An Efficient Synthesis of the Novel Triazoloquinazoline Adenosine Antagonist, CGS 15943

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An efficient synthesis of the novel triazoloquinazoline adenosine antagonist, CGS 15943, is reported in five steps in approximately 50% overall yield. A key reaction in the synthetic sequence is the double cyclization of an *N*-(substituted-2-cyanophenyl)carbamate with a carboxylic acid hydrazide to afford a [1,2,4]triazolo-[1,5-*c*]quinazolin-5(6*H*)-one in high yield without either a Dimroth or "translocative" rearrangement occurring. Another key reaction is the condensation of a 2-(1*H*-1,2,4-triazol-5-yl)benzenamine with cyanamide under acidic conditions to prepare a guanidine.

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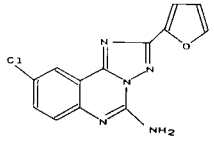
Introduction.

During a program of screening benzodiazepine receptor antagonists and other potential anxiomodulators as possible adenosine antagonists, it was discovered that the triazoloquinazoline structure **1** (CGS 15943) was more potent than any adenosine antagonist reported at that time (January 1983) [2]. It was approximately 500 times as active as theophylline and 250 times as potent as the benzodiazepine receptor antagonist **2** (CGS 8216) in blocking the adenosine activation in guinea pig synaptoneurosomes [3]. We recently required large amounts of **1** for further evaluation. Although **1** is available through the described synthesis [2] and each individual step proceeds in moderate yield, several of the reagents used may have posed health and safety problems during scale up. In addition, the required starting materials were cost prohibitive in quantities larger than lab scale. We now report two syntheses of **1** from readily available, inexpensive starting materials that avoid the potential health and safety problems.



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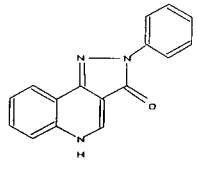

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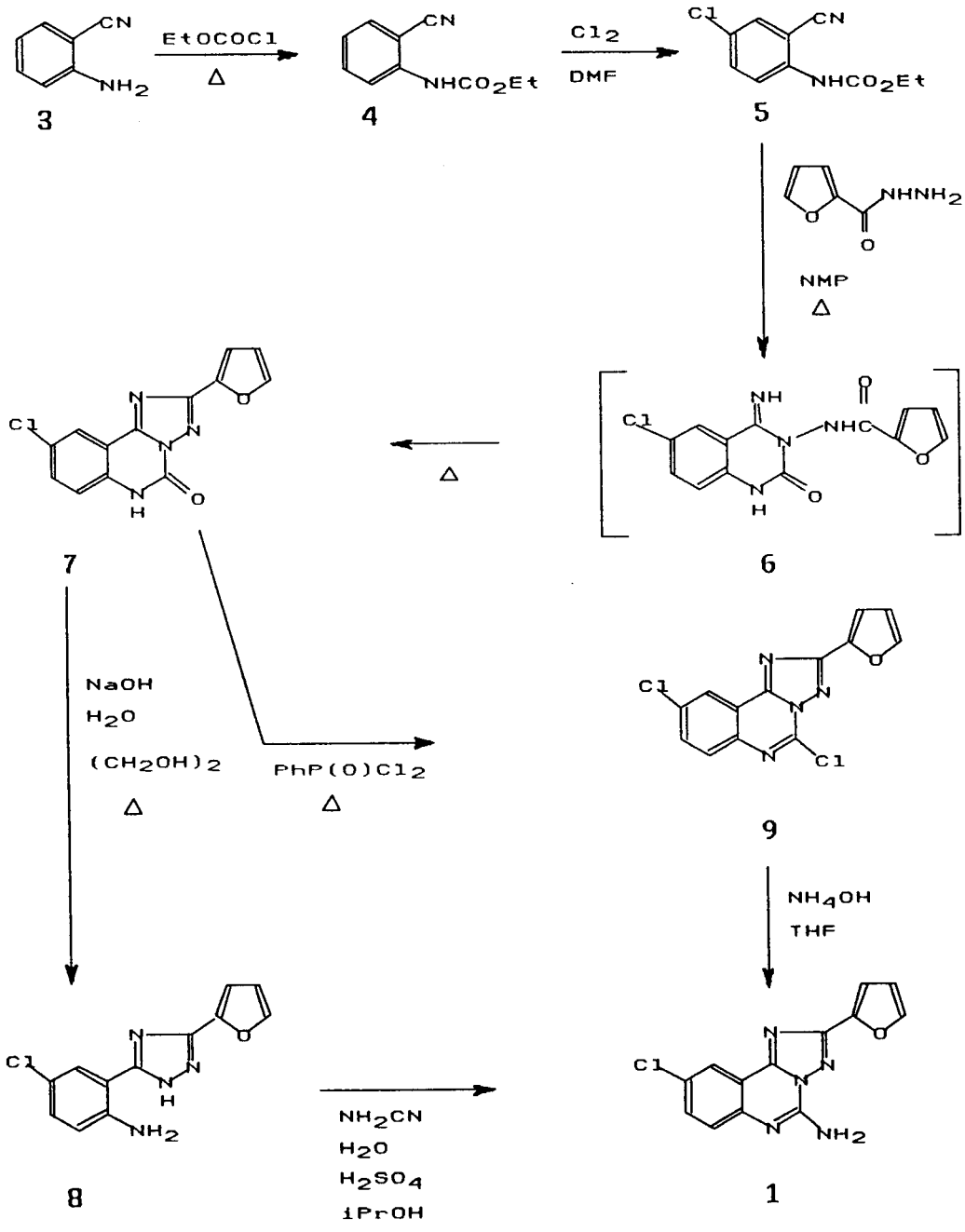
Results and Discussion.

Method 1.

The acylation of anthranilonitrile, **3**, in refluxing ethyl chloroformate with the concomitant evolution of hydrogen chloride gas, afforded the desired crystalline urethane, **4**, in 92% yield. A second crop (6% of acceptable **4**) was obtained by concentrating and then cooling the combined mother/wash liquor. Attempts to acylate **3** under milder conditions (*ie.* ethyl chloroformate and triethylamine in acetonitrile or ethyl chloroformate in a biphasic mixture of aqueous sodium bicarbonate and methylene chloride) led to the formation of a bright yellow, highly insoluble urea. *N*-Chlorination of **4** in *N,N* dimethylformamide (DMF) with chlorine gas, followed by an Orton rearrangement [4] gave **5** in 90% yield.

The condensation of **5** with 2-furoic acid hydrazide in hot 1-methyl-2-pyrrolidinone (NMP) sequentially produced a volatile by-products mixture consisting of ethanol at 90-110° internal temperature followed by water at 160°. After cooling the reaction mixture to 100° and diluting it with water, the triazolo-urea, **7**, was isolated in 94% yield. The formation of intermediate **6** seemed likely and a distinct, extremely polar reaction intermediate was observed by a tlc analysis of the NMP reaction solution at 110°. Attempts to isolate and purify this intermediate led to its cyclization. Since the double cyclization occurred so readily, it seemed likely that no Dimroth-type rearrangement [5] occurred. While the Dimroth rearrangement leading to isomeric triazoles is known [6] and there are several examples of the facile rearrangement of the triazolo[4,3-*c*]-quinazoline to the triazolo[1,5-*c*]quinazoline ring system [7], the reverse rearrangement has not been reported. There was no evidence for a "translocative" rearrangement which has been documented to readily occur during the addition of methyl hydrazine to methyl *N*-(2-cyanophenyl)methanimidate under much milder conditions [8]. The **7** isolated from this procedure was virtually identical, by spectroscopic analysis, to the material prepared from the isocyanate [2]. In addition, the ultimate structure proof was the direct conversion of **7** to **1** without opening the urea linkage, as described in Method 2.

The original procedure for the hydrolysis of **7** required the use of refluxing 2-methoxyethanol (methyl Cellosolve,



a known teratogen [9]) as the solvent [2]. After a protracted workup, **8** was isolated in 84% yield. Simple aqueous hydrolysis did not work and a higher boiling protic solvent was needed. Ultimately, the hydrolysis of **7** was achieved by refluxing a mixture of **7**, sodium hydroxide, water and ethylene glycol followed by neutralizing the cooled reaction medium with acetic acid to afford the known triazole **8** in 99% yield. Refluxing a mixture of **8**, excess 50% aqueous cyanamide and aqueous sulfuric acid in isopropanol, initially produced a solution from which the cyclized product began to precipitate after 10 minutes. The desired product, **1**, was isolated in 65% yield after adjusting the *p*H to 6.5, filtering the slurry and recrystallizing the crude product (containing urea) with a decolorizing carbon treatment, from hot acetic acid. The purified **1** was rinsed with water and ethanol to remove the last traces of acetic acid. The unreacted starting material remained in the isopropanol filtrate and could be recovered and recycled through the process to increase the yield for this step to >90%.

Method 2.

Additional proof that no rearrangement occurred during the double cyclization reaction was the direct conversion of the tricyclic urea intermediate, **7**, to the desired product, **1**, without opening the urea linkage. When **7** was heated to 185° in phenylphosphonic dichloride [11], the known **9** [2] was obtained in 90% (*ca.*) yield. This compound proved to be moisture sensitive, partially hydrolyzing back to **7** during an attempt to isolate and dry the crystalline product. This instability problem was avoided by subsequently reacting the crude **9** with the desired nucleophile (in this case, NH_3). A solution of crude **9** in THF was converted to **1** by treatment with concentrated aqueous ammonia in an overall yield of 77% from the common intermediate **7**.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer model 457 spectrometer. Proton nmr were obtained on a Varian EM-390 instrument using tetramethylsilane as an internal standard. Elemental analyses were obtained from Robertson Laboratory, Inc., P. O. Box 927, Madison, New Jersey 07940.

Ethyl *N*-(2-Cyanophenyl)carbamate (**4**).

CAUTION: This reaction should be conducted in an efficient fume hood as ethyl chloroformate is a potent irritant and lachrymator. In addition, the outlet gasses should be vented through a caustic scrubber since one molar equivalent of hydrogen chloride is evolved.

A vigorously stirred suspension of anthranilonitrile, **3**, (60.2 g, 0.5 mole) in ethyl chloroformate (246 ml, 2.5 moles) was heated at reflux. A clear solution was obtained after 3 hours and the reaction was complete by tlc analysis (silica gel with toluene:ethyl acetate, 85:15) after 6 hours. The excess ethyl chloroformate (150 ml) was distilled from the reaction mixture at atmospheric pressure and toluene (30 ml) was added to the reaction mixture as a chaser solvent. When the head temperature reached 110° (an additional 45 ml of distillate removed), toluene (130 ml) was added in one portion. The reaction mixture was cooled to *ca.* 80° and cyclohexane (380 ml) was slowly added to induce crystallization. The suspension was slowly cooled to room temperature and additional cyclohexane (140 ml) was added. The solid was collected by filtration, rinsed with cyclohexane (2 x 100 ml) and dried *in vacuo* at 50-55° to provide 87.2 g (92%) of the title compound as a white solid, mp 104-105°; ^{1}H nmr (deuteriochloroform): δ 8.10 (d, 1H), 7.45 (m, 2H), 7.06 (m, 2H), 4.15 (q, 2H) and 1.28 ppm (t, 3H); ir (nujol): 2240 (CN), 1710 (urethane CO), 1535 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.11; N, 14.90.

Concentrating the toluene/cyclohexane mother liquor to 35 ml and cooling this solution to −5° afforded a second crop of product which was isolated by filtration, washed with chilled cyclohexane and dried *in vacuo* at 50-55° to provide an additional 5.6 g (6%) of the title compound as a white solid, mp 104-106°.

Ethyl *N*-(4-Chloro-2-cyanophenyl)carbamate (**5**).

CAUTION: This reaction should be run in an efficient fume hood.

Into a vigorously stirred solution of **4** (47.55 g, 0.25 mole) in *N,N*-dimethylformamide (DMF, 100 ml) was bubbled chlorine gas (36.2 g, 0.51 mole) at such a rate as to keep the internal temperature at 30 ± 2° (~12 g/hour) until the reaction was complete as shown by tlc analysis (silica gel with toluene: ethyl acetate, 85:15). Nitrogen was bubbled through the reaction mixture for 1 hour. Cold water (200 ml, ~5°) was added to the reaction mixture to induce crystallization. The crude product was collected by filtration, washed with water (200 ml) and dried *in vacuo* at 60° to provide 55.1 g of crude **5** which was recrystallized from 2:1 ethanol:water to produce 50.7 g (90%) of the title compound as an off white solid, mp 131-133°; ^{1}H nmr (deuteriochloroform): δ 8.25 (s, 1H), 7.55 (m, 2H), 7.15 (s, 1H), 4.30 (q, 2H) and 1.35 ppm (t, 3H).

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.03; N, 12.47. Found: C, 53.25; H, 3.95; N, 12.42.

9-Chloro-2-(2-furanyl)-5,6-dihydro[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (**7**).

To a three necked, 500 ml round bottomed flask equipped with a mechanical stirrer, thermometer adapter with a nitrogen inlet and a Dean-Stark trap was charged a solution of **5** (15.0 g, 0.07 mole) and 2-furoic acid hydrazide (8.42 g, 0.07 mole) in 1-methyl-2-pyrrolidinone (NMP, 75 ml). A gentle nitrogen sweep was established through the apparatus and the stirred solution was heated at 160° (oil bath temperature) for 3 hours during which time the ethanol and water which formed, distilled from the reaction. At this point, the reaction was complete by tlc analysis (silica gel with chloroform:methanol, 95:5). The reaction mixture was cooled to below 100° and water (150 ml) was added slowly. The slurry was cooled to 25°, stirred for 15 minutes and the product was collected by filtration, washed with water (100 ml) then with 2-propanol (50 ml) and dried *in vacuo* at 75° to produce 18.0 g (94%) of the title compound as a light tan solid, mp >350° (lit mp [2] 375-377°); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.00 (s, 1H), 7.85 (s, 1H), 7.65 (dd, 1H), 7.30 (m, 1H), 7.10 (m, 1H), 6.70 (m, 1H) and 3.20 ppm (s, 1H, exchanges with deuterium oxide); ir (potassium bromide): 3120, 1760, 1740, 1640, 1550, 1470, 1425, 1320, 1210 cm^{-1}.

Anal. Calcd. for $C_{13}H_7ClN_4O_2$: C, 54.47; H, 2.46; N, 19.54. Found: C, 54.30; H, 2.70; N, 19.28.

4-Chloro-2-[3-(2-furanyl)-1*H*-1,2,4-triazol-5-yl]benzenamine (**8**).

To a well stirred slurry of **7** (180.0 g, 0.63 mole) in ethylene glycol (700 ml) which was heated at 100°, was added a solution of sodium hydroxide (51.2 g, 1.28 moles) in water (126 ml). The slurry was heated at reflux (~130-135°) for 18 hours. The resulting solution was cooled to 27° and the product began to crystallize. Water (700 ml) and 1-octanol (10 ml) were added to the suspension. The *p*H of the suspension was adjusted to 6.5 by the *slow* addition of glacial acetic acid (75 ml). Note: the reaction may foam due to the evolution of carbon dioxide. The slurry was stirred at room temperature for 30 minutes. The product was collected by filtration, washed with water (3 x 500 ml), 2-propanol (500 ml) and dried *in vacuo* at 80° to produce 162.7 g (99%) of the title compound as an off white solid, mp 250-252° (lit mp [2] 246-248°); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.80-8.00 (cp, 2H) and 6.60-7.30 (cp, 7H); ir (potassium bromide): 3475, 3340, 3125,

2925, 2850, 1615, 1550, 1495 cm^{-1}.

Anal. Calcd. for $C_{12}H_9ClN_4O$: C, 55.29; H, 3.48; N, 21.49. Found: C, 54.92; H, 3.27; N, 21.39.

9-Chloro-2-(2-furanyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5-amine (**1**) (Method 1).

To a slurry of **8** (100.0 g, 0.384 mole) in 2-propanol (1 l) was added 50% aqueous cyanamide (50 ml, 0.595 mole) followed by dilute sulfuric acid (25.0 g of concentrated acid dissolved in 30 ml of water) [10]. The slurry was heated at reflux for 8 hours and then cooled to room temperature, and the *p*H adjusted to 6.5 by the addition of 5 ml of 25% aqueous sodium hydroxide. The slurry was cooled to 5° and the product was collected by filtration, washed with 2-propanol (2 x 500 ml), air dried and then dried *in vacuo* at 80° to afford 92.3 g of crude product. The crude product was dissolved in hot (110°) acetic acid (1.5 l) containing decolorizing carbon (1 g). The solution was clarified through a pad of Hyflo Supercel, the filter cake was rinsed with hot acetic acid (100 ml) and the filtrate was allowed to cool to room temperature and stirred for 18 hours. The product was collected by filtration, washed with water (1 l), ethanol (500 ml) then dried *in vacuo* at 80° to produce 72.1 g (66%) of the title compound as a white fluffy powder, mp 271-272° (lit mp [2] 278-279°); ^1H nmr (dimethyl sulfoxide-d_6): δ8.05 (m, 1H), 7.70-7.85 (m, 3H), 7.42-7.65 (m, 2H), 7.20 (d, 1H) and 6.70 ppm (m, 1H); ir (nujol): 3440, 1675, 1608, 1580, 1550, 1525, and 1500 cm^{-1}.

Anal. Calcd. for $C_{13}H_8ClN_5O$: C, 54.66; H, 2.80; N, 24.51. Found: C, 54.51; H, 2.77; N, 24.35.

9-Chloro-2-(2-furanyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5-amine (**1**) (Method 2).

A well stirred suspension of **7** (3.00 g, 0.011 mole) in phenylphosphonic dichloride (75 ml) was heated to 185° for 24 hours. The reaction was cooled to 100° (*ca.*) and the excess phenylphosphonic dichloride was removed by vacuum distillation. The residue was cooled to room temperature, dissolved in methylene chloride and filtered to recover the unreacted **7** (0.26 g). The methylene chloride filtrate, containing **9**, was concentrated to dryness at reduced pressure and the resulting white crystalline, air sensitive solid was dissolved in dry THF (100 ml). The resulting solution was cooled to −5° in an ice-methanol bath and concentrated aqueous ammonia (50 ml of a 28% solution) was slowly added. The reaction mixture was stirred for 2 hours. The resulting thin slurry was diluted with water (100 ml) and the product was isolated by filtration, washed with acetone (50 ml) and dried *in vacuo* at 65° to produce 2.30 g (77%) of the title product, mp 272-273° (lit mp [2] 278-279°). The product was identical as shown by ir, nmr, tlc and mixed melting point with the product obtained from Method 1.

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[10] The concentration was found to be critical. If the *p*H was not 2 or below, all the cyanamide was consumed and the reaction only proceeded to 30% conversion to **1**. The reaction could then be driven to completion by charging additional cyanamide and sulfuric acid.

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