and 4.69 Hz, pyrid.part H-7), 8.15 (dd, H, ^3J = 7.72 Hz, ^4J = 1.95 Hz, pyrid.part H-6), 8.55 (dd, H, ^3J = 4.69 Hz, ^4J = 1.95 Hz, pyrid.part H-8) . – ^{13}C-NMR ($CDCl_3$): δ = 166.5 (C=O), 156.6 (C-9a), 151.8 (C-2), 151.5 (C-8), 140.7 (C-6), 133.4 (C-5a), 124.4 (C-7), 114.5 (CN), 113.4 (C-3), 35.7 (N-CH_3), 29.7 (SCH_2), 15.1 (CH_3) . – MS; *m/z* (%): 279 (M+2, 4; two sulfur atoms), 277 (M^+, 44), 217 (100), 210 (23), 204 (12), 182 (18), 152 (19), 105 (13), 77 (16), 67 (58). – $C_{12}H_{11}N_3OS_2$ (277.4): calcd. C 51.96, H 4.00, N 15.15; found C 51.81, H 3.89, N 15,21.

4-Methoxy-3-methylthio-6-nitro-2-benzothiopyran-1-thione (Isothiochromene-1-thione) (**6**): Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-*N*-cyanomethyl-*N*-methyl-5-nitrobenzamide (**5**) (1.27 g, 5 mmol) and carbon disulfide (0.38 g, 0.3 ml, 5 mmol) in dry DMF (20 ml) at –10 °C. After the addition, the mixture was warmed up to room temperature and stirred for 6 h at 150 °C. After this time it was cooled to –10 °C. Iodomethane (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at room temp. Then the solution was poured into ice water. The precipitate was filtered off and dried. This material (2.12 g) obtained was dissolved in dichloro methane and purified by column chromatography on silica gel (Merck, Kieselgel 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 0.2 g of an oil. Recrystallization from ethanol gave the pure sample (0.18 g, yield: 12%) as a colourless solid (R_f = 0.68, ethyl acetate/*n*-hexane 1:1), m.p. 170–171 °C. – IR (KBr): $\tilde{\nu}$ = 2922, 2852, 1673, 1583, 1549, 1419, 1380, 1335, 1288, 1254, 1197, 1143, 1119, 1089, 1059, 952, 845, 833, 759, 677, 602 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.52 (s, 3 H, SCH_3), 3.90 (s, 3 H, OCH_3), 6.87 (d, H, ^4J = 1.95 Hz, aromatic H-6), 7.216 (dd, H, ^3J = 8.59 Hz, ^4J = 1.95 Hz, aromatic H-8), 8.17 (d, H, ^3J = 8.59 Hz, aromatic H-9) . – ^{13}C-NMR ($CDCl_3$): δ = 192.0 (C=S), 160.3 (C-6), 148.5 (C-8a), 136.9 (C-4), 131.6(C-8), 124.7 (C-4, C-7), 118.8 (C-4a), 116.3 (C-3), 34.7 (O-CH_3), 14.6 (SCH_3) . – MS; *m/z* (%): 255 [M^+-CS] (49), 222 (4), 182 (100), 167 (7), 153 (8), 139 (22), 122 (9), 95 (16), 69 (10), 63 (13). – $C_{11}H_9NO_3S_3$ (299.3): calcd. C 44.13, H 3.03, N 4.67; found C 44.07, H 3.30, N 4.72.

4-Methyl-6-methylthio-7-nitro-5(4H)-oxo-1,4-benzothiazepine-3-carbonitrile (**7**): Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-*N*-cyanomethyl-*N*-methyl-5-nitrobenzamide (**5**) (1.27 g, 5 mmol) and carbon disulfide (0.38 g, 0.3 ml, 5 mmol) in dry DMSO (20 ml) at 10 °C. After the addition, the mixture was warmed up to room temperature and stirred for 6 h at 50–60 °C. After this time it was cooled to room temp. Iodomethane (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 2 h at room temp. Then the solution was poured onto ice water containing some drops of conc. hydrochloric acid. The oily precipitate was three times extracted with ethyl acetate and dried with sodium sulfate. The material (2.12 g) obtained by evaporation of the solvent was dissolved in dichloromethane and purified by column chromatography on silica gel (Merck 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 0.21 g of a yellow solid. Recrystallization from methanol gave the pure sample (0.18 g, yield: 12%) as yellow crystals, m.p. 180 °C (decomp.). – IR (KBr): $\tilde{\nu}$ = 3098, 3076, 2989, 2928, 2856, 2212, 1929, 1812, 1655, 1594,

1583, 1521, 1466, 1443, 1423, 1394, 1352, 1303, 1291, 1246, 1166, 1121, 1061, 1033, 981, 955, 926, 909, 874, 848, 788, 766 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.61 (s, 3 H, SCH_3), 3.30 (s, 3 H, NCH_3), 5.78 (s, H, H-2) 7.47 (d, H, ^3J = 8.83 Hz, aromatic H-9), 8.38 (d, H, ^3J = 8.83 Hz, aromatic H-8) . – ^{13}C-NMR (125,705 MHz, [D$_6$]DMSO): δ = 164.5 (C=O), 149.3 (C-7), 138.4 (C-6), 133.2 (C-5a), 127.7 (d, *J* (C, H) = 169.8 Hz, C-8), 127.6 (C-9a), 126.1 (d, *J* (C, H) = 169.8 Hz, C-9), 113.8 (d, *J* (C=CH) = 10 Hz, C-3), 112.5 (CN), 52.0 (d, *J* (C, H) = 156.8 Hz, C-2), 27.6 (q, *J* (C, H) = 140 Hz, N-CH_3), 13.5 (q, *J* (C, H) = 141 Hz, SCH_3) . – MS; *m*/*z* (%): 277 (14), 263 (100), 246 (18), 233 (15), 216 (65), 200 (13), 186 (34), 170 (14), 159 (30), 142 (29), 121 (14), 91 (32), 75 (29), 50 (62). – $C_{12}H_9N_3O_3S_2$ (307.4): calcd. C 46.90, H 2.95, N 13.67, S 20.80; found C 47.21, H 3.17, N 14.32, S 20.78.

3,3-Bis(methylthio)-2-[N-(2-chloro-5-nitrobenzoyl)-N-methylamino]acrylonitrile (**8**): Sodium hydride (0.5g 80% suspension in paraffin oil, 10 mmol) was added with stirring and in an argon atmosphere to a solution of 2-chloro-*N*-cyanomethyl-*N*-methyl-5-nitrobenzamide (**5**) (1.27g, 5 mmol) and carbon disulfide (0.38 g, 0.3 ml, 5 mmol) in DMF (30 ml, dried with CaH_2 and stored over molecular sieves) at 0°C. After the addition, the mixture was stirred for 2 h. Iodomethane (1.53 g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at room temp. Then the solution was poured into ice water and acidified by adding hydrochloric acid. The precipitate was extracted with ethyl acetate. This material (2.07 g) obtained after evaporation was purified by column chromatography on silica gel (Merck 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 0.96 g of a yellow oil. Recrystallization from ethanol gave the pure sample (0.86 g, yield: 48%) as yellow crystals (R_f = 0.44, ethyl acetate/*n*-hexane 1:1), m.p. 91–109 °C. – IR (KBr): $\tilde{\nu}$ = 3094, 2928, 2204, 1669, 1597, 1530, 1477, 1424, 1347, 1292, 1255, 1186, 1139, 1121, 1108, 1075, 1055, 1029, 974, 928, 895, 874, 838, 780, 760, 745, 721, 661, 490, 413 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.23 (s, 2.4 H, SCH_3), 2.43 (s, 2.4 H, SCH_3), 2.51 (s, 0.6 H, SCH_3), 2.57 (s, 0.6 H, SCH_3), 3.00 (s, 0.6 H, NCH_3), 3.28 (s, 2.4 H, NCH_3), 8.1 (dd, 0.8 H, ^4J = 2.15 Hz, ^3J = 8.5 Hz, H-4, aromatic), 7.56 (d, 0.2 H, ^3J = 8.5 Hz, H-3, aromatic), 7.63 (d, 0.8 H, ^3J = 8.5 Hz, H-3, aromatic), 8.21 (dd, 0.2 H, ^4J = 2.15 Hz, ^3J = 8.5 Hz, H-4, aromatic), 8.27 (d, 0.8 H, ^4J = 2.15 Hz, H-6, aromatic), 8.31 (d, 0.2 H, ^4J = 2.15 Hz, H-6, aromatic) . – MS; *m*/*z* (%): 310 (M^+-SCH_3, 100), 264 (9), 184 (13), 173, (18), 138 (13), 91 (25). $C_{13}H_{12}ClN_3O_3S_2$ (357.8): calcd. C 43.64, H 3.38, N 11.74; found C 43.54, H 3.03,N 11.85.

Crystal Structure Analysis[45]. – *Crystal Data*: $C_{12}H_{11}N_3OS_2$, M_r = 277.36, monoclinic, space group *Pn* (No. 7), *a* = 4.5810(3), *b* = 14.094(1), *c* = 10.3379(8) Å, β = 95.033(7)°, *V* = 664.89(9) Å^3, *Z* = 2, μ = 0.391 mm^{-1}, d_{calcd} = 1.385 g/cm^3; *Data collection*: Stoe STADI4 diffractometer, crystal size 0.42 × 0.25 × 0.17 mm, *T* = 293(2) K, Mo-*Kα* radiation (graphite monochromator, λ = 0.71073 Å), Θ/2Θ scan mode, Θ range 2.45–30.00°, *h*,*k*,*l* range $\bar{6}$/6,$\bar{19}$/19,$\bar{14}$/14, 3930 measured reflections, 2732 unique observed reflections [$I > 2\sigma(I)$]; *Structure solution and refinement*: Heavy atom method, full-matrix least-squares refinement on F^2, hydrogen atoms at geometrically calculated positions and treated according to the riding model, all non-hydrogen atoms refined anisotropically, 23.8 reflections/parameter, max. and min. electron density in last difference Fourier synthesis 0.369 and −0.333 e/Å^3, $(\Delta/\sigma)_{max}$ in last l.s. cycle 0.000, *R*1 = 0.0581 for $I > 2\sigma(I)$, *wR*2 = 0.1379 and *S* = 1.178 for all data, $w = 1/[\sigma^2(F_o^2)+(a\cdot P)^2+b\cdot P]$ with $P = 1/3(F_o^2+2F_c^2)$ and *a* = 0.0304, *b* = 0.3477, absolute configuration [Flack parameter[46] = −0.08(11)]. *Programs used*: SHELXS-86[47], SHELXL-93[48], XP/PC[49].

[1] R. B. Silverman, *Medizinische Chemie für Organiker, Biochemiker und Pharmazeutische Chemiker*, VCH Verlagsgesellschaft, Weinheim, New York, Basel, Cambridge, Tokyo, **1995**, p. 91.
[2] R. K. Husa, M. F. Rafferty, T. J. Hagen, E. A. Hallinan (G. D. Searle and Co., USA), US 5304644 A , 1994; *Chem. Abstr.* **1994**, *121*, 134165.
[3] J. R. Housley, J. E. Jeffery, K. J. Nichol, B. J. Sargent (Boots Co PLC), PCT Int. Appl. 9411360, 1994; *Chem. Abstr.* **1994**, *121*, 134167.
[4] T. Oosawa, H. Murooka, A. Miwa (Kirin Brewery), JP 05271208, 1993; *Chem. Abstr.* **1994**, *120*, 245182.
[5] S. Kakehi, S. Ito (Kissei Pharmaceutical, Japan), JP 06025257 A2 , 1994; *Chem. Abstr.* **1994**, *121*, 134166.
[6] L.E. Brieaddy (Wellcome Foundation Ltd., UK), PCT Int. Appl. 9605188, **1996**; *Chem. Abstr.* **1996**, *125*, 114724.
[7] L. E. Brieaddy (Wellcome Foundation Ltd.), PCT Int. Appl. 9316055, 1993; *Chem. Abstr.* **1994**, *120*, 164244.
[8] G. Walther, H. Daniel, W. D. Bechtel, K. Brandt, *Arzneim.-Forsch.* **1990**, *40*, 440–446.
[9] W. Dölling, V. Birkner, H. Hartung, M. Biedermann, *Proceedings of the 17th International Symposium on the Organic Chemistry of Sulfur*, Tsukuba, Japan, July 1996, in *Phosphorus, Sulfur, Silicon* **1997**, *120 & 121*, 467–469.
[10] W. Dölling, *Phosphorus, Sulfur, Silicon* **1997**, *122*, 71–86.
[11] J. T. Sharp, *Seven-membered Rings with Two or More Heteroatoms* in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, **1984**, vol. 7, chapter 5.18.6, p. 631–636.
[12] K.-H. Wünsch, A. Ehlers, *Z. Chem.* **1970**, *10*, 361–370.
[13] A. Lévai, *Khim. Geterotsikl. Soedin.* **1986**, 1443–1452.
[14] A. Lévai, *Trends Heterocycl. Chem.* **1995**, *4*, 51–69.
[15] A. Chimirri, R. Gitto, S. Grasso, A. M. Monforte, M. Zappala, *Adv. Heterocycl. Chem.* **1995**, *63*, 61–101.
[16] A. Couture, E. Huguerre, P. Grandclaudon, *J. Org. Chem.* **1990**, *55*, 4337–4339.
[17] A. Couture, E. Deniau, P. Grangclaudon, C. Simion, *Synthesis* **1996**, 986–990.
[18] A. Garofalo, G. Campiani, S. M. Ciani, I. Fiorini, V. Nacci, *Tetrahedron* **1996**, *52*, 7745–7754.
[19] A. Garofalo, V. Nacci, F. Corelli, G. Campiani, *Heterocycles* **1990**, *31*, 1291–1300.
[20] F. L. Merchan, J. Garín, E. Melendez, T. Tejero, *Synthesis* **1983**, 154–156.
[21] A. Kamal, M. V. Rao, P. B. Sattur, *Heterocycles* **1986**, *24*, 3075–3078.
[22] A. Ohno, A. Tsutsumi, Y. Kawai, N. Yamazaki, Y. Mikata, M. Okamura, *J. Am. Chem. Soc.* **1994**, *116*, 8133–8137.
[23] T. R. Kelly, J. J. Walsh, *J. Org. Chem.* **1992**, *57*, 6657–6658.
[24] H. Yoshida, S. Shimano, S. Mochizuki, K. Konishi, K. Koike, T. Nakagawa (Nippon Kayaku Co., Ltd., Japan), EP Ep 246507 A1, 1987; *Chem. Abstr.* **1988**, *108,* 167312.
[25] Y. Watanabe, K. Konishi, S. Shimano, K. Koike, T. Yonekawa (Nippon Kayaku Co., Ltd., Japan), JP JP 04112872 A2, 1992; *Chem. Abstr.* **1992**, *117*, 145310.
[26] K. Takahashi, T. Masuda, K. Ogura, H. Iida, *Synthesis* **1983**, 1043–1045.
[27] F. H. Allen, O. Kennard, R. Taylor, *Acc. Chem. Soc.* **1983**, *16*, 146–152.
[28] M. Sbit, L. Dupont, O. Dideberg, J.-F. Liegelois, J. Delarge, *Acta Cryst.,* **1988**, *C44*, 319–321.
[29] P. Rademacher, *Strukturen organischer Moleküle*, VCH Verlagsgesellschaft, Weinheim, **1987**, p. 56.
[30] M. Makosza, *Chemie in unserer Zeit* **1996**, *30*(3), 134–140.
[31] O. N. Chupakhin, V. N. Charushin, H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, **1994**.
[32] F. Terrier, *Nucleophilic Aromatic Substitutions. the Influence of the Nitro Group*, VCH Verlagsgesellschaft, Weinheim, **1991**.
[33] M. F. Semmelhack, *Transition Metal Arene Complexes: Nucleophilic Addition* in *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegedus), Pergamon , **1995**, vol. 12, chapter 9.1, p. 979–1015.
[34] G. A. Artamkina, M. P. Egorov, I. P. Beletskaya, *Chem. Rev.* **1982**, *82*, 427–459.
[35] C. Paradisi, *Arene Substitution via Nucleophilic Addition to Electron Deficient Arenes* in *Comprehensive Organic Chemistry* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon

Press, Oxford, New York, Seoul, Tokyo, **1991**, vol. 4, p. 423−450.
[36] J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, **1968**.
[37] N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, P. A. Wade, *J. Org. Chem.* **1976**, *41*, 1560−1564.
[38] J. F. Bunnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273−412.
[39] R. D. Clark, A. Jahangir, *Org. React.* **1995**, *47*, 1−314.
[40] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879−899.
[41] H. W. Gschwend, H. R. Rodriguez, *Org. React.* **1979**, *26*, 1−120.
[42] L. Legrand, N. Lozac′h, *Bull. Soc. Chim. Fran.* **1964**, 1787, 1791, 1793.
[43] V. Prey, B. Kerres, H. Berbalk, *Monatsh. Chem.* **1960**, *91*, 774, 788.
[44] K. Nagarajan, C. L. Kulkarni, A. Venkateswarlu, R. K. Shah, *Indian J. Chem.* **1974**, *12*, 258−262.
[45] Further details of the crystal structure determination are available on request from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-407350, the names of the authors, and the journal citation.
[46] H. D. Flack, *Acta Crystallogr. Sect. A* **1983**, *A 39*, 876−881.
[47] G. M. Sheldrick, *SHELXS-86, Program for the Solution of Crystal Structures*, Universität Göttingen, **1986**.
[48] G. M. Sheldrick, *SHELXL-93, Program for the Refinement of Crystal Structures*, Universität Göttingen, **1993**.
[49] *XP/PC, Molecular Graphics Program Package for Display and Analysis of Stereochemical Data, Version 4.2 for MS-DOS*, Siemens Analytical X-Ray Instruments, Inc., Madison, Wisconsin, USA, **1990**.
[50] W. Dölling, A. Perjéssy, I. Schaller, A. Kolbe, *J. Heterocycl. Chem.*, **1998** in press.

[97263]