3250-3160 (NH), 1550-1525, 1345, 1320-1305, and 945-910 cm^{-1} (NCS I, II, III, and IV amide bands, respectively) (11); ^{1}H-NMR of II ($CDCl_3$): δ 2.82 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 3.68 (q, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.41 (d, 2, J = 5 Hz, $C_6H_5CH_2$—), 5.64 (s, distorted, 1, 2-phenethyl-NH, exchangeable), 6.07 (s, distorted, 1, benzyl-NH, exchangeable), and 7.13 ppm (m, 10, ArH).

2-Arylimino-4-aryl-3-(2-phenethyl)-2,3-dihydrothiazole Hydrobromides (VIII–XXXIII)—A mixture of *N*-aryl-*N'*-(2-phenethyl)thioureas (II–VII) (0.001 mol) and phenacyl bromide or the appropriately substituted phenacyl bromide (0.0011 mol) in absolute ethanol (10 mL) was heated at reflux for 4 h. Some of the products separated during the heating, while others crystallized after cooling the mixture. The products were removed by filtration, dried, and recrystallized from benzene containing a few drops of absolute ethanol. The yields and physical constants of the products (VIII–XXXIII) are listed in Table I. IR (mineral oil) ν: 2780–2670 (—NH) and 1610–1590 cm^{-1} (C=N); ^{1}H-NMR of XXIII (Me_2SO-d_6): δ 2.41 (s, 3, CH_3), 2.94 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.46 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 7.26 (m, 10, ArH and C_5—H of the thiazoline ring), 7.70 (d, 2, J = 9 Hz, ArH, *meta* to nitro group), and 8.44 ppm (d, 2, J = 9 Hz, ArH, *ortho* to nitro group); ^{1}H-NMR for XXVIII: δ 2.41 (s, 3, CH_3), 2.87 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.34 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 6.87 (s, 1, C_5-thiazoline proton), and 7.25 ppm (m, 13, ArH); ^{1}H-NMR for XXX: δ 2.81 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.27 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 6.80 (s, 1, C_5-thiazoline proton), and 7.29 ppm (m, 14, ArH). MS, *m/z* (relative abundance %) for XXIII: M^+ at 415(7), 312(22), 311(100), 310(20), 134(19), 105(47), 104(22), 103(26), 91(49), and 89(28). For XXVIII: M^+ at 404 and M + 2 at 406(8), 302(36), 301(22), 300(100), 299(15), 149(27), 148(51), 147(74), 134(27), 118(31), 115(28), 105(52), 104(21), 103(29), and 91(48). For XXX: M^+ at 435 and M + 2 at 437(0.9), 332(57), 331(17), 330(50), 139(22), 135(31), 134(100), 105(41), 104(49), 103(32), 102(23), 91(86), 90(24), 89(20), and 82(16).

Antihypertensive Testing—Rats, maintained in an incubator (32–35°C) for 20–40 min, were restrained to measure systolic blood pressure and heart rate indirectly by the tail cuff method[4]. Each determination was the mean of at least six recordings. Groups of four animals were used, and measurements were made predose (time zero) 1, 2, 4, and 6 h after administration of the products, with occasional readings at 24 h.

Anticonvulsant Testing—The compounds suspended in 1% methylcellulose were administered orally (1 mL/100 g) to CD-1 male mice (18–25 g), 10 per group, 1 h before intravenous infusion of 8 mg/mL of pentylenetetrazol in saline at a rate of 0.5 mL/min. The time of infusion required to elicit a tonic extensor spasm was noted, and the dose of pentylenetetrazol administered was calculated. The results (Table I) are expressed as the percentage change compared with controls treated with vehicle only. Statistical significance was determined using the Student's t test.

[4] W, W8005 B.P. recorder.

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Synthesis of *N*,*N'*-Disubstituted *N''*-2-(2-Quinolinylmethylthio)ethylguanidines as Potential Anticancer Agents

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Abstract □ A simple method for obtaining the title compounds was found in the alkaline rearrangement of *S*-2-aminoethylisothiouronium salts, which were obtained from the condensation of thiourea or substituted thioureas with 2-bromoethylamine hydrobromide. No activity was found for the substituted guanidines against P388 lymphocytic leukemia in mice, or as H_2-receptor antagonists.

Keyphrases □ *N,N'*-Disubstituted *N''*-2-(2-quinolinylmethylthio)ethylguanidines—anticancer activity, potential H_2-receptor antagonist □ Anticancer agents—potential, *N,N'*-disubstituted *N''*-2-(2-quinolinylmethylthio)ethylguanidines, H_2-receptor antagonist activity

A number of strongly basic compounds have shown appreciable anticancer activity. Bis(guanidines) and guanylhydrazones are active in leukemia systems (1, 2), and bis(guanylhydrazones) of anthracene-9,10-dicarboxaldehydes (3) have a particularly broad spectrum of anticancer activity. Recently, synthesized bis(*S*-alkyl) (4), and *S*-alkyl cycloalkylamino (5) derivatives of *N*-methylquinolinium dithioacetic acid showed reproducible activity against P388 lymphocytic leukemia in mice, the best activity being shown by one of the basic (morpholino) derivatives. It appeared that further increase in basicity of this series was warranted. The basic side chain of the cimetidine molecule was selected for inclusion in the quinoline-2-methyl structure because of the reported cytostatic and immunosuppressive activities of some guanidine derivatives (6). Modification of the basicity by inclusion of electron-attracting or -releasing functions on the guanidine moiety was

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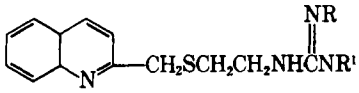
Table I—Physical Properties of *N,N'*-Disubstituted *N''*-2-(2-Quinolinylmethylthio)ethylguanidines (I·HX) and Antileukemic Activities in Mice [a]

Compound	R	R'	HX	Formula[b]	mp, °C	Yield, %	Dose, mg/kg[c]	Weight Difference (T − C)	Median Survival Time, T/C%[d]
Ia	H	H	2HCl	$C_{13}H_{16}N_4S\cdot 2HCl\cdot 1.5H_2O$	189–191	44[e]	100.0	−1.1	101
							50.0	0.6	94
Ib	H	CH_3	2HCl	$C_{14}H_{18}N_4S\cdot 2HCl\cdot 3H_2O$	220–223	43[f]			
Ic	CH_3	CH_3	2HCl	$C_{15}H_{20}N_4S\cdot 2HCl\cdot H_2O$	158–160	63[g]	50.0	−3.3	112
							25.0	−0.5	118
							12.5	−0.5	115
Id	CH_3	$C_6H_5CH_2$	2HCl	$C_{21}H_{24}N_4S\cdot 2HCl\cdot 1.5H_2O$	122 (dec.)	84[h]	50.0	−2.0	101
							25.0	−0.3	109
							12.5	−0.4	98
Ie	CH_3	$C_6H_5SO_2$	2HBr	$C_{20}H_{22}N_4O_2S_2\cdot 2HBr\cdot 2H_2O$	80–90 (dec.)	77	200.0	−0.5	100
							100.0	0.4	106
							50.0	0.7	106
If	CH_3	CN		$C_{15}H_{17}N_5S$		93	100.0	−1.2	94
							50.0	0.0	115

[a] CD_2F_1 mice were inoculated with P388 lymphocytic leukemia. [b] All compounds were analyzed for C, H, and N; in addition, Ia was analyzed for Cl, and Ib–d were analyzed for S. All values were within ±0.4% of the theoretical values. [c] Drugs were administered intraperitoneally on days 1, 5, and 9. [d] A T/C% value of ≥125 is considered a positive result. [e] Recrystallized from MeOH. [f] Recrystallized from MeOH–EtOAc. [g] Recrystallized from acetone–water. [h] Recrystallized from ether.

made, giving compounds of the I series. Since quinoline-2-methyl analogues of cimetidine have not been prepared or tested as H_2-receptor antagonists, this activity was also investigated for these derivatives.



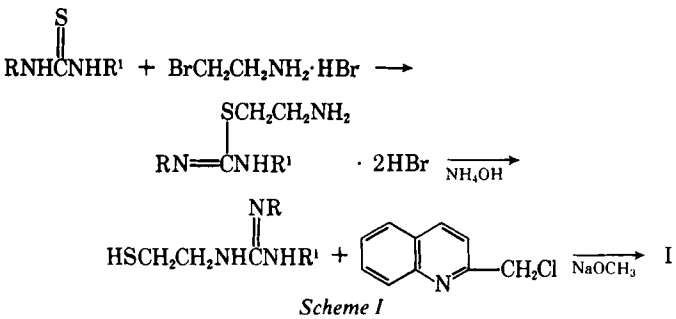
R=H, CH_3, $C_6H_5CH_2$ CN, $C_6H_5SO_2$
R'=H, CH_3

I

DISCUSSION

Chemistry—Most synthetic methods used for cimetidine analogues have involved the use of cyanamide (7, 8) or a derivative such as *N*-cyanoiminodithiocarbonic acid dimethyl ester (9) or *N*-methyldicyanodiamide (10) and treatment with appropriate amines or halides. It was found more convenient to synthesize the guanidinoethylmercapto moiety by alkaline rearrangement of *N,N'*-disubstituted *S*-2-aminoethylisothiouronium salts (11). These were prepared by condensation of *N,N'*-disubstituted thioureas with 2-bromoethylamine hydrobromide. When an electron-withdrawing function was present on the thiourea, salts were not formed, and rearrangement was carried out on the neutral molecule. The resulting mercapto compounds were converted to the sodium salts and condensed with 2-chloromethylquinoline. Yields of the *N*-2-(2-quinolinylmethylthio)ethylguanidines ranged from 42 to 93%, based on the isothiuronium compounds. Physical constants of the compounds obtained are recorded in Table I. This method of synthesis is shown in Scheme I. It may be considered an improvement over previously used methods for cimetidine analogues because of fewer synthetic steps and more stable starting materials.

^{1}H-NMR spectra of the products agreed with the proposed structures. Quinoline protons appeared at δ 8.46–8.60 ppm as salts and at δ 7.68–7.76 ppm as neutral molecules. The 2-quinolinylmethyl protons appeared as singlets at δ 4.52–4.64 ppm for the salts and at δ 3.90–3.99 ppm for the neutral molecules. The S—CH_2 protons were seen at δ 2.78–3.55 ppm for the salts and at δ 2.59–2.65 ppm for the neutral compounds. The N—CH_2 protons had chemical shifts at δ 3.50–3.55 ppm for the salts and at δ 3.41–3.43 ppm for the nonsalt forms. The N—CH_3 protons were found at δ 2.75–2.96 ppm for the salts and at δ 2.74–2.78 ppm for the nonsalts. The doublet of the N—CH_3 protons became a singlet in the presence of D_2O, indicating the proximity of N—H.



Scheme I

Biological Test Results—Antileukemia testing of the *N*-2-(2-quinolinylmethylthio)ethylguanidines was done at the National Cancer Institute in mice with P388 lymphocytic leukemia using the NCI protocol (12). Details regarding dose and survival of the treated animals are recorded in Table I. None of the compounds showed positive activity (a T/C × 100 ratio of ≥125), and all were appreciably toxic. Doses >100 mg/kg were generally fatal.

Screening of the compounds for possible H_2-receptor antagonism was carried out with guinea pig atria at doses of 10^{-4}–10^{-5} M. Cimetidine and tripelennamine were employed as H_2- and H_1-antagonists, respectively, and histamine was used as the H_2-agonist. None of the compounds had the ability to interact with the H_2-receptor, as determined by an isolated right atrial preparation from the guinea pig. The *N*-benzyl-*N'*-methylguanidine derivative slowed atrial rate but was not acting *via* an H_2-receptor.

EXPERIMENTAL SECTION[1]

***N*-Methyl-*S*-2-aminoethylisothiouronium Bromide Hydrobromide**—A mixture of *N*-methylthiourea (4.5 g, 0.05 mol) and absolute ethanol (50 mL) was refluxed for 30 min, 2-bromoethylamine hydrobromide (10.25 g, 0.05 mol) was added, and the mixture was refluxed for 2 h. The mixture was cooled, and the white precipitate was removed by filtration, dried at reduced pressure, and recrystallized from methanol to give 13.39 g (91%), mp 220–222°C; R_f 0.60. IR(KBr): 3300, 3260, 3080 (NH, NH_2^+, and NH_3^+), 1940 (amine·HBr), and 1648 (N—C=N) cm^{-1}; ^{1}H-NMR: δ 8.90 (br s, 6, NH, NH_2^+ and NH_3^+), 3.55 (t, 2, N—CH_2), 3.19 (t, 2, S—CH_2), and 2.99 ppm (s, 3, CH_3).

Anal.—Calc. for $C_4H_{11}N_3S\cdot 2HBr$: C, 16.28; H, 4.44; N, 14.24. Found: C, 16.43; H, 4.61; N, 14.37.

***N,N'*-Dimethyl-*S*-2-aminoethylisothiouronium Bromide Hydrobromide**—To a solution of *N,N'*-dimethylthiourea (5.20 g, 0.05 mol) in absolute ethanol (50 mL) was added 2-bromoethylamine hydrobromide (10.25 g, 0.05 mol) and the solution was refluxed for 2 h. The mixture was cooled (ice-bath), and the white solid was isolated and dried at reduced pressure. Recrystallization from methanol gave 12.59 g (82%), mp 215–216°C (dec.); R_f 0.59. IR(KBr): 3260, 3120, 3070 (NH_2^+, NH_3^+), 2020 (amine·HBr), 1630, and 1620 (N—C=N, NH_3^+) cm^{-1}; ^{1}H-NMR: δ 8.70 (br s, 5, NH_2^+ and NH_3^+), 3.68 (t, 2, N—CH_2), 3.18 (t, 2, S—CH_2), and 3.04 ppm (s, 6, $2CH_3$).

Anal.—Calc. for $C_5H_{13}N_3S\cdot 2HBr$: C, 19.43; H, 4.89; N, 13.60. Found: C, 19.65; H, 5.01; N, 13.46.

***N*-Benzyl-*N'*-methyl-*S*-2-aminoethylisothiouronium Bromide Hydrobromide**—*N*-Benzyl-*N'*-methylthiourea was prepared in 95% yield from benzylamine and methyl isothiocyanate in methanol, stirring for 20 h and recrystallizing from aqueous methanol to give white crystals, mp 71–73°C. The thiourea (9.01 g, 0.05 mol) was refluxed in absolute ethanol (50 mL) for 30 min, 2-bromoethylamine hydrobromide (10.25 g, 0.05 mol) was added, and

[1] Melting points were determined in capillary tubes with a Mel-Temp block and are uncorrected. ^{1}H-NMR spectra were obtained in Me_2SO-d_6 with a Varian T-60 spectrometer using Me_4Si as internal standard. IR spectra were obtained on a Perkin-Elmer 457A grating spectrophotometer using KBr pellets. TLC was carried out using Eastman silica gel plates with fluorescent indicator and a solvent system of 1-butanol–acetone–water (4:5:1). Elemental analyses were done by F. B. Strauss, Oxford, England. Organic reagents were supplied by Aldrich Chemical Co. and Fisher Scientific Co., and the hydrogen chloride by Matheson Gas Products.

the mixture was refluxed until it became homogeneous. It was cooled (ice-bath), and the white precipitate was removed by filtration and dried at reduced pressure. A second crop resulted on reducing the volume of the filtrate to 20 mL and cooling at −20°C. The combined solids were recrystallized from methanol to give 13.66 g (72%), mp 219–221°C; R_f 0.65. IR(KBr): 3330, 3230, 3100 (NH_2^+ and NH_3^+), 2020 (amine·HBr), 1620, and 1615 (N—C=N, NH_3^+) cm^{-1}; ^{1}H-NMR: δ 8.53 (bs, 5, NH_2^+ and NH_3^+), 7.93 (s, 5, ArH), 4.74 (s, 2, CH_2), 3.67 (t, 2, N—CH_2), 3.18 (t, 2, S—CH_2), and 3.09 ppm (s, 3, CH_3).

Anal.—Calc. for $C_{11}H_{17}N_3S{\cdot}2HBr$: C, 34.30; H, 4.97; N, 10.91. Found: C, 34.52; H, 5.18; N, 10.82.

***N*-Benzenesulfonyl-*N'*-methyl-*S*-2-aminoethylisothiourea**—To a solution of benzenesulfonamide (8.65 g, 0.055 mol) in dimethylformamide (30 mL) at 4°C was added a solution of sodium hydroxide (2.22 g) in water (3 mL) and methyl isothiocyanate (4.02 g, 0.055 mol), and the solution was stirred for 30 min. 2-Bromoethylamine hydrobromide (10.25 g, 0.05 mol) in dimethylformamide (20 mL) was added and stirring was continued at room temperature for 7 h. The mixture was added to water (500 mL) and extracted with 1-butanol (350 mL), and the extract was washed with water (2 × 250 mL). The organic phase was evaporated and the resulting syrup solidified on storage at −20°C. The white solid was recrystallized from methanol, to yield 4.23 g (28%), mp 114–116°C; R_f 0.50. IR(KBr): 3340, 3260 (NH and NH_2), 1570 (NH), 1200, and 1135 (SO_2) cm^{-1}; ^{1}H-NMR: δ 7.62 (m, 5, ArH), 7.20 (br t, 2, NH_2), 3.35 (m, 2, N—CH_2), 2.72 (d, 3, CH_3), and 2.60 ppm (m, 2, S—CH_2).

***N*-Cyano-*N'*-methyl-*S*-2-aminoethylisothiourea**—To a solution of cyanamide (2.31 g, 0.055 mol) in dimethylformamide (30 mL) at 4°C were added a solution of sodium hydroxide (2.2 g) in water (3 mL) and methyl isothiocyanate (4.02 g, 0.055 mol), and the solution was stirred for 30 min. 2-Bromoethylamine hydrobromide (10.25 g, 0.05 mol) in dimethylformamide (20 mL) was added, and the mixture was stirred at room temperature for 18 h. The solvent was evaporated at reduced pressure and the residue was extracted with 1-butanol (2 × 30 mL). The extract was washed with water (2 × 30 mL), and the organic phase was evaporated at reduced pressure to give 4.50 g (52%) of a syrup; R_f 0.81. IR(KBr film): 3350, 3240, 3170 (NH and NH_2), 2180 (CN), 1580; and 1540 (NH and NH_2) cm^{-1}; ^{1}H-NMR: δ 6.80 (br s, 3, NH and NH_2), 3.35 (m, 2, N—CH_2), 2.72 (d, 3, CH_3), and 2.60 ppm (m, 2, S—CH_2).

Representative Procedures for the Preparation of *N,N'*-Disubstituted *N''*-2-(2-Quinolinylmethylthio)ethylguanidines—*N-2-(2-Quinolinylmethylthio)ethylguanidine Dihydrochloride*—*S*-2-Aminoethylisothiouronium bromide hydrobromide (11) (28.10 g, 0.1 mol) in 50 mL of water was treated with concentrated ammonium hydroxide (15 mL, 0.25 mol) and stirred at room temperature for 2 h. The mixture was evaporated to dryness, and the residue was dried at reduced pressure. This material was dissolved in 25 mL of methanol, and a solution of sodium methoxide (5.40 g, 0.1 mol) in methanol (50 mL) was added. To the solution of the sodium salt of 2-mercaptoethylguanidine was added a solution of 2-chloromethylquinoline, prepared from the hydrochloride (21.41 g, 0.1 mol) and sodium methoxide (5.40 g, 0.1 mol), in methanol (50 mL). The mixture was stirred at room temperature for 18 h, the sodium chloride was removed by filtration, and the filtrate was evaporated to dryness. The residue was extracted with water (75 mL) and ether (75 mL), and the residual oil was reextracted with water (50 mL) and ether (50 mL). The aqueous extracts were evaporated to a syrup and dried at reduced pressure. The residue was treated with methanolic hydrogen chloride (75 mL), prepared by saturation at 0°C for 20 h. The methanol was evaporated, and the residue was recrystallized from methanol to give 14.59 g (44%) of beige crystals, mp 189–191°C; R_f 0.52. IR(KBr): 3380, 3300, 3120 (NH and NH_2), 2720–2600 (amine·HCl), and 1630 (N—C=N and NH_3^+) cm^{-1}; ^{1}H-NMR: δ 11.58 (br s, 1, quinoline·NH^+), 8.47 (m, 6, quinoline), 7.48 (br s, 5, NH, NH_2, and NH_2^+), 4.59 (s, 2, CH_2), 3.50 (q, 2, N—CH_2), 3.20 (s, H_2O), and 2.78 ppm (t, 2, S—CH_2).

N-Benzenesulfonyl-N'-methyl-N''-2-(2-quinolinylmethylthio)ethylguanidine Hydrobromide—*N*-Benzenesulfonyl-*N'*-methyl-*S*-2-aminoethylisothiourea (2.73 g, 0.01 mol) was added to 30 mL of methanol saturated with ammonia at 0°C, and stirred at 0°C for 18 h. The mixture was evaporated to dryness, and the residue was treated with acetone (20 mL) and sodium hydroxide (0.4 g) in water (10 mL). To the resulting solution was added 2-chloromethylquinoline (1.78 g, 0.01 mol) and stirring was continued at room temperature for 4 h. The mixture was evaporated to half volume, water (20 mL) was added, and the solution was extracted with 1-butanol (2 × 30 mL). The extract was washed with water (2 × 30 mL), evaporated to a syrup, and dried at reduced pressure to give 3.21 g (77%), which was converted to the hydrobromide, mp 68°C (color change), 80–90°C (dec.); R_f 0.84. ^{1}H-NMR ($CDCl_3$): δ 7.68 (m, 11, ArH), 6.60 (br s, 2, 2 NH), 3.90 (s, 2, CH_2), 3.41 (q, 2, N—CH_2), 2.74 (d, 3, CH_3), and 2.59 ppm (t, 2, S—CH_2).

N-Cyano-N'-methyl-N''-2-(2-quinolinylmethylthio)ethylguanidine—*N*-Cyano-*N'*-methyl-*S*-2-aminoethylisothiourea (3.35 g, 0.021 mol) was added to methanol (30 mL) saturated with ammonia at 0°C, and stirred at 0°C for 18 h. The mixture was evaporated to a syrup and dried at reduced pressure. The residue was added to a solution of sodium methoxide (0.81 g) in methanol (30 mL), 2-chloromethylquinoline (2.67 g, 0.015 mol) was added, and the solution was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was evaporated to a syrup which was dried at reduced pressure. The residue was extracted with 1,2-dichloroethane (50 mL), washed with water (2 × 30 mL), dried (Na_2SO_4), and filtered. The filtrate was evaporated to a syrup and dried at reduced pressure to give 4.18 g (93%); R_f 0.84. IR (film): 3280, 3160 (NH), and 2170 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.76 (m, 6, quinoline), 6.18 (br s, 2, 2 NH), 3.99 (s, 2, CH_2), 3.43 (m, 2, N—CH_2), 2.78 (d, 3, CH_3), and 2.65 ppm (m, 2, S—CH_2).

H_2-Receptor Antagonist Test—Compounds were tested for H_2-receptor antagonist activity using the guinea pig right atrial preparation described by Yellen *et al.* (13) and Lumley and Broadley (14). The isolated atrium was placed in a 50-mL tissue bath at 30°C and filled with Krebs-bicarbonate solution oxygenated with oxygen-carbon dioxide (95:5). Connected to a Grass Force displacement transducer, a 750-mg tension was applied to the atrium, and the tissue was allowed to equilibrate for 60–90 min. Cumulative dose-response curves were constructed using 10^{-7} 10^{-4} M histamine[2] in the presence or absence of cimetidine[3], tripelennamine dihydrochloride[2], or propranolol hydrochloride[4]. None of the compounds tested was capable of shifting the cumulative dose-response curve to histamine.

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