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Synthesis of 2-Substituted Thiobenzimidazoles as Potential Anthelminthics[1)]

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The 2-substituted thiobenzimidazoles **7–19** have been synthesized and tested for their anthelminthic activity against *Ancylostoma ceylanium* and *Hymenolepsis nana* in hamsters and rats, respectively.

Synthese 2-substituierter Thiobenzimidazole als potentielle Anthelminthica

Die 2-substituierten Thiobenzimidazole **7–19** wurden synthetisiert und auf ihre anthelminthische Aktivität gegen *Ancylostoma ceylanium* und *Hymenolepsis nana* an Hamster und Ratte getestet.

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Although introduction of an alkyl or arylthio pharmacophore at 2 and 5 positions of benzimidazole is generally associated with a broad spectrum of anthelminthic activity[2-4], this has not been fully explored in the chemotherapy of intestinal nematodes. These observations led us to synthesize the structurally related 2-substituted thiobenzimidazoles **7–19** which have been evaluated for their anthelminthic activity.

The benzimidazole-2-thiones **5–7** and **9** have seen synthesized by the reaction of carbon disulphide with the corresponding o-phenylenediamines[5-7], of which **5** and **6** were treated with 1-chloro-3-(N-phenyl-piperazinyl)propane[8] to yield 2-[3-(1-phenyl-4-piperazinyl)propyl]thiobenzimidazole **(10)** and 5(6)-nitro-2-[3-(1-phenyl-4-piperazinyl)propyl]thiobenzimidazole **(11)**, respectively. Similarly, treatment of the potassium salts of **7** and **9** with ethyl chloroformate resulted in the formation of 1-carbethoxy-2-carbethoxythio-5-phenylthiobenzimidazole **(12)** and 1-methyl-2-carbethoxy-thiobenzimidazole **(13)**, respectively. A similar reaction of the potassium salt of **7** with methyliodide gave 2-methylthio-5-phenylthiobenzimidazole **(8)**, while reaction of the potassium salt of **9** with 2-bromoacetylfuran[9] afforded 1-methyl-2-(methylcarbonyl-2-furyl)-thiobenzimidazole **(14)** which was reduced with sodium borohydride to give 1-methyl-2-[2-hydroxy-2-(2-furyl)ethyl]thiobenzimidazole **(15)**. Treatment of **15** with thionyl chloride did not give the desired compound **16**, instead 1-methylbenzimidazole-2-thione **9** was isolated.

Reaction of the potassium salt of **7** with 1-chloro-4-nitrobenzene gave 2-[(4-nitrophenyl)thio]-5-phenylthiobenzimidazole **(17)**. Catalytic hydrogenation of **17** afforded the corresponding amino compound **18** which was allowed to react with thiophosgene to yield 2-[(4-isothiocyanatophenyl)thio]-5-phenyl thiobenzimidazole **(19)**.

Anthelminthic Activity

All the compounds were evaluated for their antihookworm and anticestode activity against *Ancylostoma ceylanicum* and *Hymenolepis nana* in Hamsters and rats, respectively. The screening was done using the method of *Steward* with slight modifications[10-12]. In this test none of the compounds showed noteworthy activity up to an oral dose of 250 mg/kg given for 1–3 days. Compounds **7** and **14** were toxic to rats infected with *H.nana* at 100 mg/kg.

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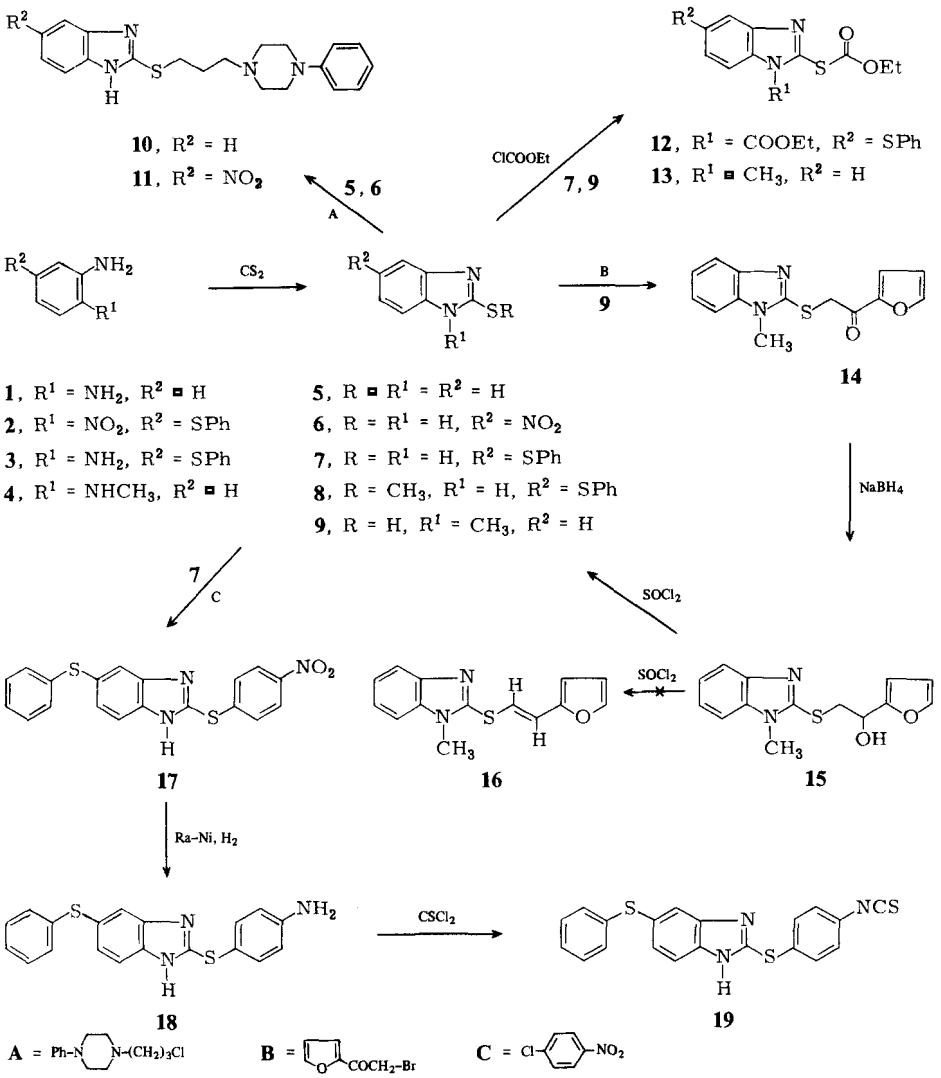
Experimental Part

The structure of all compounds were checked by *IR* on Perkin-Elmer 157 infracord spectrophotometer. *NMR*: Varian A-60D and Perkin-Elmer R-32 spectrometers, TMS int. ref.. *MS*: Jeol-JMS D-300 spectrometer. The *purity* of the compounds was checked on silica gel G-plates and spots were located by iodine vapours or $KMnO_4$ spray. *MP*: in sulphuric acid bath, uncorr. The *analysis* of the compounds are tabulated in Table 1.

2-Nitro-5-phenylthioaniline **(2)**

A mixture of 1.1 g (10 mmol) thiophenol, 0.56 g (10 mmol) potassium hydroxide and 1.7 g (10 mmol) 2-nitro-5-chloroaniline in 30 ml ethanol was refluxed for 4 h. The separated solid was washed with



water, crystallised from ethanol, yield 2 g (83 %), m.p. 115 °C. IR (KBr): 1320, 1560 (NO_2), 3300, 3400 cm^{-1} (NH_2).

5-Phenylthiobenzimidazole-2-thione **(7)**

A mixture of 2.4 g (10 mmol) **2** and Raney-nickel (about 0.5 g) in 50 ml ethanol was shaken with hydrogen in a Parr hydrogenator at 3.5 kg/cm^2 for 12 h. The catalyst was removed and 1.1 g (15 mmol) carbon disulfide and 0.56 g (10 mmol) potassium hydroxide added to the above filtrate. The reaction mixture was refluxed for 4 h, acidified with dil. HCl, the separated solid was crystallised from ethanol, yield 2 g (77 %), m.p. 236 °C. IR (KBr): 2610 cm^{-1} (SH). MS: m/e = 258.

Table 1: *Analytical Data*

Compd. No.	Molecular formula	(M.W.)	Calculated			Found		
			C	H	N	C	H	N
2	$C_{12}H_{10}N_2O_2S$	(246)	58.5	4.06	11.4	58.4	4.00	11.2
7	$C_{13}H_{10}N_2S_2$	(258)	60.5	3.87	10.9	60.3	3.91	10.8
8	$C_{14}H_{12}N_2S_2$	(272)	61.8	4.41	10.3	61.5	4.30	10.4
10	$C_{20}H_{24}N_4S$	(352)	68.2	6.81	15.9	67.9	6.61	15.7
11	$C_{20}H_{23}N_5O_2S$	(397)	60.5	5.79	17.6	60.2	5.50	17.4
13	$C_{11}H_{12}N_2O_2S$	(236)	55.9	5.08	11.9	55.7	5.24	11.6
14	$C_{14}H_{12}N_2O_2S$	(272)	61.8	4.41	10.3	61.6	4.27	10.1
15	$C_{14}H_{14}N_2O_2S$	(274)	61.3	5.10	10.2	61.2	5.00	10.4
17	$C_{19}H_{13}N_3O_2S_2$	(379)	60.2	3.43	11.1	60.0	3.32	11.4
18	$C_{19}H_{15}N_3S_2$	(349)	65.3	4.29	12.0	65.2	4.40	12.3
19	$C_{20}H_{13}N_3S_3$	(391)	61.4	3.32	10.7	61.1	3.23	10.5

2-Methylthio-5-phenylthiobenzimidazole **(8)**

A solution of 2.84 g (20 mmol) methyl iodide in 15 ml dry acetone was added to a stirred and ice cooled solution of 2.97 g (10 mmol) potassium salt of **7** in 20 ml dry acetone. Stirring was continued for 5 h and then the solvent was removed under reduced pressure; the residue was taken in ethylacetate, washed with 2 × 5 ml water, dried (Na_2SO_4) and concentrated to get a sticky product which was triturated with ethylacetate hexane, yield 1.7 g (62.5 %), m.p. 118 °C. NMR ($CDCl_3$): δ (ppm) = 2.60 (s, 3H, S-CH_3), 6.96–7.50 (m, 8H, Ar-H).

2-[3-(1-Phenyl-4-piperazinyl)propyl]thiobenzimidazole **(10)**

A solution of 1.5 g (10 mmol) **5** and 2 ml 20 % NaOH in 30 ml DMF was stirred for 30 min and 2.38 g (10 mmol) 1-chloro-3-(N-phenyl-piperazinyl)propane **(A)** was added. The reaction mixture was heated at 60–70 °C with stirring for 12 h and then poured into water. The separated solid was crystallized from chloroform, yield 1.7 g (50 %), m.p. 145 °C. NMR ($CDCl_3$): δ (ppm) = 1.84–2.13 (m, 2H, $SCH_2C\underline{H}_2$), 2.64 [t, 6H, $N(CH_2)_3$], 3.14–3.50 (m, 6H, Ar-N-($C\underline{H}_2)_2$, S-CH_2], 6.80–7.40 (m, 10H, Ar-$\underline{H}$ and $N\underline{H}$).

Similarly 5(6)-Nitro-2-[3-(1-phenyl-4-piperazinyl)propyl]thiobenzimidazole **(11)** was prepared by treating **6** with 1-chloro-3-(N-phenylpiperazinyl)propane **(A)** in 56 % yield, m.p. 125 °C. NMR (DMSO-d_6): δ (ppm) = 1.81–2.18 (m, 2H, $SCH_2C\underline{H}_2$), 2.40–2.70 [m, 6H, $N(C\underline{H}_2)_3$], 3.04–3.31 (m, 6H, Ar-$N(C\underline{H}_2)_2$, S-$C\underline{H}_2$], 6.67–7.37 (m, 6H, N-Ar-$\underline{H}$ and $N\underline{H}$), 7.54 (d, 1H, 4H of benzimidazole, J = 9 Hz), 8.00 (dd, 1H, 5H of benzimidazole, J = 2 Hz, J = 9 Hz), 8.25 (d, 1H, 7H of benzimidazole, J = 1.5 Hz).

1-Carbethoxy-2-carbethoxythio-5-phenylthiobenzimidazole **(12)**

A solution of 2.16 g (20 mmol) ethyl chloroformate in 10 ml dry acetone was added to a stirred solution of 2.97 g (10 mmol) potassium salt of **7** in 20 ml dry acetone under ice cooling. Stirring was continued for 5 h and then the solvent was removed i.vac. The residue was taken in ethyl acetate, washed with 2 × 25 ml water, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel column using hexane as eluant to get the product as an oil, yield 1.5 g (45 %). IR (Neat): 1750 cm^{-1} ($COOC_2H_5$). NMR ($CDCl_3$): δ (ppm) = 1.20–1.60 [m, 6H, $(CH_2C\underline{H}_3)_2$], 4.15–4.65 [m, 4H, $(C\underline{H}_2CH_3)_2$], 7.08–7.90 (m, 8H, Ar-H).

Similarly 1-methyl-2-carbethoxy-thiobenzimidazole **(13)** was prepared by the reaction of 1.08 g (10 mmol) ethylchloroformate with 2.0 g (10 mmol) potassium salt of **9** and purified by chromatography on a silica gel column using benzene as eluant in 43 % yield, m.p. 106 °C. IR (KBr): 1720 cm^{-1} ($COOC_2H_5$). NMR ($CDCl_3$): δ (ppm) = 1.45 (t, 3H, $CH_2\underline{CH_3}$), 3.62 (s, 3H, N-CH_3), 4.46 (q, 2H, $\underline{CH_2}CH_3$), 6.90–7.22 (m, 3H, Ar-H), 7.67 (dd, 1H, Ar-H, J = 2 Hz, J = 9 Hz).

1-Methyl-2-(methylcarbonyl-2-furyl)thiobenzimidazole **(14)**

A solution of 1.8 g (10 mmol) 2-bromoacetylfuran **(B)** in 20 ml dry acetone was added to a stirred solution of 2.0 g (10 mmol) potassium salt of **9** in 20 ml dry acetone at room temp. After the addition was finished, the reaction mixture was further stirred for 3 h and then refluxed for 4 h. The solvent was removed i.vac. The residue taken in ethyl acetate, washed with 2 × 5 ml water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified chromatographically on a silica gel column using hexane benzene (1 : 1) as eluant, yield 1 g (37 %), m.p. 126 °C. IR (KBr): 1685 cm^{-1} (CH_2CO). NMR ($CDCl_3$): δ (ppm) = 3.68 (s, 3H, N-CH_3), 4.74 (s, 2H, CH_2), 6.41–6.60 (m, 1H, 4-H of furan ring), 7.09–7.70 (m, 6H, Ar-H). MS: m/e = 272.

1-Methyl-2-[2-hydroxy-2-(2-furyl)ethyl]thiobenzimidazole **(15)**

0.38 g (10 mmol) sodium borohydride was added in portions to a stirred mixture of 2.7 g (10 mmol) **14** and 150 ml methanol at 0 °C. After the addition was complete, the reaction mixture was stirred for 2 h at room temp. The solvent was removed i.vac. and the residue treated with 20 ml water. The product was crystallized from chloroform, yield 2 g (72 %), m.p. 105 °C. IR (KBr): 3150 cm^{-1} (OH). MS: m/e = 274.

2-[(4-Nitrophenyl)thio]-5-phenylthiobenzimidazole **(17)**

A mixture of 2.97 g (10 mmol) potassium salt of **7** and 1.5 g (10 mmol) 1-chloro-4-nitrobenzene **(C)** in 25 ml dry DMF was refluxed for 24 h. The reaction mixture was poured into water. The separated solid was purified on a silica gel column using benzene as eluant, yield 0.8 g (26 %), m.p. 90 °C. IR (KBr): 1340, 1550 cm^{-1} (NO_2). MS: m/e = 379.

2-[(4-Aminophenyl)thio]-5-phenylthiobenzimidazole **(18)**

A mixture of 3.7 g (10 mmol) **17** and Raney-nickel (about 0.5 g) in 50 ml methanol was shaken with hydrogen in a Parr hydrogenator at 3.5 kg/cm^2 for 12 h. The catalyst was removed and the filtrate was concentrated i.vac. to get the product as solid which was crystallized from methanol, yield 3.0 g (88 %), m.p. 180 °C. IR (KBr): 3400 cm−1 (NH_2).

2-[(4-Isothiocyanatophenyl)thio]-5-phenylthiobenzimidazole **(19)**

A solution of 1.1 g (10 mmol) thiophosgene in 10 ml dry acetone was added dropwise to a stirred solution of 3.5 g (10 mmol) **18**, 2.0 g (20 mmol) triethylamine in 20 ml dry acetone at room temp. Stirring was continued for 2 h. The solvent was removed i.vac. The residue was taken in ethyl acetate, washed with 2 × 5 ml water, dried (Na_2SO_4) and concentrated. The crude product was purified on a silica gel column using benzene as eluant. It was crystallized from hexane, yield 3 g (76 %), m.p. 110 °C. IR (KBr): 2150 cm^{-1} (NCS). MS: m/e = 391.

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Neue Abbauprodukte des Didrovaltrats und des Homodidrovaltrats

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Bei der Umsetzung von Didrovaltrat **(1a)** bzw. Homodidrovaltrat **(1b)** mit BF_3-Etherat werden die 2,9-Dioxatricyclodecane **2b** und **2c** gebildet.

New Degradation Products of Didrovaltrate and Homodidrovaltrate

The 2,9-dioxatricyclodecanes **2b** and **2c** are formed by reaction of didrovaltrate **(1a)** and homodidrovaltrate **(1b)** with BF_3 etherate.

Wagner und *Jurcic*[2)] vermuteten, daß für die Wirkung des Didrovaltrats **(1a)**, ein Valepotriat vom Monoen-Typ, lipophilere Umwandlungsprodukte, z.B. 2,9-Dioxatricyclodecane **2** von Bedeutung sind. Die Halogen- bzw. Rhodan-Derivate **2a** wurden von *Thies* und Mitarb.[3,4)] durch Umsetzung von **1a** mit Halogen- bzw. Rhodanwasserstoff dargestellt. Die Alkohole **2b** und **2c** sind bisher nicht bekannt; sie konnten nach Umsetzung von **1a**, welches zusätzlich noch **1b** enthielt, mit Bortrifluorid-Etherat, chromatographisch isoliert werden.

Nach dem Massenspektrum besitzt **2b** gegenüber **1a** ein um 84 Einheiten verringertes Molgewicht mit der Summenformel $C_{17}H_{24}O_7$. Das IR-Spektrum zeigt, daß Oxiran- und

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