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Benzimidazole Condensed Ring Systems, VI [1]: Organic Azides in Heterocyclic Synthesis, X [2]: Synthesis of Some Substituted Pyrimido[1,6-a]-benzimidazoles as Potential Antimicrobial Agents

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Summary. The syntheses of 3-chloro derivatives of 2-alkyl-pyrimido[1,6-a]benzimidazol-1(2*H*)-ones **2a, b** as well as of 4,4-dichloro and 4,4-dibromo derivatives of 2-alkylpyrimido[1,6-a]benzimidazole-1,3(2*H*,4*H*)-diones **3a, b** and **4** are reported. Methods for converting some of the chloro compounds to azido (**5, 6**), amino (**8**), morpholino (**9a**,**10**,**11**), piperidino (**9b**), cyano (**12**), and methoxy (**13**) derivatives of the adopted tricyclic system are also described.

Keywords. Condensed benzimidazo-uracils; Tricyclic pyrimido[1,6-a]benzimidazoles; Geminal diazido compounds; "Staudinger reaction".

Kondensierte Ringsysteme des Benzimidazols, 6. Mitt. [1]: **Organische Azide in der Heterocyclen-Synthese, 10. Mitt.** [2]: **Synthese von substituierten Pyrimido[1,6-a]benzimidazolen als mögliche antimikrobielle Wirkstoffe**

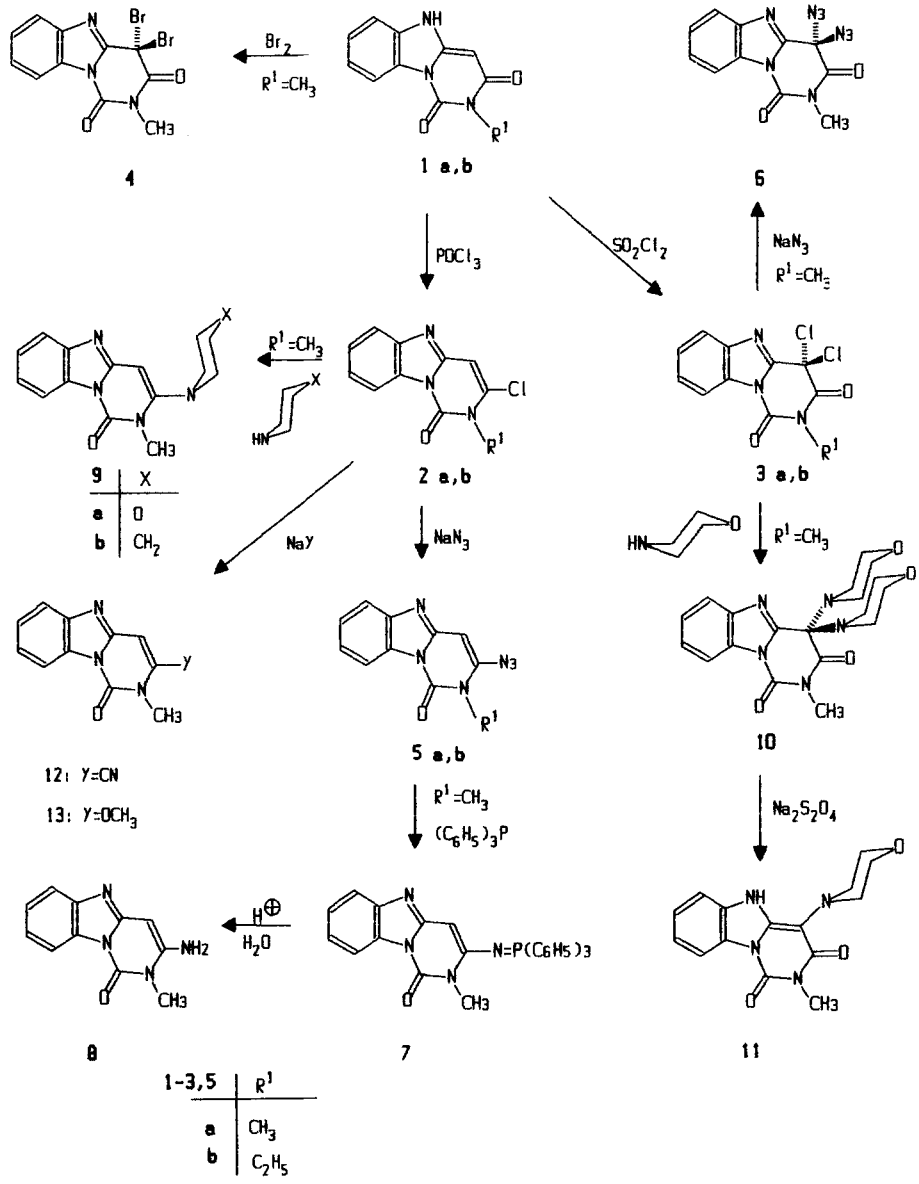
Zusammenfassung. Die Synthese von 3-Chlor-2-alkyl-pyrimido[1,6-a]benzimidazol-1(2*H*)-onen (**2a, b**) und von 4,4-Dichlor- und 4,4-dibrom-pyrimido[1,6-a]benzimidazol-1,3(2*H*,4*H*)-dionen (**3a, b, 4**) wird beschrieben. Diese Verbindungen lassen sich zu den entsprechenden Azido- (**5, 6**), Amino- (**8**), Morpholino- (**9a, 10, 11**), Piperidino- (**9b**), Cyano- (**12**) und Methoxy- (**13**) Derivaten umwandeln.

Introduction

Recently we have described the synthesis of 2-methyl- and 2-ethyl-pyrimido-[1,6-a]benzimidazole-1,3(2*H*,5*H*)-diones (**1a, b**) [1]. As a result of the biological interest in this tricyclic system which comprises an uracil residue within its structure [1, 3], we describe the synthesis of some derivatives of **1** as potential antimicrobial agents.

Results and Discussion

Chlorination of **1** with phosphoryl chloride affords 2-alkyl-3-chloropyrimido-[1,6-a]benzimidazol-1(2*H*)-ones (**2a, b**) in good yields, whereas chlorination of **1** with excess of sulfuryl chloride yielded 2-alkyl-4,4-dichloro-pyrimido[1,6-a]benz-



imidazole-1,3(2*H*,4*H*)-diones (**3 a, b**). On the other hand, 4,-dibromo-2-methyl-pyrimido[1,6-a]benzimidazole-1,3(2*H*,4*H*)-dione (**4**) was prepared by bromination of **1 a** with excess of bromine in glacial acetic acid. Reacting the 3-chloro derivatives **2 a, b** with sodium azide in dimethylformamide at 60 °C furnished the corresponding 3-azido compounds **5 a, b** in excellent yields. Reaction of the 4,4-dichloro derivative **3 a** with sodium azide at room temperature resulted in the 4,4-diazido compound **6**. The 3-amino-2-methylpyrimido[1,6-a]benzimidazole-1(2*H*)-one (**8**) was obtained by Staudinger-reaction [4] starting with the azide **5 a**. The phosphine-imine intermediate **7**, readily accessible from the azido derivative **5 a** and triphenylphosphine, was hydrolized with 2*N* hydrochloric acid to give **8** in 89% yield. The 3-(1-morpholino) and 3-(1-piperidino) analogs **9 a** and **9 b** were prepared by refluxing 3-chloro-2-methyl-pyrimido[1,6-a]benzimidazol-1(2*H*)-one **2 a** with an excess of morpholine or piperidine in dimethylformamide. 2-Methyl-4,4-dimorpholino-pyri-

mido[1,6-a]benzimidazole-1,3(2*H*,4*H*)-dione (**10**) was obtained by treating the 4,4-dichloro compound **3** with an excess of morpholine at room temperature. Reductive desamination of **10** using sodium dithionite yielded 2-methyl-4-(1-morpholino)pyrimido[1,6-a]benzimidazole-1,3(2*H*,5*H*)-dione (**11**). Nucleophilic displacement of the 3-chloro atom in compound **2a** with sodium cyanide and sodium methoxide gave the 3-cyano and 3-methoxy derivatives **12** and **13**, respectively.

Compounds **5a**, **7**, and **8** were screened for *in vitro* activities against three *Staphylococcus aureus* strains (S 14, S 17, S 18) as Gram-positive bacteria, two *Escherichia coli* (E 21, E 41) as Gram-negative bacteria and one *Candida albicans* (M 1). The disc method was adopted to determine the inhibition zones and compounds which showed inhibition zones $\geqslant 8$ mm in diameter were evaluated for their minimal inhibitory concentrations (MIC) against the most sensitive organisms [5]. From the compounds screened, only **8** showed activity against *E. coli* with an inhibition zone 14 mm in diameter but its MIC was $> 250\,\mu$g/ml.

Experimental Part

Melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. The NMR spectra were recorded in hexadeuteriodimethylsulfoxide (unless otherwise indicated) with *TMS* as an internal standard; the instruments used were the Varian EM-360 at 60 MHz and the XL-200 at 200 MHz.

3-Chloro-2-methylpyrimido[1,6-a]benzimidazol-1(2H)-one (**2a**)

Compound **1a** [1] (2.15 g, 10 mmol) was refluxed with phosphoryl chloride (20 ml) for 1 hour. Excess phosphoryl chloride was then distilled under vacuum and the yellowish residue was treated with cold water. The mixture was neutralized with sodium hydroxide (2*N*) and the product was filtered, washed with water and dried, m.p. 215–216° (dimethylformamide); the yield was almost quantitative. IR: 3100 m, 1700 s (CO), 1640 m, 1600 m, 1590 w cm^{-1}. ^{1}H-NMR (200 MHz): δ 3.6 (s, CH_3), 7.05 (s, H at C-4), 7.3–7.5 (m, 2 *Ar*H at C-7 and 8), 7.7 (d, H at C-6), 8.3 (d, H at C-9). Anal. calcd. for $C_{11}H_8ClN_3O$: C 56.54, H 3.45, Cl 15.17, N 17.98; found: C 56.50, H 3.65, Cl 15.21, N 17.87.

3-Chloro-2-ethylpyrimido[1,6-a]benzimidazol-1(2H)-one (**2b**)

It was similarly prepared from **1b** [1] (2.29 g, 10 mmol) and phosphoryl chloride (20 ml), yield 1.83 (74%), m.p. 190–192° (dimethylformamide). IR: 3110 m, 1700 s (CO), 1640 s, 1600 s, 1540 w cm^{-1}. ^{1}H-NMR (200 MHz): δ 1.3 (t, CH_3), 4.25 (q, CH_2), 7.07 (s, H at C-4), 7.3–7.5 (m, 2 *Ar*H at C-7 and 8), 7.7 (d, H at C-6), 8.25 (d, H at C-9). Anal. calcd. for $C_{12}H_{10}ClN_3O$: Cl 14.32, N 16.97; found: Cl 14.39, N 16.79.

4,4-Dichloro-2-methylpyrimido[1,6-a]benzimidazole-1,3(2H,4H)-dione (**3a**)

To a suspension of **1a** (2.15 g, 10 mmol) in dioxane (15 ml), sulfuryl chloride (2.02 ml, 25 mmol) was carefully added so that the reaction temperature did not exceed 60 °C. The temperature was maintained at 60 °C for 15–20 min, then the reaction mixture was poured onto crushed ice and the precipitated product was filtered, washed with water and dried; yield 1.82 g (64%), m.p. 192–194 °, dec. (methanol). IR: 1760 s (C_3=O); 1710 s (C_1=O), 1615 w, 1500 m cm^{-1}. ^{1}H-NMR (CF_3COOH): δ 3.65 (s, CH_3), 7.7–8.2 (m, 3 *Ar*H), 8.6 (d, H at C-9). Anal. calcd. for $C_{11}H_7Cl_2N_3O_2$: C 46.50, H 2.48, N 14.79; found: C 46.42, H 2.51, N 14.73.

4,4-Dichloro-2-ethylpyrimido[1,6-a]benzimidazole-1,3(2H,4H)-dione (**3b**)

It was similarly prepared from **1b** (2.29 g, 10 mmol) and sulfuryl chloride (2.02 ml, 25 mmol), yield 2.53 g (85%), m.p. 177–180°, dec. (methanol). IR: 1760 s ($C_3=O$), 1710 s ($C_1=O$), 1610 m, 1550 s cm^{-1}. ^{1}H-NMR (CF_3COOH): δ 1.45 (t, J = 7 Hz, CH_3), 4.3 (q, J = 7 Hz, CH_2), 7.7–8.2 (m, 3 *Ar*H), 8.55 (d, H at C-9). Anal. calcd. for $C_{12}H_9Cl_2N_3O_2$: C 48.34, H 3.04, Cl 23.78, N 14.10; found: 48.60, H 3.10, Cl 24.33, N 13.98.

4,4-Dibromo-2-methylpyrimido[1,6-a]benzimidazole-1,3(2H,4H)-dione (**4**)

Bromine (1 ml, 20 mmol) was added, in one portion, to a stirred suspension of **1a** (1.08 g, 5 mmol) in glacial acetic acid (20 ml). After stirring at room temperature for 30 min, water was added and the product was filtered, washed with water and purified by washing with hot ethanol, yield 1.83 g (98%), m.p. 180°, dec. IR: 1760 s ($C_3=O$), 1710 s ($C_1=O$), 1610 w, 1600 w, 1540 m, 1840 w cm^{-1}. Anal. calcd. for $C_{11}H_7Br_2N_3O_2$: C 35.42, H 1.89, N 11.27; found: C 35.15, H 1.94, N 11.02.

3-Azido-2-methylpyrimido[1,6-a]benzimidazol-1(2H)-one (**5a**)

Sodium azide (0.52 g, 8 mmol) was added to a stirred suspension of **2a** (1.17 g, 5 mmol) in dimethylformamide (30 ml) and the mixture was heated at 60–70 °C for 30 min. After cooling and addition of cold water, a yellowish-brown product was separated out. This was filtered, washed with water and dried protected from light and heat; yield 1.0 g (83%), m.p. 158°, dec. (methanol). IR: 2120 s (N_3), 1720 s (CO), 1630 s, 1600 m, 1590 w, 1550 w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.4 (s, CH_3), 6.15 (s, H at C-4), 7.2–7.8 (m, 3 *Ar*H), 8.25 (d, H at C-9). Anal. calcd. for $C_{11}H_8N_6O$: C 55.00, H 3.36, N 34.99; found: C 54.96, H 3.40, N 35.09.

3-Azido-2-ethylpyrimido[1,6-a]benzimidazol-1(2H)-one (**5b**)

This was likewise prepared from **2b** (1.24 g, 5 mmol) and sodium azide (0.52 g, 8 mmol); yield 1.0 g (78%), m.p. 150–153°, dec. (methanol). IR: 2120 s (N_3), 1710 s (CO), 1640 s, 1600 s, 1590 w, 1550 w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.4 (t, J = 7 Hz, CH_3), 4.1 (q, J = 7 Hz, CH_2), 6.25 (s, H at C-4), 7.3–7.8 (m, 3 *Ar*H), 8.35 (d, H at C-9). Anal. calcd. for $C_{12}H_{10}N_6O$: C 56.68, H 3.96, N 33.06; found: C 56.40, H 3.94, N 33.12.

4,4-Diazido-2-methylpyrimido[1,6-a]benzimidazole-1,3(2H,4H)-dione (**6**)

A suspension of **3a** (2.27 g, 8 mmol) in methanol (40 ml) was stirred with sodium azide (1.3 g, 20 mmol) for 1 hour at room temperature, during which a clear solution was initially formed followed by the separation of the product. After addition of water, the product was filtered, washed with water and dried protected from heat and light; yield 1.84 g (77%), m.p. 140–142°, dec. (ethanol). IR: 2120 s (N_3), 1760 s ($C_3=O$), 1710 s ($C_1=O$), 1610 w, 1590 w, 1560 m cm^{-1}. ^{1}H-NMR (CDCl): δ 3.5 (s, CH_3), 7.2–8.0 (m, 3 *Ar*H), 8.2 (d, H at C-9). Anal. calcd. for $C_{11}H_7N_9O_2$: C 44.45, H 2.37, N 42.41; found: C 44.05, H 2.55, N 42.4.

2-Methyl-3-(triphenylphosphoranylideneamino)pyrimido[1,6-a]-benzimidazol-1(2H)-one (**7**)

A solution of triphenylphosphine (0.5 g, 2 mmol) in benzene (10 ml) was added to a stirred suspension of **5a** (0.24 g, 1 mmol) in benzene (10 ml) at room temperature. Immediately a yellowish-brown solution was formed with evolution of nitrogen gas followed by the precipitation of the product. After stirring for 30 min, the product was filtered, washed with benzene and dried; yield 0.42 g (85%), m.p. 243–245° (methanol or ethanol). IR: 3400 w, 3000 w, 1690 s, 1620 s, 1580 s, 1570 s cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.9 (s, CH_3), 5.35 (s, H at C-4), 7.0–8.0 (m, 18 *Ar*H), 8.3 (d, H at C-9). Anal. calcd. for $C_{29}H_{23}N_4OP \cdot {}^1/_2\,C_2H_5OH$: C 72.42, H 5.3, N 11.26; found: C 72.60, H 5.45, N 10.91.

3-Amino-2-methylpyrimido[1,6-a]benzimidazol-1(2H)-one (**8**)

This was prepared by refluxing **7** (1 g) with hydrochloric acid (2 *N*) (20 ml)-ethanol (20 ml) mixture for 1 hour. Subsequently most of the alcohol was evaporated and the reaction mixture was neutralized with ammonium hydroxide. The liberated amine was filtered, washed with water and dried; yield 0.38 g (89%), m.p. 290–295°, dec. (aqueous ethanol). IR: 3 500–2 700 bm, 1 690 s, 1 660 s (CO), 1 630 s, 1 600 s, 1 560 m cm^{-1}. ^{1}H-NMR: δ 3.45 (s, CH_3), 5.6 (s, H at C-4), 6.9 (s, NH_2), 7.0–7.6 (m, 3 *Ar*H), 8.15 (d, H at C-9). Anal. calcd. for $C_{11}H_{10}N_4O$: C 61.67, H 4.71, N 26.16; found: C 62.03, H 4.80, N 26.29.

2-Methyl-3-(4-morpholino)pyrimido[1,6-a]benzimidazol-1(2H)-one (**9a**)

It was prepared by refluxing **2a** (0.92 g, 4 mmol) with morpholine (1 ml, 12 mmol) in dimethylformamide (10 ml) for 30 minutes. After cooling and addition of few ml of water, the product was filtered, washed with water and dried; yield 1.0 g (88%), m.p. 232–235° (dimethylformamide). IR: 3 100 w, 2 900 w, 1 700 s (CO), 1 635 s, 1 600 s, 1 590 m, 1 540 w cm^{-1}. ^{1}H-NMR (CF_3COOH): δ 3.5 (s, 4 H, CH_2-N-CH_2 in morpholino), 3.8 (s, CH_3), 4.25 (s, 4 H, CH_2-O-CH_2 in morpholino), 6.5 (s, H at C-4), 7.4–7.9 (m, 3 *Ar*H), 8.5 (d, H at C-9). Anal. calcd. for $C_{15}H_{16}N_4O_2$: C 63.37, H 5.67, N 19.71; found: C 63.36, H 5.49, N 19.85.

2-Methyl-3-(1-piperidino)-pyrimido[1,6-a]benzimidazol-1(2H)-one (**9b**)

It was similarly prepared from **2a** (0.92 g, 4 mmol) and piperidine (1.2 ml, 12 mmol), yield 1.03 g (91%), m.p. 160–162° (aqueous dimethylformamide). IR: 2 950 w, 1 700 s (CO), 1 645 s, 1 600 m, 1 550 m cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.7 (s, 6 H, $CH_2-CH_2-CH_2$ in piperidino), 2.9 (s, 4 H, CH_2-N-CH_2 in piperidino), 3.8 (s, CH_3), 6.05 (s, H at C-4), 7.2–7.8 (m, 3 *Ar*H), 8.3 (d, H at C-9). Anal. calcd. for $C_{16}H_{18}N_4O$: C 68.06, H 6.43, N 19.84; found: C 68.16, H 6.31, N 19.57.

4,4-Di(4-morpholino)-2-methylpyrimido[1,6-a]benzimidazole-1,3(2H,4H)-dione (**10**)

Morpholine (3.5 ml, 40 mmol) was added dropwise to a stirred solution of **3a** (2.27 g, 8 mmol) in dimethylformamide (20 ml) at room temperature. An exothermic reaction took place and a colorless crystalline product separated out. After stirring for 1 hour at room temperature, water was added and the product was filtered, washed with water and dried; yield 2.42 g (74%), m.p. 185–189°, dec. (ethanol). IR: 3 000–2 900 w, 1 750 s ($C_3=O$), 1 700 s ($C_1=O$), 1 610 w, 1 540 m cm^{-1}. Anal. calcd. for $C_{19}H_{23}N_5O_4 \cdot {}^1/_2 C_2H_5OH$: C 58.81, H 6.42, N 17.20; found: C 58.52, H 5.99, N 17.87.

2-Methyl-4-(4-morpholino)-pyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione (**11**)

To a suspension of **10** (0.41 g, 1 mmol) in ethanol (20 ml)-water (20 ml) mixture, sodium dithionite (1 g) was added, portionwise while warming, over a period of 15–20 minutes. After concentration and addition of water, the product was filtered and dried; yield 0.28 g (90%), m.p. 258–261°, dec. (*n*-butanol). IR: 3 100–2 800 bm, 1 710 s ($C_1=O$), 1 670 s ($C_3=O$), 1 620 s, 1 480 m cm^{-1}. ^{1}H-NMR (200 MHz): δ 3.0 (s, 4 H, CH_2-N-CH_2 in morpholino), 3.2 (s, CH_3), 3.8 (s, 4 H, CH_2-O-CH_2 in morpholino), 7.1 (m, 2 *Ar*H), 7.3 (d, H at C-6), 8.1 (d, H at C-9). Anal. calcd. for $C_{15}H_{16}N_4O_3 \cdot {}^1/_2 H_2O$: C 58.24, H 5.54, N 18.11; found: C 58.87, H 5.59, N 18.05.

3-Cyano-2-methylpyrimido[1,6-a]benzimidazol-1(2H)-one (**12**)

A mixture of **2a** (1.17 g, 5 mmol) and sodium cyanide (0.49 g, 10 mmol) was stirred in dimethylformamide (15 ml) at 80–100 °C for 30 minutes. After cooling and addition of water, a dark brown product separated out. It was filtered, washed with water and dried; yield 0.5 g (45%), m.p. > 300° (dime-

thylformamide). IR: 3080 m, 2220 s (CN), 1720 s (CO), 1630 s, 1610 w, 1560 m cm^{-1}. ^{1}H-NMR (CF_3COOH): δ 4.0 (s, CH_3), 7.65–8.1 (m, 3 *Ar*H), 8.65 (d, H at C-9), 8.75 (s, H at C-4). Anal. calcd. for $C_{12}H_8N_4O$: C 64.28, H 3.60, N 24.99; found: C 63.98, H 3.62, N 25.07.

3-Methoxy-2-methylpyrimido[1,6-a]benzimidazol-1(2H)-one (**13**)

It was prepared by refluxing **2a** (1.17 g, 5 mmol) with a solution of sodium (0.14 g, 6 mmol) in absolute ethanol (30 ml) for 2 hours. After concentration and cooling, the product was filtered, washed with water and dried, yield 0.6 g (52%), m.p. 209–211° (methanol). IR: 3100 w, 1720 s (CO), 1640 s, 1600 m, 1560 m, 1250 s, 1040 w cm^{-1} (C–O–C). ^{1}H-NMR ($CDCl_3$): δ 3.5 (s, N–CH_3), 3.9 (s, O–CH_3), 5.8 (s, H at C-4), 7.1–7.8 (m, 3 *Ar*H), 8.3 (d, H at C-9). Anal. calcd. for $C_{12}H_{11}N_3O_2$: C 62.87, H 4.84, N 18.33; found: C 63.03, H 4.86, N 18.53.

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References and Notes

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