Unusual Products from the Synthesis of 3-(2-Phenylethyl)pyridines by the Hydrosulfite Reduction of Nitrosamines

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The Overberger hydrosulfite reduction of *N*-nitroso[(3-phenylmethylamino)methyl]pyridine gave 3-(2-phenylethyl)pyridine and, as determined by nmr, glc and mass spectral studies, about 15% of a mixture which consisted of the 2-, 4-, and 6-(phenylmethyl)-3-methylpyridines, and the 3-[2-, 3-, and 4-(methylphenylmethyl)]pyridines. These by-products resulted from the coupling of an arylmethyl fragment with the opposite aryl group. A concerted reaction is suggested for the *ortho* couplings and a radical rearrangement for the *para* couplings. Authentic samples of three of these by-products were prepared for comparison. A similar reduction of (+)-*N*-nitroso-3-[(phenylethylamino)methyl]pyridine gave (+)3-(2-phenylpropyl)pyridine of undetermined optical purity and by-products which were not examined but whose nmr spectrum indicated them to be of analogous origin.

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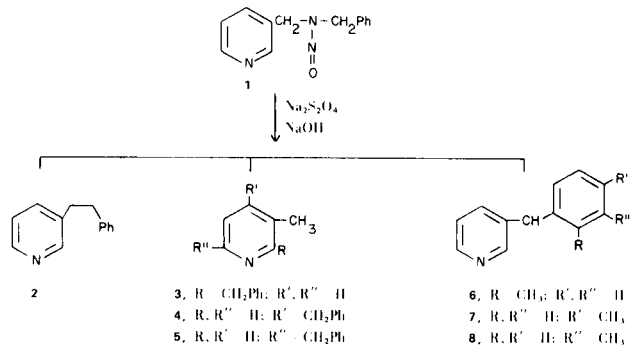
The search for an inexpensive synthesis of 3-(2-phenylethyl)pyridine, an intermediate for an antihistamine (1), led to an application of the Overberger hydrosulfite reduction of diarylmethylnitrosamines (2) shown in Scheme I.

Scheme I



This facile, widely applicable procedure has been neglected as a preparative method for 1,2-diarylethanes. However, in this instance, the product contained in addition to **2**, approximately 15% of a mixture of compounds **3**, **4**, **6**, and **7**; probably **5**, and possibly **8**. The character of these by-products was detected from the aromatic methyl and diarylmethyl signals found in a 3/2 ratio in the nmr spectrum of the mother liquid from which most of **2** had been removed. In addition, when this liquid was quaternized with methyl tosylate and hydrogenated to convert pyridines to piperidines, the product still contained aromatic methyl, *i.e.*, tolyl groups.

This liquid portion was examined by combined gas chromatography and mass spectrometry (GC/MS) employing both OV-1 and OV-17 columns operated isothermally at 120°. The introduction of the GC effluent into the mass spectrometer (Varian MAT CH-5) was effected through a Biemann-Watson separator maintained at 250°. The mixture on OV-1 gave a chromatogram with six peaks. The first two peaks were completely resolved but there was only partial resolution of the last four. An OV-17 column afforded resolution of peak six and a somewhat different overlap of peaks three, four and five than was obtained on the OV-1 column. By making GC/MS runs on both OV-1 and OV-17 columns while making approximately twenty complete MS scans per GC peak a representative mass spectrum was obtained for each compound in the mixture. Seven compounds were found, see Table I. The GC peak for compound **4** also contained some compound **2** that had not been completely removed from the mixture. Although these two com-

Table I

Significant Mass Spectral Data

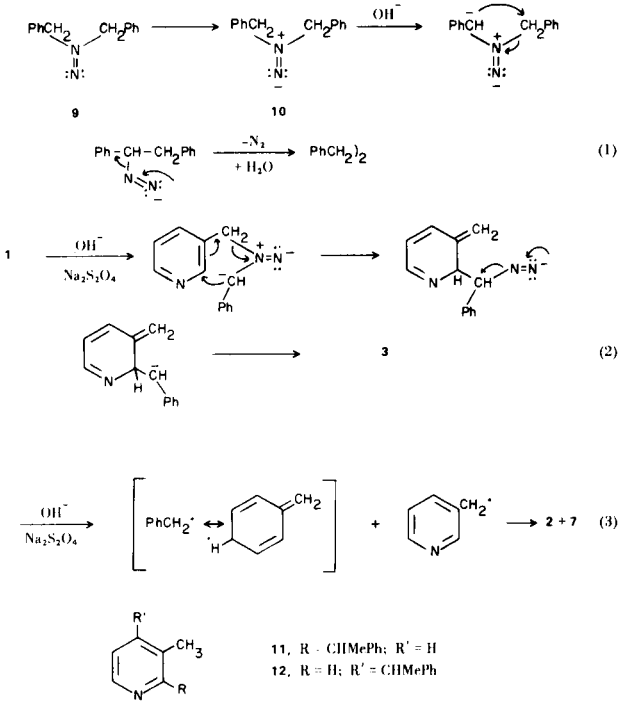
Compound	Found in GC Peak	Relative Intensities of Mass Spectral Peaks, M = Molecular ion			
		M	M-1	Mass 91	M/M-1
2	3	24	1	100	24.
3	1	34	100	7	0.34
4	3	100	70	6	1.42
5	2	27	100	3	0.27
6	4	100	44	14	2.27
7	5	100	50	28	2.00
8	6	100	35	46	2.87
2-(Phenylmethyl)pyridine		23	100		0.23
3-(Phenylmethyl)pyridine		86	100		0.86
4-(Phenylmethyl)pyridine		100	74		1.35

pounds were not resolved by GC, the multiple MS scans effected the resolution of their spectra.

The structures shown in Scheme I were assigned to the compounds in this mixture by comparing the mass spectra of these unknowns with those of authentic **2, 3, 6,** and **7** (prepared by unambiguous routes) and of the 2-, 3-, and 4-(phenylmethyl)pyridines (3). The most significant feature of the mass spectra of these compounds was the relative intensity of the molecular ion (M), the (M) minus one (M-1), and the mass 91 peaks, see Table I. One unknown gave a M/M-1 ratio similar to that of both 2-(phenylmethyl)pyridine and of **3**, and accordingly was assigned structure **5**. The compound which gave a M/M-1 ratio almost identical to that of 4-(phenylmethyl)pyridine was assigned structure **4**. Additionally, there was a benzylic proton signal at δ 4.12 (4-(phenylmethyl)pyridine signals appear here) in the nmr spectrum of the mixture. Compounds **6, 7,** and **8** all gave much greater M/M-1 ratios and also larger mass 91 peaks than did any of the 2- and 4-(phenylmethyl)pyridines.

Overberger suggested (3b) that **9** and/or a resonance form **10** were intermediates in the hydrosulfite reduction of dibenzylnitrosamines (eq 1). Presumably analogous intermediates were formed in the mercuric oxide oxidation of 1,1-dibenzylhydrazines (4), and in the basic decomposition of their tosyl hydrazides (5); reactions which also gave 1,2-diarylethanes. Products analogous to **3-8** inclusive were not reported in any of these reactions although in two instances (2c), (4d), in the oxidation of dibenzylhydrazines, a specific search for by-products was made. Our present sophisticated physical analytical methods were not then generally available but if such by-products indeed were absent, compounds **3-8** must have been formed by a different mechanism.

The compounds **2-8** probably were formed by a concerted reaction, or from radicals within a solvent cage, since there was negligible, if any, product from the coupling of like fragments. A reaction as typified by (eq 2) would account for compounds **3, 4,** and **6.** The rearrangement of a radical (eq 3) and subsequent coupling would give **7**, and a similar rearrangement of the 3-pyridylmethyl radical would give **5.** We are unable to suggest a plausible mechanism for the formation of **8** if, indeed, it is the seventh product of this reaction.



The optical activity of a carbon atom bonded to the nitrosamine was retained to some degree in the coupled product of the Overberger reduction (2b). Similarly, we found that (+)*N*-nitroso-(3-pyridylmethyl)(phenylethyl)-amine gave optically active 3-(2-phenylpropyl)pyridine in low yield. Its optical purity was not determined. This reaction was run before nmr was available and, except for a small sample, the mixture of by-products was discarded. A subsequent nmr spectrum of this sample indicated that at least four by-products, including compounds **11** and **12** were present. If **11** and **12** retained optical activity it would be evidence for their formation by a concerted mechanism. The possible racemization of the nitrosamine, which may form carbanions in the strong alkali (6), was not checked.

Circumstances were such that further work, *i.e.*, the synthesis of authentic **8** for comparison, the isolation of **11** and/or **12**, *etc.*, could not be done on this interesting reaction.

EXPERIMENTAL

The melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

3-[(Phenylmethylamino)methyl]pyridine.

Under nitrogen, 106 g. (1 mole) of benzaldehyde was added with stirring to 108 g. (1 mole) of (3-pyridylmethyl)amine in 500 ml. of methanol. After 0.5 hours the warm solution was cooled and kept at 0-5° while 24 g. (0.63 mole) of sodium borohydride was added in small portions (2-3 hours). The solution was kept at 5° for 0.5 hours, warmed slowly to 25° and after 1 hour the methanol was distilled. Water was added carefully and the product was extracted with ether, dried over potassium carbonate and distilled, b.p. 145-150° (2 mm.), yield 173 g. (87%).

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.74; H, 7.11; N, 14.13. Found: C, 78.51; H, 7.34; N, 13.97.

N-Nitroso-3[(phenylmethylamino)methyl]pyridine (**1**).

Nitrosation, (*CAUTION*) (7), of 173 g. of 3-[(phenylmethylamino)methyl]pyridine by the method of Hatt (8) gave, when the reaction mixture was made alkaline, 193 g. (97%) of greenish yellow crystals, m.p. 67-68°.

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.48. Found: C, 68.83; H, 5.97; N, 18.23.

3-(2-Phenylethyl)pyridine (**2**) and By-products.

Nitrogen was passed through a solution of 96 g. (0.422 mole) of **1** in 2.5 l. of a 1:1 mixture of ethanol and 20% aqueous sodium hydroxide at 58-60° for 0.5 hours. Sodium hydrosulfite, 165 g. (0.95 mole) of purified grade, was added in one portion and the mixture was stirred at 60-65° (slight cooling was required at first) for 7 hours. Most of the ethanol was distilled through a short column and the suspension was filtered. The filter cake was stirred with three 500 ml. portions of ether and was filtered and washed with ether each time. The aqueous filtrate was extracted with three 500 ml. portions of ether and all of the ether solutions were combined, washed with water, dried with potassium carbonate, and distilled. The yield was 60-65 g. (77-84%) of material, b.p. 100-103° (1 mm.) and 3-4 g. of residue. In the nmr spectrum of this crude product, the combined integration of the diarylmethyl singlets at δ 4.18, 4.12, 3.94, and 3.87 relative to that of the 4H singlet of **2** at δ 2.87 indicated *ca.* 15% of these by-products was present. The combined integration of the aromatic methyl singlets at δ 2.20 and 2.29 relative to that of the diarylmethyls was in the ratio of 3 to 2. The product from two runs, 120 g., was seeded with **2**, kept at 25° for 24 hours and the liquid was decanted. This procedure was repeated with the decanted liquid at 4° and again at -15°. The solid obtained in each case was melted and processed similarly at the next highest temperature, or, if completely solid at 4°, decanted at 25°. The material which was solid at 25° was recrystallized from a little hexane with much loss by slowly cooling the solution to 4° and decanting. The compounds in this mother liquor were recovered and treated as was the original product. There was obtained 71 g. of **2** (9), m.p. 31-32°; nmr (deuteriochloroform): δ 2.87 (s, 4H, CH_2CH_2), 7.10-7.40 (m, 7H, 5 Ph and 3 and 4 py), 8.44 (m, 2H, 2 and 6 py); mass spectrum: (70 eV) m/e (relative intensity) 183 (24), 182 (0.8), 167 (0.5), 91 (100), 65 (24), 51 (6).

A 20 g. fraction of the most liquid material from all of these manipulations was used for the GC/MS studies. A 5 g. sample and 5.2 g. of methyl tosylate were heated on a steam bath for 3 hours. The cooled mixture was dissolved in 150 ml. of water and extracted with ether. This aqueous solution of the quaternary salt was warmed to remove the dissolved ether, stirred with 0.5 g. of charcoal, filtered and hydrogenated at 2 atmospheres with 0.5 g. of 5% palladium-carbon. Hydrogenation was complete in 2 hours. The product was recovered as the free base in the usual manner and its complex nmr spectrum showed five signals (arylmethyl and *N*-methyl) from δ 2.18 to 2.28.

α-Phenyl-(3-methyl-2-pyridyl)acetonitrile.

The sodamide prepared from 48.3 g. (2.1 moles) of sodium and liquid ammonia was suspended in 500 ml. of toluene and added slugwise (frothing) to a stirred solution of 127.6 g. (1 mole) of 2-chloro-3-methylpyridine and 123 g. (1.05 moles) of phenylacetonitrile in 1.5 l. of toluene at 85-90° in a 5 l. flask in a mantle. After 1 hour at 90° the mixture was cooled to 10° in an ice bath and 500 ml. of water was added cautiously below 20°. The toluene was separated, washed with water and distilled to give 166.5 g. (80%) of the nitrile, b.p. 130-132° (1 mm.), m.p. 123-124° when crystallized from ethanenitrile.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.72; H, 5.80; N, 13.45. Found: C, 80.70; H, 5.87; N, 13.40.

2-(Phenylmethyl)-3-methylpyridine (**3**).

α-Phenyl-(3-methyl-2-pyridyl)acetonitrile (15 g.) was hydrolyzed and decarboxylated by refluxing it with 150 ml. of concentrated hydrochloric acid for 15 hours. The mixture was basified and an ether extract was dried and distilled to give 9.5 g. (73%) of **3**, b.p. 98-99° (1 mm.); nmr (deuteriochloroform): δ 2.20 (s, 3, CH_3), 4.18 (s, 2, CH_2), 7.00-7.40 (m, 7, Ph and py), 8.47 (q, 1.6 py H); mass spectrum: (70 eV) m/e (relative intensity) 183 (34), 182 (100), 181 (12), 180 (14), 168 (13), 167 (21), 91 (7), 77 (6).

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 85.35; H, 7.17; N, 7.34.

2-(Phenylmethyl)-3-methylpyridine Picrate.

This compound crystallized from acetone and had m.p. 140-141°.

Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.28; H, 4.01; N, 13.70.

(2-Methylphenyl)(3-pyridyl)methanone.

Nicotinonitrile, 26 g. (0.25 mole) in 250 ml. of ether was added under reflux with stirring to a Grignard reagent prepared from 57 g. (0.31 mole) of *o*-bromotoluene and 7.5 g. (0.31 mole) of magnesium in 500 ml. of ether. A yellow gummy complex formed which made stirring difficult, but refluxing was continued for 2 hours. Water was added carefully and then 500 ml. of 20% hydrochloric acid and the ether was distilled. The mixture was refluxed for 10 hours to hydrolyze the imine, made strongly basic with aqueous ammonia and extracted with ether (emulsions). The extract, dried over potassium carbonate and then distilled gave 21 g. (42%) of the ketone, b.p. 130-134° (1 mm.).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.46; H, 5.75; N, 7.32.

α-(4-Methylphenyl)-3-pyridinemethanol.

To a Grignard reagent made from 85.5 g. (0.5 mole) of *p*-bromotoluene and 12.3 g. (0.505 mole) of magnesium in 500 ml. of ether was added 58.5 g. (0.5 mole) of 3-pyridinecaldehyde in 200 ml. of ether. Stirring and refluxing was continued for 2 hours and the complex was decomposed by the addition of 1 l. of 15% ammonium chloride solution. The ether was separated, the aqueous phase extracted with 500 ml. of ether, and the combined

ether solutions were dried and the ether was distilled. The residue was crystallized from ethanenitrile and gave 80 g. (81%) of α-(4-methylphenyl)-3-pyridinemethanol, m.p. 130-132°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 77.99; H, 6.60; N, 6.90.

(4-Methylphenyl)(3-pyridyl)methanone.

A mixture of 20.5 g. (0.103 mole) of α-(4-methylphenyl)-3-pyridinemethanol, 300 ml. of water, 200 ml. of purified dioxane and 3 g. of potassium hydroxide was stirred at 40-50° and 10.8 g. (0.068 mole) of powdered potassium permanganate was added in 0.5 g. portions. The color discharged rapidly after each addition until the last portion was added; it then persisted for 10 minutes. The mixture was heated at 90° for 45 minutes to coagulate the manganese hydroxide and was extracted, without filtering, with three 300 ml. portions of ether. The ether extract was washed with water, dried, and evaporated. The product was crystallized from isopropyl ether, yield, 18 g. (90%), m.p. 78-80°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.06; H, 5.76; N, 7.32.

3-(2-Methylphenylmethyl)pyridine (**6**).

Wolff-Kischner reduction of 15 g. (2-methylphenyl)(3-pyridyl)-methanone with 15 ml. of 85% hydrazine and 21 g. of potassium hydroxide in 120 ml. of triethylene glycol for 1 hour at 100° and 5 hours at 200° gave, after the usual workup, 11 g. (79%) of **6**, b.p. 98-99° (1 mm.), nmr (deuteriochloroform): δ 2.20 (s, 3, CH_3), 3.94 (s, 2, CH_2), 7.12 (s, 4, Ph), 7.10-7.40 (m, 2, 4 and 5 py H), 8.40-8.44 (m, 2, 2 and 6 py H); mass spectrum: (70 eV) m/e (relative intensity) 183 (100), 182 (44), 181 (5), 180 (12), 168 (88), 167 (44), 105 (14), 104 (19), 91 (14), 77 (15).

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 85.14; H, 7.37; N, 7.24.

3-(2-Methylphenylmethyl)pyridine Picrate.

This salt, crystallized from ethanol, melted at 110-112°.

Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.58. Found: C, 55.21; H, 4.27; N, 13.30.

3-(4-Methylphenylmethyl)pyridine (**7**).

The reduction of 17.5 g. of (4-methylphenyl)(3-pyridyl)methanone as described for **6** gave 13.5 g. (78%) of **7**, b.p. 102-104° (1 mm.), m.p. 38-40°; nmr (deuteriochloroform): δ 2.29 (s, 3, CH_3), 3.87 (s, 2, CH_2), 7.07 (s, 4, Ph), 7.00-7.40 (m, 2, 4 and 5 py H), 8.43-8.45 (m, 2, 2 and 6 py H); mass spectrum: (70 eV) (relative intensity) 183 (100), 182 (50), 181 (6), 180 (8), 168 (66), 167 (39), 105 (9), 104 (4), 91 (28), 77 (6).

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 84.97; H, 7.27; N, 7.97.

(+)3-[(Phenylethylamino)methyl]pyridine.

By the procedure used to prepare [(3-phenylmethylamino)-methyl]pyridine, 59 g. (0.55 mole) of 3-pyridinealdehyde and 66.5 g. (0.55 mole) of (+)phenylethylamine was reduced with 13.2 g. (0.35 mole) of sodium borohydride. This reaction gave 44 g. (40%) of the desired amine, b.p. 125-130° (1 mm.), $[\alpha]_D^{25}$ +25.5° neat. The reason for this low yield is unknown, but the preparation of the Schiff base previous to the reduction may be preferable in this instance.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.12; H, 7.59; N, 13.19. Found: C, 78.91; H, 7.73; N, 13.47.

(+)3-[(Phenylethylamino)methyl]pyridine Maleate.

This salt was crystallized from 2-butanone, m.p. 122-125°, $[\alpha]_D^{25}$ -29.7° c = 1% in methanol.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.83; H, 6.13; N, 8.54. Found: C, 65.67; H, 6.42; N, 8.59.

(+)3-(2-Phenylpropyl)pyridine and By-products.

(+)3-[(Phenylethylamino)methyl]pyridine, 33 g. (0.132 mole), was nitrosated by Hatt's procedure (8) and gave 36.5 g. (98%) of (+)*N*-nitroso-3-[(phenylethylamino)methyl]pyridine as an orange gum which could not be crystallized. This gum was dissolved in 850 ml. of a 1:1 mixture of ethanol and 20% aqueous sodium hydroxide and reduced with 54 g. (0.31 mole) of sodium hydrosulfite as described for **2**. Distillation of the product gave 20.2 g. (77%) of amine, b.p. 101-105° (0.5 mm.); $[\alpha]_D^{26}$ 22.2° neat. This material was assumed to be a mixture of the optical isomer and racemate.

(+)3-(2-Phenylpropyl)pyridine Hydrochloride.

The above base gave with dry hydrogen chloride in ethanol a salt melting at 123-130°, which after several recrystallizations from both ethanol and ethanenitrile yielded 7 g. of material, m.p. 130-133°; $[\alpha]_D^{25}$ +17.6° c = 2% in ethanol. Its optical purity was not determined.

Anal. Calcd. for $C_{14}H_{16}ClN$: C, 71.94; H, 6.91; N, 5.99. Found: C, 72.31; H, 6.74; N, 6.21.

(+)3-(2-Phenylpropyl)pyridine.

The base was recovered from the 7 g. of salt and distilled, b.p. 107-109° (1 mm.); $[\alpha]_D^{26}$ +21.4° c = 5% in ethanol; nmr (deuteriochloroform): δ 1.27 (d, 3, CH_3, J = 7 Hz), 2.86 (s, 2, CH_2), 2.90 (m, 1, CH, J = 7 Hz), 7.18 (m, 7, 5 Ph and 3 and 4 py), 8.32 (m, 2, 2 and 6 py H).

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.51; H, 7.60; N, 6.92.

The basic material was recovered from the salts in the ethanol and ethanenitrile liquors and, except for a small sample, eventually was discarded. An nmr (deuteriochloroform) spectrum of this sample, taken subsequent to the study of the products in Scheme I, showed three sets of aliphatic proton signals. One set was identical to that of the 3-(2-phenylpropyl)pyridine just described; a second set was assigned to compounds **11** and **12**, δ 1.67, 1.68 (d, 3, CH_3), 2.17, 2.22 (s, 3, 3-py CH_3), 4.25 (q, 1, diarylmethine H); the third set was assigned to the possible by-products 3-(2- and 4-ethylphenylmethyl)pyridines, δ 1.10, 1.18 (t, 3, CH_3), 2.60 (q, 2, -CH_2Me), 3.90, 3.98 (s, 2, diarylmethyl).

Mass spectra of unknowns assigned the following structures.

2-(Phenylmethyl)-5-methylpyridine (**5**).

This compound had MS: (70 eV) m/e (relative intensity) 183 (27), 182 (100), 181 (14), 168 (4), 167 (17), 91 (3).

4-(Phenylmethyl)-3-methylpyridine (**4**).

This compound had MS: (70 eV) m/e (relative intensity) 183 (100), 182 (70), 181 (5), 168 (83), 167 (45), 105 (14), 104 (15), 91 (6), 77 (11).

3-(3-Methylphenylmethyl)pyridine (**8**).

This compound had MS: (70 eV) m/e (relative intensity) 183 (100), 182 (35), 181 (8), 168 (46), 167 (29), 105 (34), 104 (9), 91 (46), 77 (9), 52 (14).

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