# Synthesis of Chiral 5-Substituted 2-Pyrrolidones, Metabolites of the Antipsychotic Benzamides Remoxipride and Raclopride

Lars Gawell,* Peter Ström† and Thomas Högberg†

Department of Medicinal Chemistry, CNS, Astra Arcus AB, S-151 85 Södertälje, Sweden

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Three of the major human metabolites of remoxipride (**1**) and raclopride (**6**) have been synthesized in optically active form. Starting from L-pyroglutamic acid, the two pyrrolidones (+)-(5S)-5-(aminomethyl)-2-pyrrolidone (**10**) and (+)-(5*S*)-5-(aminomethyl)-1-ethyl-2-pyrrolidone (**12**) were prepared. Acylation of **10** or **12** with the appropriate benzoyl chloride then led to the metabolites **2** and **3** from remoxipride and metabolite **7** from raclopride.

In the group of substituted benzamides, a number of derivatives have been found that selectively inhibit the dopamine $D_2$ receptors and possess potential antipsychotic properties.[1] Remoxipride {(−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide, **1**} has been developed in the Astra laboratories[2] and found to have an antipsychotic efficacy comparable to that of haloperidol and to be associated with a considerably lower degree of adverse effects, in particular motoric (extrapyramidal) side effects (EPS).[3]

In rodents, remoxipride is primarily metabolized in the aromatic moiety giving demethylated and/or oxidized compounds.[1,4] However, in man and dog, α-oxidations in the pyrrolidine ring are the predominant metabolic reactions.[4] These and *N*-dealkylation lead to the pyrrolidones **2** and **3** and hydroxypyrrolidones **4** and **5** (Fig. 1). Syntheses of the hydroxypyrrolidones have recently been described.[5] This paper details the synthesis of the chiral lactams **2** and **3**.

Raclopride[1,6]{(−)-(*S*)-3,5-dichloro-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide, **6**} is another antipsychotic dopamine $D_2$ antagonist under investigation (Fig. 2).[7] Furthermore, raclopride in $^{11}$C-labelled form is a well established radiotracer for positron emission tomography studies in man.[8,9] Therefore, it is of importance to have access to the major human metabolite[10] **7** for various studies. The synthetic strategy used for the remoxipride metabolite **2** could easily be applied to this molecule.

## Results and discussion

Initially, remoxipride metabolite **2** was prepared in the racemic form to be used as reference sample for analytical purposes. This was easily accomplished by reduction of the previously reported metabolite 5-[(3-bromo-2, 6-dimethoxybenzamido)methyl]-1-ethyl-5-hydroxy-2-pyrrolidone[5] with sodium cyanoborohydride.[11] However, for pharmacological evaluation, the metabolites **2** and **3** from remoxipride, and metabolite **7** from raclopride, were required in optically pure forms.

The two structurally related benzamides remoxipride and raclopride possess the *S*-configuration at the asymmetric centre. This stereochemistry should also apply to the metabolites **2**, **3** and **7** since the metabolic conversions leading to these compounds, take place at positions remote from the asymmetric centre. Therefore, syntheses of these metabolites, starting from materials with the desired *S*-configuration, were elaborated.

L-Pyroglutamic acid, was converted into (*S*)-5-(bromomethyl)-2-pyrrolidone (**8**) according to the procedure of Silverman and Levy[12] (Scheme 1). Nucleophilic substitution on the bromide **8**, with sodium azide in the presence of 18-crown-6 ether, gave the crystalline (*S*)-5-(azidomethyl)-2-pyrrolidone (**9**), previously isolated in the race-

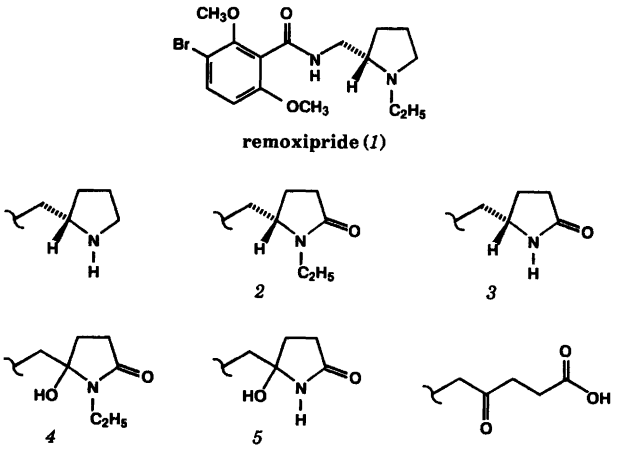



*Fig. 1.* Major human and canine metabolites of remoxipride.[4]

† Present address: Department of Medicinal Chemistry, Astra Draco AB, P.O. Box 34, S-221 00 Lund, Sweden.
* Author to whom correspondence should be addressed.

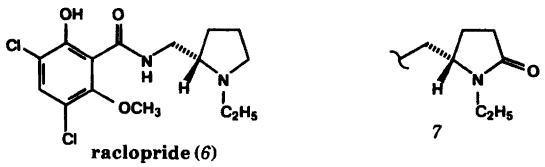



*Fig. 2.* Raclopride and its major human metabolite.[10]

mic form as an oil.[13] Hydrogenation of the azide **9** over palladium-on-carbon gave the amine **10**, which was acylated with 3-bromo-2,6-dimethoxybenzoyl chloride[5] to furnish the remoxipride metabolite **3**.

The *N*-substituted metabolites **2** and **7**, were prepared analogously from the amine **12**. The sodium salt of compound **9** was *N*-alkylated with ethyl iodide in *N,N*-dimethylformamide (DMF), to form the azide **11**. The following hydrogenation of **11** in ethanol produced a mixture of products, from which the desired amine **12** was isolated as an oxalate. Formation of the 'dimeric' by-product, bis[(1-ethyl-5-oxo-2-pyrrolidinyl)methyl]amine (**13**), was found to be dependent on the concentration of the substrate **11**. By running the hydrogenation in a 3 % solution, the 'dimerization' was minimized and a 90:10 ratio of the amines **12** and **13** was formed according to GLC. The enantiomeric purity of the amine **12** was determined by capillary GLC after derivatization with (−)-(*R*)- and (+)-(*S*)-α-methoxyphenylacetyl chloride and was found to be high, i.e. 99 % e.e. Treatment of the oxalate of the amine **12** with the appropriate benzoyl chloride under basic conditions, furnished the metabolites **2** and **7** from remoxipride and raclopride respectively.

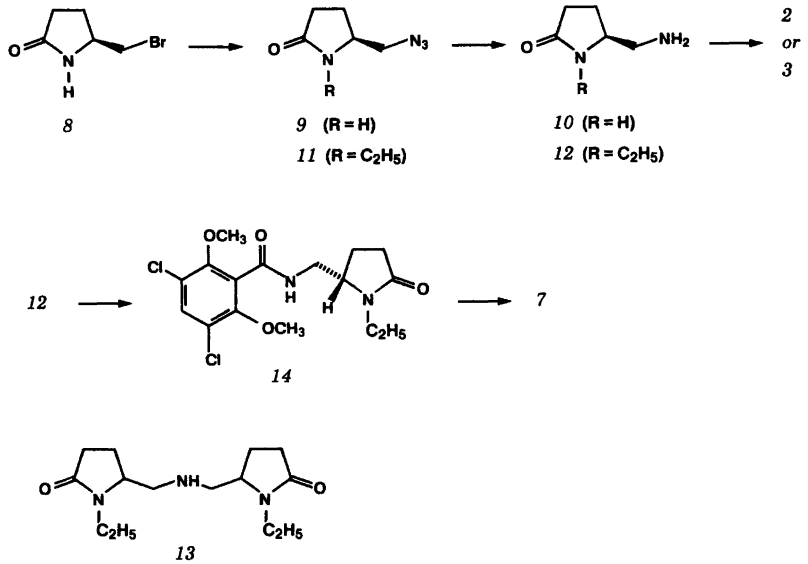
## Experimental

Melting points were determined on a Mettler FP 61 apparatus and are uncorrected. NMR spectra ($^1$H at 300 MHz and $^{13}$C at 75 MHz) were obtained on a Varian Gemini-300 instrument with $Me_4Si$ (TMS) or sodium 3-(trimethylsilyl)-propanoate (TSP) as the internal reference. Mass spectra were recorded on a Finnigan Mat ITD instrument at an electron energy of 70 eV. Optical rotations were measured on an AA-100 Polarimeter, Optical Activity Ltd., England. Elemental analyses, performed by *Analytische Laboratorien,* Elbach, West Germany and Mikro Kemi AB, Uppsala, Sweden were within ± 0.4 % of the theoretical values unless otherwise noted.

(−)-(S)-*5-(Bromomethyl)-2-pyrrolidone* (**8**) was synthesized as described previously.[12] M.p. 72–74 °C; $[\alpha]_D^{20}$ −31° (*c* 1.2, ethanol) [lit.[12] m.p.71–74 °C]; $[\alpha]_D^{20}$ −33° (*c* 5.0, ethanol).

(+)-(S)-*5-(Azidomethyl)-2-pyrrolidone* (**9**). A mixture of the bromide **8** (10.0 g, 56 mmol), sodium azide (7.0 g, 103 mmol) and 18-crown-6 (590 mg) in acetonitrile (40 ml) was stirred at 85 °C. After 16 h, the reaction mixture was filtered and concentrated. The residue was dissolved in ethyl acetate and filtered through a column of $SiO_2$. The filtrate was concentrated by evaporation at reduced pressure to yield the azide **9** (7.0 g, 89 %) as a crystalline solid. A portion was taken out and recrystallized from ethyl acetate/diisopropyl ether to give an analytically pure sample: M.p. 65–66 °C; $[\alpha]_D^{25}$ +72° (*c* 1.1, ethanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.80–1.90 (1 H, m), 2.23–2.44 (3 H, m), 3.31 (1 H, dd, *J* 12.3 and 6.6 Hz), 3.47 (1 H, dd, *J* 12.3 and 4.5 Hz) 3.78–3.90 (1 H, m) and 6.94 (1 H, br s). $^{13}$C NMR ($CDCl_3$, TMS): δ 24.10, 29.90, 53.86, 56.16, 179.33. MS [*m/z* (% rel. int.)]: 141 (22, *M*+1), 113 (3), 85 (4), 84 (100). Anal. ($C_5H_8N_4O$): C, H, O.

(+)-(S)-*5-(Aminomethyl)-2-pyrrolidone* (**10**). A solution of the azide **9** (717 mg, 5.1 mmol) in ethanol (5 ml) was stirred under an atmosphere of hydrogen in the presence of 5 % Pd/C as a catalyst. In the course of the reaction, the reaction flask was flushed three times with hydrogen gas in order to remove the nitrogen gas produced. After 18 h the




*Scheme 1.*

catalyst was removed by filtration. Evaporation of the solvent at reduced pressure left the pure amine **10** (540 mg, 93%) as an oil, $[\alpha]_D^{23}$ +53° (*c* 1.0, ethanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.60–1.85 (1 H, m), 2.15–2.45 (3 H, m), 2.60–2.75 (1 H, m), 2.80–2.90 (1 H, m), 3.40 (2 H, br s), 3.65–3.80 (1 H, m), 7.85 (1 H, br s). $^{13}$C NMR ($CDCl_3$, TMS): δ 24.32, 30.40, 47.01, 56.83, 179.96. MS [*m/z* (% rel. int.)]: 115 (11, *M*+1), 97 (19), 85 (84), 84 (100).

(+)-(S)-*5-(Azidomethyl)-1-ethyl-2-pyrrolidone* (**11**). To a suspension of NaH (430 mg, 18 mmol) in DMF (20 ml), was added a solution of azide **9** (1.97 g, 14 mmol) in DMF (2 ml) at ice-water temperature. The cooling bath was removed and the mixture was stirred at room temperature for 2 h, to form an emulsion. Ethyl iodide (2.50 g, 16 mmol) in DMF (2 ml) was added and the stirring was continued. After 1 h, the emulsion had dissolved and the reaction mixture was filtered and concentrated. Water was added and the mixture extracted with $CH_2Cl_2$. The organic solution was washed with brine, dried ($Na_2SO_4$) and evaporated to dryness. The residue was dissolved in ethyl acetate and filtered through a column of $SiO_2$. The filtrate was concentrated and the residue dried under vacuum to give the azide **11** (1.92 g, 82%) as an oil, $[\alpha]_D^{22}$ +50° (*c* 1.6, ethanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.14 (3 H, t, *J* 7.2 Hz), 1.75–1.95 (1 H, m), 2.05–2.25 (1 H, m), 2.27–2.37 (1 H, m), 2.40–2.55 (1 H, m), 2.90–3.15 (1 H, m), 3.42 (1 H, dd, *J* 12.7 and 4.9 Hz), 3.54 (1 H, dd, *J* 12.7 and 4.6 Hz) and 3.62–3.75 (1 H, m), 3.75–3.85 (1 H, m). $^{13}$C NMR ($CDCl_3$, TMS): δ 12.88, 22.33, 30.05, 35.63, 53.53, 56.53, 175.58. MS [*m/z* (% rel. int.)]: 169 (43, M+l), 141 (9), 113 (6), 112 (100), 84 (27).

(+)-(S)-*5-(Aminomethyl)-1-ethyl-2-pyrrolidone* (**12**). A solution of the azide **11** (1.0 g, 6 mmol) in ethanol (15 ml) was stirred overnight under an atmosphere of hydrogen in the presence of 10% Pd/C as a catalyst. The catalyst was removed by filtration and the solvent evaporated off to leave a 1:1 mixture of compounds **12** (99% e.e.) and **13** as indicated by GLC. To a part (520 mg) of this mixture in methanol (2 ml) was added oxalic acid (335 mg, 3.7 mmol) in the same solvent. After 15 min a precipitate had formed which was redissolved in methanol–$H_2O$ with heating. Crystallization overnight at 4 °C furnished the oxalate of **13** (235 mg). Recrystallization from methanol–$H_2O$ gave an analytically pure sample. M.p. 211–212 °C; $[\alpha]_D^{20}$ −27° (*c* 1.1, $H_2O$). $^1$H NMR ($D_2O$, TSP): δ 1.11 (3 H, t), 1.95–2.10 (1 H, m), 2.25–2.65 (3 H, m), 3.00–3.15 (1 H, m), 3.20–3.50 (2 H, m), 3.50–3.65 (1 H, m), 4.10–4.25 (1 H, m), 4.84 (3 H, s). $^{13}$C NMR ($D_2O$, TSP): δ 14.51, 24.84, 24.93, 32.23, 38.94, 52.52, 57.70, 57.78, 168.95, 181.41. MS [*m/z* (% rel. int.)] of base **13**: 269 (15), 268 (*M*+l, 100), 267 (10), 266 (7), 155 (13), 126 (11), 113 (8), 112 (82), 98 (14). Anal. ($C_{16}H_{28}N_3O_6$): C, H, N.

The mother liquor from above was evaporated to dryness and the residue was crystallized from $H_2O$–methanol to yield the oxalate of **12** (240 mg). A portion was taken out and recrystallized from methanol to give an analytically sample. M.p. 173–174 °C; $[\alpha]_D^{20}$ −8° (*c* 1.0, $H_2O$). $^1$H NMR ($D_2O$, TSP): δ 1.10 (3 H, t), 1.85–1.95 (1 H, m), 2.30–2.43 (1 H, m), 2.45–2.60 (1 H, m), 3.00–3.15 (1 H, m), 3.20–3.28 (1 H, dd, *J* 13.5 and 7.2 Hz), 3.30–3.38 (1 H, dd, *J* 13.5 and 2.9 Hz), 3.50–3.65 (1 H, m), 4.10–4.20 (1 H, m), 4.83 (4 H, br s). $^{13}$C NMR ($D_2O$, TSP): δ 14.26, 23.70, 32.41, 38.69, 43.06, 58.18, 168.99, 181.67. MS [*m/z* (% rel. int.)] of base **12**: 144 (7), 143 (*M*+l, 100), 126 (7), 112 (32). Anal. ($C_9H_{16}N_2O_5$): C, H, N.

(S)-5-[(3,5-Dichloro-2,6-dimethoxybenzamido)methyl]-1-ethyl-2-pyrrolidone (**14**). A mixture of 3,5-dichloro-2,6-dimethoxybenzoic acid (121 mg, 0.48 mmol), $SOCl_2$ (100 µl) and DMF (1 drop) in toluene (1 ml) was stirred at 50 °C for 1 h. The solvent was evaporated off and the residue was redissolved in toluene (2 ml) and evaporated. This was repeated twice. The residual acyl chloride was dissolved in $CH_2Cl_2$ (1 ml) and added with cooling to a mixture of the oxalate of **12** (70 mg, 0.30 mmol), $K_2CO_3$ (65 mg) and triethylamine (100 µl) in $CH_2Cl_2$ (1 ml). After 30 min, 2 M NaOH (1 ml) was added and the organic layer was separated. Drying ($Na_2SO_4$) and evaporation of the solvent left a solid residue. Recrystallization twice from ethyl acetate–diisopropyl ether gave 69 mg (38% yield) of the benzamide **14**. M.p. 108.0–108.5 °C; $[\alpha]_D^{25}$ −14° (*c* 0.9, methanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.11 (3 H, t), 1.79–1.96 (1 H, m), 2.00–2.20 (2 H, m) 2.35–2.50 (1 H, m), 2.92–3.05 (1 H, m), 3.35–3.45 (1 H, m), 3.65–3.75 (1 H, m), 3.85–3.95 (2 H, m), 3.88 (6 H, s), 6.77 (1 H, br t), 7.43 ( 1 H, s). $^{13}$C NMR ($CDCl_3$, TMS): δ 12.67, 21.46, 29.98, 35.25, 40.91, 56.45, 62.74, 124.43, 129.57, 132.04, 152.70, 165.08, 175.77. MS [*m/z* (% rel. int.)]: 380 (5), 379 (13), 378 (24), 377 (57), 376 (31), 375 (48), 374 (14), 341 (8), 309 (5), 308 (7), 307 (12), 235 (8), 233 (7), 232 (8), 165 (6), 126 (11), 125 (6), 113 (22), 112 (100), 84 (16). Anal. ($C_{16}H_{20}Cl_2N_2O_4$): C, H, N.

(S)-*5-[(3,5-Dichloro-2-hydroxy-6-methoxybenzamido)-methyl]-1-ethyl-2-pyrrolidone* (**7**). To the benzamide **14** (330 mg, 0.8 mmol) in $CH_2Cl_2$ (5 ml) was added $BBr_3$ (1 mmol, 1 M in $CH_2Cl_2$) with stirring at −70 °C. A tar was formed and the stirring was continued at room temperature for 6 h. The reaction mixture was cooled in an ice–water bath and an excess of 2 M $NH_3$ was added. The organic layer was separated and the aqueous phase was washed with $CH_2Cl_2$. The organic solutions were combined and dried ($Na_2SO_4$). Evaporation of the solvent left a residue which was purified by chromatography on $SiO_2$ ($CH_2Cl_2$–acetone 9:1) and provided 220 mg (76% yield) of the benzamide the **7** as an oil. $[\alpha]_D^{25}$ −29° (*c* 0.9, methanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.19 (3 H, t), 1.80–1.95 (1 H, m), 2.15–2.35 (1 H, m), 2.37–2.50 (2 H, m), 3.00–3.15 (1 H, m), 3.40–3.55 (1 H, m), 3.65–3.80 (1 H, m), 3.85–4.05 (2 H, m), 3.90 (3 H, s), 7.51 (1 H, s), 8.63 (1 H, br t). $^{13}$C NMR ($CDCl_3$, TMS): δ 12.89, 22.01, 30.16, 35.62, 40.92, 56.25, 62.18, 109.59, 117.35, 119.82, 134.65, 153.97, 158.51, 169.83, 175.59. MS [*m/z* (% rel. int.)]: 361 (3), 143

(4), 113 (7), 112 (100), 99 (6), 98 (8), 97 (8), 96 (3), 86 (5), 85 (16), 84 (33), 83 (4), 82 (6), 72 (4), 71 (3), 70 (8), 69 (9), 68 (6).

(S)-*5-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-1-ethyl-2-pyrrolidone* (**2**) was prepared analogously to benzamide **14** from 3-bromo-2,6-dimethoxybenzoic acid.[2] M.p. 110–112 °C; $[\alpha]_D^{25}$ −19° (*c* 1.1, ethanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.13 (3 H, t), 1.88–2.05 (1 H, m), 2.10–2.27 (2 H, m), 2.35–2.55 (1 H, m), 2.95–3.10 (1 H, m), 3.35–3.45 (1 H, m), 3.65–3.75 (1 H, m), 3.81 (3 H, s), 3.85–3.95 (2 H, m), 3.87 (3 H, s), 6.29 (1 H, br t), 6.61 (1 H, d, *J* 8.9 Hz), 7.49 (1 H, d, *J* 8.9 Hz). $^{13}$C NMR ($CDCl_3$, TMS): δ 12.71, 21.51, 30.09 35.25, 40.85, 56.37, 56.59, 62.72, 108.54, 108.87, 123.18, 134.62, 155.11, 156.99, 166.01, 175 84. MS [*m/z* (% rel. int.)]: 387/385 (14/14) 262/260 (7/6), 125 (5), 113 (7), 112 (100), 84 (15). Anal. ($C_{16}H_{21}BrN_2O_4$): C, H, N, O.

*Racemic* **2**. To a solution of 5-[(3-bromo-2,6-dimethoxybenzamido)methyl]-1-ethyl-5-hydroxy-2-pyrrolidone[5] (100 mg, 0.25 mmol) in methanol–$H_2O$ (3:1) was added sodium cyanoborohydride (100 mg, 1.6 mmol) followed by a crystal of methyl orange. Aqueous 2 M HCl was added dropwise until the yellow solution turned red and the addition was continued to maintain the red colour. After 2 h of stirring at room temperature the reaction mixture was evaporated to dryness. The residue was extracted with $CH_2Cl_2$. The organic solution was washed with 1 M HCl and brine and dried ($Na_2SO_4$). Evaporation of the solvent left the racemic title compound (86 mg, 90 %) with NMR and MS spectra identical with those of the *S*-enantiomer **2**.

(S)-*5-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-2-pyrrolidone* (**3**). To a mixture of (*S*)-5-(aminomethyl)-2-pyrrolidone (**10**, 1.17 g, 10 mmol) and triethylamine (2.0 g, 14 mmol) in $CH_2Cl_2$ (10 ml) was added dropwise at ice–water temperature, a solution of 3-bromo-2,6-dimethoxybenzoyl chloride[5] (2.6 g, 10 mmol) in the same solvent (20 ml). After 3 h the reaction mixture was successively washed with 2 M HCl, $H_2O$, 2 M NaOH and brine and dried ($Na_2SO_4$). Evaporation to dryness left a residue (2.4 g) which was purified by column chromatography on $SiO_2$ ($CH_2Cl_2$–methanol, 9:1). From the main fraction, the title compound **3** was isolated as a glass (1.37 g, yield 38 %). $[\alpha]_D^{25}$ −11° (*c* 1.1, ethanol). $^1$H NMR ($CDCl_3$, TMS): δ 1.75–1.85 (1 H, m), 2.00–2.30 (3 H, m), 3.20–3.35 (1 H, m), 3.63–3.75 (1 H, m), 3.80 (3 H, s), 3.85 (3 H, s), 3.90–4.00 (1 H, m), 6.59 (1 H, d, *J* 8.9 Hz), 6.90 (1 H, br s), 7.15 (1 H, br t), 7.46 (1 H, d, *J* 8.9 Hz). $^{13}$C NMR ($CDCl_3$, TMS): δ 24.14, 29.90, 44.58, 54.47, 56.42, 67.70, 108.33, 108.93, 123.37, 134.41, 154.86, 156.99, 165.92, 179.18. MS [*m/z* (% rel. int.)]: 359/357 (13/12), 282 (6), 280 (18), 279 (100), 265 (15), 260 (7), 259 (11), 249 (9), 196 (6), 195 (6), 182 (36), 180 (7), 168 (10), 167 (9), 165 (14), 158 (9), 139 (11), 115 (14), 101 (31), 84 (32).

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