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Synthesis of Substituted Benzimidazoles as Potential Anthelminthics[1)]

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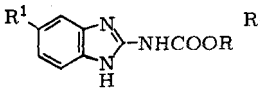
The substituted biphenyls **8–13**, 5(6)-phenyl-2-substituted benzimidazoles **7, 14–18**, 9-phenylbenzimidazo[1,2-*c*]quinazolin-6-one **19a**, and -thione **20** as well as the 1-aroyl-2-mercapto-5-phenylbenzimidazoles **21, 24, 25** have been synthesized. Their anthelminthic activities are reported.

Synthese substituierter Benzimidazole als potentielle Anthelminthika

Die substituierten Biphenyle **8–13**, 5(6)-Phenyl-2-substituierten Benzimidazole **7, 14–18,** 9-Phenylbenzimidazo[1,2-*c*]chinazolin-6-one und -thione **19–20** und 1-Aroyl-2-mercapto-5-phenylbenzimidazole **21, 24, 25** wurden synthetisiert. Eine dieser Verbindungen zeigt Aktivität gegen Helminthen.

Introduction of 2-carbalkoxyamino function in an appropriately substituted benzimidazole is known to yield compounds **1** with marked anthelminthic activity[2)]. Despite the introduction of thiabendazole **2**[3)], cambendazole **3**[4)] and HOE-33258 **4**[5)] in the chemotherapy of animal and human helminthiasis, a detailed study directed towards exploring the potentiality of 2-aryl benzimidazole is lacking[6)]. Accordingly the synthesis and anthelmintic activity of a series of 5(6)-phenyl-2-substituted benzimidazoles **7, 14–16, 21, 24, 25** and their cyclic analogs **19** and **20** are reported in this communication.



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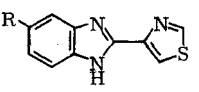
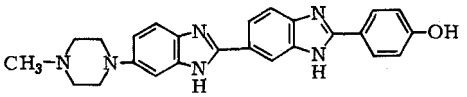


2, R = H
3, R = NHCOOPr^i



4 (HOE-33258)

Reaction of 3,4-diaminobiphenyl **(6)**, obtained by reduction of 4-amino-3-nitrobiphenyl **(5)**, with 1,3-dicarbethoxy-S-methylisothiourea gave ethyl 5(6)-phenylbenzimidazole-2-carbamate **(7)**.

Condensation of **5** with substituted benzoyl chlorides yielded the corresponding 4-N-(aroylamino)-3-nitrobiphenyls **8–10** which were reduced with hydrazine hydrate/Ra-

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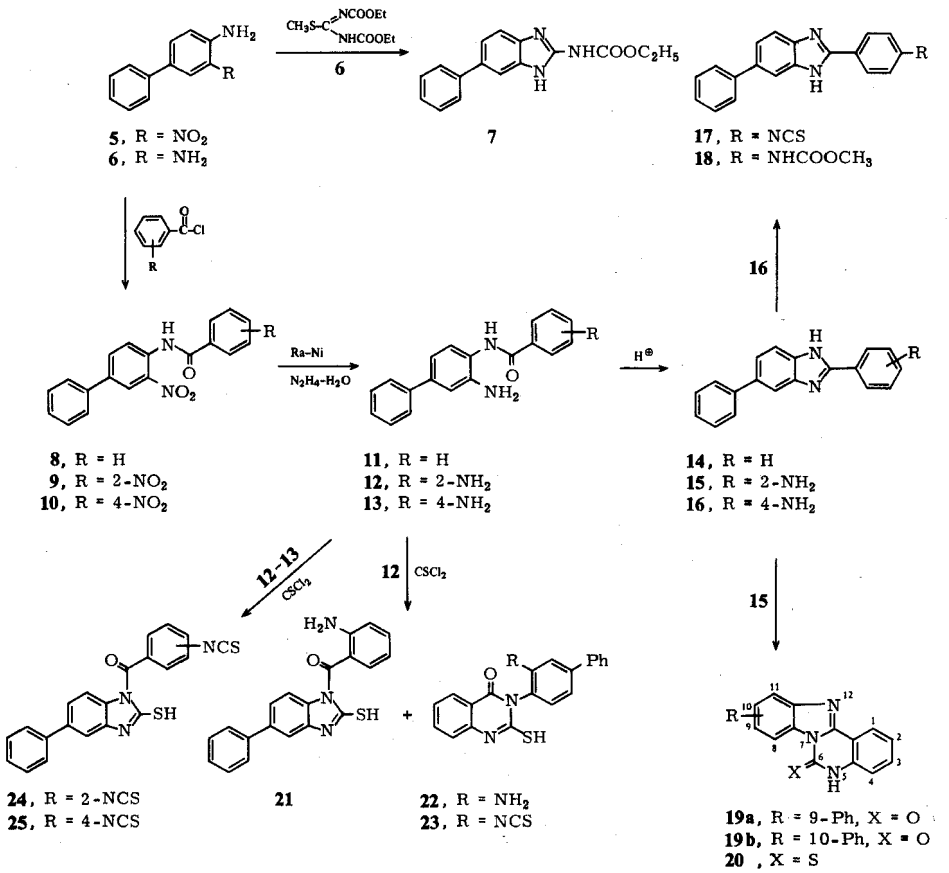
ney-nickel to afford the corresponding amines **11–13**. Acid catalysed cyclization of **11–13** gave the 2,5(6)-diphenylbenzimidazoles **14–16** of which 2-(4-aminophenyl)-5(6)-phenylbenzimidazole **(16)** was treated with thiophosgene or methylchloroformate to yield 2-(4-isothiocyanatophenyl)-5(6)-phenylbenzimidazole hydrochloride **(17)** and 2-(4-carbmethoxyaminophenyl)-5(6)-phenylbenzimidazole **(18)**. Reaction of 2-(2-aminophenyl)-5(6)-phenylbenzimidazole **(15)** with ethyl chloroformate or potassium ethyl xanthate in pyridine resulted in the exclusive formation of 9-phenylbenzimidazo[1,2-*c*]quinazoline-6-one **(19a)** and the corresponding-6-thione **20**. The structure of **19a** was established by its ^{13}C-NMR spectrum.

The ^{13}C-NMR spectrum of **19** showed the chemical shift of C-9 at 135,31 ppm which was in agreement with the calculated value (136,1 ppm) if structure **19a** is taken into account. If the cyclization would occur through the other nitrogen to yield **19b**, the calculated value for that carbon (now C-10) ought to be δ = 130.0 ppm. The calculation is based on the effect of various groups present in 5-phenylbenzimidazole fused with a quinazoline nucleus[7,8]. The structure of **19a** was further supported by the fact that ^{13}C-NMR of 5-phenylbenzimidazole and 2-(2-aminophenyl)-5(6)-phenylbenzimidazole **(15)** showed the absorption for 5(6)-carbon at δ = 133.14 and 132.98 ppm.



5, R = NO_2
6, R = NH_2

7

17, R = NCS
18, R = $NHCOOCH_3$

8, R = H
9, R = 2-NO_2
10, R = 4-NO_2

11, R = H
12, R = 2-NH_2
13, R = 4-NH_2

14, R = H
15, R = 2-NH_2
16, R = 4-NH_2

24, R = 2-NCS
25, R = 4-NCS

21

22, R = NH_2
23, R = NCS

19a, R = 9-Ph, X = O
19b, R = 10-Ph, X = O
20 , X = S

The reaction of **12** and **13** with two moles of thiophosgene directly yielded the 1-(2-isothiocyanatobenzoyl) and 1-(4-isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazoles **(24)** and **(25)**, and no intermediate could be isolated.

The structures of **24** and **25** were confirmed by the study of their IR and mass spectra. IR spectra of **24** and **25** had sharp bands at 1635 and 1640 cm^{-1} corresponding to C=N absorption of benzimidazole ring. The mass spectra of the two compounds clearly indicated the loss of a thiol group (32) from the molecular ion at m/e 355 in **24** and from $(M\text{-}161)^+$ at m/e 194 in **25** which is not possible otherwise.

However, reaction of **12** with one mole of thiophosgene resulted in the formation of only 1-(2-aminobenzoyl)-2-mercapto-5-phenylbenzimidazole **21** out of the two possible isomers **21** and **22,** along with the small amount of its corresponding isothiocyanate **24.** The structure of **21** was confirmed by its mass (m/e 345) and IR absorption (1690 cm^{-1} for $NCON\text{-}C_6H_4\text{-}2\text{-}NH_2$)[9].

Furthermore, isolation of **24** from the reaction mixture can only be accounted by formation of **21** as intermediate. The possibility of formation of alternative intermediate **22** was ruled out, since no quinazolino-isothiocyanate **23** could be isolated during the reaction of **12** with two moles of thiophosgene.

Anthelminthic Activity

Most of the compounds were tested for their anthelminthic activity against experimental infections of *Ancylostoma ceylanicum* (hamsters), *Hymenolepis nana* (mice) and *Nippostrongylus brasiliensis* (rats)[10, 11]. None of the compounds caused any noteworthy reduction in the worm load upto an oral dose of 250 mg/kg daily for 3 days, except **7** which caused 100 % reduction of *A. ceylanicum* at an oral dose of 25 x 3 mg/kg. These results indicate that introduction of an aryl function at 2-position of 5(6)-phenylbenzimidazoles does not lead to biological activity.

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Experimental

The structures of all the compounds were checked by *IR* on Perkin-Elmer 157 and 177 infracord spectrophotometers. *NMR*: Varian A-60D and R-32 spectrophotometers, 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. Melting points were taken in sulfuric acid bath, uncorr. The analysis of the compounds are tabulated in Table 1.

4-Amino-3-nitrobiphenyl **(5)** was prepared starting from biphenyl by lit. method[12] and reduced with Raney-nickel/hydrazine hydrate to yield 3,4-diaminobiphenyl **(6)**.

Table 1: Microanalytic Data of Compounds **7–21, 24** *and* **25**

Compd. No.	Molecular formula (M. W.)		Calculated (%) C	H	Found (%) C	H
7	$C_{16}H_{15}N_3O_2$	(281)	68.3	5,33	68.5	4.95
8	$C_{19}H_{14}N_2O_3$	(318)	71.7	4.46	72.0	4.42
9	$C_{19}H_{13}N_3O_5$	(363)	62.9	3.57	63.3	3.83
10	$C_{19}H_{13}N_3O_5$	(363)	62.9	3.57	62.8	3.68
11	$C_{19}H_{16}N_2O$	(288)	79.1	5.55	79.4	5.28
12	$C_{19}H_{17}N_3O$	(303)	75.2	5.61	75.6	5.78
13	$C_{19}H_{17}N_3O$	(303)	75.2	5.61	75.4	5.46
14	$C_{19}H_{14}N_2$	(270)	84.1	5.18	83.7	5.53
15	$C_{19}H_{15}N_3$	(285)	80.0	5.26	80.3	5.48
16	$C_{19}H_{15}N_3$	(285)	80.0	5.26	80.2	5.12
17	$C_{20}H_{13}N_3S \cdot HCl$	(363.5)	66.2	3.85	66.4	3.62
18	$C_{21}H_{17}N_3O_2$	(343)	73.5	4.95	73.7	5.22
19	$C_{20}H_{13}N_3O$	(311)	77.2	4.14	77.4	4.53
20	$C_{20}H_{13}N_3S$	(327)	73.4	3.97	73.5	4.26
21	$C_{20}H_{15}N_3OS$	(345)	69.6	4.34	70.1	4.15
24	$C_{21}H_{13}N_3OS_2$	(387)	65.1	3.35	65.4	3.25
25	$C_{21}H_{13}N_3OS_2$	(387)	65.1	3.35	65.2	3.50

Ethyl 5(6)-phenylbenzimidazole-2-carbamate **(7)**

A mixture of 1.0 g (5,4 mmol) **6** and 1.26 g (6 mmol) 1,3-dicarbethoxy-S-methylisothiourea in 50 ml ethanol was refluxed for 12 h. The reaction mixture was cooled and the separated solid washed with 3 x 10 ml ethanol, dried and crystallized from acetic acid-water, yield 0.9 g (60 %), m.p. 220°C. IR (KBr): 1720 cm^{-1} (CO). NMR (TFA): δ (ppm) = 1.0 (t, 3, $CH_2C\underline{H}_3$, J = 8Hz), 4.0 (q, 2, -$C\underline{H}_2$-CH_3, J = 8Hz), 6.8–7.3 (m, 8, Ar-$\underline{H}$).

4-N-(Benzoylamino)-3-nitrobiphenyl **(8)**

A solution of 0.77 g (5,5 mmol) benzoyl chloride in 20 ml dry benzene was added dropwise to a refluxing solution of 1.0 g (4,6 mmol) **5** in 30 ml dry benzene and refluxing was continued for 12 h. The reaction mixture was successively washed with water and 10 % $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated to get a crystallized solid, yield 1.2 g (81 %), m.p. 140°C. IR (KBr): 1680 (CO), 1320, 1580 cm^{-1} (NO_2). NMR (DMSO-d_6): δ (ppm) = 7.25–7.95 (m, 12, Ar-$\underline{H}$), 8.18 (d, 1, o to NO_2, J = 2Hz).

Similarly the compounds **9** and **10** were prepared from **5** and the corresponding acid chlorides in dry benzene.
9, yield 75 %, m.p. 151°C. IR (KBr): 1685 (CO), 1320, 1520 cm^{-1} (NO_2). NMR (DMSO-d_6): δ (ppm) = 7.32–8.0 (m, 11, Ar-$\underline{H}$), 8.12 (d, 1, PhC=C$\underline{H}$-C-NO_2, J = 2Hz).
10, yield 76 %, m.p. 244°C. IR (KBr): 1680 (CO), 1340, 1520 cm^{-1} (NO_2).

4-N-(Benzoylamino)-3-aminobiphenyl **(11)**

To a warm mixture of 1.0 g (3,1 mmol) **8** and Raney-nickel (~ 0.2 g) in 50 ml ethanol-THF (2 : 1), 1.25 g (0.0248 mol) hydrazine hydrate in 20 ml ethanol was added dropwise and refluxing was continued for 1 h. The catalyst was filtered off and the mother liquor was concentrated to get a solid which was

crystallized from ethanol, yield 0.65 g (72 %), m.p. 198–200°C. IR (KBr): 3200-3400 (NH,NH_2), 1635 cm^{-1} (CO).

In similar manner **12** and **13** were prepared from **9** and **10.**
12, yield 64 %, m.p. 188°C. IR (KBr): 3200-3300 (NH, NH_2), 1620 cm^{-1} (CO).
13, yield 68 %, m.p. 228°C. IR (KBr): 3200–3300 (NH,NH_2), 1625 cm^{-1} (CO).

2,5(6)-Diphenylbenzimidazole **(14)**

A solution of 1.0 g (3,4 mmol) **11** in 10 ml ethanol and 20 ml concentrated hydrochloric acid was refluxed for 8 h. The reaction mixture was cooled and the separated solid was filtered, and basified with ammonia solution. The aqueous layer was extracted with 2 x 30 ml ethyl acetate, dried (Na_2SO_4) and the solvent removed to get the pure compound, yield 0.58 g (62 %), m.p. 196°C (lit[13] m.p. 197–198°C). IR (KBr): 1620 cm^{-1} (Arom). MS: m/e = 270.

Compounds **15** and **16** were prepared as above.
15, yield 63 %, m.p. 215°C. IR (KBr): 3150–3420 (NH,NH_2), 1605 cm^{-1} (Arom). MS: m/e = 285.
16, yield 58 %, m.p. 227–228°C. IR (KBr): 3200–3400 (NH,NH_2), 1600 cm^{-1} (Arom). MS: m/e = 285.

2-(4-Isothiocyanatophenyl)-5(6)-phenylbenzimidazole hydrochloride **(17)**

A solution of 0.268 ml (3,5 mmol) thiophosgene in 10 ml dry acetone was added dropwise to a stir solution of 1.0 g (3,5 mmol) **16** in 35 ml dry acetone at room temp. The stirring was continued for 8 h and the separated hydrochloride washed with 3 x 10 ml ethyl acetate and dried, yield 0.78 g (65 %), m.p. 295–298°C. IR (KBr): 2050 cm^{-1} (NCS).

2-(4-Carbmethoxyaminophenyl)-5(6)-phenylbenzimidazole **(18)**

0.4 g (4,2 mmol) methyl chloroformate was added to a solution of 1.0 g (3,5 mmol) **16** in 20 ml pyridine and the reaction mixture heated at 100°C for 1 h. The reaction mixture was cooled and diluted with 100 ml water. The separated solid was washed with water, dried and crystallized from ethanol, yield 1.0 g (85 %), m.p. 210°C. IR (KBr): 1710 cm^{-1} (CO); NMR (TFA): δ (ppm) = 3.5 (s, 3, OCH_3), 6.8–7.6 (m, 12, Ar-H).

9-Phenylbenzimidazo[1,2-c]quinazolin-6-one **(19)**

A mixture of 1.0 g (3,5 mmol) **16** and 0.38 g (3,5 mmol) ethyl chloroformate in 20 ml pyridine was refluxed for 2 h. The reaction mixture was cooled and diluted with water. The separated solid was dried and crystallized from DMSO, yield 0.83 g (75 %), m.p. 296°C. IR (KBr): 1710 (CO), 1620 cm^{-1} (C=N). MS: m/e = 311. This reaction does not complete even at refluxing temp. when acetone was used as solvent.

Similarly, *9-phenylbenzimidazo[1,2-c]quinazoline-6-thione* **(20)** was prepared by reaction of **15** with potassium ethyl xanthate in pyridine, yield 72 %, m.p. 255–256°C. IR (KBr): 1630 (C=N), 1160 cm^{-1} (C=S). MS: m/e = 327.

1-(2-Aminobenzoyl)-2-mercapto-5-phenylbenzimidazole **(21)**

0.127 ml (1,6 mmol) thiophosgene in 20 ml acetone was added dropwise to a stir solution of 0,5 g (1,6 mmol) **12** in 30 ml dry acetone and 0.32 ml (3,2 mmol) triethylamine at room temp. Stirring was continued for 5 h and the solid separated was crystallized from DMSO-water, yield 0.24 g (45 %), m.p.

275°C. IR (KBr): 3200–3400 (NH_2), 1690 cm^{-1} (CO). MS: m/e = 345. Mother liquor yielded 15 % of **24.**

1-(4-Isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazole **(25)**

To a stirred solution of 0.5 g (1,6 mmol) **13** in 30 ml dry acetone and 0.65 ml (6,5 mmol) triethylamine, 0.253 ml (32 mmol) thiophosgene in 30 ml dry acetone was added dropwise at room temp. Stirring was continued for 10 h. The solvent was removed completely and the residue crystallized from benzene, yield 0.41 g (65 %), m.p. 195°C. IR (KBr): 2060 (NCS), 1680 cm^{-1} (CO). MS: m/e = 387, base peak 162.

Similarly **24** was prepared from **12** and two moles of thiophosgene. It was purified by column chromatography using silica gel column and ethyl acetate-benzene (1 : 4) as eluant, yield 50 %, m.p. 255–256°C. IR (KBr): 2080 (NCS), 1710 cm^{-1} (CO). MS: m/e = 387, base peak 329.

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