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4-Methallyl Substituted 1,2,4-Triazoline-3-thiones as a Source of N-Bridgehead Heterocycles

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Abstract: 4-Methallyl substituted 1,2,4-triazoline-3-thiones **1** upon treatment with sulfuric acid or bromine cyclize to derivatives of thiazolo[2,3-c]-1,2,4-triazole **2** and **3**, respectively. However, after methylation of the thiocarbonyl-sulfur by methyl trifluoromethanesulfonate and further treatment with bromine, compounds **1** undergo a cyclization to the imidazo[2,1-c]-1,2,4-triazoline-3-thiones **5**.

Dedicated to Prof. Dr. H. Suschitzky on the occasion of his 80th birthday.

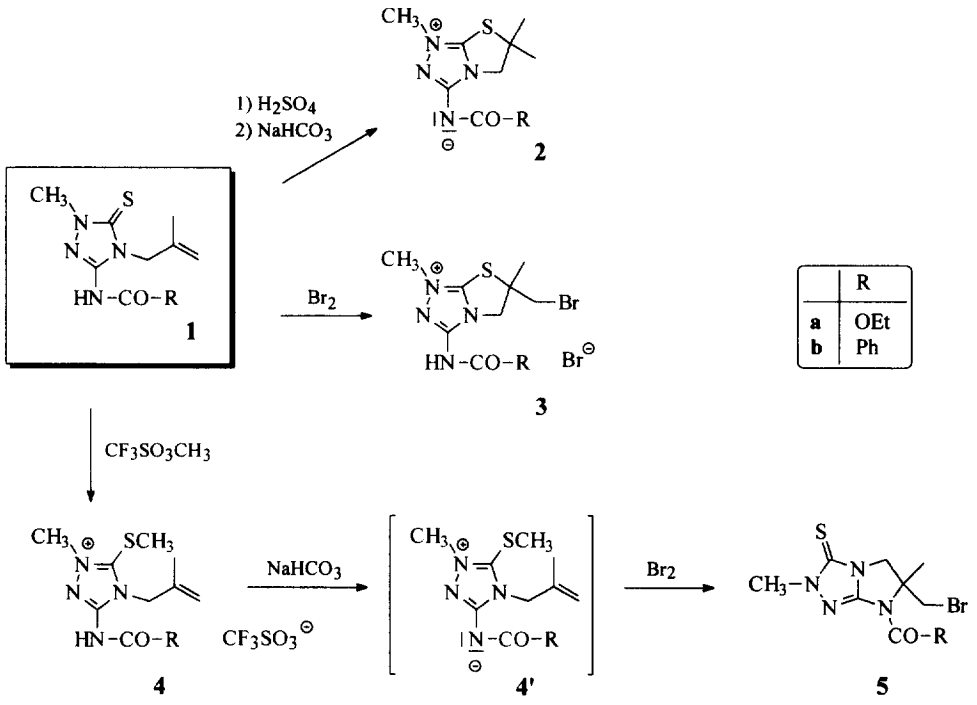
As a continuation of our study on the synthesis and reaction of 1,2,4-triazolidine-3-thiones and 1,2,4-triazoline-3-thiones we now describe a new synthesis of mesoionic thiazolo[2,3-c]-1,2,4-triazolium-3-acylaminides and imidazo[2,1-c]-1,2,4-triazoline-3-thiones.

Although numerous thiazolo[2,3-c]-1,2,4-triazole derivatives are known, until now no mesoionic compounds of this type were reported in the literature. A convenient route to thiazolo[2,3-c]-1,2,4-triazoles includes the cyclization of hydrazinosubstituted thiazoles[1,2]. In a similar manner the imidazo[2,1-c]-1,2,4-triazoles were prepared from hydrazinosubstituted imidazoles[3,4]. On the other hand, compounds incorporating a methallylthiocarbamoyl group were shown to be suitable precursors of 1,3-thiazolines[5]. Thus, upon treatment with strong acids, the proton induced cationic π-cyclization leads to the formation of the thiazoline ring. This was verified for different methallyl substituted thiosemicarbazides, thioureas[5] and 1,2,4-triazolidine-3-thiones[6]. In the present work we apply this reaction on methallyl substituted 1,2,4-triazoline-3-thiones **1** resulting in a new entry to N-bridgehead heterocycles.

RESULTS AND DISCUSSION

The treatment of **1** with sulfuric acid afforded water-soluble products, which after neutralization with sodium bicarbonate finally gave the thiazolo[2,3-c]-1,2,4-triazolium-3-acylaminides **2** in 73 % yield

(Scheme 1). Presumably, the formation of **2** involves a Markovnikov-orientated addition of a proton on the methallyl group and the nucleophilic ring closure through the thiocarbonyl-sulfur atom. In contrast to the 1,2,4-triazolidine-3-thiones which underwent a ring cleavage while forming the thiazolines[6], in the case of the triazoline analogues no ring opening products were detected.



Scheme 1

Similarly, the action of bromine on **1** afforded the thiazolo[2,3-c]-1,2,4-triazolium bromides **3** in more than 80 % yield. The ^1H NMR spectra of **2a** and **2b** show the typical singlet of the geminal dimethyl groups at 1.74 and 1.70 ppm, respectively. Since the methylene protons in compounds **3a** and **3b** are diastereotopic, each of them gives a separate doublet. Evidence for the acylaminide substructure in **2** is given by ^{13}C NMR spectroscopy. The carbonyl carbons appear in a lower field compared with the corresponding signals of the starting materials **1** or the salts **3**. Furthermore, the benzoyl compound **2b** shows the *ipso*-carbon atom at 139.3 ppm, while the *para*-carbon atom appears at 130.6 ppm. This is fully compatible with the ^{13}C NMR values of acylaminides reported in earlier papers[7,8].

In order to apply the cationic π-cyclization for the preparation of imidazo[2,1-c]-1,2,4-triazoline-3-thiones **5** the reversible protection of the thiocarbonyl-sulfur in compounds **1** is necessary, e. g. by alkylation. Thus, we treated **1** with methyl trifluoromethanesulfonate to give the stable 3-methylmercapto-1,2,4-triazolium

trifluoromethanesulfonates **4** in quantitative yield. The acylamino-nitrogen becomes a nucleophile by deprotonation of **4** to the 3-methylmercapto-1,2,4-triazolium-5-acylaminide **4'**, which was isolated in the case of **4'b**. In the next step the intermediate compounds **4'** were treated with bromine to give directly the desired imidazo[2,1-c]-1,2,4-triazoline-3-thiones **5** in moderate yields. This one-pot reaction probably includes the Markovnikov-orientated addition of Br^+ to the methallyl group, cyclization by an intramolecular nucleophilic attack of the aminide-nitrogen and subsequent demethylation of the sulfur. The last reaction, namely the regeneration of the thiocarbonyl-group is initiated by a nucleophilic attack of the Br^- ion on the S-methyl group resulting in the elimination of methyl bromide. 3-Methylmercapto-1,2,4-triazolium salts containing a nucleophilic anion, like Br^- or I^- would be unstable[9]. Because of this we used methyl trifluoromethanesulfonate rather than an alkyl halide in the S-methylation of compounds **1**.

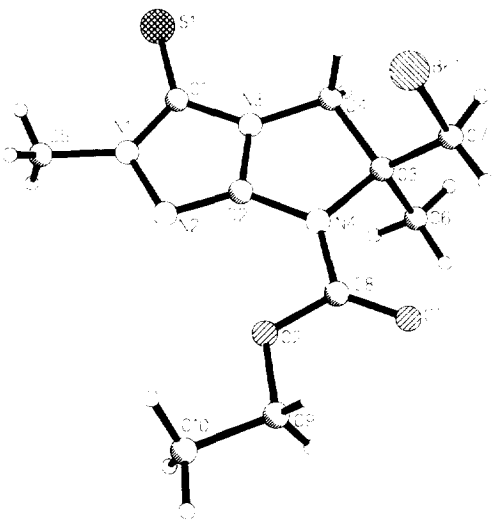


Figure 1. Molecular Structure of **5a** with crystallographic numbering[10]

The structure of the imidazo[2,1-c]-1,2,4-triazoline-3-thione **5a** was correctly determined by X-ray crystallography as shown in Fig. 1. The ring system is nearly planar, only the C(4) atom is forced out of the plane of the imidazole-ring. The C-S bond length [1.675(5) Å] is longer as calculated for compounds having an exact C=S double bond. Furthermore, the C-N bond lengths within the triazoline-ring [C(1)-N(1) = 1.334(6) Å and C(1)-N(3) = 1.369(6) Å] are intermediate between single-bond and double-bond length, indicating considerable conjugation with the C=S bond.

EXPERIMENTAL SECTION

All melting points were determined on a Boëtius melting point apparatus. NMR spectra were recorded on the Varian Gemini-200 (^{1}H NMR: 200 MHz, ^{13}C NMR: 50 MHz) and Unity-400 (^{1}H NMR: 200 MHz, ^{13}C NMR: 50 MHz) spectrometer. The chemical shifts given in ppm are referenced to the deuterated solvent. Mass spectra were measured with the V6 12-250 mass spectrometer of Analytical Instruments Manchester. The elemental analyses were performed using the CHN-Rapid Heraeus Elemental Analyzer. The 1,2,4-triazoline-3-thiones **1a** and **b** were prepared as described in ref. 7.

Thiazolo[2,3-c]-1,2,4-triazolium-3-acylaminides (2). General Procedure. The 1,2,4-triazoline-3-thiones **1** (10 mmol) were added in portions under stirring to concentrated sulfuric acid (8 ml), keeping the temperature below 45°C. The clear solution was gradually added to 50 g of crushed ice[11] and the resulting mixture treated with sodium bicarbonate (25 g). After extraction with trichloromethane (3×15 ml), drying the organic phase with sodium sulfate and removing the solvent *in vacuo*, compounds **2** were obtained as an oil. The crude materials were allowed to crystallize on standing and were recrystallized from chlorobenzene (for **2a**) and toluene (for **2b**).

5,6-Dihydro-1,6,6-trimethyl-thiazolo[2,3-c]-1,2,4-triazolium-3-ethoxycarbonylaminide (2a) (73%), m.p. 141-143°C (colourless leaflets). (Found: C, 46.69; H, 6.19; N, 21.64. $C_{10}H_{16}N_4O_2S$ requires: C, 46.86; H, 6.29; N, 21.86); ^{1}H NMR δ ($CDCl_3$): 1.25 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.74 (s, 6H, $C(CH_3)_2$), 3.66 (s, 3H, NCH_3), 4.05 (s, 2H, CH_2), 4.09 (q, 2H, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_2CH_3), 28.6 ($C(CH_3)_2$), 37.1 (NCH_3), 56.7 (C), 59.3 (CH_2CH_3), 69.6 (CH_2), 147.9, 156.3, 160.2 (CO); MS m/z (%): 256 (M^+, 100), 241 (42), 223 (31), 201 (80), 173 (41).

5,6-Dihydro-1,6,6-trimethyl-thiazolo[2,3-c]-1,2,4-triazolium-3-benzoylaminide (2b) (73%), m.p. 91-95°C (colourless needles). (Found: C, 58.26; H, 5.46; N, 19.66. $C_{14}H_{16}N_4OS$ requires: C, 58.31; H, 5.59; N, 19.43); ^{1}H NMR δ ($CDCl_3$): 1.70 (s, 6H, $C(CH_3)_2$), 3.62 (s, 3H, NCH_3), 4.22 (s, 2H, CH_2), 7.30-8.18 (m, 5H, C_6H_5); ^{13}C NMR δ ($CDCl_3$): 29.8 ($CCH_3)_2$), 38.2 (NCH_3), 60.3 (C), 70.8 (CH_2), 128.0, 129.4, 130.6 (para), 139.3 (ipso), 150.4, 157.7, 172.7 (CO); MS m/z (%): 288 (M^+, 53), 105 (100), 91 (46), 77 (44).

Thiazolo[2,3-c]-1,2,4-triazolium Bromides (3). General Procedure. To a solution of the appropriate 1,2,4-triazoline-3-thione **1** (10 mmol) in dry dichloromethane (20 ml) was added a solution of bromine (1.60 g, 10 mmol) in dichloromethane (5 ml) at a temperature of 0 - 5°C. The mixture was stirred at room temperature

until a precipitate of the hydrobromide occured. It was then filtered off, washed with dichloromethane and dried *in vacuo*.

6-Bromomethyl-5,6-dihydro-1,6-dimethyl-3-ethoxycarbonylamino-thiazolo[2,3-c]-1,2,4-triazolium Bromide (3a) (84%), m.p. 168-170°C (colourless powder). (Found: C, 28.73; H, 3.71; N, 13.13; $C_{10}H_{15}BrN_4O_2S \cdot HBr$ requires: C, 28.86; H, 3.88; N, 13.46); ^1H NMR δ (DMSO-d_6): 1.26 (t, 3H, J=7.1 Hz, CH_2CH_3), 1.91 (s, 3H, CCH_3), 3.84 (s, 3H, NCH_3), 4.21 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.29 (d, 1H, J=10.5 Hz, CH_2), 4.37 (d, 1H, J=10.5 Hz, CH_2), 4.44 (d, 1H, J=12.2 Hz, CH_2), 4.70 (d, 1H, J=12.4 Hz, CH_2); ^{13}C NMR δ (DMSO-d_6): 14.5 (CH_2CH_3), 25.5 (CCH_3), 38.9 (NCH_3), 41.0 (CH_2Br), 56.8 (NCH_2), 62.7 (CH_2CH_3), 72.9 (C), 145.5, 152.2 (CO), 155.3; MS m/z (%): 336/334 (M^+-HBr, 21), 255 (100), 209 (69), 183 (39).

3-Benzoylamino-6-bromomethyl-5,6-dihydro-1,6-dimethyl-thiazolo[2,3-c]-1,2,4-triazolium Bromide (3b) (85%), m.p. 122-123°C (colourless hygroscopic powder). ^1H NMR δ (DMSO-d_6): 1.93 (s, 3H, CCH_3), 3.91 (s, 3H, NCH_3), 4.25 (d, 1H, J=10.5 Hz, CH_2), 4.32 (d, 1H, J=10.5 Hz, CH_2), 4.52 (d, 1H, J=12.4 Hz, CH_2), 4.72 (d, 1H, J=12.4 Hz, CH_2), 7.61 (t, 2H, J=7.3 Hz, C_6H_5), 7.73 (t, 1H, J=7.3 Hz, C_6H_5), 8.05 (d, 2H, J=6.9 Hz, C_6H_5); ^{13}C NMR δ (DMSO-d_6): 25.6 (CCH_3), 38.5 (NCH_3), 41.1 (CH_2Br), 57.6 (NCH_2), 73.1 (C), 128.9, 129.0, 131.5 (ipso), 133.7 (para), 145.9, 155.8, 166.3 (CO); MS m/z (%): 288 (M^+-Br_2, 69), 105 (100), 77 (58).

3-Methylmercapto-1,2,4-triazolium Trifluoromethanesulfonates (4). General Procedure. To a stirred solution of the appropriate 1,2,4-triazoline-3-thione **1** (10 mmol) in dry dichloromethane (40 ml) was added methyl trifluoromethanesulfonate (1.64 g, 10 mmol). After 1 h stirring at room temperature the solvent was distilled off. The resulting triflates may be used in the next step without further purification, only small samples were recrystallized from ethanol/ether.

5-Ethoxycarbonylamino-4-methallyl-2-methyl-3-methylmercapto-1,2,4-triazolium Trifluoromethanesulfonate (4a) (100%), m.p. 111-113°C (colourless leaflets). (Found: C, 34.33; H, 4.56; N, 13.47. $C_{11}H_{18}N_4O_2S \cdot CF_3SO_3H$ requires: C, 34.28; H, 4.55; N, 13.33); ^1H NMR δ (DMSO-d_6): 1.28 (t, 3H, J=7.1 Hz, CH_2CH_3), 1.78 (s, 3H, CCH_3), 2.64 (s, 3H, SCH_3), 4.10 (s, 3H, NCH_3), 4.23 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.63 (s, 1H, $=CH_2$), 4.83 (s, 2H, NCH_2), 5.01 (s, 1H, $=CH_2$), 11.15 (bs, 1H, NH); ^{13}C NMR δ (DMSO-d_6): 14.4 (CH_2CH_3), 17.5 (SCH_3), 20.0 (CCH_3), 39.4 (NCH_3), 50.8 (NCH_2), 62.6 (CH_2CH_3), 113.1 ($=CH_2$), 138.0 (>C=), 147.8, 149.5, 152.3 (CO); MS m/z (%): 270 (M^+-CF_3SO_3H, 22), 256 (M^+-$CF_3SO_3CH_3$, 32), 210 (74), 177 (48), 149 (64), 82 (53), 69 (100).

5-Benzoylamino-4-methallyl-2-methyl-3-methylmercapto-1,2,4-triazolium Trifluoromethanesulfonate (4b) (100%), m.p. 163-165°C (colourless needles). (Found: C, 42.46; H, 4.08; N, 12.55. $C_{15}H_{18}N_4OS{\cdot}CF_3SO_3H$ requires: C, 42.47; H, 4.23; N, 12.38); ^{1}H NMR δ (DMSO-d_6): 1.73 (s, 3H, CCH_3), 2.71 (s, 3H, SCH_3), 4.18 (s, 3H, NCH_3), 4.73 (s, 1H, $=CH_2$), 4.90 (s, 2H, NCH_2), 5.01 (s, 1H, $=CH_2$), 7.62 (t, 2H, J=7.3 Hz, C_6H_5), 7.73 (t, 1H, J=7.1 Hz, C_6H_5), 7.97 (d, 2H, J=7.0 Hz, C_6H_5); ^{13}C NMR δ (DMSO-d_6): 17.5 (SCH_3), 19.9 (CCH_3), 39.6 (NCH_3), 51.9 (NCH_2), 114.3 ($=CH_2$), 128.6, 129.1, 131.9, 133.6, 137.6 (>C=), 148.0, 150.9, 167.1 (CO); MS m/z (%): 302 (M^+-CF_3SO_3H, 21), 288 (M^+-$CF_3SO_3CH_3$, 31), 105 (100), 77 (76).

4-Methallyl-2-methyl-3-methylmercapto-1,2,4-triazolium-5-benzoylaminide (4'b). The triflate **4b** (4.52 g, 10 mmol) was dissolved in ethanol (15 ml) under heating. The ethanolic solution was diluted with water (25 ml) and treated with sodium bicarbonate (0.84 g, 10 mmol). After further addition of water (25 ml) crystallization took place. The crystals were filtered off and allowed to dry in air to give **4'b·1/2CF_3SO_3Na** (86%) as colourless needles, m.p. 191-195°C. (Found: C, 47.89; H, 4.65; N, 14.24. $C_{15}H_{18}N_4OS{\cdot}1/2$ CF_3SO_3Na requires: C, 47.93; H, 4.67; N, 14.42); ^{1}H NMR δ (DMSO-d_6): 1.81 (s, 3H, CCH_3), 2.57 (s, 3H, SCH_3), 4.03 (s, 3H, NCH_3), 4.66 (s, 1H, $=CH_2$), 4.73 (s, 2H, NCH_2), 4.96 (s, 1H, $=CH_2$), 7.38-8.16 (m, 5H, C_6H_5); ^{13}C NMR δ (DMSO-d_6): 17.7 (SCH_3), 20.4 (CCH_3), 38.0 (NCH_3), 48.9 (NCH_2), 112.3 ($=CH_2$), 127.8, 128.8, 130.1 (para), 139.97 (CF_3), 140.04 (ipso), 142.7, 157.9, 170.0 (CO).

6-Bromomethyl-2,6-dimethyl-7-ethoxycarbonyl-2,3,5,6-tetrahydro-7*H*-imidazo[2,1-c]-1,2,4-triazole-3-thione (5a). To a stirred solution of the triflate **4a** (4.2 g, 10 mmol) in water (50 ml) was gradually added sodium bicarbonate (0.84 g, 10 mmol). When the evolution of carbon dioxide had ceased, the solution was extracted with trichloromethane (3 ×15 ml). The combined organic phases were dried with sodium sulfate and the solvent was removed under reduced pressure. The resulting oily residue was dissolved in acetonitrile (50 ml) and a solution of bromine (1.6 g, 10 mmol) in 5 ml of acetonitrile was slowly added at a temperature between 0 and 5°C. The reaction mixture was then heated to reflux for 5 h. After removal of the solvent *in vacuo* the residue was chromatographed on silica gel (65 g) using a mixture of trichloromethane/n-hexane (20:1) as eluent. The crude product was recrystallized from *tert*-butyl methyl ether to give **5a** (47%) as colourless prisms, m.p. 123-125°C. (Found: C, 36.19; H, 4.58; N, 16.33. $C_{10}H_{15}BrN_4O_2S$ requires: C, 35.83; H, 4.51; N, 16.71); ^{1}H NMR δ ($CDCl_3$): 1.34 (t, 3H, J=7.1 Hz, CH_2CH_3), 1.80 (s, 3H, CCH_3), 3.59 (d, 1H, J=11.1 Hz, CH_2), 3.64 (s, 3H, NCH_3), 3.81 (d, 1H, J=11.1 Hz, CH_2), 4.15 (d, 2×1H, J=11.1 Hz, CH_2), 4.33 (q, 2H, J=7.1 Hz, CH_2CH_3); ^{13}C NMR δ ($CDCl_3$): 14.8 (CH_2CH_3), 24.4 (CCH_3), 36.8 (NCH_3), 38.0 (CH_2Br), 52.5 (NCH_2), 64.3 (CH_2CH_3), 71.8 (C), 149.9 (>C=N-), 150.0 (CO), 162.2 (CS); MS m/z (%): 336/334 (M^+, 100), 197 (57), 183 (42), 169 (77).

X-ray diffraction analysis of ***5a***[12]: Crystals were obtained from ethyl acetate/n-hexane. A platelet (0.4 x 0.4 x 0.7 mm^3) was selected. The measurement was carried out at room temperature, STADI4 (Stoe) diffractometer, ω-θ-scan, graphite monochromator, Mo Kα (λ = 0.71073 Å). The structure was solved by direct methods[13], monclinic, space group $P2_1/c$, a = 7.742(1) Å, b =17.920(5) Å, c = 10.286(1) Å, ß = 100.41(1)°, V = 1403.6(5) $Å^3$, Z = 4, ρ_{calc} = 1.586g/cm^{-3}, 2490 data, 214 parameters; the C, O, N, S and Br atoms were refined with anisotropic temperature factors, and the hydrogen atoms with isotropic temperature factores; all hydrogen atoms have been found except H6A, H6B, H6C which have been refined at calculated positions, agreement factor R/wR2 = 0.0947/0.1813, R_w /wR_w 2 = 0.0607/0.1578[14]. The molecular shape is presented in Fig. 1.

7-Benzoyl-6-bromomethyl-2,6-dimethyl-2,3,5,6-tetrahydro-7*H*-imidazo[2,1-c]-1,2,4-triazole-3-thione (5b). A solution of **4'b** (3.88 g, 10 mmol) in acetonitrile (50 ml) was prepared. The further reaction with bromine and isolation was performed as described for the preparation of **5a** (see above). After column chromatography the solid material was recrystallized from ethanol to give **5b** (48%) as colourless prisms, m.p. 174-178°C. (Found: C, 45.90; H, 4.10; N, 14.89. $C_{14}H_{15}BrN_4OS$ requires: C, 45.78; H, 4.12; N, 15.26); ^1H NMR δ ($CDCl_3$): 1.99 (s, 3H, CCH_3), 3.49 (s, 3H, NCH_3), 3.73 (d, 1H, J=11.2 Hz, CH_2), 3.88 (d, 1H, J=11.0 Hz, CH_2), 4.28 (d, 1H, J=11.1 Hz, CH_2), 4.50 (d, 1H, 11.2 Hz, CH_2), 7.43 (t, 2H, J=7.2 Hz, C_6H_5), 7.57 (t, 1H, J=7.4 Hz, C_6H_5), 7.62 (d, 2H, J=8.3 Hz, C_6H_5); ^{13}C NMR δ ($CDCl_3$): 24.1 (CCH_3), 36.8 (NCH_3), 37.4 (CH_2Br), 52.4 (NCH_2), 74.0 (C), 128.7, 128.9, 133.0 (para), 133.6 (ipso), 150.1 (>C=N-), 162.4 (CS), 167.8 (CO); MS m/z (%): 368/366 (M^+, 12), 105 (100), 77 (43).

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