Sulfonylcarbamimidic Azides from Sulfonyl Chlorides and 5-Aminotetrazole

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Treatment of *o*-nitrobenzenesulfonyl chloride (**3**) with 5-aminotetrazole (5-AT) gave [(2-nitrophenyl)sulfonyl]carbamimidic azide (**6**), a ring-opened isomer of the expected *N*-(1*H*-tetrazol-5-yl)-2-nitrobenzenesulfonamide (**4**). Sulfonylcarbamimidic azide **6** was converted to 2-amino-*N*-(aminoiminomethyl)benzenesulfonamide (**7**) with ethanolic stannous chloride, and to 3-amino-1,2,4-thiadiazine 1,1-dioxide (**8**) with sodium dithionite. Methanesulfonyl chloride (**9**) and 5-AT gave 2-(methylsulfonyl)carbamimidic azide (**10**), which isomerized to 5-[(methylsulfonyl)amino]-1*H*-tetrazole (**11**) in warm ethanol. Attempted cycloaddition of 2-(phenylsulfonyl)carbamimidic azide (**13**) and ethyl vinyl ether led only to alkylated tetrazole products. In addition, other tetrazole-alkylating reactions are described. Isomers produced from these alkylations were differentiated with ^{13}C nmr spectroscopy.

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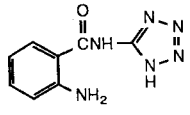
N-1*H*-Tetrazol-5-yl-2-aminobenzamide (**1**) has been a versatile intermediate in our laboratories for the preparation of antiallergic agents [1-4]. Sulfonamide **2** is a closely related structure which we also proposed to prepare. This report describes our attempts to synthesize **2** which led to the isolation, characterization and further study of novel sulfonylcarbamimidic azides.



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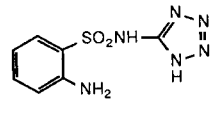
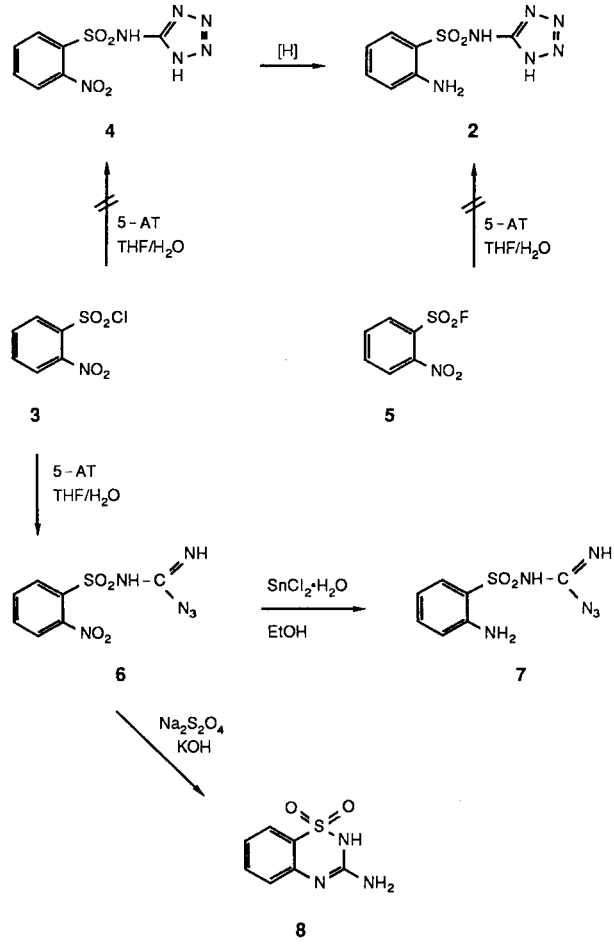


2

Treatment of 5-aminotetrazole (5-AT) with *o*-nitrobenzenesulfonyl chloride (**3**) in aqueous tetrahydrofuran did not provide the expected sulfonylaminotetrazole **4**, which we envisioned as a precursor of **2**. This reaction produced, instead, [(2-nitrophenyl)sulfonyl]carbamimidic azide (**6**), a ring-opened version of tetrazole **4** (Scheme I). The infrared spectrum of **6** displayed intense absorption bands in the cumulated double bond region, at 2210 and 2150 cm^{-1}. We also were unable to prepare **2** from *o*-aminobenzenesulfonyl fluoride (**5**), since **5** failed to react with 5-aminotetrazole.

Reduction of **6** with ethanolic stannous chloride gave 2-amino-*N*-(aminoiminomethyl)benzenesulfonamide (**7**), a compound resulting from reduction of both nitro and azide groups to amino groups. Stannous chloride has recently been described as a selective reducing agent for aromatic nitro groups in the presence of additional, reducible functionality [5]. This selectivity, as we have determined with our reduction of **6**, does not include the carbamimidic azide functionality. When the reduction was

Scheme I



effected with sodium dithionite in a basic, aqueous medium, 3-amino-1,2,4-benzothiadiazine 1,1-dioxide (**8**) was produced. In this procedure, the production of **7** is ap-

parently followed by a base-induced cyclization to produce **8** *via* elimination of ammonia.

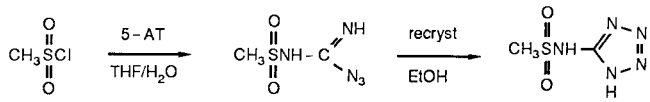
Both **7** and **8** have been previously prepared by other routes. Sulfonylguanidine **7** has been synthesized from the corresponding 2-nitro compound using iron and ferrous chloride [6,7]. Benzothiadiazine **8** has been prepared by Topliss and Konzelman [8] by three routes, all initiating from *o*-aminobenzenesulfonamide.

Ring-opening reactions of tetrazoles have been previously documented. 5-Alkyl-1-arylaminotetrazoles thermally rearrange to 1-alkyl-5-arylaminotetrazoles, *via* ring-opened intermediates [9,10], in a process reminiscent of the Dimroth rearrangement [11,12]. Likewise, 5-mercapto-1-phenyl-1*H*-tetrazole thermally rearranges to 5-(phenylamino)-1,2,3,4-thiatriazole [13]. We have recently shown that 2-carbomethoxyphenyl isocyanate and 5-aminotetrazole give 2-[((5-amino-1*H*-tetrazol-1-yl)carbonyl)amino]benzoic acid methyl ester, which thermally rearranges to 2-[((1*H*-tetrazol-5-ylamino)carbonyl)amino]benzoic acid methyl ester [14]. In addition, a recent report describes the formation of tetrazolotriazines and their *in situ* rearrangement to azidotriazines [15].

5-[(4-Methylphenylsulfonyl)amino]tetrazole has previously been reported [16], with no mention of the corresponding ring-opened carbamimidic azide, as have the 1-methyl and 2-methyl derivatives [17], 1-aryl derivatives [18], and the 1-dimethylamino derivative [19]. The latter compound was unstable, and eliminated nitrogen at room temperature. Also reported are sulfonylazidoformamidines (alternate nomenclature for sulfonylcarbamimidic azides), which were prepared from hydrazoic acid and *N*-sulfonylcarbodiimides [20]. The latter compounds, on heating in toluene, cyclized to the corresponding tetrazoles.

We decided to investigate the reactions of an alkylsulfonyl chloride with 5-aminotetrazole, since alkylsulfonylcarbamamidic azides have not been previously reported. Scheme II shows the reaction we observed with methanesulfonyl chloride and 5-aminotetrazole. We initially isolated carbamimidic azide **10**, mp 99-100°, which was evident from the intense absorption bands at 2205 and 2160 cm^{-1}. However, upon recrystallization from ethanol, carbamimidic azide **10** cyclized to tetrazole **11**, mp 194-195° dec. The infrared spectrum of **11** displayed typical 1*H*-tetrazole NH stretching at 3400-2400 cm^{-1}, and lack of absorption in the cumulated double bond region. Isomeric compounds **10** and **11** displayed different ^1H and ^{13}C nmr spectra in dimethylsulfoxide-d_6. The methyl signal for **10** appeared at δ 2.97, while the methyl signal for **11** was more deshielded, appearing at δ 3.29. In the carbon spectrum, the imino carbon of **10** appeared at δ 157.5, in a slightly deshielded position with respect to the corresponding tetrazole carbon of **11**, which appeared at δ 152.7. Both **10** and **11** displayed mass spectral molecular ions in the electron impact mode. Fragmentation patterns were similar, but fragment intensities were quite different.

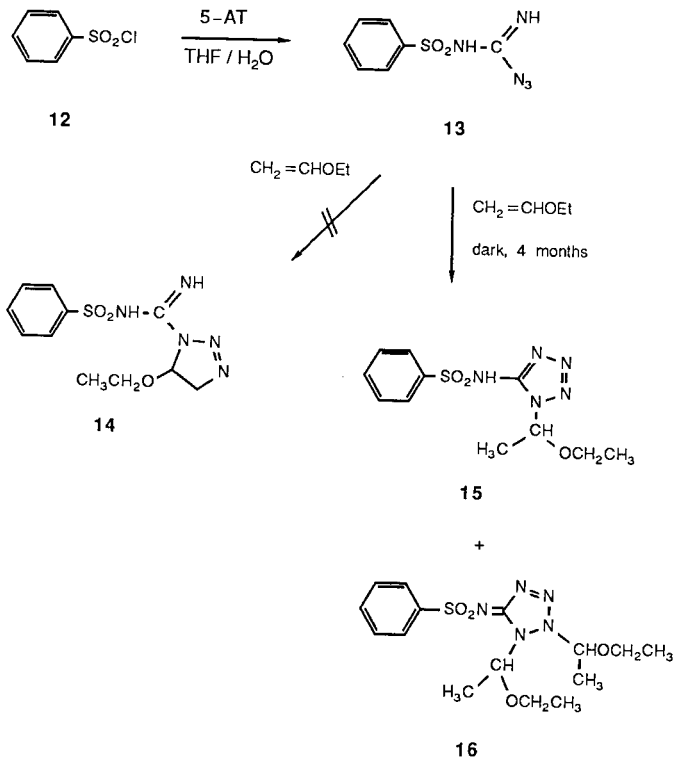
Scheme II



9 **10** **11**

Since azides are good 1,3-dipolarophiles, we attempted a 1,3-dipolar cycloaddition reaction with a carbamimidic azide. We chose 2-(phenylsulfonyl)carbamimidic azide (**13**) as our 1,3-dipolarophile, whose synthesis is shown in Scheme III. Again, infrared spectroscopy confirmed that **13** was a carbamimidic azide rather than a tetrazole, from the intense absorption bands at 2185 and 2130 cm^{-1} and the lack of NH absorption characteristic of 1*H*-tetrazoles.

Scheme III



12 **13** **14** **15** **16**

Enol ethers are electron-rich enes which are susceptible to 1,3-cycloaddition reactions [21]. Ethyl vinyl ether and *p*-nitrophenylazide, for example, undergo cycloaddition to give 5-ethoxy-1-*p*-nitrophenyl-1,2,3-triazoline [22]. Thus, we were interested to see whether triazoline **14** would form from carbamimidic azide **13** and ethyl vinyl ether.

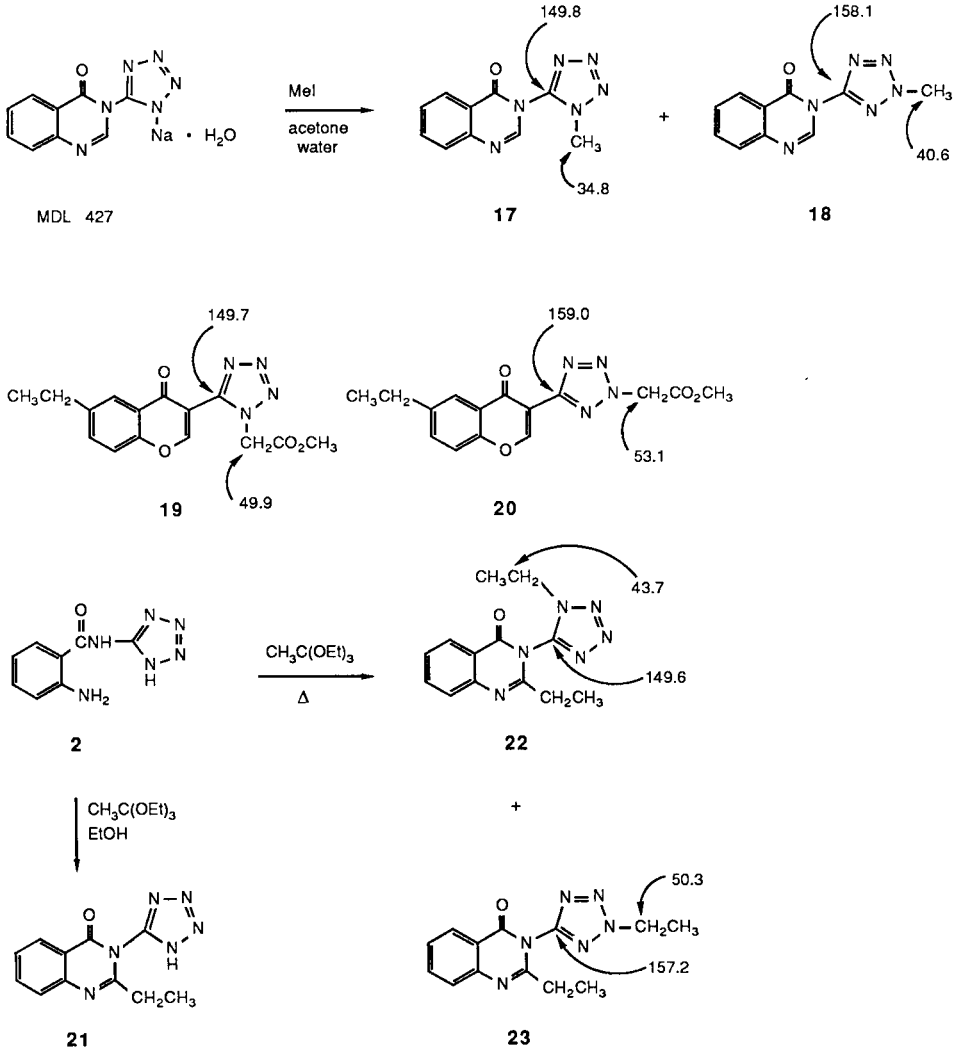
Treatment of **13** with excess ethyl vinyl ether in tetrahydrofuran in the absence of light for 4 months produced two products, which were separated by silica gel flash

chromatography. It was clear from spectral data that neither of these products was triazoline **14**, or a product resulting from elimination of ethanol from **14**, and that the products obtained were mono- and dialkylated versions of the tetrazole corresponding to **13**.

To the fast moving component we propose structure **16**, namely, *N*-[1,2-bis(1-ethoxyethyl)-1,2-dihydro-5*H*-tetrazol-5-ylidene]benzenesulfonamide. The infrared spectrum (Nujol) of **16** displayed no NH stretching, and intense ether stretching at 1075 cm^{-1}. Mass spectrometry (electron impact) showed a weak, protonated molecular ion at m/e 370, apparently produced *via* a self-chemical ionization process, and a more intense fragment ion at m/e 324, corresponding to loss of ethoxide radical from the molecular ion. The nmr spectrum (deuteriochloroform) of **16** displayed methine quartets, J = 6 Hz, at δ 5.95 and 5.30, with corresponding methyl doublets, J = 6 Hz, at δ 1.85 and 1.20. We feel that the downfield set of methyl-methine signals corresponds to the ethoxyethyl group closest to the deshielding sulfonamide group. The nonequivalence of the ethoxyethyl groups in **16** rules out a symmetrical dialkylated structure.

To the slower moving, mono-alkylated product we propose structure **15**, namely, *N*-[1-(1-ethoxyethyl)-1*H*-tetrazol-5-yl]benzenesulfonamide. The infrared spectrum (Nujol) of **15** showed broad NH stretching at 3120 cm^{-1} and ether stretching at 1050 cm^{-1}. Methane chemical ionization mass spectrometry showed a protonated molecular ion at m/e 298, with an adduct at m/e 326. The nmr spectrum (deuteriochloroform) of **15** displayed a methine quartet, J = 6 Hz, at δ 5.85, with the corresponding methyl doublet, J = 6 Hz, at δ 1.75. We assigned the position of the alkyl group on the tetrazole in **15** on the basis of chemical shifts of the methyl-methine signals, which

Scheme IV



were close to the downfield set of methyl-methine signals in **16**.

We have also studied other tetrazole-alkylation reactions. 3-(1*H*-Tetrazol-5-yl)-4(3*H*)-quinazolinone sodium salt (MDL 427), an antiallergic agent whose synthesis and biological activity we have recently described [1], when treated with methyl iodide in aqueous acetone gave a mixture of methylated species which was separated by fractional recrystallization to provide 3-(1-methyl-1*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone (**17**), mp 220-221°, and the corresponding 2-methyl isomer **18**, mp 120-121° (Scheme IV). These conditions have been used previously for the methylation of 5-amino-1*H*-tetrazole sodium salt [23] and 5-(nitroamino)-1*H*-tetrazole potassium salt [24].

Structural assignments for **17** and **18** were made on the basis of ^{13}C nmr spectroscopy. It has been shown by Elguero, Marzin and Roberts [25] that the resonances for both C-5 and NCH_3 in 2-methyl-2*H*-tetrazole are downfield with respect to those resonances in 1-methyl-1*H*-tetrazole. The same phenomenon has been reported by Hart and Ford [26] in their ^{13}C nmr study on several pairs of methylated 5-aryltetrazoles. Nohara, *et al.* [27] used ^{13}C nmr spectroscopy to assign structures to pairs of alkylated tetrazolylchromones, such as AA-344 derivatives **19** and **20**. The ^{13}C assignments for the tetrazole carbon atoms and the methylene groups attached to the tetrazole nitrogen atoms for the monoalkylated products obtained from both AA-344 and MDL 427 are shown in Scheme IV. Thus we differentiated **17** and **18** on the basis of ^{13}C field positions of the tetrazole carbon atoms and NCH_3 groups, which are also listed in Scheme IV.

The alkylation procedure developed for MDL 427 was modified to efficiently work in biological solutions. Methylated derivatives **17** and **18** could be extracted from the biological fluids and quantitated by vapor phase chromatography to provide an assay method for MDL 427.

We have also observed tetrazole ethylation by transesterification with triethyl orthoesters. When we treated tetrazolamide **2** with triethyl orthopropionate in ethanol, we obtained quinazolinone **21**, as we reported earlier [1]. However, in the absence of solvent, we observed *N*-ethylation of the tetrazole ring in addition to quinazolinone formation, with triethyl orthopropionate. The mixture of ethylated tetrazoles was separated by fractional crystallization to give the 1-methyl compound **22**, mp 152-154°, and, predominantly, the 2-methyl isomer **23**, mp 116-119°. Again, these structural assignments were made on the basis of ^{13}C nmr spectroscopy. The compound displaying downfield resonances for the tetrazole carbon and the attached methylene group was assigned as **23** (Scheme IV).

In summary, we were unable to prepare sulfonamides **2** or **4** as shown in Scheme 1. However, we did prepare the interesting carbamimidic azide **6**, which was reduced to sulfonylguanidine **7** and was reductively cyclized to thiadiazine **8**. The reduction of **6** to **7** demonstrates the utility of the aminotetrazole unit as a latent guanidine. Carbamamidic azides **10** and **13** were also synthesized and studied. The preparation of carbamamidic azides from sulfonyl chlorides and 5-aminotetrazole has not previously been reported. Azide **13** underwent alkylation with ethyl vinyl ether rather than cycloaddition. Alkylation reactions of MDL 427 and a related tetrazole produced pairs of monoalkylated tetrazoles, whose structures were assigned with ^{13}C nmr spectroscopy.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 710B, 727B and 1310 spectrophotometers, ^1H nmr spectra were recorded with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 spectrometers, ^{13}C spectra were recorded with a Varian FT-80A spectrometer, 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.

[(2-Nitrophenyl)sulfonyl]carbamimidic Azide (**6**).

To a warm solution of 10.3 g (0.100 mole) of 5-aminotetrazole monohydrate (5-AT) in 250 ml of tetrahydrofuran and 15 ml of water was added 11.1 g (50.0 mmoles) of *o*-nitrobenzenesulfonyl chloride (**3**). The solution was diluted with water, which did not produce a precipitate, and concentrated. The residue was partitioned between methylene chloride and water and the organic layer was dried and concentrated to give 10.3 g (76%) of **6**, mp 134-135° dec (ethanol-water); ir (Nujol): 3430, 3290, 3210, 2210, 2150, 1640 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 9.10 (br s, 1H, NH), 8.30-8.10 (m, 1H, aromatic), 8.10-7.60 (m, 4H, aromatic and NH); ms: (70 eV, electron impact) m/e 270 (molecular ion).

Anal. Calcd. for $C_7H_6N_6O_4S$: C, 31.11; H, 2.24; N, 31.10. Found: C, 31.12; H, 2.35; N, 31.03.

2-Amino-*N*-(aminoiminomethyl)benzenesulfonamide (**7**).

A 2.70 g (10.0 mmoles) quantity of **6** was added to a solution of 11.3 g (50.0 mmoles) of stannous chloride dihydrate in 20 ml of ethanol, under a nitrogen atmosphere. The mixture was heated at 70°, and the solution which resulted was heated at this temperature for 20 minutes. The solution was cooled and poured onto ice. The mixture was basified with sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated to a small volume. The resulting solid was collected and dried to give 1.18 g (55%) of **7**, mp 204-205° (ethyl acetate) (lit [6] mp 203-204°); ir (Nujol): 3420, 3330, 3230, 1640 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 7.43 (dd, J = 7 Hz, J = 2 Hz, 1H, H *ortho* to SO_2), 7.06 (dt, J = 7 Hz, J = 2 Hz, 1H, H *para* to SO_2), 6.77-6.28 (m, 6H, remaining aromatic and 4 NH protons), 5.67 (s, 2H, NH_2); ms: (70 eV, chemical ionization) 215 ($M^+ + 1$), 243 ($M^+ + 29$), 255 ($M^+ + 41$).

Anal. Calcd. for $C_7H_{10}N_4O_2S$: C, 39.25; H, 4.71; N, 26.16. Found: C, 39.12; H, 4.70; N, 26.11.

3-Amino-1,2,4-benzothiadiazine 1,1-Dioxide (**8**).

To a solution of 11.1 g (41.0 mmoles) of **6** in 100 ml of 10% aqueous potassium hydroxide was added, in portions with stirring, 40.0 g of sodium dithionite. Temperature was maintained at 35-40°. After 30 minutes, the solution was acidified with hydrochloric acid and heated on the steam bath for 3 hours. The resulting precipitate was collected, washed with water and dried to give a quantitative yield of **8**, mp 309-310° (lit [8] mp 344-345°); ir (Nujol): 3410, 3320 and 3210 (NH), 1645 (C = N) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.65 (br s, 1H, NH, deuterium oxide-

exchangeable), 7.80-7.40 (m, 2H, aromatic), 7.40-7.05 (m, 2H, aromatic), 6.95 (s, 2H, NH_2, deuterium oxide-exchangeable); ms: (chemical ionization, 70 eV) m/e 198 (molecular ion).

2-(Methylsulfonyl)carbamimidic Azide (**10**) and 5-[(Methylsulfonyl)amino]-1*H*-tetrazole (**11**).

To a warm solution of 20.6 g (0.200 mole) of 5-aminotetrazole monohydrate (5-AT) in 250 ml of tetrahydrofuran was added a solution of 11.5 g (0.100 mole) of methanesulfonyl chloride (**9**) in 50 ml of tetrahydrofuran. After heating on the steam bath for 1 hour, the clear solution was evaporated and partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate) and concentrated to give 3.34 g (20%) of **10**, mp 99-100° dec with gas evolution; ir (potassium bromide): 3440, 3310, 3250 and 3190 (NH), 2205, 2160, 1640 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.74 (s, 1H, NH), 7.61 (s, 1H, NH), 2.97 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 157.49 (C=NH), 41.09 (CH_3); ms: (70 eV, electron impact) m/e 163 (molecular ion).

Azide **10** was recrystallized from ethanol to give tetrazole **11**, mp 194-195° dec; ir (potassium bromide): 3400-2400 (NH), 1590 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ *ca.* 13 (very broad s, 2H, both NH), 3.29 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 152.66 (tetrazole C), 41.09 (CH_3); ms: (70 eV, electron impact) m/e 163 (molecular ion).

Anal. Calcd. for $C_2H_5N_5O_2S$: C, 14.72; H, 3.08; N, 42.92. Found: C, 14.85; H, 3.20; N, 43.09.

2-(Phenylsulfonyl)carbamimidic Azide (**13**).

To a warm solution of 20.6 g (0.200 mole) of 5-aminotetrazole monohydrate (5-AT) in 250 ml of tetrahydrofuran and 5 ml of water was added a solution of 17.6 g (0.100 mole) of benzenesulfonyl chloride (**12**) in 20 ml of tetrahydrofuran. After 30 minutes of warming, the clear solution was stirred at room temperature for 15 hours and concentrated. The residue was triturated with water and the resulting solid was collected and air-dried to give 16.4 g (73%) of **13**, mp 135° (ethanol); ir (Nujol): 3515, 3310 and 3240 (NH), 2185, 2130, 1635, 1545 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.80 (s, 1H, NH), 8.00-7.36 (m, 5H, aromatic); ms: (100 eV, chemical ionization) 226 ($M^+ + 1$), 254 ($M^+ + 29$), 266 ($M^+ + 41$).

Anal. Calcd. for $C_7H_7N_5SO_2$: C, 37.32; H, 3.13; N, 31.10. Found: C, 37.36; H, 3.23; N, 30.99.

3-(1-Methyl-1*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone (**17**) and 3-(2-Methyl-2*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone (**18**).

A mixture of 10.0 g (37.9 mmoles) of MDL 427, 30 ml of water, 100 ml of acetone and 5.73 g (40.4 mmoles) of methyl iodide was heated at reflux for 3 hours. The resulting clear solution was concentrated until crystallization commenced, and cooling resulted in more crystallization. The solid was collected and washed with acetone-water to give 7.10 g of a mixture of **17** and **18**. Recrystallization from ethanol gave, as a first crop, 1.20 g of **17**, mp 220-221°; nmr (dimethylsulfoxide-d_6): δ 8.40 (s, 1H, C2-H), 8.30 (dd, 1H, C5-H), 8.10-7.55 (m, 3H, remaining aromatic), 4.07 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8N_6O$: C, 52.63; H, 3.53; N, 36.83. Found: C, 52.72; H, 3.72; N, 36.83.

A second crop gave 1.95 g, which was recrystallized to give **18**, mp 120-121°; nmr (dimethylsulfoxide-d_6): δ 8.50 (s, 1H, C2-H), 8.27 (dd, 1H, C5-H), 8.17-7.50 (m, 3H, remaining aromatic), 4.55 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8N_6O$: C, 52.63; H, 3.53; N, 36.83. Found: C, 52.25; H, 3.67; N, 37.00.

2-Ethyl-3-(1-methyl-1*H*-tetrazol-5-yl)-4(3*H*)-quinazolinone (**22**) and 2-Ethyl-3-(2-methyl-2*H*-tetrazol-5-yl)-4-(3*H*)-quinazolinone (**23**).

A mixture of 5.00 g (24.4 mmoles) of **2** [1] and 40 ml of triethyl orthopropionate was heated and the resulting clear solution was heated at reflux for 16 hours. The solution was concentrated to a small volume. After 2 days, 800 mg of solid was removed by filtration and recrystallized from ethanol to give 150 mg of **22**, mp 152-154°; ir (Nujol) 1685 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.18 (dd, 1H, C5-H), 8.10-7.50 (m, 3H, remaining aromatic), 4.40 (q, J = 7 Hz, 2H, NCH_2), 2.55-2.20 (m, 2H, CCH_2), 1.45 (t, J = 7 Hz, 3H, CH_3), 1.17 (t, J = 7 Hz, 3H, CH_3); ms: (70 eV, electron impact) m/e 270 (molecular ion).

Anal. Calcd. for $C_{13}H_{14}N_6O$: C, 57.76; H, 5.22; N, 31.10. Found: C, 57.60; H, 5.27; N, 31.26.

The filtrate deposited another crop of crystals which was collected and recrystallized (benzene-hexane) to give 3.95 g of **23**, mp 116-119°; nmr (dimethylsulfoxide-d_6): δ 8.15 (dd, 1H, C5-H), 4.90 (q, J = 7 Hz, 2H, NCH_2), 2.35 (q, J = 7 Hz, 2H, CCH_2), 1.63 (t, J = 7 Hz, 3H, CH_3), 1.17 (t, J = 7 Hz, 3H, CH_3); ms: (70 eV, electron impact) m/e 270 (molecular ion).

Anal. Calcd. for $C_{13}H_{14}N_6O$: C, 57.76; H, 5.22; N, 31.10. Found: C, 57.80; H, 5.27; N, 31.34.

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