A Versatile Synthesis of Functionalised 2-Aminoquinolines by Mercury Controlled Cyclisation of 2-Vinylphenylthioureas

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4-(4-Hydroxyphenyl)-2-phenylamino-1,8-naphthyridine was prepared *via* cyclisation of *N*-phenyl-*N'*-3-(4-hydroxyphenethen-1-yl)pyridin-2-ylthiourea in the presence of mercuric oxide. Derivatives of 4-methyl-2-aminoquinolines were prepared in a similar manner from 2-vinylphenylthioureas.

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Introduction.

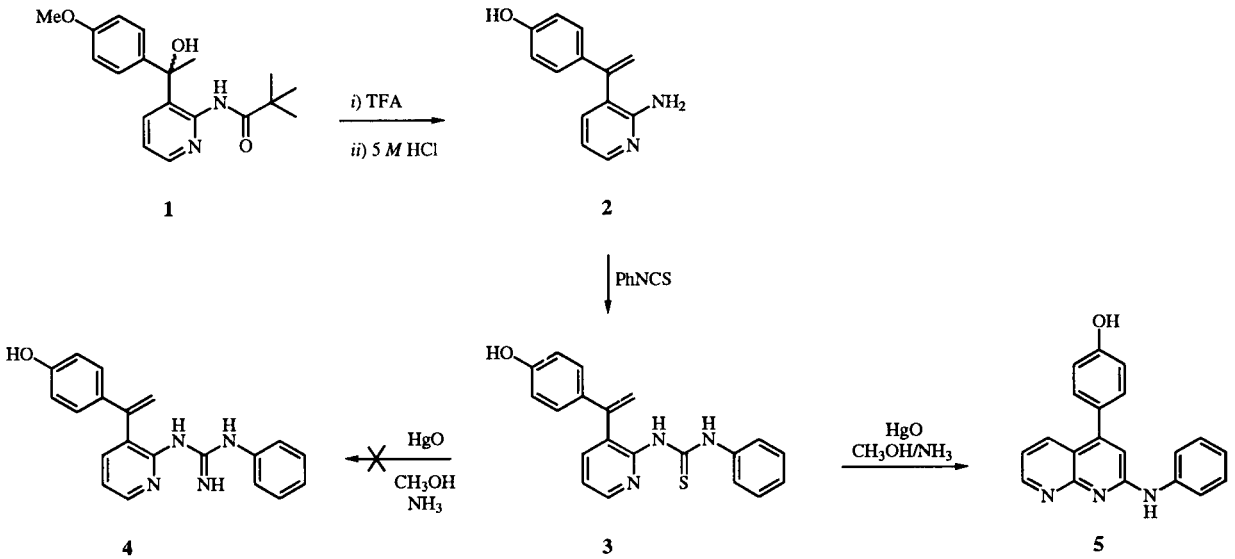
The synthesis of 2-aminoquinolines may be achieved in a number of ways, although many of the available methods employ high temperatures, acidic [1,2,3] or basic [4] conditions. We now report our results on the synthesis of such compounds *via* the intramolecular cyclisation and desulfuration of thioureas derived from 2-isopropenylaniline, a process which gives clean products in high yields under mild conditions at room temperature.

Results and Discussion.

In connection with the preparation of some biologically active compounds, we recently required access to *bis*-arylguanidines *e.g.* **4**. These are usually prepared *i*) from the corresponding *bis*-arylthioureas and methanolic ammonia in the presence of a Hg(II) salt or *ii*) from a thiomethyl-*N*-arylisothiourea and an aniline derivative. Thus, **1**, prepared according to the method of Turner [5], was treated with trifluoroacetic acid to eliminate water and then deprotected by heating in hydrochloric acid. The aminopyridine **2** was then converted into the thiourea **3** as shown in Scheme 1. On treatment with mercuric oxide and methanolic ammonia however, **3** failed to give the guanidine **4** but rather gave the naphthyridine **5** formally *via* a cyclisation between C2 and C3 (naphthyridine numbering). Such cyclisations are not unprecedented for the formation of naphthyridines and quinolines and previous reports have dealt with thermal [6], photochemical [7,8] and chemical ring closure reactions [9]. Rarely, however, do they involve such mild conditions.

In order to explore the generality of this cyclisation reaction, we investigated thioureas derived from 2-isopropenylaniline **6** which lacks the 4-hydroxyphenyl group present in **3**. Arylthioureas have been prepared by several

Scheme 1



methods, but the procedure reported by Rasmussen [10] was of general use and involved heating an isothiocyanate and an aniline together under reflux for 15-30 minutes in acetone. We found that good yields of **7** could also be obtained by allowing a mixture of the isothiocyanate and aniline to stand at room temperature for 24 hours in dichloromethane.

The thiourea **7a** was stirred in methanol overnight with red mercuric oxide, the same conditions as those used for the preparation of guanidines. In this case the reaction gave two products, the required quinoline **8a** and methyl *N*-benzoyl-*N'*-(2-isopropenylphenyl)isourea **9** (Scheme 2). This, however, was not altogether surprising since methanol may act as a nucleophile in the substitution of mercury bound sulfur. When **7d** was reacted with mercuric oxide in methanolic ammonia solution, the product was the benzylguanidine **10**, obtained in 85% yield.

Thus the functionality on the alkenyl group appears to control the ease of cyclisation. When an electron donating group such as the 4-hydroxyphenyl residue in **3** is present, then cyclisation occurs readily even in the presence of strong nucleophiles such as ammonia. In the case of the less electron rich isopropenyl group, where, also, the pyridine ring has been replaced by benzene, as in **7a-d**, then cyclisation only occurs cleanly where there is no such competition, as shown in Scheme 2.

We therefore examined a range of non-nucleophilic solvents to see which would give aminoquinolines without the interference of side reactions. In this instance it was found that dichloromethane was clearly favourable for our purposes, as the reaction proceeded cleanly to the desired product. The table shows the products from several cyclisations performed in dichloromethane using a variety of thioureas prepared from **6** and different isothiocyanates.

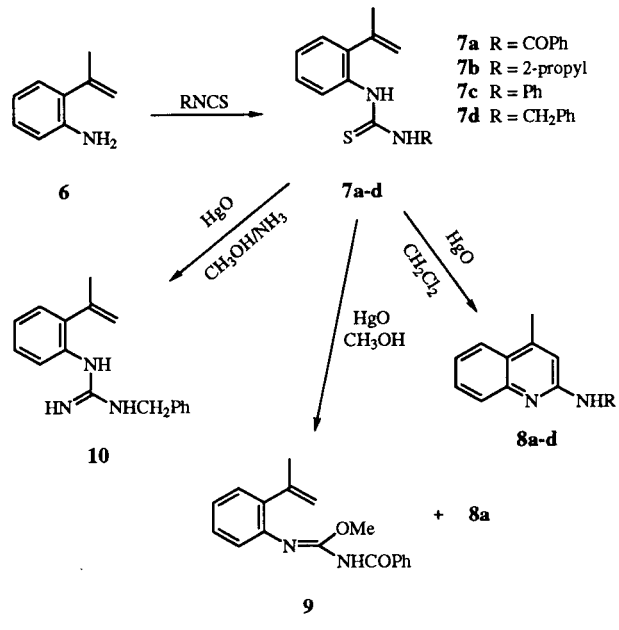
Table [a]

Isothiocyanate	7	%	8	%
benzoyl	**a**	93	**a**	91
2-propyl	**b**	37	**b**	38
phenyl	**c**	97	**c**	85
benzyl	**d**	80	**d**	85

[a] The yields quoted refer only to crystalline isolated yields and are unoptimised.

We believe that mercury covalently binds to the thiourea sulfur atom, facilitating nucleophilic attack at carbon and displacement of mercuric sulfide. It may also be possible for the carbodiimide, formed *via* 1,2-elimination of mercuric sulfide, to act as an intermediate in this reaction. In our case the alkenyl bond is conveniently placed and sufficiently reactive in solvents such as dichloromethane to perform the intramolecular displacement, where subsequent loss of a proton and aromatisation gives the quinolines **8a-d**.

Scheme 2



In conclusion, it is apparent that the ability of the alkenyl bond to intercept the activated thiourea depends on a variety of factors. Intramolecular cyclisation occurs, even in the presence of nucleophiles such as ammonia or methanol, if there is an electron rich group adjacent to the alkenyl bond. Where no such group is present, a competitive reaction with solvents such as methanol is observed. However, if this same reaction is performed in a non-nucleophilic solvent, such as dichloromethane, then the cyclisation proceeds in a clean and facile manner to give the products in high overall yield. It is anticipated that the cyclisation would be effective for a range of substituents at C-4 of the quinoline, and that additional groups on the aniline would also be tolerated.

EXPERIMENTAL

All starting materials were purchased from Aldrich, Lancaster or Fisons companies. Melting points were determined in a capillary tube on a Buchi SMP-20 apparatus and are uncorrected. Mass spectra were determined using a VG analytical 70-VSEQ instrument for both EI and FAB. The nmr spectra were recorded at 250 MHz on a Bruker AM 250 instrument or at 400 MHz on a Bruker ARX 400 instrument. Infrared spectroscopy was performed using a Hewlett Packard 1700 instrument.

3-(4-Hydroxyphenethen-1-yl)-2-aminopyridine (**2**).

Compound **1** (12.0 g, 0.037 mole) was stirred in trifluoroacetic acid (200 ml) for 2 hours and then concentrated. The residue was diluted with water, basified with 2*N* sodium hydroxide solution and extracted with ethyl acetate. The organic solu-

tion was concentrated, then heated under reflux in 5*N* hydrochloric acid for 48 hours. The solution was cooled, neutralised with 2*N* sodium hydroxide solution and extracted with dichloromethane. The organic layer was dried and evaporated to a solid. Recrystallisation from acetonitrile gave **2**, 5.3 g, (70%), mp 177-179°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.12 (d, 1H, J = 1.60 Hz), 5.19 (s, 2H, N*H*$_2$), 5.64 (d, 1H, J = 1.60 Hz), 6.61 (dd, 1H, J_1 = 7.20 Hz, J_2 = 4.80 Hz), 6.74 (m, 2H), 7.13 (m, 2H), 7.24 (dd, 1H, J_1 = 7.20 Hz, J_2 = 1.60 Hz), 7.95 (dd, 1H, J_1 = 5.00 Hz, J_2 = 1.80 Hz), 9.59 (s, 1H, O*H*); ms: m/z (relative intensity) 212 (M+), 211 (100), 195 (20), 119 (20); ir: (nujol): ν 3469 (NH), 3315 (OH), 3244 (NH), 1627, 1612, 1582, 1567, 1511, 1269, 1211, 839, 777 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.23; H, 5.78; N, 13.16.

N-Phenyl-*N'*-3-(4-hydroxyphenethen-1-yl)pyridin-2-ylthiourea (**3**).

A mixture of **2** (1.0 g, 4.7 mmoles) and phenyl isothiocyanate (1.13 g, 8.4 mmoles) was heated under reflux in toluene overnight. Flash chromatography (silica gel, 1% methanol in dichloromethane) and crystallisation from ether gave **3**, 0.5 g, 31%, mp 168-170°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.34 (s, 1H), 5.98 (s, 1H), 6.80 (m, 2H), 7.20 (m, 2H), 7.23 (m, 1H), 7.27 (dd, 2H, J_1 = 7.48 Hz, J_2 = 5.14 Hz), 7.40 (m, 2H), 7.68 (m, 2H), 7.76 (dd, 1H, J_1 = 7.50 Hz, J_2 = 1.82 Hz), 8.05 (br singlet, 1H), 8.42 (dd, 1H, J_1 = 1.76 Hz, J_2 = 5.09 Hz), 9.78 (br singlet, 1H, N*H*), 13.71 (br singlet, 1H, N*H*); ms: m/z (FAB) 348 (M+H$^+$); ir: (nujol): ν 3384 (NH), 3248 (OH), 1619, 1610, 1584, 1574, 1511, 1362, 1281, 1215, 1150, 912, 839 cm^{-1}.

Anal. Calcd. for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.09. Found: C, 69.14; H, 5.08; N, 12.16.

4-(4-Hydroxyphenyl)-2-phenylamino-1,8-naphthyridine (**5**).

A mixture of **3** (0.5 g, 1.44 mmoles) and mercuric oxide (0.34 g, 1.57 mmoles) was stirred in methanolic ammonia solution in a sealed flask for 18 hours. The mixture was filtered through celite and evaporated to a bright yellow oil which was crystallised from ethanol-ether to afford **5**, 0.3 g, (69%), mp 280-282°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 6.95-7.03 (m, 4H), 7.29 (dd, 1H, J_1 = 8.05 Hz, J_2 = 4.34 Hz), 7.34-7.39 (m, 4H), 8.03-8.08 (m, 3H), 8.80 (dd, 1H, J_1 = 4.20 Hz, J_2 = 1.70 Hz), 9.70 (s, 1H, O*H*), 9.85 (br singlet, N*H*); ms: (FAB) m/z 314 (M+H$^+$); ir: ν 3356 (NH), 1619, 1611, 1599, 1536, 1520, 1391, 1379, 1240, 787, 752 cm^{-1}.

Anal. Calcd. for $C_{20}H_{15}N_3O$ + 0.6% water: C, 74.10; H, 5.04; N, 12.96. Found: C, 74.15; H, 5.33; N, 12.76.

N-Benzoyl-*N'*-2-isopropenylphenylthiourea (**7a**).

To a solution of **6** (1.33 g, 10 mmoles) in acetone (25 ml) was added benzoyl isothiocyanate (1.8 g, 11 mmoles). The mixture was stirred at room temperature for 1 hour, concentrated and the residue triturated with hexane-dichloromethane to give **7a**, 2.7 g, (93%), mp 120-121°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.04 (s, 3H), 5.03 (m, 1H, J = 0.84 Hz), 5.27 (quintet, 1H, J = 1.62 Hz), 7.38-7.50 (m, 3H), 7.54 (m, 2H), 7.67 (m, 1H), 7.76 (d, 1H, J = 7.72 Hz), 8.00 (m, 2H), 11.63 (br singlet, N*H*), 12.43 (br singlet, N*H*); ms: (FAB) m/z 297 (M+H$^+$); ir: (nujol): ν 3241 (NH), 1652, 1536, 1509, 1155, 724 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.93; H, 5.58; N, 9.53.

General Method for the Synthesis of Thioureas **7b-d**.

A mixture of **6** (1.33 g, 10 mmoles) and the appropriate isothiocyanate (11 mmoles) in dichloromethane (50 ml) was stirred for 24 hours. The mixture was filtered through celite and evaporated. The thioureas were purified by crystallisation from hexane.

N-Propan-2-yl-*N'*-2-isopropenylphenylthiourea (**7b**).

Compound **7b** was obtained in 37% yield (0.81 g), mp 93-94°; ^{1}H nmr (deuteriochloroform): δ 1.19 (d, 6H, J = 6.56 Hz), 2.06 (dd, 3H, J_1 = 0.88 Hz, J_2 = 0.64 Hz), 4.58 (octet, 1H, J = 7.36 Hz), 5.02 (sextet, 1H, J_1 = 0.88 Hz, J_2 = 0.80 Hz), 5.28 (quintet, 1H, J = 1.56 Hz), 5.67 (br doublet, N*H*, J = 6.80 Hz), 7.22-7.37 (m, 4H); ms: m/z (relative intensity) 234 (M$^+$), 201 (66), 188 (100), 133 (45); ir: (nujol): ν 3165 (NH), 1535, 1510, 1250, 895, 773 cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95. Found: C, 66.53; H, 7.57; N, 11.97.

N-Phenyl-*N'*-2-isopropenylphenylthiourea (**7c**).

Compound **7c** was obtained in 97% yield (2.6 g), mp 143-144°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.03 (singlet, 3H), 5.01 (m, 1H, J = not resolved), 5.20 (m, 1H, J = not resolved), 7.14 (m, 1H), 7.22-7.34 (m, 5H), 7.48 (m, 1H), 7.50 (m, 2H), 9.20 (br singlet, N*H*), 9.65 (br singlet, N*H*); ms: m/z (relative intensity) 268 (M$^+$), 235 (68), 222 (100), 132 (32), 93 (39), 77 (35); ir: (nujol): ν 3358, 3150 (NH), 1592, 1541, 1506, 1286, 911, 762 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.68; H, 6.10; N, 10.61; S, 11.85.

N-Benzyl-*N'*-2-isopropenylphenylthiourea (**7d**).

Compound **7d** was obtained in 80% yield (2.27 g), mp 98-100°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.99 (s, 3H), 4.71 (d, 2H, J = 4.80 Hz), 4.98 (s, 1H), 5.16 (s, 1H), 7.23-7.38 (m, 9H), 8.0 (br singlet, N*H*), 9.03 (br singlet, N*H*); ms: m/z (relative intensity) 282 (M$^+$), 236 (40), 175 (62), 141 (46), 133 (49), 106 (86), 91 (100), 77 (42); ir: (nujol): ν 3370 (NH), 3148, 1641, 1536, 1512, 1301, 1235, 1089, 969, 767 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92; S, 11.35. Found: C, 72.31; H, 6.48; N, 10.20; S, 11.01.

General Method for the Synthesis of 2-Aminoquinolines **8a-d**.

A mixture of the thiourea and red mercuric oxide (10% molar excess) was stirred in dichloromethane for 24 hours. The mixture was filtered through celite and evaporated. The crude product was purified by recrystallisation from hexane unless otherwise stated.

2-Benzoylamino-4-methylquinoline (**8a**).

Compound **8a** was obtained as crystals from ethyl acetate-hexane, 0.81 g, (91%), mp 125-126°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.77 (s, 3H), 7.46-7.63 (m, 4H), 7.67 (dd, 1H, J = 6.49 Hz), 7.84 (d, 1H, J = 8.44 Hz), 7.95-8.01 (m, 3H), 8.24 (s, 1H), 11.05 (br singlet, N*H*); ms: m/z (relative intensity) 262 (M$^+$), 233 (58), 105 (77), 77 (100); ir: ν 1689, 1674 (C=O signal split), 1600, 1579, 1378, 1363, 710 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.37; N, 10.68. Found: C, 77.83; H, 5.58; N, 10.75.

2-Propan-2-ylamino-4-methylquinoline (**8b**).

Compound **8b** was obtained in 38% yield (0.13 g), mp 108-

109°; ^{1}H nmr (deuteriochloroform): δ 1.28 (d, 6H, J = 6.25), 2.56 (s, 3H), 4.20 (octet, 1H, J = 6.44 Hz), 4.55 (br doublet, N*H*), 6.48 (s, 1H), 7.21 (dd, 1H, J = 8.13 Hz), 7.51 (dd, 1H, J = 8.33 Hz), 7.65 (d, 1H, J = 7.59 Hz), 7.75 (d, 1H, J = 9.49 Hz); ms: m/z (relative intensity) 200 (M^+), 185 (21), 158 (20), 28 (100); ir: ν 3252 (NH), 1626, 1543, 1507, 1419, 1400, 1296, 1217, 750 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.63; H, 8.01; N, 13.96.

2-Phenylamino-4-methylquinoline (**8c**).

Compound **8c** was obtained in 85% yield (1.0 g), mp 120-121°; ^{1}H nmr (deuteriochloroform): δ 2.58 (s, 3H), 6.83 (m, 2H, NH + quinoline C3 H), 7.07 (dd, 1H, J = 7.36 Hz), 7.27-7.38 (m, 3H), 7.52-7.60 (m, 3H), 7.76-7.82 (m, 2H); ms: m/z (relative intensity) 234 (M^+), 233 (100), 219 (14), 116 (14); ir: ν 3386 (NH), 1595, 1527, 1378, 765, 752 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.78; H, 6.19; N, 11.96.

2-Benzylamino-4-methylquinoline (**8d**).

Compound **8d** was obtained in 85% yield (2.1 g), mp 75-76°; ^{1}H nmr (deuteriochloroform): δ 2.53 (s, 3H), 4.70 (d, 2H, J = 5.57 Hz), 5.09 (br triplet, N*H*), 6.46 (s, 1H), 7.20-7.41 (m, 6H), 7.52 (dd, 1H, J = 8.34 Hz), 7.69-7.77 (m, 2H); ms: m/z (relative intensity) 248 (M^+), 171 (15), 143 (49), 106 (48); ir: (nujol): ν 3240 (NH), 1622, 1377, 1353, 763, 731 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 81.85; H, 6.59; N, 11.32.

Methyl *N*-Benzoyl-*N'*-(2-isopropenylphenyl)carbamimidate (**9**).

A mixture of **7a** (0.29 g, 1.1 mmoles) and red mercuric oxide (0.3 g, 1.39 mmoles) was stirred in methanol for 24 hours. The mixture was filtered through celite and the solvent removed under reduced pressure. Chromatography (silica gel, chloroform) gave the quinoline **8a**, 90 mg, (34%), whose spectral characteristics agreed with those described earlier, and **9**, 60 mg, (20%), mp 86-88°; ^{1}H nmr (deuteriochloroform): δ 2.08 (s, 3H), 4.08 (s, 3H), 5.05 (m, 1H, J = 1.54 Hz), 5.37 (m, 1H, J = 1.54 Hz), 7.18-7.31 (m, 3H), 7.40-7.54 (m, 4H), 8.28-8.32 (m, 2H), 11.79 (br singlet, N*H*); ms: (FAB) m/z 295 ($M+H^+$); ir: (nujol): ν 3201 (NH), 1615, 1592 (C=O signal split), 1574, 1380, 1349, 1059, 771 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.44; H, 6.30; N, 9.58.

N-2-Isopropenylphenyl-*N'*-benzylguanidine (**10**).

A mixture of **7d** (0.26 g, 0.93 mmole) and red mercuric oxide (0.3 g, 1.39 mmoles) was stirred in methanolic ammonia for 2 hours at room temperature. The mixture was filtered through celite and the solvent removed under reduced pressure. Recrystallisation from hexane-ether gave **10**, 212 mg, (85%), mp 95-97°; ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 3H), 4.00 (br singlet, 3H, N*H*), 4.43 (s, 2H), 4.97 (s, 1H), 5.05 (s, 1H), 6.92 (d, 1H, J = 7.60 Hz), 6.98 (dd, 1H, J = 7.60 Hz), 7.16-7.36 (m, 7H); ms: (FAB) m/z 266 ($M+H^+$); ir: ν 3417 (NH), 3292 (OH), 1639, 1615, 1586, 1536, 1350, 901, 759, 724, 695 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 77.06; H, 7.21; N, 16.01.

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