Development of a New Synthesis of 3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolinone, Sodium Salt *via* an Amidine Intermediate

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A new synthesis of the recently reported 3-(1*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone, sodium salt (**1**, MDL-427), an experimental mediator release inhibitor, was developed from: (1) reaction of 5-aminotetrazole **3** and triethyl orthoformate **6** to give ethyl *N*-(1*H*-tetrazol-5-yl)formimidate **8**, (2) reaction of methyl anthranilate and imidate **8** to give amidine **11**, and (3) treatment of **11** with base to give **1**. Investigation of each of these steps independently led to a significantly more efficient, facile and higher-yielding 1-pot process. A brief examination of anthranilic acid **13** and its salts and derivatives **14** to **17** in this process found them to have dissimilar reactivities. The formation of amidine **11** as an isolable intermediate was unusual, as was its failure to cyclize under standard neutral or acidic conditions. The absolute requirement for base to effect cyclization of **11** appears to be unprecedented.

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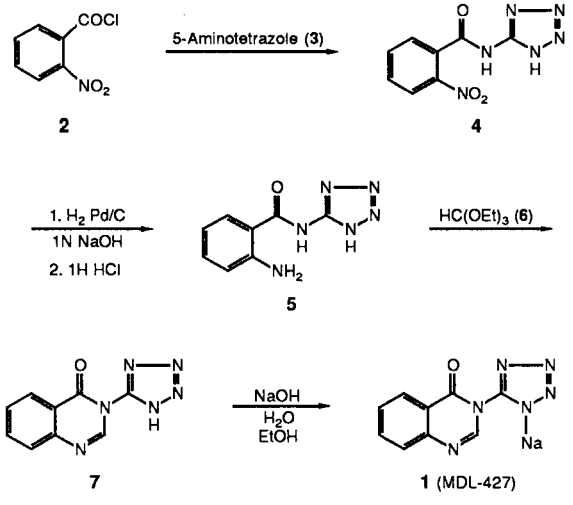
The synthesis and interesting pharmacological properties of 3-(1*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone, sodium salt (**1**, MDL-427) were recently described [1-2]. Compound **1** is an anti-asthma and anti-allergy agent which acts by inhibiting mediator release. The synthesis is shown in Scheme I.

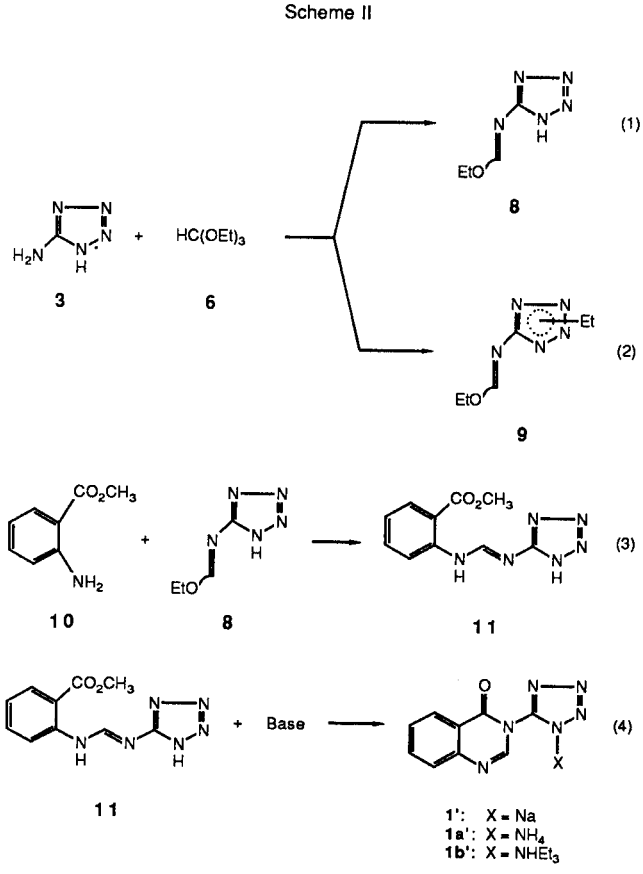
Scheme I



For large scale preparation, an alternate synthesis was desired, in which the nitro-containing materials, **2** and **4**, and hence the subsequent reduction step, might be avoided. With this constraint in mind, synthesis *via* amidine **11** (Scheme II) was explored.

Ethyl *N*-(1*H*-tetrazol-5-yl)formimidate **8** was obtained by reacting 5-aminotetrazole **3** and triethyl orthoformate **6** in hexane and azeotropically removing ethanol (Equation 1,

Scheme II



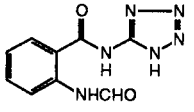
Scheme II). The imidate **8** was fairly insoluble under these conditions and was isolated in 95% yield by filtration directly from the reaction medium. The reaction could also be carried out in carbon tetrachloride or neat triethyl orthoformate at temperatures lower than 100°. In triethyl or-

thoformate at temperatures greater than 100°, mixtures of the *N*-alkylated isomers **9** were obtained (Equation 2, Scheme II). This is an interesting example of the relatively rare circumstances where triethyl orthoformate appears to act as an alkylating agent [3]. It should be noted that on one occasion while distilling **9**, a minor explosion occurred; see Experimental for details.

Studies of the reaction of primary amines with trialkyl orthoformates have shown that by varying conditions, one may obtain either an imidate or the amidine arising from reaction of the starting amine with the intermediate imidate [4]. In particular, catalytic amounts of acid were shown to favor imidate formation. When one equivalent of triethyl orthoformate was used with **3**, conversion was incomplete and other products were observed. However, even with acid present and azeotropic removal of ethanol, complete conversion of 5-aminotetrazole could not be effected in most solvents without the use of excess triethyl orthoformate. In contrast, it was found that only one equivalent of triethyl orthoformate was necessary in *N,N*-dimethylformamide. Since both **3** and **8** were soluble in *N,N*-dimethylformamide, this would be a good solvent for *in situ* preparation of **8**.

Reaction of formimidate **8** with one equivalent of methyl anthranilate **10** in ethyl acetate at room temperature gave 68% yield of crude *N*-(1*H*-tetrazol-5-yl)-*N'*-(2-carbomethoxyphenyl)formamidine **11**. With formamidine **11** in hand, experiments to effect ring closure were undertaken. These were directed initially toward the protonated intermediate **7**, but a considerable variety of neutral and acidic conditions failed [5]. This was quite surprising since *N*-acylation of amidines under similar conditions is well known, is facile even in intermolecular systems and in many cases is faster than *N*-acylation of amines [6]. One would thus expect that in intramolecular cases, such as amidine **11**, the reaction would be even more facile.

By contrast, treatment of amidine **11** with one equivalent of sodium hydroxide at room temperature in 2-propanol effected instantaneous conversion directly to the ring-closed quinazolinone as the desired tetrazolate sodium salt **1**. The reaction mixture was heterogeneous and **1** could be isolated analytically pure in 80-85% yield merely by filtration from the reaction medium. Cyclization of amidine **11** could be effected with other bases and in a variety of solvents [7]. With sodium bases, **1** was generally the sole product (99.9% by hplc), sometimes accompanied by the sodium salt of **12**. This was of no concern, since it had been shown [2] that this byproduct could be converted to **1** upon recrystallization from aqueous 2-propanol.



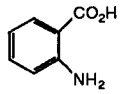
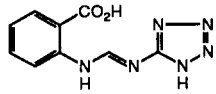
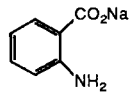
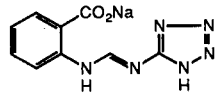
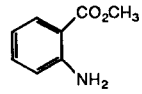
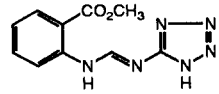
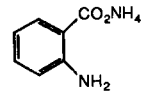
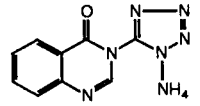
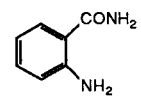
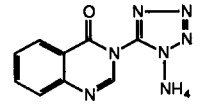
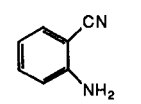
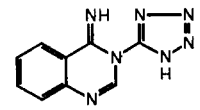
12

Imidate **8** was found to be highly susceptible to hydrolysis and reactions with it generally gave rise to **3** as an undesired byproduct. In view of this, a synthesis of **11** was sought which avoided isolation of **8**. This was accomplished by simultaneous mixing of equimolar amounts of 5-aminotetrazole **3**, triethyl orthoformate **6** and methyl anthranilate **10** in carbon tetrachloride or hexane and refluxing overnight, which effected complete conversion to amidine **11** as the sole product. Filtration directly from the carbon tetrachloride reaction mixture gave analytically pure **11** in 93% yield. Analysis of the filtrate showed only **11**. Hence, the reaction could be deemed quantitative.

The first plan in developing the 1-pot process was to carry out the overall sequence in one vessel as a 2-phase system. It was hoped that synthesis of amidine **11** in carbon

TABLE I

Products from the Reaction of Anthranilates with Imidate 8 in DMF

Anthranilate Starting material	Product	Yield (%)
 **13**	 **18**	61 91 (CCl_4)
 **14**	 **19**	34
 **10**	 **11**	44 89 (CCl_4)
 **15**	 **1a**	9
 **16**	 **1a**	28
 **17**	 **20**	20

tetrachloride or hexane, as just described, could be followed by *in situ* treatment with aqueous base. This would generate **1**, which would partition into the aqueous phase and thus be ready for recrystallization after phase separation. In spite of the success of the 3-component reaction to give amidine **11** in these solvents, difficulties were encountered at the basification stage, and a solvent was then sought for the amidine conversion with which the aqueous base required for ring closure would be miscible.

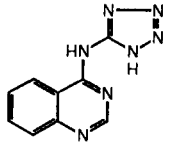
2-Propanol was found to be such a solvent. Reaction of **3**, **6** and **10** to give amidine **11** was complete in 24 hours at room temperature or in 1 hour upon heating at reflux. The mixture was heterogeneous at room temperature and the product could be isolated in high purity simply by filtration from the reaction medium. Analysis of the filtrate showed only amidine **11**. Hence, here also the reaction could be deemed essentially quantitative. Addition of small volumes of water to the mixture prior to base addition was required to give smooth conversion to the desired **1**. Optimized conditions for the 1-pot process were thus found to be: simultaneous mixing of 5-aminotetrazole **3**, triethyl orthoformate **6** and methyl anthranilate **10** in equivalent amounts in 2-propanol, heating at 70° for 1-2 hours, cooling to room temperature and adding first, water, then base [8]. The amorphous **1** could be filtered directly from the medium at this point and was generally found to be greater than 99.9% pure by hplc. Alternatively, the mixture could be heated to 75° to effect dissolution. Addition of 2-propanol followed by cooling to room temperature gave recrystallized **1** as a hydrate in 80-85% yield of greater than 99.9% pure **1**. The degree of hydration varied partly as a function of the rate of cooling.

During the course of this work, a cursory probe of the behavior of anthranilic acid **13**, its sodium and ammonium salts **14** and **15**, anthranilamide **16** and anthranilonitrile **17** (Table I) was undertaken to explore their feasibility as alternate starting materials for synthesis of **1** in the method described above. Since preliminary results indicated that the anthranilate esters were most suitable for this purpose, yields and reaction conditions were not optimized in this part of the study.

In contrast with anthranilate ester **10**, simultaneous mixing of each of **13** through **17** with 5-aminotetrazole **3** and triethyl orthoformate **6** in hexane or carbon tetrachloride led to mixtures of products. However, when **13** through **17** were each added to a hot *N,N*-dimethylformamide solution of the imidate **8** preformed *in situ*, the reactions generally proceeded to a single product. With concentrations of 1-2*M*, the products precipitated from the reaction media in varying amounts and were collected by filtration and analyzed. An exception was amidine **18**, which remained in solution upon cooling. Most compounds in this study had appreciable solubility in *N,N*-dimethylformamide, and accordingly, the yields of these precipitated products were low. Filtrate aliquots were concentrated for analysis and in general showed a sole or predominant compound identical with that which precipitated from the reaction medium. This suggested that although recovery was not optimized, these conditions gave good conversion to the products identified.

Table I lists the compounds isolated from these reactions and shows comparative yield data of methyl anthranilate **10** and anthranilic acid **13** in carbon tetrachloride. The acid **13** and its sodium salt **14** gave the respective amidine products, **18** and **19** [9]. By contrast, ammonium anthranilate **15** underwent ring closure directly to the quinazolinone tetrazolate ammonium salt **1a**, as did anthranilamide **16**. Anthranilonitrile **17** led initially to iminoquinazolinone **20**, which underwent rearrangement to *N*-(1*H*-tetrazol-5-yl)-*N*-(quinazolin-4-yl)amine **21** on longer reaction or heating. For completeness, the ester **10** was submitted to these conditions. It gave the sole product amidine **11**, as it had in the 3-component reaction.

It was felt that quinazolinone **1a** was most likely arising through an amidine-type intermediate such as **22**, and that this intermediate should be accessible from acid amidine **18**. However, attempts to effect the transformation of **18** to **1a** failed.



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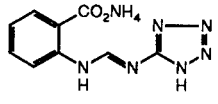
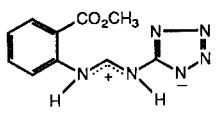
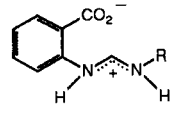


22

The appearance of the amidines **11**, **18** and **19** is highly unusual. All reported reactions of acid and ester anthranilates with imidates give quinazolinones directly, frequently under extremely mild conditions [11-19]. Amidines as intermediates which can undergo cyclization have been postulated [11] and sought without success [16] in these reactions. To the best of our knowledge, there is only one other case where an amidine was observed and isolated [19]. Furthermore, in that case, cyclization of the amidine to the quinazolinone was accomplished merely by heating in ethanol, a property not shared by any of the amidines **11**, **18** or **19**. Thus, the ring closed products observed with ammonium anthranilate **15**, anthranilamide **16** and anthranilonitrile **17** are quite consistent with precedent. The appearance and reactivity of the amidines **11**, **18** and **19** departs from precedent. In particular, the extreme resistance of acid amidine **18** to ring closure is anomalous and the absolute requirement for base to effect the ring closure of ester amidine **11** is without precedent.



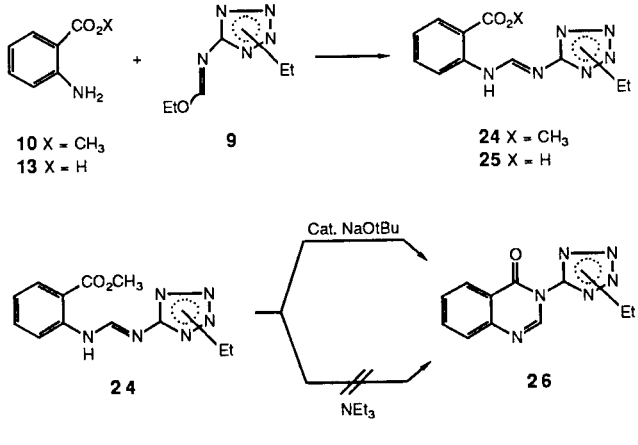
11a



23
(R = alkyl or aryl)

We could find no satisfactory explanation for the reactivity differences of these anthranilate derivatives. In seeking one, we noted that some properties of the ester amidine **11** were quite similar to those of amidinium carboxylates [20], and we explored briefly the possibility that **11** might exist as an amidinium tetrazolate **11a** which could require deprotonation of the amidinium moiety for ring closure. Amidinium carboxylates **23** were first identified as intermediates in the formation of quinazolinones from primary amines and benzoxazinones [20]. They were extremely insoluble under the reaction conditions and were found to cyclize to quinazolinones under very mild basic conditions, as does **11**. They also cyclize in toluene, a property not shared by amidine **11**. A broad signal between 3100-2300 cm^{-1} in the ir spectrum of **11** is consistent with a zwitterion, but the carbonyl region is complicated due to the presence of the tetrazole. Proton nmr spectra recorded at $-30°$ in deuterated *N,N*-dimethylformamide show signals consistent with the presence of at least two isomeric species. As yet, there is no obvious evidence in the nmr spectra for a zwitterionic species. A more detailed analysis of ester amidine **11** by nmr is under way.

Scheme III



Whether zwitterionic or not, the acidic tetrazole proton does appear to influence the ring-closure requirements. Reaction of ester anthranilate **10** and imidate **9** gave amidine **24** (Scheme III). This amidine cannot be zwitterionic since it lacks the acidic tetrazole proton. Treatment of **24** with catalytic sodium *t*-butoxide led to instantaneous ring closure at 0°. This finding was quite consistent with the behavior observed for ester amidine **11**. However, **25** failed to undergo ring-closure on treatment with triethylamine, even when in excess, and this is contrary to the behavior of ester amidine **11** where ring-closure was facile with either ammonium hydroxide or triethylamine. In addition, the acid amidine **25**, which is most nearly comparable to the amidinium carboxylates, behaved as its *N*-unsubstituted analogue **18** and failed to ring-close under any conditions tried. An understanding of these behavioral differences awaits further investigation.

In summary, we have developed a new, highly efficient 1-pot synthesis of 3-(1*H*-tetrazol-5-yl)-4(3*H*)-quinazolin-4-one, sodium salt (**1**, MDL-427) from 5-aminotetrazole **3**, triethyl orthoformate **6** and methyl anthranilate **10**. The reaction proceeds through *N*-(1*H*-tetrazol-5-yl)-*N'*-(2-carbomethoxyphenyl)formamidine **11**, an isolable intermediate. While amidines have frequently been postulated as intermediates in reactions of anthranilates with imidates, this appears to be only the second case in which an amidine is observed. The absolute requirement for base to effect the cyclization of **11** is unprecedented. A probe of the chemistry of anthranilic acid **13** and some of its salts and derivatives under similar conditions revealed that these structurally similar materials have dissimilar reactivities.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 283 spectrophotometer, and nmr spectra on IBM NR80 and Varian XL-200 spectrometers. Chemical shifts are quoted in ppm downfield from tetramethylsilane as an internal standard.

3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolin-4-one, Sodium Salt (**1**, MDL-427) (By 1-Pot, 3-Component Reaction).

A mixture of 10.0 g (0.117 mole) of 5-aminotetrazole, 18.2 g (0.123 mole) of triethyl orthoformate and 18.0 g (0.119 mole) methyl anthranilate in 90 ml of 2-propanol was heated with stirring at 70° for 1.5 hours under nitrogen. The mixture was then cooled to ambient and treated with 23 ml of water. The mixture was stirred for 15 minutes and then treated with 24 ml of 5*N* sodium hydroxide (0.117 mole). After stirring for 15 minutes at ambient, the mixture was brought to reflux and treated with 180 ml 2-propanol at a rate to keep the temperature above 70°, then stirred at reflux for 1 hour. The mixture was then cooled to ambient temperature with stirring and crystallizaton occurred. The crystals were collected by filtration, washed with 2-propanol and vacuum-oven dried to give 27 g (80%) of **1** as a trihydrate. (The degree of hydration varied somewhat from experiment to experiment), mp 300°; ir (potassium bromide): 3600-2900 (spikes at 3600 and 3400), 1680, 1650, 1610 (s), 1560 (w), 1485 (m), 1470, 1450 (s), 1410 (m), 1325 (s) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.28 (s, 1H, C2-H), 8.22 (d, 1H, J = 7.82), 7.91-7.63 (m, 3H, quinazolinone), 3.51 (s, 6H, water).

Anal. Calcd. for $C_9H_5N_6ONa\cdot 3H_2O$: C, 37.24; H, 3.82; N, 28.96. Found: C, 37.19; H, 3.72; N, 29.06.

3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolin-4-one, Ammonium Salt **1a** from *N*-(1*H*-Tetrazol-5-yl)-*N*-(2-carbomethoxyphenyl)formamidine **11**.

A slurry of 3.0 g (12.1 mmoles) of **11** in 10 ml of methanol was stirred at room temperature and treated with 0.8 ml (12.2 mmoles) of concentrated ammonium hydroxide. The mixture was stirred for 1 hour. The white solid was then collected by filtration, washed with aqueous 2-propanol, and vacuum-oven dried to give 2.51 g (89%) of **1a** as white needles identical with **1a** prepared from **16** described below.

3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolin-4-one, Ammonium Salt **1a** from Ammonium Anthranilate **15**.

A solution of 10.0 g (0.117 mole) of 5-aminotetrazole in 50 ml of *N,N*-dimethylformamide was heated to 100° and treated with 17.3 g (0.117 mole) of triethyl orthoformate under nitrogen. The mixture was stirred at 100° for 2 hours, then treated with a solution of 17.6 g (0.114 mole) of ammonium anthranilate (prepared from 16.0 g (0.114 mole) of anthranilic acid and 7.8 ml (0.114 mole) of concentrated ammonium hydroxide in methanol) in 40 ml of *N,N*-dimethylformamide. After stirring at 100° for 1 hour, the mixture was cooled to room temperature, then further cooled with an ice bath to induce crystallization. White crystals were collected by filtration, washed with *N,N*-dimethylformamide, then carbon tetrachloride, and vacuum-oven dried to give 2.42 g (9%) of **1a** identical with **1a** prepared from **16** described below.

3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolin-4-one, Ammonium Salt **1a** from Anthranilamide **16**.

A mixture of 10.0 g (0.117 mole) of 5-aminotetrazole in 100 ml of *N,N*-dimethylformamide was heated to 90° and treated with 21.3 g (0.144 mole) of triethyl orthoformate and stirred for 3 hours under nitrogen. A solution of 16.0 g (0.117 mole) of anthranilamide in 20 ml of *N,N*-dimethylformamide was then added to the mixture. The mixture was cooled to 85°, heated at 85° for 1 hour, then cooled to room temperature. White crystals were collected by filtration, washed with cold *N,N*-dimethylformamide, then vacuum-oven dried to give 7.6 g (28%) of **1a**, mp 235-237°; ir (potassium bromide): 3220, 2960, 2940, 2860, 1680, 1620, 1485, 1470, 1440, 1420, 1330, 1270 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.21 and 8.18 (s overlying br d, 2H, C2-H and C5-H, J = 7.45), 7.73 (m, 3H, C6/7/8-H), 7.25 (br s, 3H, NH).

Anal. Calcd. for $C_9H_9N_7O$: C, 46.75; H, 3.92; N, 42.41. Found: C, 46.61; H, 3.99; N, 42.59.

3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolin-4-one, Triethylammonium Salt **1b**.

A slurry of 5.0 g (20 mmoles) of **11** in 25 ml of 2-propanol was stirred at room temperature and treated with 2.0 g (20 mmoles) of triethylamine. The mixture was heated at reflux for 24 hours, then cooled to room temperature. The white crystals were filtered, washed with 2-propanol and dried to give 0.6 g (10%) of **1b**, mp 112-115°. (A further 3.4 g (53%) of crude **1b** was obtained by evaporation of the filtrate *in vacuo* and trituration of the residue with carbon tetrachloride); ir (potasium bromide): 3080, 3050, 2930, 2860, 2650, 2500, 1690, 1610, 1470, 1460, 1420, 1325, 1270, 1250, 1190 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.22 and 8.17 (s overlying br d, 2H, C2-H, C5-H), 7.73 (m, 3H, C6/7/8-H), 3.11 (q, 2H, CH_2, J = 7.71), 1.22 (t, 3H, CH_3, J = 7.71).

Anal. Calcd. for $C_{15}H_{21}N_7O$: C, 56.70; H, 6.62; N, 31.23. Found: C, 57.10; H, 6.71; N, 31.09.

Ethyl *N*-(1*H*-Tetrazol-5-yl)formimidate **8**.

A mixture of 50.0 g (0.587 mole) of 5-aminotetrazole and 347 g (2.34 mole) of triethyl orthoformate in 500 ml of hexane was heated in an apparatus with a take-off distillation head. The mixture was heated and distillate collected until proton nmr of aliquots filtered from the mixture showed no further aminotetrazole. This took approximately 6 hours. Hexane was replenished in the reaction vessel as necessary. The mixture was then cooled to room temperature. Fine white crystals were collected by filtration, washed with hexane and vacuum-oven dried to give 78.7 g (95%) of **8**, mp 124°, resolidifies, re-melts at 170°; ir (potassium bromide): 3300-2200 (s with minima at 2900, 2700, 2600 and 2500), 1620, 1570 (shoulder), 1450, 1400, 1380, 1325, 1260, 1230 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.7 (s, 1H, methine), 4.4 (q, 2H, OCH_2, J = 6.7), 1.3 (t, 3H, CH_3, J = 6.7); ei hrms: Calcd. for $C_4H_7N_5O$: 141.0650. Found: 141.0648.

Ethyl *N*-(*N*-Ethyltetrazol-5-yl)formimidate **9**.

A slurry of 30.0 g (0.353 mole) of 5-aminotetrazole in 300 ml (1.8 moles) of triethyl orthoformate was heated under nitrogen at reflux (76°) for 4 hours. Distillate was then collected until the head temperature reached 120°. The mixture was cooled and distillation was continued under aspirator pressure until most of the excess triethyl orthoformate was removed. The red residue was Kugelrohr distilled. (**CAUTION**. On two occasions, the residue was distilled under aspirator pressure in conventional distilling apparatus. On one of these occasions, the reaction went out of control. Approximately 30 minutes after excess triethyl orthoformate had distilled and the pot temperature had been raised, a popping sound was heard and clouds of white smoke emanated from space between the flask and the condenser which had become separated. The head temperature was 130° and the pot temperature was 160°. The residual material in the reaction flask had become a black tacky solid, which could not be stirred). Three fractions were collected between 85-95° (0.1 mm Hg). The second and third fractions gave 12.2 g and 14.2 g (44%) of **9**, each consisting of an approximately 95:5 ratio of isomers; ir (carbon tetrachloride): 3000, 1640 (s), 1510, 1495 (s), 1475, 1450, 1400, 1350, 1320, 1310, 1230 (s) cm^{-1}; ^1H nmr (chloroform-d_6): δ 8.29 (s, 1H, imino methine), 4.32 (q, 2H, CH_2, J = 7.34), 4.16 (q, 2H, CH_2, J = 7.17), 1.34 (t, 3H, CH_3, J = 7.34), 1.12 (t, 3H, CH_3, J = 7.10).

Anal. Calcd. for $C_6H_{11}N_5O$: C, 42.59; H, 6.55; N, 41.39. Found: C, 42.17; H, 6.32; N, 41.10.

N-(1*H*-Tetrazol-5-yl)-*N'*-(2-carbomethoxyphenyl)formamidine **11**.

A mixture of 71.3 g (0.481 mole) of triethyl orthoformate, 12.2 g (0.118 mole) of 5-aminotetrazole monohydrate and 22.3 g (0.146 mole) of methyl anthranilate in 100 ml of carbon tetrachloride was refluxed for 16 hours under nitrogen. The mixture was cooled to room temperature. The white crystals were collected by filtration, washed with carbon tetrachloride and vacuum-oven dried to give 27.0 g (93%) of **11**, mp 200°; ir (potassium bromide): 3250 (w), 3150-2300 (with many spikes), 1700 (m), 1630, 1600, 1580 (s), 1510, 1460, 1440, 1400, 1390 (m), 1320, 1270 (s) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 15.40, 12.20, 10.75 (br, 1H, NH), 9.20-8.10 (br with maxima at 9.0 and 8.4, 2H), 8.0 (d, 1H, C6-H, J = 7.8), 7.68 (t, 1H, C4-H, J = 7.4, 8.1), 7.26 (t, 1H, C5-H, J = 7.6, 7.4).

Anal. Calcd. for $C_{10}H_{10}N_6O_2$: C, 48.78; H, 4.09; N, 34.13. Found: C, 48.40; H, 3.82; N, 34.44.

Compound **11** was also prepared in *N,N*-dimethylformamide according to the procedure described above for preparation of **1a** from **15**. Using 10.0 g (0.117 mole) of 5-aminotetrazole and 19.5 ml (0.117 mole) of triethyl orthoformate in 50 ml of *N,N*-dimethylformamide to which a solution of 16.95 g (0.117 mole) of methyl anthranilate in 15 ml of *N,N*-dimethylformamide was added, there was obtained 12.64 g (44%) of **11**, identical with that described above.

N-(1*H*-Tetrazol-5-yl)-*N'*-(2-carboxyphenyl)formamidine **18**.

A mixture of 10.0 g (0.117 mole) of 5-aminotetrazole and 35.0 g (0.234 mole) of triethyl orthoformate in 300 ml of carbon tetrachloride was heated with stirring under nitrogen in apparatus with a take-off distilling head until distillate appeared. Distillation was continued for approximately 5 hours, replenishing carbon tetrachloride as necessary until complete conversion of 5-aminotetrazole was noted in the proton nmr. A warm solution of 16.1 g (0.117 mole) of anthranilic acid in 35 ml 2-propanol was added to the hot mixture. The mixture was stirred for two hours, then cooled to ambient. The fine white crystals were collected by filtration, washed with 2-propanol and dried to give 24.9 g (91%) of **18**. An analytical sample was recrystallized from hot *N,N*-dimethylformamide, mp 210°; ir (potassium bromide): 3450, 3080, 2960, 2860, 1725-1625, 1600, 1500, 1420, 1390, 1275 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 14.0-10.5 (br, 1.5H), 9.0 (br s, 1H), 8.40 (br, 1H), 8.04 (d, 1H, C6-H, J = 6.72), 7.61 (dt, 1H, C5-H, J = 2.56, 6.72), 7.18 (t, 1H, C4-H, J = 8.0).

Anal. Calcd. for $C_9H_8N_6O_2$: C, 46.55; H, 3.47; N, 36.17. Found: C, 46.15; H, 3.45; N, 35.79.

Compound **18** was also prepared in *N,N*-dimethylformamide as described above for preparation of **1a** from **15**. Using 20.0 g (0.235 mole) of 5-aminotetrazole and 39 ml (0.235 mole) of triethyl orthoformate in 100 ml of *N,N*-dimethylformamide to which 32.3 g (0.235 mole) of anthranilic acid was added, there was obtained 33.3 g (61%) of **18**.

N-(1*H*-Tetrazol-5-yl)-*N'*-(2-carboxyphenyl)formamidine, Sodium Salt **19**.

A solution of 5.2 g (61.2 mmoles) of 5-aminotetrazole and 9.1 g (61.4 mmoles) of triethyl orthoformate in 20 ml of *N,N*-dimethylformamide was heated to 100°. To this mixture was added a 1.6 *M* solution of sodium anthranilate in *N,N*-dimethylformamide. (The sodium anthranilate was prepared by adding 23 ml of 21 wt% sodium ethoxide in ethanol (62.0 mmoles) to a solution of 8.40 g (62.0 mmoles) of anthranilic acid in 10 ml of *N,N*-dimethylformamide, concentrating the mixture and re-dissolving the residue in 40 ml of *N,N*-dimethylformamide.) The mixture was heated at 100° for 30 minutes, then cooled to room temperature and stirred overnight. The homogeneous mixture was concentrated *in vacuo*. The oily residue was stirred with acetone, which gave an off-white solid. This was collected by filtration, washed with acetone and dried to give 5.40 g (34%) of crude **19**. Spectra of this material were identical in essentials with those of **19** prepared from **18** described below.

N-(1*H*-Tetrazol-5-yl)-*N'*-(2-carboxyphenyl)formamidine, Sodium Salt **19**, from **18**.

A slurry of 0.5 g (2.2 mmoles) of **18** in 10 ml of 2-propanol was stirred at room temperature under nitrogen as 0.8 ml (2.2 mmoles) of a solution (21 weight %) of sodium ethoxide in ethanol was added. The mixture remained heterogeneous. After stirring at room temperature for 30 minutes, the solid was collected by filtration, washed with 2-propanol and vacuum-oven dried to give 0.46 g (84%) of **19** as a white powder, mp >290°; ir (potassium bromide): 3600-2600, 1700-1530 (with minimum at 1600), 1470, 1380, 1280 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.9 (br, 2/3 H, NH), 9.80 (br, 2-1/3 H, NH and amidine methine), 8.10 (d, 2H, J = 7.57, C3/6-H), 7.36 (t, 1H, J = 7.76, 7.62, C4-H), 7.01 (t, 1H, J = 7.57, 7.52, C5-H).

Anal. Calcd. for $C_9H_7N_6O_3Na \cdot H_2O$: C, 39.71; H, 3.33; N, 30.88. Found: C, 39.81; H, 2.96; N, 30.18.

3-(1*H*-Tetrazol-5-yl)-4(3*H*)-iminoquinazolinone **20**.

A solution of 20.0 g (0.235 mole) of 5-aminotetrazole and 39 ml (0.234 mole) of triethyl orthoformate in 125 ml of *N,N*-dimethylformamide was heated at 110° for 1.5 hours under nitrogen. A solution of 28.6 g (0.234 mole) of anthranilonitrile in 20 ml of *N,N*-dimethylformamide was added to the mixture. The oil bath used for heating was immediately removed. When the temperature had dropped to 40°, the off-white crystals were collected by filtration, washed with with *N,N*-dimethylformamide and dried to give 8.5 g (17%) of **20**, mp 280°; ir (potassium bromide): 3100, 2950, 2860, 1700, 1640, 1620, 1590, 1560, 1475, 1430, 1410, 1385, 1330, 1260 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 9.28 (s, 1H, C2-H), 8.72 (d, 1H, C5-H, J = 7.98), 7.97 (m, 3H, C6/7/8-H).

Anal. Calcd. for $C_9H_7N_7$: C, 50.70; H, 3.32; N, 45.99. Found: C, 50.63; H, 3.22; N, 45.91.

N-(1*H*-Tetrazol-5-yl)-*N*-(quinazolin-4-yl)amine **21**.

A mixture of 16.0 g (0.188 mole) of 5-aminotetrazole and 32 ml (0.192 mole) of triethyl orthoformate in 150 ml of *N,N*-dimethylformamide was heated at 95° for 1.5 hours under nitrogen. A solution of 23.0 g (0.188 mole) of anthranilonitrile in 20 ml of *N,N*-dimethylformamide was added to the hot mixture, which was then cooled to room temperature. The mixture was heated at 110° for 24 hours, then cooled to room temperature. Crystals were collected by filtration, washed with *N,N*-dimethylformamide then 2-propanol and vacuum-oven dried to give 11.6 g (29%) of **21** as flocculent white crystals, mp 315°; ir (potassium bromide): 3450 (w), 3300-2200 with minima at 3050 and 2960, 1630, 1610, 1580, 1550, 1500, 1430, 1380, 1350, 1310, 1260 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.50 (s overlying d, 2H, C2-H and C5-H, J = 7.48), 7.73 (m, 3H, C6/7/8-H).

Anal. Calcd. for $C_9H_7N_7$: C, 50.70; H, 3.32; N, 45.99. Found: C, 50.55; H,3.40; N, 46.10.

N-(*N*-Ethyltetrazol-5-yl)-*N'*-(2-carbomethoxyphenyl)formamidine **24**.

A solution of 7.1 g (42.2 mmoles) of ethyl *N*-(*N*-ethyltetrazol-5-yl)formimidate **9** in 3 ml of ethyl acetate was stirred at room temperature as a solution of 6.4 g (42 mmoles) of methyl anthranilate in 1 ml of ethyl acetate was added followed by 3 drops of formic acid. The mixture was stirred for 18 hours at room temperature. The solid was collected by filtration and recrystallized from ethyl acetate/hexane to give 5.8 g (50%) of **24**, mp 89-90°; ir (potasium bromide): 3450 (w), 3280, 1700, 1635, 1610, 1490, 1460, 1450, 1325, 1315, 1295, 1260 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 12.0 and 10.63 (br, 1H, NH), 8.96 (br, 1H, amidine methine), 7.27 (br, 1H, C3-H), 6.93 (dd, 1H, C6-H, J = 2.40, 7.74), 6.60 (dt, 1H, C5-H, J = 2.40, 7.74), 6.13 (t, 1H, C4-H, J = 7.74), 4.60 (q, 2H, CH_2, J = 6.67), 3.86 (s, 3H, OCH_3), 1.47 (t, 3H, CH_3, J = 6.67).

Anal. Calcd. for $C_{12}H_{14}N_6O_2$: C, 52.55; H, 5.24; N, 30.64. Found: C, 52.17; H, 5.13; N, 30.76.

N-(*N*-Ethyltetrazol-5-yl)-*N'*-(2-carboxyphenyl)formamidine **25**.

A solution of 0.41 g (3 mmoles) of anthranilic acid and 0.5 g (3 mmoles) of **9** was stirred in 5 ml of ethyl acetate at room temperature under nitrogen. A solid precipitated within 5 minutes. After 20 minutes, the solid was collected by filtration, washed with 2-propanol and vacuum-oven dried to give 0.30 g (39%) of **25** as a white powder, mp 151-153°; ir (potassium bromide): 3150-2650 and 2650-2100 (w), 1680, 1625 (s), 1595, 1480, 1315, 1255 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 14.5-10.5 (br, 2H, NH and OH), 9.06-7.63 (complex, 4H, 3 aromatic and amidine methine), 7.21 (t, 1H, J = 7.6, phenyl), 4.64 (q, 2H, J = 6.8, CH_2), 1.56 (t, 3H, J = 6.8, CH_3).

Anal. Calcd. for $C_{11}H_{12}N_6O_2$: C, 50.76; H, 4.65; N, 32.29. Found: C, 50.44; H, 4.73; N, 32.00.

N-(*N*-Ethyltetrazol-5-yl)-4(3*H*)-quinazolinone **26** from 3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolinone.

A slurry of 1.07 g (22.4 mmoles) of sodium hydride as a 50% oil dispersion was washed twice with 10 ml volumes of toluene then stirred with 20 ml of dry THF under nitrogen. To this was added 4.0 g (18.7 mmoles) of **7** [2] as a solid and the mixture was stirred at room temperature for 2 hours. The heterogeneous mixture was then treated with 6 ml (74.8 mmoles) of ethyl iodide and stirred for a further 4 hours at room temperature. The solids were dissolved by addition of 30 ml of *N,N*-dimethylformamide. The mixture was heated at 60° for 48 hours, then cooled to room temperature and poured onto ice. A yellow solid formed, was collected by filtration and vacuum-oven dried to give 2.82 g (62%) of crude **26**. An analytical sample was obtained as fine white needles by recrystallization from aqueous *N,N*-dimethylformamide, mp 109-110°; ir (potassium bromide): 3000 (w), 2880, 1670, 1590, 1500, 1450, 1400, 1370, 1300, 1250 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.50 (s, 1H, C2-H), 8.26 (br d, 1H, C5-H, J = 7.98), 7.83 (m, 3H, C6/7/8-H), 4.83 (q, 2H, CH_2, J = 6.70), 1.62 (t, 3H, CH_3, J = 6.70).

Anal. Calcd. for $C_{11}H_{10}N_6O$: C, 54.54; H, 4.16; N, 34.69. Found: C, 54.43; H, 4.15; N, 34.62.

3-(*N*-Ethyltetrazol-5-yl)-4(3*H*)-quinazolinone **26** from *N*-(*N*-Ethyltetrazol-5-yl)-*N*-(carbomethoxyphenyl)formamidine **24**.

A mixture of 0.57 g (2.1 mmoles) of **24** was stirred in 10 ml of 2-propanol and cooled to 0°. A solution of 10 mg (0.1 mmole) of sodium *t*-butoxide in 1 ml of *N,N*-dimethylformamide was added to the mixture. Tlc (1:1 ethyl acetate/hexane, silica gel) of an aliquot immediately after base addition showed conversion complete. The solvent was evaporated *in vacuo* from the bulk of the reaction mixture to give 0.3 g (57%) of **26** whose spectra were identical with those described above.

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REFERENCES AND NOTES

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[1] N. P. Peet and S. Sunder, U. S. Patent 4,419,357 (Dec. 6, 1983).

[2] N. P. Peet, L. E. Baugh, S. Sunder, J. E. Lewis, E. H. Matthews, E. E. Olberding and D. Shah, *J. Med. Chem.*, **29**, 2403 (1986).

[3] R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives", Academic Press, New York, 1970, pp 192-194.

[4] R. M. Roberts and R. H. DeWolfe, *J. Am. Chem. Soc.*, **76**, 2411 (1954).

[5] From refluxing ethyl acetate for 4 days, Dowanol PM (glycol ether products) at 100° for 4 days, refluxing toluene (in a Dean Stark apparatus for removal of solvent) for 24 hours, or from slow heating in diphenyl ether at 190°, the sole material found was unreacted amidine **11**. Neither **11** nor **7** were recovered from diphenyl ether upon brief heating at 240°. Heating in *N,N*-dimethylformamide at 140° for 24 hours gave products of amidine bond cleavage. When fusion was attempted by brief immersion of **11** in an oil bath between 200-210°, spectra showed no **7** or **11** present. Proton nmr of spectra of aliquots concentrated from acidic media (catalytic hydrochloric acid, Dowanol PM, 80°; catalytic *p*-toluenesulfonic acid, refluxing toluene) showed no **11** or **7**.

[6] R. H. De Wolfe in "The Chemistry of Amidines and Imidates", S. Patai, ed, John Wiley & Sons, NY 1975, p 373.

[7] Other bases employed were sodium methoxide, ammonium hydroxide and triethylamine. Other solvents found satisfactory were toluene, *N,N*-dimethylformamide and methanol.

[8] A. P. Vinogradoff, U. S. Patent 4,644,065 (Feb. 17, 1987).

[9] Amidine **19** is shown as the sodium carboxylate salt, but since the p*Ka*'s of the tetrazolyl and carboxyl functions are very similar, **19** more likely exists as a mixture of carboxylate and tetrazolate salts.

[10] By treatment of **18** with one equivalent of ammonium hydroxide in methanol, methanol/*N,N*-dimethylformamide or *N,N*-dimethylformamide alone, anion formation occurred, as shown by differences in the nmr spectra, but was followed by loss of the amidine bond. This was slow in methanol and almost instantaneous in *N,N*-dimethylformamide in which **18** was most soluble. The same behaviour was found with anhydrous ammonia continuously bubbled through a heterogeneous mixture of **18** in tetrahydrofuran. Treatment of acid amidine **18** with sodium bases also failed to give ring closure.

[11] W. Ried and J. Valentin, *Ann. Chem.*, **707**, 250 (1967).

[12] H. A. Burch, *J. Med. Chem.*, **9**, 408 (1966).

[13] W. Ried and W. Stephan, *Chem. Ber.*, **95**, 3042 (1962).

[14] C. Runti, C. Nisi, and L. Sindellari, *Ann. Chim.* (Rome), **51**, 719 (1961).

[15] S. Petersen and E. Tietze, *Ann. Chem.*, **623**, 166 (1959).

[16] R. Andrisano and G. Modena, *Gazz. Chim. Ital.*, **80**, 321 (1950).

[17] S. Rajappa and B. G. Advani, *Tetrahedron*, **29**, 1299 (1973).

[18] H. Finger and L. Schupp, *J. Prakt. Chem.*, **74**, 154 (1906).

[19] A. Singh, A. S. Uppal, T. K. Bindal, and M. Singh, *Indian J. Chem.*, **19B**, 37 (1980).

[20] L. A. Errede, *J. Org. Chem.*, **41**, 1763 (1976).