SYNTHESIS AND RING CLOSURE REACTIONS OF SOME N-(o-AMINOPHENYL)-N-METHYL-N′,N″-DISUBSTITUTED-GUANIDINES AND OF N-(2-AMINO-4--METHOXYPHENYL)-N-METHYL-N'-PHENYLTHIOUREA*)

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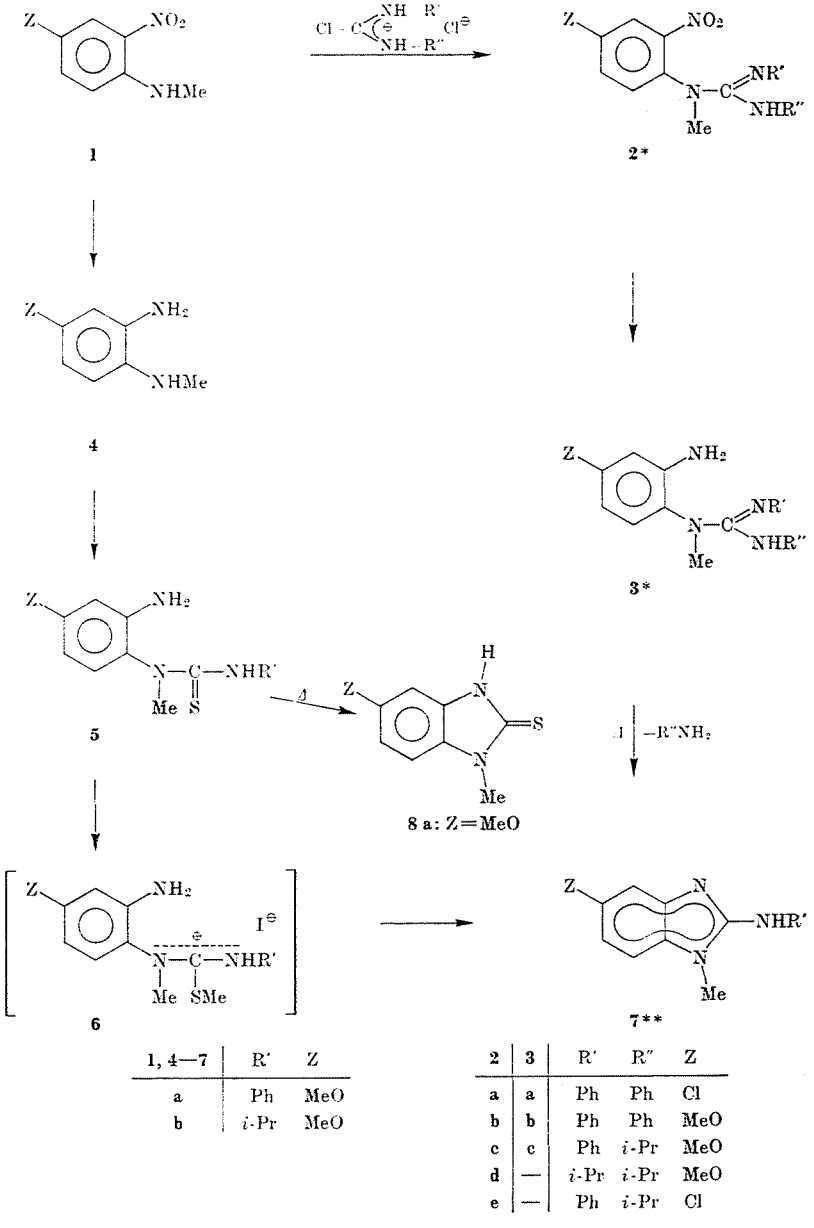
In connection with another research project we were interested in the ring closure reactions of *N*-(*o*-aminophenyl)-*N*-methyl-*N′*,*N″*-disubstituted--guanidines (3) with suitable C_1 components, namely, whether these reactions result in the formation of five- or seven-membered rings.

No compounds of type **3** have been known prior to our work. The first step of our method devised for the synthesis of type **3** compounds consisted in the reaction of *N*-methyl-*o*-nitranilines (**1**) with the appropriate *N*,*N′*--disubstituted chloroformamidinium chlorides which are easily available by allowing to react disubstituted ureas or thioureas with phosgen [1]. Part of the resulting nitrophenylguanidines **2** were catalytically reduced to the corresponding aminophenylguanidines **3**. In the Z = Cl series the reaction temperature must not exceed room temperature since, already at slightly elevated temperatures, the chloro substituent may easily be replaced by hydrogen. In addition, at elevated temperatures, ring closure of the compounds **3** may take place under formation of the corresponding 2-aminobenzimidazoles **7** even in the presence of excess hydrogen chloride.

The free bases **3** are thermally unstable. When **3b** was heated above its m.p., an exothermic reaction started at 130 °C**. The resulting change in weight exactly corresponded to the loss of one molecule of aniline, and the product proved identical with an authentic sample of 2-anilino-5-methoxy-1-methylbenzimidazole (**7a**). **3c**, when refluxed in anisole, furnished a mixture of the two theoretically possible benzimidazoles **7a** and **7b**. Similar ring closures took place on prolonged standing of the aminophenylguanidines **3** at room temperature.

* Partly based on the Chem. Eng. Thesis by P. Lugosi, Technical University Budapest, 1972.

** The thermolyses were followed by DTA. The authors are grateful to Dr. T. Meisel and Mrs. F. Csonka for having performed these experiments.



1, 4—7	R'	Z
a	Ph	MeO
b	*i*-Pr	MeO

2	3	R'	R''	Z
a	a	Ph	Ph	Cl
b	b	Ph	Ph	MeO
c	c	Ph	*i*-Pr	MeO
d	—	*i*-Pr	*i*-Pr	MeO
e	—	Ph	*i*-Pr	Cl

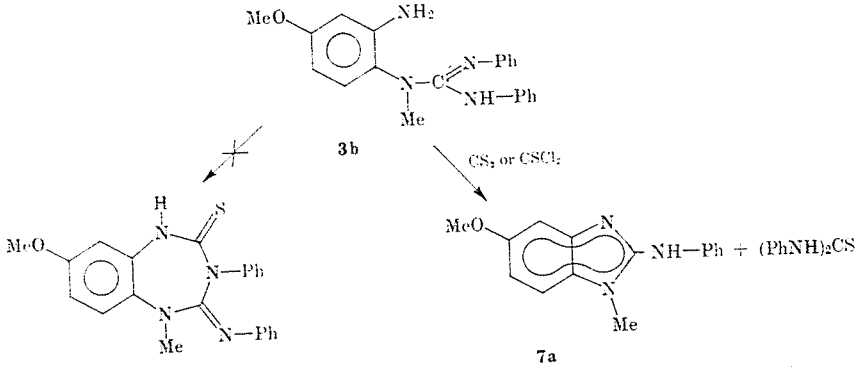
* Two tautomeric forms are conceivable if $R' \neq R''$. The positions of the tautomeric equilibria have not been studied.

** Potentially tautomeric compound. For establishment of the tautomeric structure see [2].

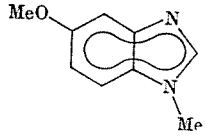
Authentic samples of the benzimidazoles **7** were obtained by allowing to react the N-methylphenylenediamine **4a** with the appropriate isothiocyanates to yield the thioureas **5.** The site of attack of the reagent in the reaction with phenyl isothiocyanate was unequivocally established on the basis of the IR and NMR spectra of the product. The IR spectrum (KBr) exhibited a pair of bands at 3497 and 3408 cm^{-1} (ν_{as} and ν_s NH_2), and the signal of the *N*--methyl group in the NMR spectrum ($CDCl_3$) appeared at δ 3.65 ppm to be compared with the position of the *N*-methyl signals in the NMR spectra ($CDCl_3$) of *N*-methylaniline (δ 2.5 ppm) and *N*-methyl-*N,N'*-diphenylthiourea (δ 3.7 ppm) used as model compounds.

5a was subsequently allowed to react with methyl iodide in methanol, whereby **7a** was obtained as a result of the ring closure of the intermediate thiouronium salt **6a** under evolution of methanethiol. **7b** was prepared similarly and isolated in form of its hydriodide.

As model reactions, the reactions of **3b** with carbon disulfide, thiophosgen and triethyl orthoformate were studied. In no case was formation of products containing a seven-membered heterocyclic ring noticed, the benzimidazole **7a** being the only heterocyclic product isolated.



The reactions of *N*-(2-amino-4-methoxyphenyl)-*N*-methyl-*N'*-phenylthiourea (**5a**) with C_1 components have also been studied. When **5a** was allowed to react with triethyl orthoformate in boiling dioxane, 5-methoxy-1-methylbenzimidazole (**9**) was obtained as the main product. In addition, the reaction mixture contained, according to its TLC, small amounts of 5-methoxy-1--methyl-2-benzimidazolinethione (**8a**), 2-anilino-5-methoxy-1-methylbenzimidazole (**7a**), thiocarbanilide, as well as some unreacted **5a.** When the above reaction was performed in benzene, **7a** became the main product. When **5a** was allowed to react with thiocarbonylbiimidazole, **8a** was obtained in 74% yield.



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Experimental

Preparation of N-methyl-N-(o-nitrophenyl)-N′,N″--disubstituted-guanidines 2 (see Table I)

Mixtures of the appropriate *N*-methyl-*o*-nitranilines (**1a** [4] and **1b** [5]; 20 mmoles) and chloroformamidinium chloride [1] (10 mmoles) were heated and stirred at 130—140 °C for 30 to 60 min until, according to TLC (adsorbent: Kieselgel G; application: $CHCl_3$ solutions; development: benzene-methanol, 10 : 2; detection: iodine vapour), the starting compounds **1** completely disappeared. The melts were allowed to cool and solidify and were boiled for 10 minutes with water (100 ml). The insoluble residues were filtered off, and the filtrate was treated, after being allowed to cool, with N/1 NaOH aqu. (40 ml) to yield compounds **2a** and **b** as crystalline products and compounds **2c**—**e** as viscous oils which resisted all attempts of crystallization. Compound **2d** was transformed into a crystalline hydrogen oxalate, while the purity of compounds **2c** and **2e** was checked by TLC and their structure was established on the basis of their NMR spectra.

Reduction of N-methyl-N-(o-nitrophenyl)-N′,N″--disubstituted-guanidines

a) Compounds **2a**, **2b** and **2c** (10 mmoles) were dissolved in ethanolic (40 ml) hydrogen chloride (1.1 g; 30 mmoles) and reduced catalytically in the presence of Pd-on-charcoal catalysts with activity and amount chosen so as to avoid too high reaction rates and warming up of the reaction mixtures. The products were isolated after conventional work-up of the reaction mixtures in form of their dihydrochlorides. Since the dihydrochlorides of **3b** and **3c** proved hygroscopic, they were dissolved in a small amount of MeOH, and the solutions were treated with N/1 aqueous NaOH (pH = 9) to give the corresponding free bases which were recrystallized from gasoline (see Table II).

b) **2a** (3.8 g; 10 mmoles) was dissolved in a mixture of EtOH (60 ml) and conc. hydrochloric acid (5 ml) and *rapidly* reduced in the presence of a Pd/C catalyst so that a marked rise of the temperature of the mixture took

Table I

Preparation of the *N*-methyl-*N*-(*o*-nitrophenyl)-*N'*,*N''*-disubstituted-guanidines **2a – e**

	Yield	m.p., °C	Solvent of recryst.	Formula (Mol. wt.)	Calc/Found			NMR Spectra ($CDCl_3$, TMS, δ values)		
					C%	H%	N%	MeO	MeN	Me_2(CH)
a	71%[a]/	130 – 1	gasoline	$C_{20}H_{17}ClN_4O_2$ (380.8)	d/		14.71		3.4	—
b	70%[a]/	167 – 8	benzene-gasoline	$C_{21}H_{20}N_4O_3$ (376.4)	67.00 67.25	5.36 5.36	14.89 15.08	3.8	3.4	—
c	80%[b]/	oil	—					3.8	3.3	0.85, d, J = 6 Hz
d	42%[c]/	188 – 9[c]/	EtOH	$C_{17}H_{20}H_4O_7$[c]/ (398.4)	51.21 51.52	6.58 6.64	14.06 14.31	4.0[e]/	3.5[e]/	1.2, d,[e]/ J = 6 Hz
e	90%[b]/	oil	—					—	3.32	0.95, d, J = 6 Hz

a) Based on amount of recrystallized product
b) Based on amount of crude product
c) Hydrogen oxalate
d) Cl, calc 9.31, found 9.45%
e) Solvent water

place. 940 ml of H_2 was consumed (the reduction of the nitro group would have required 720 ml). Conventional work-up of the reaction mixture furnished 2.2 g (84.5%) of crude 7 (R′ = Ph, Z = H) hydrochloride, colourless crystals, whose IR spectrum (KBr) was identical with that of a pure product prepared by treating the free base 7 (R′ = Ph, Z = H) with hydrogen chloride.

The crude hydrochloride (2.0 g) was triturated at room temperature with a mixture of water (100 ml) and 20% aqueous NaOH (13 ml) to yield 1.2 g (71%) of the free base, colourless crystals, m.p. 197—198 °C (aqueous MeOH).

$C_{14}H_{13}N_3$ (222.3). Calc C 75.31, H 5.87, N 18.82. Found C 75.96, H 5.82, N 18.93%.

The base was reconverted in 90% yield into the hydrochloride, m.p. 236—237 °C (EtOH—Et_2O).

$C_{14}H_{14}ClN_3$ (259.7). Calc. C 64.74, H 5.43, Cl 13.65, N 16.18. Found C 64.21, H 5.70, Cl 14.16, N 16.06%.

N-(2-Amino-4-methoxyphenyl)-N-methyl-N′-phenylthiourea (**5** a)

To a solution of **4a** [5] (4.5 g; 30 mmoles) in $CHCl_3$ (30 ml) a solution of phenyl isothiocyanate (4.05 g; 30 mmoles) in $CHCl_3$ (20 ml) was added at room temperature. The mixture was allowed to stand for 20 min at room temperature and the solvent was distilled off. The resulting pink oil turned crystalline on scratching. Yield: 8.0 g (93.5%), colourless crystals, m.p. 125 °C (EtOH).

$C_{15}H_{17}N_3OS$ (287.4). Calc. N 14.62, S 11.15. Found N 14.51, S 11.49%.

2-*Anilino*-5-*methoxy*-1-*methylbenzimidazole* (**7a**)

A methanolic (40 ml) solution of **5a** (4.8 g; 16.7 mmole) was refluxed with MeI (1.2 ml; 19.5 mmole) for 4 hrs until the evolution of methanethiol ceased. The deposition of the colourless crystalline product started on cooling and was completed by the addition of ether (50 ml). 5.0 g (78%) of the hydriodide of the title compound, m.p. 218—220 °C were obtained.

The hydriodide was dissolved in a mixture of ethanol (20 ml) and water (40 ml). To the boiling solution 10% aqueous NaOH (15 ml) was added, and the mixture was refluxed for 10 min. The colourless crystalline product was filtered off after the mixture had been allowed to cool, and it was washed with water until neutral to yield 3.0 g (75%) of **7a**, m.p. 213 °C (EtOH).

$C_{15}H_{15}N_3O$ (253.3). Calc. C 71.12, H 5.97, N 16.98. Found C 71.06, H 6.10, N 16.52%.

Table II

Preparation of the *N*-(*o*-aminophenyl)-*N*-methyl-*N'*,*N''*-disubstituted-guanidines **3a–c**

	Yield	m.p., °C	Solvent of recryst.	Formula (Mol. wt.)	Calc/Found			NMR Spectra ($CDCl_3$, TMS, δ values)		
					C%	H%	N%	MeO	MeN	Me_2(CH)
a	75%[a]	b)	EtOH/Et_2O	$C_{20}H_{19}ClN_4 \cdot 2HCl$ (423.8)	56.68 56.69	4.99 4.91	13.22 12.93			
b	80%	100	gasoline	$C_{21}H_{22}N_4O$ (346.4)	72.80 72.97	6.40 6.29	16.17 16.20	3.61	3.2	—
c	65%	66—67	gasoline	$C_{18}H_{24}N_4O$ (312.4)	69.20 69.88	7.74 7.90	17.94 18.19	3.73	3.08	0.75, d, J = 6 Hz

a) Dihydrochloride
b) The dihydrochloride turns black without melting above 200°C

2-Isopropylamino-5-methoxy-1-methylbenzimidazole hydriodide (**7b**·HI)

4a [5] (4.5 g; 30 mmole) was allowed to react with isopropyl isothiocyanate (3.0 g; mmole) in $CHCl_3$ solution as described above for the reaction with phenyl isothiocyanate. The residue, obtained on evaporation of the solvent, was dissolved in EtOH (50 ml). Methyl iodide (2.5 ml; 40 mmoles) was added, and the solution was refluxed for 4 hrs to yield, after being allowed to cool, 6.3 g (60%) of a crystalline product, m.p. 208—210 °C (water).

$C_{12}H_{17}N_3O \cdot HI$ (347.2). Calc. C 41.51, H 5.22, N 12.10 Found C 41.47, H 5.79, N 11.89%.

Thermolyses of the guanidines **3**

a., **3b** (3.46 g; 10 mmole) was heated at 150 °C *in vacuo*. Aniline distilled from the melt which solidified on cooling. Recrystallization from ethanol furnished 2.0 g (80%) of 2-anilino-5-methoxy-1-methylbenzimidazole (**7a**), m.p. 212—213 °C, identical with the product prepared starting with **5a**.

b., A solution of **3c** in anisole was refluxed until the starting compound disappeared completely (TLC). The product proved, according to TLC (adsorbent: Kieselgel G, solvent: benzene-methanol, 7 : 3), to be a mixture of **7a** and **7b**.

Reaction of N-(2-amino-4-methoxyphenyl)-N--methyl-N',N''-diphenylguanidine (**3b**) *with carbon disulfide, thiophosgen and triethyl orthoformate*

a) The dihydrochloride of **3b** (2.1 g; 5 mmole) was dissolved at 0 °C in an anhydrous methanolic (20 ml) solution of metallic sodium (0.23 g; 10 mmole), and CS_2 (10 ml) was simultaneously added. The mixture was allowed to stand overnight at room temperature and the solvent was distilled off *in vacuo* (bath temperature: 20 °C). The crystalline residue was triturated with two portions of ether (20 ml, each) to yield 1.2 g (95%) of 2-anilino-5-methoxy-1-methylbenzimidazole (**7a**) as the insoluble residue, m.p. 211—213 °C, which proved identical (mixed m.p., IR, TLC) with an authentic sample prepared as described above.

The combined ether solutions were evaporated to dryness *in vacuo* (bath temperature: 20 °C), and the residue was triturated at room temperature with benzene (10 ml) to yield 0.1 g of thiocarbanilide as the insoluble residue, m.p. 157—158 °C, identical (mixed m.p., IR) with an authentic sample.

The benzene solution was chromatographed through a column of silicagel

G (solvent: benzene-MeOH) to yield 0.05 g of sulfur and further 0.1 g of thiocarbanilide (total yield 40%).

The same products were obtained when the free base **3b** was liberated with the aid of aqueous NaOH.

b) When ring closure of **3b** (liberated from its dihydrochloride with the aid of aqueous NaOH) was effected with thiophosgen, **7a** and thiocarbanilide were obtained again in addition to a decomposition or polymerisation product of thiophosgen (m.p. 107—109 °C) whose structure elucidation was not attempted.

c) Triethyl orthoformate (2.5 ml) was added to a benzene solution (20 ml) of **3b** (1.0 g; 30 mmole). No reaction took place at room temperature (TLC). When the mixture was refluxed for 1 hr, 0.52 (68%) of **7a** were obtained. The mother liquor contained, according to TLC (adsorbent: Kieselgel G; solvent: benzene-methanol, 10 : 1; detection: I_2 vapour), small amounts of 5-methoxy-1-methylbenzimidazole (**9**) in addition to **7a.**

Reaction of N-(2-amino-4-methoxyphenyl)-N-methyl--N'-phenylthiourea (**5a**) *with triethyl orthoformate and thiocarbonylbiimidazole*

a) A mixture of **5a** (1.0 g; 3.5 mmole), triethyl orthoformate (2.5 ml) and anhydrous dioxane (10 ml) was refluxed for 1 hr and evaporated to dryness *in vacuo*. The residue was extracted with boiling gasoline (17 ml). From the gasoline solution a crystalline product deposited on cooling which was recrystallized to yield 0,4 g (70%) of 5-methoxy-1-methyl-benzimidazole (**9**), m.p. 113 °C which, according to mixed m.p. and IR spectra, proved identical with an authentic sample prepared by allowing to react **4a** with formic acid [5] or triethyl orthoformate.

The mother liquor of crude **9** contained, according to TLC (adsorbent: Kieselgel G; solvent: benzene—MeOH, 10 : 1; detection: iodine vapour), five compounds which were identified on the basis of their R_f values with **9, 7a, 8a** (for the preparation of an authentic sample, see below), thiocarbanilide and unreacted **5a.**

b) When the above experiment was performed in refluxing benzene, **7a** (0,62 g; 73%) was obtained as the main product.

c) Thiocarbonylbiimidazole [7] (0,53 g; 3 mmole) was added to an acetone solution (3 ml) of **5a** (0,86 g; 3 mmole). The yellow colour of the solution disappeared within 15 min. The mixture was allowed to stand for another 30 min at room temperature, the solvent was removed *in vacuo* and the residue was triturated, in order to remove the imidazole formed, with two portions of water (5 ml, each) to yield 0,43 g (74%) of **8a,** m.p. 163—164 °C (from water), identical with an authentic sample prepared as described below.

5-*Methoxy*-1-*methyl*-2-*benzimidazolinethione* (**8a**)*

5a (1,42 g; 5 mmoles) was slowly heated to 160 °C (about 10 minutes) *in vacuo* (about 20 torr). At this temperature distillation of aniline started. The mixture was heated for 5 min at 165 and for 15 min at 180 °C. The melt solidified on cooling to yield 0,90 g (99%) of **8a**, colourless crystals, m.p. 162—164 °C (water).

$C_9H_{10}N_2OS$ (194.26). Calc. C 55.65, H 5.19, N 14.43. Found C 55.88, H 5.08, N 14.61%.

Summary

Syntheses of the title compounds are described. The latter were found to be cyclized thermally into derivatives of benzimidazole. The reactions of the title compounds with C_1 components yield benzimidazole rather than 1,3,5-benzotriazepine derivatives.

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* For similar ring closures of the non-*N*-methylated analogues of **5a** and **5b** see [6].