An Unexpected Aminolysis in the Synthesis of 5-Substituted 3-(1*H*-Tetrazol-5-yl)pyrazolo[1,5-*a*]quinazolines

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A synthetic route to 5-substituted 3-(1*H*-tetrazol-5-yl)pyrazolo[1,5-*a*]quinazolines is described. An unexpected displacement of a 4-morpholinyl group from the 5-position of this system occurred during tetrazole formation by the ammonia produced by *in situ* generation of hydrazoic acid from ammonium chloride and sodium azide.

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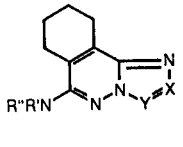
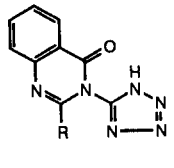
Compounds of biological interest in our laboratories include 7,8,9,10-tetrahydroimidazo[2,1-*a*]phthalazines **1a** [1], 7,8,9,10-tetrahydrotriazolo[3,4-*a*]phthalazines **1b** [2] and their corresponding fully unsaturated analogs [3], and 7,8,9,10-tetrahydrotetrazolo[5,1-*a*]phthalazines **1c** [4], all of which display bronchial-selective smooth muscle relaxant activity. A recent report from our laboratory described [5] another compound series of interest, namely, 3-(1*H*-tetrazol-5-yl)-4(3*H*)-quinazolines **2**, as antiallergic agents. With these structures as precedent, in addition to literature compounds such as the Squibb pyrazoloquinazolines [6] and the Viratek pyrazolopyrimidines [7] which display antiallergic and theophylline-like activities, respectively, it was felt that compounds of general structure **3** would possess structural features necessary to elicit the biological activities of both **1** and **2**.

This report describes the synthesis of compounds of general structure **3**. Also described is an interesting aminolysis reaction which was encountered during the course of this work.



1

a, X = Y = CH
b, X = N, Y = CR
c, X = Y = N



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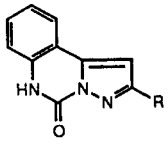
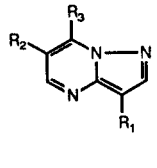
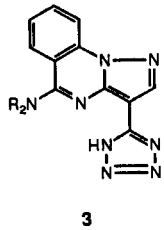


Squibb pyrazoloquinazolines



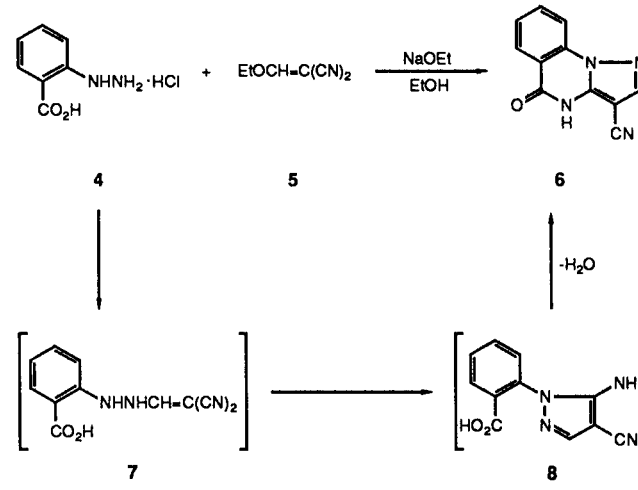
Viratek pyrazolopyrimidines



3

2-Hydrazinobenzoic acid hydrazide (**4**) was envisioned as a potential starting material for 3-(1*H*-tetrazol-5-yl)-pyrazolo[1,5-*a*]quinazolines **3**. Surprisingly, the desired pyrazolo[1,5-*a*]quinazoline skeleton could be constructed from **4** in one step. A mixture of one equivalent each of 2-hydrazinobenzoic acid hydrochloride (**4**), ethoxymethylenemalononitrile (**5**), and sodium ethoxide, when heated in ethanol at reflux for 20 hours gave a 90% yield of 4,5-dihydro-5-oxopyrazolo[1,5-*a*]quinazoline-3-carbonitrile (**6**), as shown in Scheme I [8]. Using these conditions neither **7**, the product of Michael-retro-Michael reaction [9], or the product of subsequent condensation, aminocyanopyrazole **8** [11-13], were isolated.

Scheme I

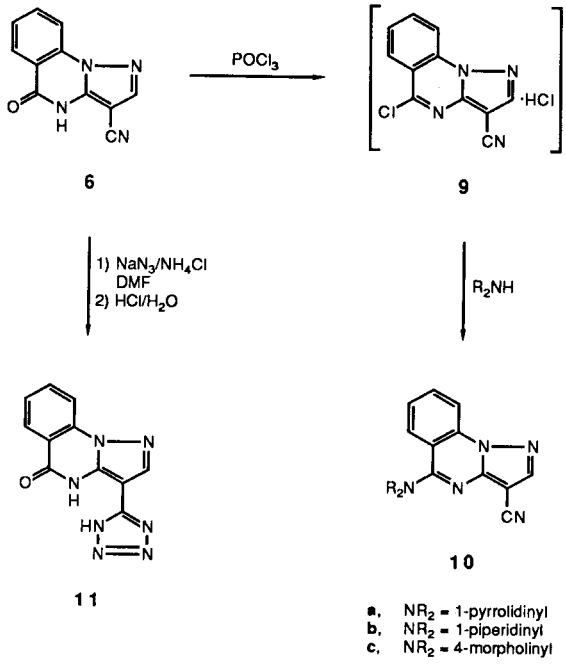


When pyrazoloquinazolinone **6** was treated with excess phosphorus oxychloride at reflux for 14 hours, concentration left a tan solid which may have been hydrochloride salt **9**. Treatment of this intermediate with water (trituration) led to a quantitative recovery of **6**. However, if this material was instead quenched by the slow addition of an excess of a secondary amine, excellent yields of 5-substituted 3-cyanopyrazolo[1,5-*a*]quinazolines were obtained. Thus, the 1-pyrrolidinyl, **10a**, 1-piperidinyl, **10b**, and

4-morpholinyl, **10c** compounds were prepared in respective yields of 97%, 91%, and 79%, as shown in Scheme II.

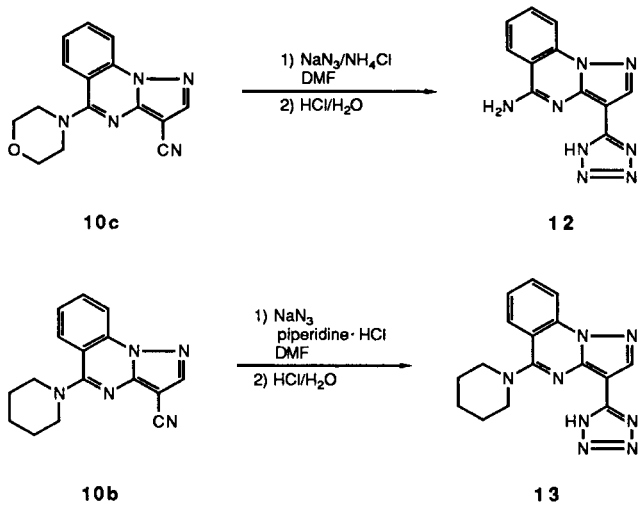
Although cycloaddition of hydrazoic acid to nitrile **6** gave a 99% yield of tetrazole **11**, it was felt that the 5-substituent needed to be incorporated prior to tetrazole formation. However, this efficient reaction suggested that cycloaddition of hydrazoic acid to nitriles **10a-c** would also succeed. The synthesis of aryl tetrazoles in this fashion is very dependent on the electronics of the aryl nitriles [14].

Scheme II



Treatment of **10c** with hydrazoic acid as shown in Scheme III gave an 85% yield of 3-(1*H*-tetrazol-5-yl)-pyrazolo[1,5-*a*]quinazolin-5-amine (**12**), a product arising from cycloaddition of hydrazoic acid plus aminolysis of the 5-substituent. In retrospect, the electrophilic nature of the 5-position which allows this displacement to occur so efficiently, by the limited amount of ammonia present, is understandable in view of the facile hydrolysis of intermediate **9**. However, the ease of aminolysis in this pyrazoloquinazoline system is noteworthy. Perhaps the efficient exchange of morpholine for ammonia occurs because morpholine is the stronger base, and is therefore protonated to a greater extent than is ammonia when it is displaced into the reaction medium. The effective concentration of nucleophilic morpholine is thus decreased, and the equilibrium in the amine exchange reaction favors **12** over the expected morpholinyl analog. It has been shown previously that hydroxide ion will displace morpholine and piperidine from electron deficient systems such as *N*-(2,4-dinitrophenyl)morpholine and *N*-(2,4-dinitrophenyl)piperidine, respectively [15].

Scheme III



Aminolysis was precluded in the cycloaddition of piperidinyl compound **10b** with hydrazoic acid, by employing piperidine hydrochloride rather than ammonium chloride for the *in situ* generation of hydrazoic acid from sodium azide. In this case, **13** was the only tetrazole produced. It is interesting to note that tetrazole formation was decidedly more sluggish with **10b** and **10c** than it was for **6**. The nitrile functionalities in **10b** and **10c** are electron-rich with respect to the nitrile in **6**, due to the electron-donating amino substituents at the 5-positions of **10b** and **10c** [14].

The pharmacology of 3-(1*H*-tetrazol-5-yl)pyrazolo[1,5-*a*]-quinazolines **11**, **12**, and **13** will be described elsewhere.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded using a Perkin-Elmer Model 710B spectrophotometer, nmr spectra with Varian EM-360A and Varian XL-300 spectrometers, and mass spectra with a Finnigan Model 4500 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H, and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, Ohio.

4,5-Dihydro-5-oxopyrazolo[1,5-*a*]quinazoline-3-carbonitrile (**6**).

To a mixture of 18.9 g (0.100 mole) of 2-hydrazinobenzoic acid hydrochloride (**4**) (Eastman), 12.2 g (0.100 mole) of ethoxymethylenemalononitrile (Aldrich), and 200 ml of absolute ethanol was added a solution of sodium ethoxide made from adding 2.3 g (0.10 mole) of sodium metal to 100 ml of absolute ethanol. After 20 hours at reflux, the warm mixture was diluted with 300 ml of water. The resulting tan crystalline solid was collected, washed with ethanol-water, and oven-dried to give 19.0 g (90%) of **6**, mp >300° (2-methoxyethanol); ir (Nujol): 3180-2000 (NH), 2215 (CN), 1660 (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 13.5 (very

broad signal, 1H, NH), 8.32 (s, 1H, C2-H), 8.30-7.40 (m, 4H, C6-H, C7-H, C8-H and C9-H); ms: (chemical ionization, methane) 211 ($M^+ + 1$), 239 ($M^+ + 29$), 251 ($M^+ + 41$).

Anal. Calcd. for $C_{11}H_6N_4O$: C, 62.85; H, 2.88; N, 26.66. Found: C, 62.71; H, 2.66; N, 26.97.

5-(1-Pyrrolidinyl)pyrazolo[1,5-*a*]quinazoline-3-carbonitrile (**10a**).

A mixture of 21.0 g (0.100 mole) of **6** and 500 ml of phosphorus oxychloride was heated at reflux for 18 hours. The resulting solution was cooled and concentrated to leave a tan solid which was cautiously added to 175 ml of pyrrolidine (exothermic). After the addition the mixture was briefly heated to reflux, cooled, and diluted with 500 ml of water. The resulting tan solid was collected, washed with water, and dried to give 25.6 g (97%) of **10a**, mp 279-280° (dimethylformamide-water); ir (potassium bromide): 2240 (C≡N), 1600 (C=N) cm^{-1}; ms: (chemical ionization, methane) 264 ($M^+ + 1$), 292 ($M^+ + 29$), 304 ($M^+ + 41$).

Anal. Calcd. for $C_{15}H_{13}N_5$: C, 68.42; H, 4.98; N, 26.60. Found: C, 68.57; H, 5.10; N, 26.81.

5-(1-Piperidinyl)pyrazolo[1,5-*a*]quinazoline-3-carbonitrile (**10b**).

A mixture of 21.0 g (0.100 mole) of **6** and 500 ml of phosphorus oxychloride was heated at reflux for 84 hours. The brown solution was concentrated to dryness and the resulting tan solid was carefully added to 150 ml of piperidine. The resulting mixture was cooled and treated with water. The resulting tan solid was collected, washed with water, and oven-dried to give 25.2 g (91%) of **10b**, mp 172-174° (dimethylformamide-water); ir (potassium bromide): 2235 (C≡N), 1600 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.37 (s, 1H, C2-H), 8.25 (d, J = 9 Hz, 1H, C6-H), 8.10-7.80 (m, 2H, C8-H and C9-H), 7.70-7.47 (m, 1H, C7-H), 3.80-3.50 (m, 4H, CH_2NCH_2), 1.90-1.50 (m, 6H, $NCH_2CH_2CH_2CH_2$); ms: (70 eV, electron impact) m/e 277 (molecular ion).

Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.26. Found: C, 69.09; H, 5.46; N, 25.23.

5-(4-Morpholinyl)pyrazolo[1,5-*a*]quinazoline-3-carbonitrile (**10c**).

A mixture of 21.0 g (0.100 mole) of **6** and 200 ml of phosphorus oxychloride was heated at reflux for 15 hours. A mixture still prevailed, so an additional 200 ml of phosphorus oxychloride was added and reflux was continued for an additional 24 hours. The mixture was filtered to remove a small amount of undissolved solid and the filtrate was concentrated. The resulting tan solid was carefully added to 100 ml of morpholine. The mixture was diluted with water and the solid was collected, washed with water, and air-dried to give 21.0 g (75%) of **10c**, mp 240-241° (dimethylformamide-water); ir (potassium bromide): 2230 (C≡N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.37 (d, J = 8 Hz, 1H, C9-H), 8.13-7.73 (m, 3H, C6-H, C7-H and C2-H singlet at δ 8.09), 7.63-7.40 (m, 1H, C8-H), 4.00-3.60 (m, 8H, morpholinyl protons); ms: (70 eV, electron impact) m/e 279 (molecular ion).

Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.50; H, 4.69; N, 25.08. Found: C, 64.40; H, 4.43; N, 25.45.

3-(1*H*-Tetrazol-5-yl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**11**).

A mixture of 21.0 g (0.100 mole) of **6**, 13.4 g (0.250 mole) of ammonium chloride, 16.3 g (0.250 mole) of sodium azide, and 200 ml of dimethylformamide was heated at 115° for 17 hours. The mixture was cooled and a brown crystalline solid was collected and air-dried to give 4.00 g of **11**. The filtrate was acidified with 1*N* hydrochloric acid and the resulting white solid was collected and air-dried to give an additional 21.0 g of **11**. Total yield of **11** was 25.0 g (99%), mp >300°; ir (Nujol): 3300-2100 (NH), 1650 (C=O), 1610 (C=N) cm^{-1}; ms: (70 eV, electron impact) m/e 253 (molecular ion).

Anal. Calcd. for $C_{11}H_7N_7O$: C, 52.17; H, 2.79; N, 38.73. Found: C, 52.40; H, 2.99; N, 39.01.

3-(1*H*-Tetrazol-5-yl)pyrazolo[1,5-*a*]quinazolin-5-amine (**12**).

A mixture of 5.22 g (97.5 mmoles) of ammonium chloride, 6.34 g (97.5 mmoles) of sodium azide, 10.9 g (39.0 mmoles) of **10c**, and 80 ml of dimethylformamide was heated at 115° under a nitrogen atmosphere for 18 hours. The mixture was cooled and acidified with 1*N* hydrochloric acid, and the solid was collected. The ir spectrum of this solid (9.59 g) still showed C≡N stretching, so it was resubjected to the original reaction conditions for an additional 47 hours. The reaction was worked up as before to give 8.33 g (85%) of **12**, mp >310° (dimethylformamide-water); ^1H nmr (dimethyl sulfoxide-d_6): δ 8.39 (d, 1H, C6-H), 8.36 (s, 1H, C2-H), 8.29 (d, 1H, C9-H), 7.97 (dt, 1H, C8-H), 7.90 (br s, 1H, tetrazole NH), 7.62 (dt, 1H, C7-H), 3.40 (br s, 2H, NH_2); ms: (chemical ionization, methane) 253 ($M^+ + 1$), 281 ($M^+ + 29$), 293 ($M^+ + 41$); HRMS Calcd. for $C_{11}H_8N_8$: 252.0872; Found: 252.0853.

Anal. Calcd. for $C_{11}H_8N_8$: C, 52.38; H, 3.20. Found: C, 52.37; H, 3.35.

5-(1-Piperidinyl)-3-(1*H*-tetrazol-5-yl)pyrazolo[1,5-*a*]quinazoline (**13**).

A mixture of 2.77 g (10.0 mmoles) of **10b**, 3.04 g (25.0 mmoles) of piperidine hydrochloride, 1.63 g (25.0 mmoles) of sodium azide, and 20 ml of dimethylformamide was heated at 115° for 16 hours. The mixture was cooled, poured into 100 ml of water, and acidified with 1*N* hydrochloric acid. After 1.5 hours of stirring the solid was collected and dried to give 2.53 g of a mixture of **10b** and **13**. This mixture was stirred vigorously with 50 ml of 1*N* sodium hydroxide for 1 hour and the solid was collected, washed with water, and dried to leave 1.09 g (39%) of **10b**, as shown by ir. The filtrate was acidified with 55 ml of 1*N* hydrochloric acid and the resulting solid was collected, washed with water, and air-dried to afford 1.47 g (46%) of **13**, mp 257-259° dec (ethanol); ir (Nujol): 3200-2400 (NH), 1625 (C=N), 1610 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.60 (s, 1H, C2-H), 8.55-7.45 (m, 4H, remaining aromatic), 3.70 (m, 4H, CH_2NCH_2), 1.78 (m, 6H, $NCH_2CH_2CH_2CH_2$); ms: (70 eV, electron impact) m/e 320 (molecular ion).

Anal. Calcd. for $C_{16}H_{16}N_8$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.69; H, 5.09; N, 35.01.

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[8] Compounds related to novel compound **6** have been reported. Thus, treatment of 2-carboxyphenylhydrazine hydrochloride with ethyl

(ethoxymethylene)cyanoacetate gave 4,5-dihydro-5-oxopyrazolo[1,5-*a*]-quinazoline-3-carboxylic acid ethyl ester [9].

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