# Synthesis of 2-Amino-7,8-dihydro-6(5*H*)-quinazolinone, 2,4-Diamino-7,8-dihydro-6(5*H*)-quinazolinone, 5,6,7,8-Tetrahydro-2,6-quinazolinediamine and 5,6,7,8-Tetrahydro-2,4,6-quinazolinetriamine Derivatives



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*N*-(2-Amino-5,6,7,8-tetrahydro-6-quinazolinyl)acetamide (**9**) and *N*-(2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinyl)acetamide (**6**) were synthesized from *N*-(4-oxocyclohexyl)acetamide (**5**) as novel peptidomimetic building blocks. With similar purpose, *N*-(6-oxo-5,6,7,8-tetrahydro-2-quinazolinyl)acetamide (**18**) and *N*-[2-(acetylamino)-6-oxo-5,6,7,8-tetrahydro-4-quinazolinyl]acetamide (**14**) were prepared from cyclohexane-1,4-dione monoethylene ketal (**11**).

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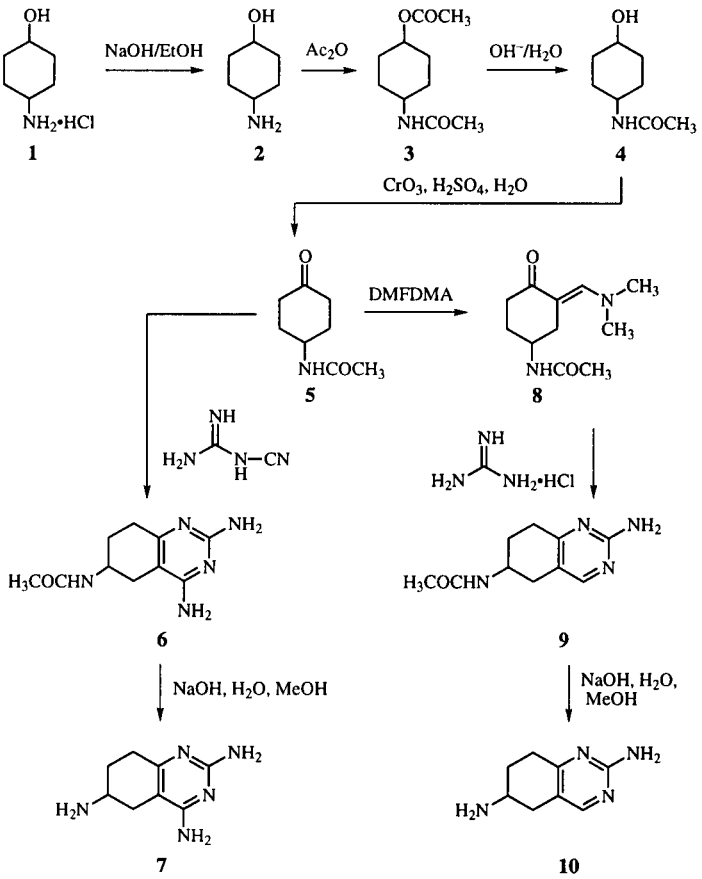
Whereas several methods are known for the synthesis of quinazolinamines bearing amino groups on both, the pyrimidine and benzene part of the molecule [1,2], the corresponding 5,6,7,8-tetrahydroquinazolinamines have not been well explored so far. We envisioned the hitherto unknown 5,6,7,8-tetrahydro-2,6-quinazolinediamine (**10**) and 5,6,7,8-tetrahydro-2,4,6-quinazolinetriamine (**7**) as interesting building blocks for the construction of peptidomimetics [3,4] since several heterocyclic amines have recently been used as mimetics of arginine [5,6].

A strategy originally designed by us to afford 5,6,7,8-tetrahydroquinazolinamines **7** and **10** comprised the synthesis of the novel acetyl protected 7,8-dihydro-6(5*H*)-quinazolinones **14** and **18** (Scheme 2) which were supposed to be easily transformed to 5,6,7,8-tetrahydroquinazolinamines **7** and **10** by reductive amination with sodium cyanoborohydride and ammonium acetate [7,8] and subsequent hydrolysis. Unfortunately, **7** and **10** could not be obtained by reductive amination of the ketones **14** and **18** in methanol, probably due to unfavorable keto-enol tautomerism as indicated by a proton nuclear magnetic resonance study [9]. Therefore, an alternative strategy for the construction of 5,6,7,8-tetrahydroquinazolinamines **7** and **10** starting from *N*-(4-oxocyclohexyl)acetamide (**5**) was devised (Scheme 1) which finally afforded *N*-(2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinyl)acetamide (**6**) and *N*-(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)-acetamide (**9**) and in reasonable yields.

The synthesis of acetyl protected 2,4-diamino-7,8-dihydro-6(5*H*)-quinazolinone **14** and 2-amino-7,8-dihydro-6(5*H*)-quinazolinone **18** started with cyclohexane-1,4-dione monoethylene ketal (**11**), a monoprotected cyclohexane-1,4-dione derivative. Cyclocondensation of **11** with cyanoguanidine performed in analogy to similar reactions of 4-methylcyclohexanone [10] and cyclohexanone-4-carboxaldehyde dimethyl acetal [11] with cyanoguanidine yielded the protected diamino derivative **12**. For the synthesis of *N*-(6-oxo-5,6,7,8-tetrahydro-2-quinazolinyl)-acetamide (**18**), compound **11** was transformed, by the use of *N*,*N*-dimethylformamide dimethyl acetal [20] to

Scheme 1

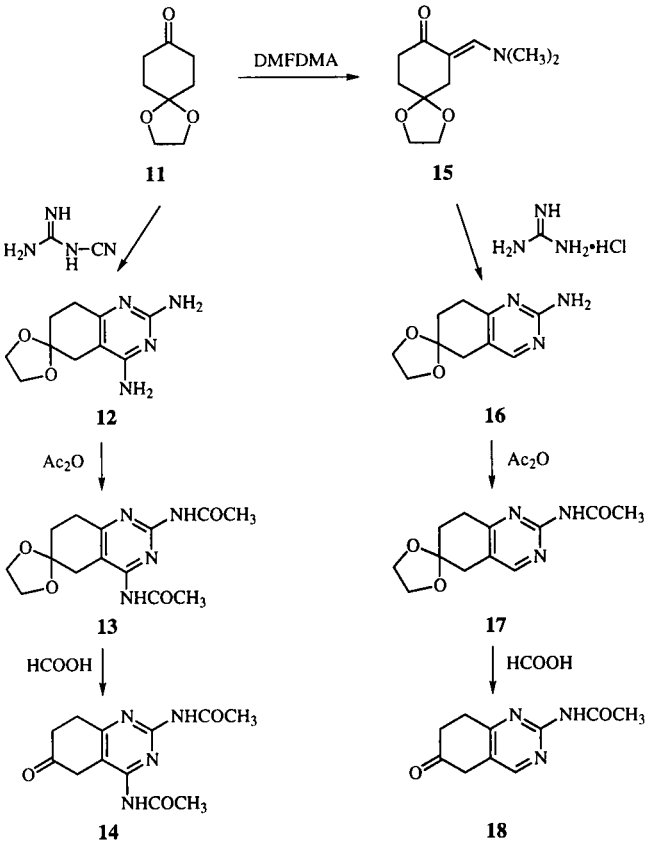



dimethylaminomethylidene derivative **15** which upon cyclization with guanidine hydrochloride afforded 2-amino-7,8-dihydro-6(5*H*)-quinazolinone ethylene ketal (**16**) in moderate yield. The deprotection of **12** and **16** by hydrolysis of the 1,3-dioxolane ring did not take place even under harsh reaction conditions (aqueous 4 *M* hydrochloric acid, reflux). Therefore, it was essential to protect the amino groups by acylation and afterwards the hydrolysis of the resulting acetamide derivatives **13** and **17** to ketones **14** and **18** was achieved in 90% formic acid.

*N*-(2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinyl)-acetamide (**6**) and *N*-(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)acetamide (**9**) were prepared from *N*-(4-oxocyclohexyl)acetamide (**5**) as shown in the Scheme 1. Compound **5** had been prepared previously by hydrogenation of 4-acetamidophenol using platinum dioxide [12, 13] or Raney nickel [14] as a catalyst. In our hands these hydrogenation procedures did not give good results and therefore alternative routes for the synthesis of **5** were sought. 4-Aminocyclohexanol (**2**) was acetylated with acetic anhydride and the resulting *O*,*N*-diacetyl derivative **3** selectively hydrolyzed to give *N*-(4-hydroxycyclohexyl)-acetamide (**4**) which was further oxidized to *N*-(4-oxocyclohexyl)acetamide (**5**) using Jones reagent [15,16] in aqueous medium [17]. Cyclocondensation of **5** with cyanoguanidine at an internal temperature of 180-185° afforded *N*-(2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinyl)-acetamide (**6**). The reaction of ketone **5** with *N*,*N*-dimethylformamide dimethyl acetal in refluxing benzene gave the enamino ketone **8** [18] which underwent cyclocondensation with guanidine hydrochloride in the presence of sodium ethoxyde to give *N*-(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)acetamide (**9**). Unexpectedly, all attempts to hydrolyze the acetamides **6** and **9** by acid hydrolysis using aqueous hydrochloric acid, hydrobromic acid or sulfuric acid with several modifications of the reaction conditions, including temperature, solvents, and concentration of acid, were unsuccessful and lead to destruction of the pyrimidine ring. Finally, the 6-acetamido group of **9** was successfully deacetylated under basic conditions, using 30 percent sodium hydroxide in a methanol – water mixture at reflux temperature to give 5,6,7,8-tetrahydro-2,6-quinazolinediamine (**10**) [21].

In conclusion, several novel 2-amino- and 2,4-diamino-7,8-dihydro-6(5*H*)-quinazolinone as well as 5,6,7,8-tetrahydro-2,6-quinazolinediamine and 5,6,7,8-tetrahydro-2,4,6-quinazolinetriamine derivatives were prepared. The application of these compounds as peptidomimetic building blocks will be reported elsewhere.

Scheme 2




## EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Proton nmr spectra were measured at 300 MHz on a Bruker AVANCE $DPX_{300}$ spectrometer. Microanalyses were performed on a Perkin-Elmer C,H,N analyser 240 C. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer.

*trans*-4-(Acetylamino)cyclohexyl Acetate (**3**).

*trans*-4-Aminocyclohexanol hydrochloride (**1**) (8.0 g, 53 mmoles) was neutralized with 0.3 *M* ethanolic sodium hydroxide (18 ml, 54 mmoles). After 0.5 hour at 0°, sodium chloride was filtered off and the filtrate was evaporated *in vacuo* to give 6.0 g (98%) of 4-aminocyclohexanol (**2**).

The title compound **3** was obtained by boiling *trans*-4-aminocyclohexanol (**2**) (6.0 g, 52 mmoles) in an excess of acetic anhydride (50 ml). After 1 hour acetic anhydride was evaporated *in vacuo* to give 10.1 g (97 %) of **3**, mp 155-157°; ir (potassium bromide): ν 3436, 3262, 2944, 1727, 1640, 1572, 1365, 1249, 1105, 1034, 902, 761, 607 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.17-1.44 (m, 4H, 2 $CH_2$), 1.77 (s, 3H, $CH_3$), 1.80-1.89 (m, 4H, 2 $CH_2$), 1.98 (s, 3H, $CH_3$), 3.46-3.58 (m, 1H, *CH*), 4.51-4.61 (m, 1H, *CH*), 7.74 (d, 1H, J = 7.16 Hz, N*H*); ms (70 eV, electron impact): m/z (%) 199 ($M^+$, 60), 80 (100).

*Anal.* Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.00; H, 8.62; N, 7.29.

*trans*-*N*-(4-Hydroxycyclohexyl)acetamide (**4**).

This product was prepared by hydrolysis of **3** (10.1 g, 51 mmoles) with an excess of 1 *M* aqueous NaOH (70 ml) at room temperature during 30 minutes. After neutralization with 1 *M* aqueous hydrochloric acid, water was removed *in vacuo*. The product **4** was isolated by continuous extraction with chloroform in a Soxhlet apparatus overnight to obtain 7.7 g (97 %) of white amorphous solid, mp 164-166° (lit [19] mp 160.0-163.5°); ir (potassium bromide): ν 3292, 2933, 1637, 1560, 1456, 1370, 1327, 1234, 1148, 1113, 1064, 959, 896, 793, 605 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.06-1.24 (m, 4H, 2 $CH_2$), 1.75 (s, 3H, $CH_3$), 1.71-1.80 (m, 4H, 2 $CH_2$), 3.31-3.49 (m, 2H, 2 *CH*), 4.50 (d, 1H, J = 4.15 Hz, O*H*), 7.63 (d, 1H, J = 7.54 Hz, N*H*); ms (70 eV, electron impact): m/z (%) 157 ($M^+$, 35), 60 (100).

*Anal.* Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.28; H, 9.47; N, 8.99.

*N*-(4-Oxocyclohexyl)acetamide (**5**).

*N*-(4-Hydroxycyclohexyl)acetamide (**4**) (7.7 g, 49 mmoles) was dissolved in water (10 ml) and a freshly prepared standard chromium trioxide-sulfuric acid reagent (Jones reagent) [15, 16] (13 ml) was added dropwise within 2 hours with stirring. The temperature was maintained at 20°C and the mixture was stirred for further 22 hours. The solution was diluted with water and the product isolated by continuous extraction with chloroform to obtain 5.6 g (74 %) of **5**, mp 136° (lit [12] mp 135-136°); ir (potassium bromide): ν 3291, 2972, 2940, 1718, 1648, 1378, 1204, 1109, 940, 740, 604 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.56-1.69 (m, 2H, C*H*$_2$), 1.82 (s, 3H, C*H*$_3$), 1.94-2.03 (m, 2H, C*H*$_2$), 2.22-2.29 (m, 2H, C*H*$_2$), 2.36-2.47 (m, 2H, C*H*$_2$), 3.96-4.06 (m, 1H, C*H*), 7.87 (d, 1H, J = 6.78 Hz, N*H*); ms (70 eV, electron impact): m/z (%) 155 ($M^+$, 44), 96 (100).

*Anal.* Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.96; H, 8.62; N, 9.22.

(±)-*N*-(2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinyl)-acetamide (**6**).

A mixture of *N*-(4-oxocyclohexyl)acetamide (**5**) (10.0 g, 65 mmoles) and cyanoguanidine (6.5 g, 77 mmoles) was heated at an internal temperature of 180° in an oil bath for 1.5 hours. A complete solution was obtained in 30 minutes and a solid started to deposit 1 hour later. The reaction mixture was cooled and triturated with 30 ml of methanol and the resulting solid was collected by filtration. Crystallization from the same solvent gave 9.0 g (63%) of **6**, mp 299-302°; ir (potassium bromide): ν 3340, 3136, 1708, 1642, 1548, 1442, 1362, 1224, 1090, 1008 959, 817 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.56-1.67 (m, 1H, C*H*$_2$), 1.76-1.81 (m, 1H, C*H*$_2$), 1.81 (s, 3H, NHCOC*H*$_3$), 1.99-2.07 (m, 1H, C*H*$_2$), 2.43-2.56 (m, 3H, C*H*$_2$, C*H*$_2$), 3.88-3.96 (m, 1H, 6-C*H*), 5.52 (s, 2H, 4-N*H*$_2$), 5.97 (s, 2H, 2-N*H*$_2$), 7.90 (d, 1H, J = 7.91 Hz, N*H*CO); ms (fast atom bombardment): m/z (%) 222 ($MH^+$, 100).

*Anal.* Calcd. for $C_{10}H_{15}N_5O$: C, 54.30; H, 6.78; N, 31.67. Found: C, 53.95; H, 6.67; N, 31.32.

(±)-*N*-[3-[(Dimethylamino)methylidene]-4-oxocyclohexyl]-acetamide (**8**).

A solution of *N*-(4-oxocyclohexyl)acetamide (**5**) (13.5 g, 87 mmoles), dimethylformamide dimethyl acetal (75 ml, 560 mmoles), and triethylamine (1.5 ml, 10 mmoles) in 350 ml of benzene was distilled over a period of 2Hours to about one-half the original volume. Benzene (150 ml) was then added to the residue, and heating was continued just below the boiling point for 2Hours. Distillation was continued to a volume one-half of the original during 1.5 hours. Benzene (150 ml) was again added, and the process was repeated a third and fourth time. The solution was cooled and product was collected by filtration to yield 10.6 g. The filtrate was chromatographed on 200 g of Florisil using $CHCl_3$/ 0-5% MeOH as eluent to give 2.58 g (total yield 72 %) of **8**, mp 132-134° (lit [18] mp 128-131°); ir (potassium bromide): ν 3477, 1630, 1522, 1414, 1363, 1273, 1135, 998, 852, 604 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.53-1.67 (m, 1H, C*H*$_2$), 1.80 (s, 3H, NHCOC*H*$_3$), 1.80-1.88 (m, 1H, C*H*$_2$), 2.17-2.23 (m, 2H, C*H*$_2$), 2.43 (dd, 1H, J = 13.94 Hz, C*H*$_2$), 2.93 (dd, 1H, J = 13.94 Hz, C*H*$_2$), 3.05 (s, 6H, N(C*H*$_3$)$_2$), 3.70-3.82 (m, 1H, 1-C*H*), 7.30 (s, 1H, C*H*N(CH$_3$)$_2$), 7.85 (d, 1H, J = 7.16 Hz, N*H*COCH$_3$); ms (FAB): m/z (%) 211 ($MH^+$, 100).

*Anal.* Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.40; H, 8.45; N, 13.01.

(±)-*N*-(2-Amino-5,6,7,8-tetrahydro-6-quinazolinyl)acetamide (**9**).

To a solution of sodium ethoxide (0.437 g, 19 mmoles) in 50 ml of absolute ethanol, guanidine hydrochloride (1.82 g, 19 mmoles) was added. After stirring for 30 minutes, a solution of *N*-[3-[(dimethylamino)methylidene]-4-oxocyclohexyl]acetamide (**8**) (4.0 g, 19 mmoles) in absolute ethanol was added and the reaction mixture was refluxed under argon atmosphere for 3 hours. The separated solid was collected by filtration to give 3.38 g (87%) of **9**, mp 256-258°, ir (potassium bromide): ν 3398, 3319, 3212, 3050, 2944, 1647, 1625, 1596, 1558, 1477, 1456, 1375, 1287, 1192, 1099, 1047, 868, 793 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.60-1.73 (m, 1H, C*H*$_2$), 1.80 (s, 3H, NHCOC*H*$_3$), 1.83-1.94 (m, 1H, C*H*$_2$), 2.33-2.41 (m, 1H, C*H*$_2$), 2.60-2.77 (m, 3H, C*H*$_2$, C*H*$_2$), 3.82-3.96 (m, 1H, 6-C*H*), 6.24 (s, 2H, 2-N*H*$_2$), 7.88 (d, 1H, J = 6.78 Hz, N*H*CO), 7.93 (s, 1H, 4-C*H*); ms (fast atom bombardment): m/z (%) 207 ($MH^+$, 40), 147 (100).

*Anal.* Calcd. for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.18. Found: C, 57.88; H, 6.77; N, 26.91.

(±)-5,6,7,8-Tetrahydro-2,6-quinazolinediamine (**10**).

A solution of *N*-(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)-acetamide (**9**) (3.0 g, 14.6 mmole) and sodium hydroxide (30 g, 0.75 mole) in a mixture of water (30 ml) and methanol (90 ml) was refluxed for 16 hours. Water was added, and the mixture was extracted with dichloromethane. The organic extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give 1.40 g (58 %) of **10**, mp 178-181°; ir (potassium bromide): ν 3412, 1652, 1602, 1558, 1487, 1428, 1362, 1258, 1209, 1103, 1060, 1013, 952, 805, 786, 752, 719 $cm^{-1}$; $^1H$ nmr (300 MHz, dimethyl sulfoxide-$d_6$): δ 1.41-1.55 (m, 1H, C*H*$_2$), 1.80-1.92 (m, 1H, C*H*$_2$), 2.16-2.24 (m, 1H, C*H*$_2$), 2.53-2.69 (m, 3H, C*H*$_2$, C*H*$_2$), 2.91-3.02 (m, 1H, 6-C*H*), 6.18 (s, 2H, 2-N*H*$_2$), 7.90 (s, 1H, 4-C*H*); ms (70 eV, electron impact): m/z (%) 164 ($M^+$, 100).

*Anal.* Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.09; H, 7.11; N, 33.91.

2,4-Diamino-7,8-dihydro-6(5*H*)-quinazolinone Ethylene Ketal (**12**).

A mixture of cyclohexane-1,4-dione monoethylene ketal (**11**) (10.0 g, 64 mmoles) and cyanoguanidine (6.4 g, 77 mmoles) were heated at an internal temperature of 180° in an oil bath for 3 hours. A complete solution was obtained in 1 hour and a solid started to deposit 1 hour later. The reaction mixture was cooled and triturated with 50 ml of methanol and the resulting solid was collected by filtration. Crystallization from the same solvent gave 8.7 g (61%) of **12**, mp > 230°; ir (potassium bromide): ν 3432, 3147, 1664, 1618, 1571, 1445, 1058 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.80 (t, 2H, J = 6.78 Hz, C*H*$_2$), 2.42 (s, 2H, 5-C*H*$_2$), 2.80 (t, 2H, J = 6.78 Hz, C*H*$_2$), 3.92 (s, 4H, O-C*H*$_2$-C*H*$_2$-O), 5.53 (s, 2H, N*H*$_2$), 5.98 (s, 2H, N*H*$_2$); ms (70 eV, electron impact): m/z (%) 222 ($M^+$, 54), 149 (100).

*Anal.* Calcd. for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.74; H, 6.49; N, 25.67.

2,4-Diacetamido-7,8-dihydro-6(5*H*)-quinazolinone Ethylene Ketal (**13**).

A mixture of 2,4-diamino-7,8-dihydro-6(5*H*)-quinazolinone ethylene ketal (**12**) (1.00 g, 4.5 mmoles) and acetic anhydride (20 ml) was heated for 1 hour at 100°. The solution was evaporated to dryness and the solid residue was dissolved in 5 ml of hot toluene. After addition of ether the precipitated yellow solid was collected; yield: 0.91 g (66%) of **13**, mp 166-169°; ir (potassium bromide): ν 3234, 2959, 1719, 1661, 1576, 1508, 1402, 1239 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.93 (t, 2H, J = 6.78 Hz, $CH_2$), 2.15 (s, 3H, $CH_3$), 2.19 (s 3H, $CH_3$), 2.67 (s, 2H, 5-$CH_2$), 2.86 (t, 2H, J = 6,78 Hz, $CH_2$), 3.93 (s, 4H, O-$CH_2$-$CH_2$-O), 10.01 (s, 1H, N*H*), 10.30 (s, 1H, N*H*); ms (70 eV, electron impact): m/z (%) 306 ($M^+$, 7), 234 (100).

*Anal.* Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.16; H, 6.09; N, 17.97.

*N*-[2-(Acetylamino)-6-oxo-5,6,7,8-tetrahydro-4-quinazolinyl]-acetamide (**14**).

A solution of 2,4-diacetamido-7,8-dihydro-6(5*H*)-quinazolinone ethylene ketal (**13**) (740 mg, 2.4 mmoles) in formic acid (15 ml) was stirred at room temperature for 12 hours. Water and the excess formic acid were removed *in vacuo*. Residue was dissolved in methanol; after addition of ether a pale orange solid ensued; yield: 420 mg (66%) of **14**, mp 215-217 °C; ir (potassium bromide): ν 3566, 1681, 1508, 1373, 1315, 793, 547 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 2.18 (s, 3H, $CH_3$), 2.19 (s, 3H, $CH_3$), 2.59 (t, 2H, J = 6.78 Hz, $CH_2$), 3.09 (t, 2H, J = 6.78 Hz, $CH_2$), 3.37 (s, 2H, 5-$CH_2$), 10.17 (s, 1H, N*H*); 10.39 (s, 1H, N*H*); ms (fast atom bombardment): m/z (%) 263 ($MH^+$, 100).

*Anal.* Calcd. for $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36. Found: C, 54.84; H, 5.13; N, 21.02.

7-[(1–Dimethylamino)methylidene]-1,4-dioxaspiro[4.5]decan-8–one (**15**).

A mixture of cyclohexane-1,4-dione monoethylene ketal (**11**) (7.80 g, 50 mmoles) and dimethylformamide dimethyl acetal (5.95 g, 50 mmoles) was refluxed under argon atmosphere for 12 hours. Solvent was removed *in vacuo* and the residue distilled in a Kugelrohr apparatus at 185°/ 0.5 Torr. The resulting yellow oil was used without further purification; yield: 5.8 g (55%) of **15**, ir (film): ν 2417, 2962, 1717, 1636, 1559, 1402, 1126, 1048 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.95 (t, 2H, J = 6.97 Hz, $CH_2$), 2.51 (t, 2H, J = 6.97 Hz, $CH_2$), 2.92 (s, 2H, 6-$CH_2$), 3.07 (s, 6H, N($CH_3$)$_2$), 4.01 (s, 4H, O-$CH_2$-$CH_2$-O), 7.50 (s, 1H, C*H*); ms (70 eV, electron impact): m/z (%) 211 ($M^+$, 36), 159 (100).

*Anal.* Calcd. for $C_{11}H_{17}NO_3$?$H_2O$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.95; H, 8.38; N, 5.84.

2-Amino-7,8-dihydro-6(5*H*)-quinazolinone Ethylene Ketal (**16**).

Guanidine hydrochloride (1.54 g, 16.1 mmoles) was added to a stirred solution of sodium ethoxide (1.10 g, 16.1 mmoles) in 100 ml of ethanol. After stirring for 30 minutes, compound **15** (3.25 g, 15.4 mmoles) was added whereupon the reaction mixture was refluxed under argon atmosphere for 10 hours. Solvent was removed under reduced pressure and the residue dissolved in water. After addition of ether, the product separated as white needles; yield: 1.74 g (55%), mp 212-213°; ir (potassium bromide): ν 3416, 3320, 2984, 1636, 1558, 1473, 1058 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.87 (t, 2H, J = 6.78 Hz, $CH_2$), 2.68 (s, 2H, 5-$CH_2$), 2.69 (t, 2H, J = 6.78 Hz, $CH_2$), 3.92 (s, 4H, O-$CH_2$-$CH_2$-O), 6.27 (s, 2H, N$H_2$), 7.91 (s, 1H, C*H*); ms (70 eV, electron impact): m/z (%) 207 ($M^+$, 96), 134 (100).

*Anal.* Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.97; H, 6.32; N, 20.29. Found: C, 57.69; H, 6.69; N, 19.94.

2-Acetamido-7,8-dihydro-6(5*H*)-quinazolinone Ethylene Ketal (**17**).

A mixture of 2-amino-7,8-dihydro-6(5*H*)-quinazolinone ethylene ketal (**16**) (2.40 g, 11.6 mmoles) and acetic anhydride (24 ml) was heated for 1 hour at 100°. The solution was evaporated to dryness and the solid residue was dissolved in 5 ml of hot toluene. After addition of ether the precipitated solid was collected by filtration to yield 2.37 g (82%) of **17**, mp 162-163°; ir (potassium bromide): ν 3151, 2983, 1674, 1598, 1516, 1443, 1379, 1058 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 1.95 (t, 2H, J = 6.41 Hz, $CH_2$), 2.14 (s, 3H, $CH_3$), 2.85 (m, 4H, 2 $CH_2$), 3.95 (s, 4H, O-$CH_2$-$CH_2$-O), 8.30 (s, 1H, C*H*), 10.34 (s, 1H, N*H*COC$H_3$); ms (70 eV, electron impact): m/z (%) 249 ($M^+$, 17), 177 (100).

*Anal.* Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.37; H, 6.34; N, 16.46.

*N*-(6-Oxo-5,6,7,8-tetrahydro-2-quinazolinyl)acetamide (**18**).

A solution of 2-acetamido-7,8-dihydro-6(5*H*)-quinazolinone ethylene ketal (**17**) (1.0 g, 4.0 mmoles) in formic acid (10 ml) was stirred at room temperature for 12 hours. Water and the excess of acid were removed *in vacuo* and the residue was dissolved in methanol; after addition of ether a pale orange solid precipitated to yield 0.51 g (62%) of **16**, mp 206-208°; ir (potassium bromide): ν 3127, 2974, 1721, 1678, 1595, 1516, 1382, 1023 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$): δ 2.17 (s, 3H, $CH_3$), 2.58 (t, 2H, J = 6.97 Hz, $CH_2$), 3.09 (t, 2H, J = 6.97 Hz, $CH_2$), 3.57 (s, 2H, 5-$CH_2$), 8.38 (s, 1H, C*H*), 10.44 (s, 1H, N*H*Ac); ms (70 eV, electron impact): m/z (%) 205 ($M^+$, 59), 134 (100).

*Anal.* Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.06; H, 5.67; N, 20.30.

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REFERENCES AND NOTES

[1] D. J. Brown, Quinazolines - Supplement 1, John Wiley & Sons, New York, 1997.

[2] D. Kikelj, in Houben - Weyl Methods of Organic Chemistry, Vol E 9b/Part 2, E. Schaumann, ed, Georg Thieme Verlag, Stuttgart, 1998.

[3] M. Goodman and S. Ro, in Burger's Medicinal Chemistry and Drug Discovery; M. E. Wolff, ed, John Wiley & Sons, New York, 1995, pp 803-861.

[4] A. Giannis, F. Rübsam, in Advances in Drug Research, Vol 29, B. Testa and U. A. Meyer, eds, Academic Press, 1997, pp 1-78.

[5] D. -M. Feng, S. J. Gardell, S. D. Lewis, M. G. Bock, Z. Chen, R. M. Freidinger, A. M. Naylor-Olsen, H. G. Ramjit, R. Woltmann, E. P. Baskin, J. J. Lynch, R. Lucas, J. A. Schafer, K. B. Dancheck, I. -W. Chen, S. -S. Mao, J. A. Krueger, T. R. Hare, A. M. Mulichak and J. P. Vacca, *J. Med. Chem.*, **40**, 3726 (1997).

[6] J. B. M. Rewinkel, H. Lucas, P. J. M. van Galen, A. B. J. Noach, T. G. van Dinther, A. M. M. Rood, A. J. S. M. Jenneboer and C. A. A. van Boeckel, *Bioorg. Med. Chem. Lett.*, **9**, 685 (1999).

[7] R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

[8] C. F. Lane, *Synthesis*, 135 (1975).

[9] $^1$H nmr spectrum of **18** in methanol-$d_4$ indicated the presence of approximately 30 percent of the 6-hydroxy tautomer.

[10] E. J. Modest, S. Chatterjee, H. K. Protopapa, *J. Am. Chem. Soc.*, **87**, 1837 (1965).

[11] A. Gangjee, N. Zaveri, S. F. Queener and R. L. Kisliuk, *J. Heterocyclic Chem.*, **32**, 243 (1995).

[12] R. R. Fraser and R. B. Swingle, *Can. J. Chem.*, **48**, 2065 (1970).

[13] E. Ferber and H. Bruckner, *Chem. Ber.*, **72**, 995 (1939).

[14] J. H. Billman and J. A. Buehler, *J. Am. Chem. Soc.*, **75**, 1345 (1953).

[15] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

[16] C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

[17] H.-J. Teuber, C. Tsaklakidis and J. W. Bats, *Liebigs Ann. Chem.*, 784 (1990).

[18] N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.*, **23**, 481 (1980).

[19] H. K. Hall, *J. Am. Chem. Soc.*, **80**, 6418 (1958).

[20] R. F. Abdulla and K. H. Fuhr, *J. Org. Chem.*, **43**, 4248 (1978).

[21] Compound **6** was also deacetylated by alkaline hydrolysis but, unfortunately, the product **7** could not be fully characterized due to its extremely bad solubility in water and organic solvents.