A Regiochemical Study of the Alkylation of 1,5- and 2,5-Substituted Tetrazoles

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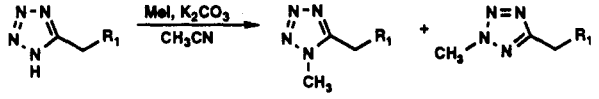
Compounds containing the tetrazole ring have demonstrated important biological activity as hypotensive agents[1] and as antibiotics,[2] where the tetrazole was introduced as a carboxylate surrogate. There are several methods available for the synthesis of tetrazoles,[3] and tetrazoles are useful as a directing group for the metalation of aromatic rings.[4] Selective functionalization of the tetrazole ring is still problematic in that alkylation of monosubstituted derivatives affords a mixture of 1,5- and 2,5-substituted tetrazoles.[5] Moody and Rees reported that N-alkyl-5-phenyltetrazoles alkylate on the N-alkyl group.[6] They recognized that "dipole-stabilized" carbanion chemistry could be applied to the unusually activated "amine" in the tetrazole.[7] Quast noted that in one example a 1,5-dialkyl derivative alkylates at the 5-position.[8] He employed the activating effect of the aromatic tetrazole ring to facilitate deprotonation of the methylene group.[9] We wish to report the results of our regiochemical study of the metalation of tetrazoles and its potential for selective functionalization of tetrazoles.

A series of readily separable 1,5- and 2,5-substituted tetrazoles, 1 and 3, were prepared by alkylating 5-substituted tetrazoles with MeI, which in turn were produced from the corresponding nitrile and $Al(N_3)_3$.[3,5] Following

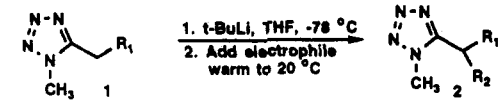


1 3

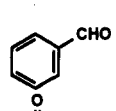
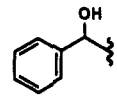
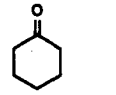
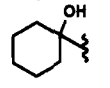
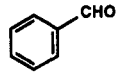
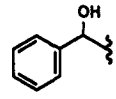
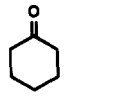
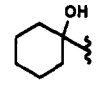
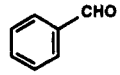
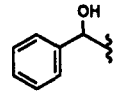
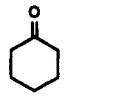
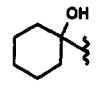
a, $R_1 = CH_3$; b, $R_1 = C_6H_5O$; c, $R_1 = C_6H_5$

the method of Moody and Rees,[6] the 1,5-isomer, 1, was metalated with *tert*-butyllithium at −78 °C in tetrahydrofuran (THF) and was quenched with various electrophiles, Table I. Reaction occurred exclusively at the 5-alkyl position. Mixtures of diastereomers were not separated except in the case of compound **2b** which was separated by flash chromatography. In one case, none of the expected product **2k** was formed. Upon reacting metalated **1a** in Et_2O with benzaldehyde, alkylation occurred on the N-alkyl portion affording **5**. For the other examples

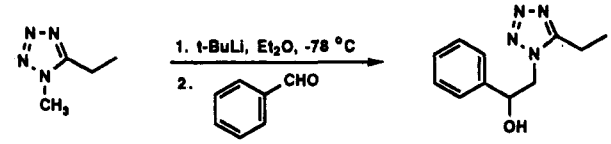
Table I. Alkylation of 1,5-Substituted Tetrazoles in THF



1 2

electrophile	R_1	R_2	yield (%)	compd
MeI	CH_3	CH_3	16 (15)	(a)
	CH_3		48 (0)	(b)
	CH_3		54	(c)
t-BuCHO	CH_3	t-Bu-CH(OH)-	59	(d)
MeI		CH_3	49 (41)	(e)
			64 (70)	(f)
			83	(g)
t-BuCHO		t-Bu-CH(OH)-	90	(h)
MeI		CH_3	72	(i)
			44	(j)
			0	(k)
t-BuCHO		t-Bu-CH(OH)-	45	(l)

reacted in Et_2O (Table I, yields in parentheses), the change of solvent did not alter the regiochemical outcome.



1a 5

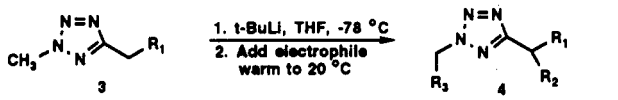
The 2,5-substituted tetrazoles **3a** and **3b** were metalated and quenched in a similar manner to yield products resulting from alkylation on the *N*-methyl site, Table II. The regiochemistry of the alkylation reaction could be altered when the phenyl-substituted derivative **3c** was employed in the reaction. The alkylation of **3a** with benzaldehyde, in Et_2O, produced **4b**, the same product produced in THF.

In summary, we have demonstrated that 1,5-substituted alkyl tetrazoles react selectively at the 5-alkyl position. For only one example, chemistry took place on the N-alkyl position with benzaldehyde in Et_2O. The 2,5-substituted tetrazoles alkylate preferentially at the N-alkyl site, unless

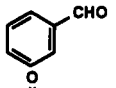
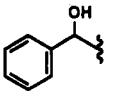
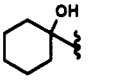
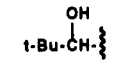
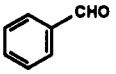
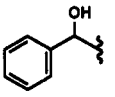
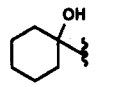
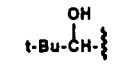
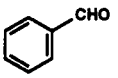
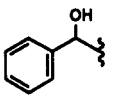
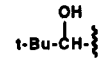
(1) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. *Hypertension* **1990**, *15*, 459-468.
(2) Saltiel, E.; Brogden, R. N. *Drugs*, **1986**, *32*, 222-259.
(3) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*, Katritsky, A. R., Ed.; Pergamon: Oxford, 1984; Vol. V, Chapter 4.13.
(4) Flippin, L. A. *Tetrahedron Lett.* **1991**, *32*, 6857-6860.
(5) Spear, R. J. *Aust. J. Chem.* **1984**, *37*, 2453-2468.
(6) Moody, C. J.; Rees, C. W.; Young, R. G. *J. Chem. Soc. Perkin Trans. 1* **1991**, 323-327.
(7) (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471-523. (b) Highsmith, T. K.; Meyers, A. I. *Advances in Heterocyclic Natural Product Synthesis* **1990**, *1*, 95-135.
(8) Quast, H.; Bieber, L.; Meichsner, G.; Regnat, D. *Chem. Ber.* **1988**, *121*, 1285-1290.
(9) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon: Oxford, 1974; Chapter 3.

0022-3263/93/1958-1623$04.00/0

Table II. Alkylation of 2,5-Substituted Tetrazoles in THF



3 4

electrophile	R_1	R_2	R_3	yield (%)	compd
MeI	CH_3	H	CH_3	48	(a)
	CH_3	H		79	(b)
	CH_3	H		51	(c)
t-BuCHO	CH_3	H		66	(d)
MeI		H	CH_3	45[a]	(e)
		H		78	(f)
		H		71	(g)
t-BuCHO		H		95	(h)
MeI		CH_3	H	54	(i)
			H	56	(j)
			H	56	(k)
t-BuCHO			H	44	(l)

[a] And bis-alkylated adduct 4e' (24%), where $R_2 = CH_3$.

a phenyl group is present on the 5-alkyl moiety to direct alkylation adjacent to it. The origin for the regioselectivity in the alkylation of 1,5- and 2,5-substituted tetrazoles is not obvious. A number of factors such as pK_a of substrate, kinetic acidity of protons, metalating agent, and solvent polarity affect a metalation reaction.[9]

Experimental Section

^1H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Melting points in open capillaries are uncorrected. Unless specified, all Burdick and Jackson solvents and reagents purchased from Aldrich were used without further purification. THF and Et_2O were dried over molecular sieves.[10] All compounds were dried over $MgSO_4$. Solvent was removed on a rotovap under reduced pressure. Unless indicated otherwise, all products were obtained as liquids.

5-Ethyl-1-methyl-1*H*-tetrazole (1a) and 5-Ethyl-2-methyl-2*H*-tetrazole (3a). A solution of 5-ethyl-1*H*-tetrazole[11] (6.54 g, 66.7 mmol) in CH_3CN (700 mL) was treated with K_2CO_3 (18.0 g, 0.130 mol) followed by addition of methyl iodide (4.2 mL, 67.5 mmol). The reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo. The residue was taken up in $CHCl_3$ (700 mL) and filtered. The filtrate was concentrated in vacuo yielding a yellow oil. The oil was chromatographed eluting with EtOAc. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield **1a** (4.67 g, 62%, more polar spot) as a yellow oil and **3a** (1.17 g, 16%, less polar spot) as a yellow oil. ^1H NMR data for **1a**:[12] ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.6 Hz, CH_2CH_3), 2.90 (q, 2 H, J = 7.6 Hz, CH_2CH_3), 4.01 (s, 3 H, NCH_3). ^1H NMR data for **3a**: ($CDCl_3$) δ 1.37 (t, 3 H, J = 7.7 Hz, CH_2CH_3), 2.93 (q, 2 H, J = 7.7 Hz, CH_2CH_3), 4.31 (s, 3 H, NCH_3).

1-Methyl-5-(phenoxymethyl)-1*H*-tetrazole (1b) and 2-Methyl-5-(phenoxymethyl)-2*H*-tetrazole (3b). A solution of 5-(phenoxymethyl)-1*H*-tetrazole[13] (8.3 g, 47.1 mmol) in CH_3CN (500 mL) was treated with K_2CO_3 (13.0 g, 94.2 mmol) followed by addition of methyl iodide (2.9 mL, 47.1 mmol). The reaction was stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was taken up in $CHCl_3$ (500 mL) and filtered. The filtrate was concentrated in vacuo yielding a yellow oil. The oil was chromatographed eluting with CH_2Cl_2. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield **1b** (2.68 g, 30%, more polar spot) as a yellow oil and **3b** (3.95 g, 44%, less polar spot) as a yellow oil. ^1H NMR data for **1b**: ($CDCl_3$) δ 4.17 (s, 3 H, NCH_3), 5.43 (s, 2 H, $PhOCH_2$), 6.98–7.07 (m, 3 H, arom), 7.27–7.35 (m, 2 H, arom). ^1H NMR data for **3b**: ($CDCl_3$) δ 4.37 (s, 3 H, NCH_3), 5.33 (s, 2 H, $PhOCH_2$), 6.97–7.05 (m, 3 H, arom), 7.26–7.34 (m, 2 H, arom).

1-Methyl-5-(phenylmethyl)-1*H*-tetrazole (1c) and 2-Methyl-5-(phenylmethyl)-2*H*-tetrazole (3c). A solution of 5-(phenylmethyl)-1*H*-tetrazole (5.9 g, 36.8 mmol) in CH_3CN (430 mL) was treated with K_2CO_3 (20.7 g, 0.150 mol) followed by addition of methyl iodide (2.3 mL, 36.8 mmol). The reaction was stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was taken up in $CHCl_3$ (430 mL) and filtered. The filtrate was concentrated in vacuo yielding an orange oil. The oil was chromatographed eluting with CH_2Cl_2. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield **3c** (1.53 g, 24%, less polar spot) as a yellow oil. The column was then eluted with 5% CH_3OH/CH_2Cl_2. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield a yellow solid. The solid was recrystallized to yield **1c** (1.75 g, 27%) as a white solid, mp 73–74 °C (lit.[12] mp 71–72 °C). ^1H NMR data for **1c**: ($CDCl_3$) δ 3.84 (s, 3 H, CH_3), 4.31 (s, 2 H, $PhCH_2$), 7.18–7.27 (m, 2 H, arom), 7.29–7.37 (m, 3 H, arom). ^1H NMR data for **3c**:[12] ($CDCl_3$) δ 4.23 (s, 2 H, $PhCH_2$), 4.29 (s, 3 H, NCH_3), 7.21–7.33 (m, 5 H, arom).

General Procedure for the Alkylation of Disubstituted Tetrazoles. β,1-Dimethyl-α-phenyl-1*H*-tetrazole-5-ethanol (2b). Tetrazole **1a** (500 mg, 4.5 mmol) was added to a flame-dried, round-bottom flask and dissolved in dry THF (38 mL). The solution was cooled to −78 °C, and t-BuLi (2.9 mL, 1.7 M in pentane) was added dropwise. The reaction was stirred at −78 °C for 30 min. Benzaldehyde (0.51 mL, 5.0 mmol) was added, and the reaction was allowed to warm to 20 °C. Et_2O (190 mL) was added. The organic layer was then washed with 15% HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and H_2O (40 mL). It was then dried, filtered, and concentrated in vacuo to yield a yellow oil. The oil was chromatographed eluting with 40% EtOAc/hexanes. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield one diastereomer of **2b** (219 mg, 22%) as a white solid: mp 100–105 °C; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 2.76 (s, 1 H, OH), 3.30 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 3.90 (s, 3 H, NCH_3), 4.89 (d, 1 H, J = 7.7 Hz, CHOH), 7.26–7.40 (m, 5 H arom); ^{13}C NMR ($CDCl_3$) ppm 156.8 (s), 141.4 (s), 128.5 (s), 128.2 (s), 126.0 (s), 77.6 (s), 37.2 (d), 33.2 (q), 15.9 (q); IR (mineral oil mull) 3319, 2923, 1602, 1528,

(10) Burfield, D. R.; Gan, G.; Smithers, R. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 23–30.
(11) Caruso, J. A.; Sears, P. G.; Popov, A. I. *J. Phys. Chem.* **1967**, *71*, 1756–1760.
(12) Quast, H.; Bieber, L.; Meichsner, G. *Liebigs Ann. Chem.* **1987**, 469–475.
(13) Buchanan, R. L.; Sprancmanis, V.; Partyka, R. A. *J. Med. Chem.* **1969**, *12*, 1001–1006.

1496, 1466, 1419, 1043, 1028, 771 cm^{-1}; MS for $C_{11}H_{14}N_4O$ *m/z* (relative intensity) 218 (M^+, 4), 203 (2), 189 (1), 168 (2), 112 (100), 79 (38). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.47; N, 25.67. Found: C, 60.85; H, 6.43; N, 25.45. The second diastereomer of **2b** (255 mg, 26%), was also isolated as a white solid: mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3 H, J = 7.0 Hz, $CHCH_3$), 3.10 (d, 1 H, OH), 3.26 (q, 1 H, J = 7.0 Hz, $CHCH_3$), 3.65 (s, 3 H, NCH_3), 5.06 (d, 1 H, CHOH), 7.18–7.21 (m, 2 H, arom), 7.26–7.31 (m, 3 H, arom); ^{13}C NMR ($CDCl_3$) ppm 156.9 (s), 141.0 (s), 128.5 (d), 128.2 (d), 125.9 (d), 75.9 (d), 37.4 (d), 33.1 (q), 14.2 (q); IR (mineral oil mull) 3337, 3103, 2923, 1621, 1602, 1526, 1493, 1455, 1018, 771, 704 cm^{-1}; MS for $C_{11}H_{14}N_4O$ *m/z* (relative intensity) 218 (M^+, 4), 203 (4), 189 (2), 162 (2), 132 (11), 112 (100), 107 (33). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.47; N, 25.67. Found: C, 60.57; H, 6.43; N, 25.70.

1-Methyl-5-(2-propyl)-1*H*-tetrazole (2a). The crude oil was chromatographed eluting with 2% CH_3OH/CH_2Cl_2 to yield **2a** (90 mg, 16%) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 6 H, J = 6.9 Hz, $CHCH_3$), 3.17 (q, 1 H, J = 6.9 Hz, $CHCH_3$), 4.02 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) ppm 159.4 (s), 33.3 (q), 24.3 (d), 20.7 (q); IR (neat) 3479, 2978, 1729, 1641, 1528, 1511, 1463, 1155, 1101, 1073, 724 cm^{-1}; MS for $C_5H_{10}N_4$ *m/z* (relative intensity) 126 (M^+, 1), 125 (2), 111 (18), 84 (19), 83 (14), 70 (58), 43 (100). Anal. Calcd for $C_5H_{10}N_4$: C, 47.60; H, 7.99. Found: C, 47.86; H, 7.86.

1-[(1-Methyl-1*H*-tetrazol-5-yl)ethyl]cyclohexanol (2c). The oil was chromatographed eluting with 1/1 EtOAc/hexanes to yield **2c** (511 mg, 54%) as a white solid: mp 78–80 °C; ^{1}H NMR ($CDCl_3$) δ 1.15–1.25 (m, 1 H, CH_2), 1.33–1.70 (m, 8 H, CH_2), 1.37 (d, 3 H, J = 7.2 Hz, CH_3), 1.78–1.88 (m, 1 H, CH_2), 3.06 (q, 1 H, J = 7.2 Hz, CH_3CH), 4.05 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) ppm 157.0 (s), 72.6 (s), 38.9 (d), 36.1 (t), 33.5 (q), 33.1 (t), 25.1 (t), 21.4 (t), 21.2 (t), 13.4 (q); IR (mineral oil mull) 3415, 2927, 1518, 1508, 1488, 1434, 1418, 1399, 1285, 970 cm^{-1}; MS for $C_{10}H_{18}N_4O$ *m/z* (relative intensity) 210 (3), 167 (12), 154 (6), 124 (2), 112 (100), 99 (10), 81 (11), 69 (26), 55 (18). Anal. Calcd for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 57.00; H, 8.70; N, 26.53.

α-(1,1-Dimethylethyl)-β,1-dimethyl-1*H*-tetrazole-5-ethanol (2d). The oil was chromatographed eluting with 1/1 EtOAc/hexanes to yield **2d** (530 mg, 59%, 1:1 mixture of diastereomers) as a white solid: mp 85–95 °C; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3.7 H, CH_3), 0.99 (s, 5.3 H, CH_3), 1.36 (d, 1.7 H, J = 7.6 Hz, $CHCH_3$), 1.47 (d, 1.3 H, J = 7.2 Hz, $CHCH_3$), 3.33–3.40 (m, 1 H, $CHCH_3$), 3.50 (d, 0.4 H, J = 2.8 Hz, CHOH), 3.70 (d, 0.6 H, J = 2.8 Hz, CHOH), 4.05 (s, 1.7 H, NCH_3), 4.06 (s, 1.3 H, NCH_3); ^{13}C NMR ($CDCl_3$) ppm 159.1 (s), 157.3 (s), 82.4 (d), 78.4 (d), 35.6 (s), 35.3 (s), 33.3 (d), 33.2 (d), 30.5 (d), 29.5 (d), 26.6 (d), 26.2 (d), 25.3 (q), 19.3 (q), 13.7 (q); IR (mineral oil mull) 3426, 2958, 1737, 1515, 1477, 1459, 1420, 1388, 1093, 1075, 1047, 1010 cm^{-1}; MS for $C_9H_{18}N_4O$ *m/z* (relative intensity) 198 (M^+, 1), 183 (10), 141 (82), 127 (27), 112 (100), 98 (34). Anal. Calcd for $C_9H_{18}N_4O$: C, 54.52; H, 9.15; N, 28.26. Found: C, 54.57; H, 9.23; N, 28.02.

1-Methyl-5-(1-phenoxyethyl)-1*H*-tetrazole (2e). The oil was chromatographed eluting with CH_2Cl_2 to yield **2e** (130 mg, 49%) as a yellow oil which solidified after several days: mp 50–54 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 4.14 (s, 3 H, NCH_3), 5.88 (q, 1 H, J = 6.7 Hz, $CHCH_3$), 6.89–6.92 (m, 2 H, arom), 6.97–7.03 (m, 1 H, arom), 7.24–7.31 (m, 1 H, arom); IR (mineral oil mull) 2925, 1596, 1586, 1496, 1485, 1474, 1223, 1085, 920, 758 cm^{-1}; MS for $C_{10}H_{12}N_4O$ *m/z* (relative intensity) 204 (M^+, 25), 189 (31), 121 (10), 111 (100), 94 (65), 77 (52). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 59.00; H, 6.03; N, 27.15.

1-Methyl-β-phenoxy-α-phenyl-1*H*-tetrazole-5-ethanol (2f). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **2f** (267 mg, 64%, 3:1 mixture of diastereomers) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.83 (d, 0.7 H, J = 4.4 Hz, OH), 2.90 (d, 0.3 H, J = 4.4 Hz, OH), 3.72 (s, 0.8 H, CH_3), 3.74 (s, 2.2 H, CH_3), 5.28 (m, 0.3 H, CHOH), 5.40 (t, 0.7 H, J = 4.4 Hz, CHOH), 5.80 (d, 0.3 H, J = 4.4 Hz, PhOCH), 5.90 (d, 0.7 H, J = 4.4 Hz, PhOCH), 6.80–6.85 (m, 2 H, arom), 6.95–7.03 (m, 1 H, arom), 7.20–7.28 (m, 3 H, arom), 7.33–7.35 (m, 4 H, arom); IR (neat) 3371, 3064, 3033, 1598, 1589, 1494, 1455, 1225, 1058, 755, 700 cm^{-1}; MS for $C_{16}H_{16}N_4O_2$ *m/z* (relative intensity) 296 (M^+, 1), 203 (2), 190 (100), 113 (25), 91 (27), 77 (49). Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44. Found: C, 64.82; H, 5.56.

1-[(1-Methyl-1*H*-tetrazol-5-yl)phenoxymethyl]cyclohexanol (2g). The oil was crystallized from EtOAc/hexanes to yield **2g** (586 mg, 83%) as a white solid: mp 128–129 °C; ^{1}H NMR ($CDCl_3$) δ 1.25–1.38 (m, 2 H, CH_2), 1.45–1.75 (m, 7 H, CH_2), 1.98–2.08 (m, 1 H, CH_2), 2.15–2.18 (m, 1 H, CH_2), 4.12 (s, 3 H, NCH_3), 5.57 (s, 1 H, PhOCH), 6.84–6.87 (m, 2 H, arom), 6.97–7.02 (m, 1 H, arom), 7.21–7.26 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 156.5 (s), 152.0 (s), 129.9 (d), 122.5 (d), 114.7 (d), 77.8 (d), 74.3 (d), 35.6 (q), 34.5 (t), 33.3 (t), 25.1 (t), 21.5 (t), 21.0 (t); IR (mineral oil mull) 3398, 2927, 1601, 1590, 1494, 1445, 1410, 1395, 1316, 1237, 1050, 754 cm^{-1}; MS for $C_{15}H_{20}N_4O_2$ *m/z* (relative intensity) 195 (5), 190 (100), 113 (17). Anal. Calcd for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.57; H, 6.95; N, 19.60.

α-(1,1-Dimethylethyl)-1-methyl-β-phenoxy-1*H*-tetrazole-5-ethanol (2h). The solid was chromatographed eluting with 20% EtOAc/hexanes to yield **2h** (598 mg, 90%, 4:1 mixture of diastereomers) as a white solid: mp 113–118 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 7.1 H, CH_3), 1.08 (s, 1.9 H, CH_3), 3.68 (d, 0.2 H, CHOH), 4.04 (d, 0.8 H, CHOH), 4.10 (s, 0.6 H, NCH_3), 4.16 (s, 2.4 H, NCH_3), 5.85 (d, 0.8 H, OCH), 5.97 (d, 0.2 H, OCH), 6.83–6.90 (m, 2 H, arom), 6.95–7.05 (m, 1 H, arom), 7.20–7.28 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 155.9 (s), 155.7 (s), 153.0 (s), 152.7 (s), 130.1 (d), 129.9 (d), 122.6 (d), 122.5 (d), 115.1 (d), 114.5 (d), 81.4 (d), 80.5 (d), 72.2 (d), 71.7 (d), 35.6 (s), 35.3 (q), 34.8 (q), 26.5 (q), 25.7 (q); IR (mineral oil mull) 3476, 3324, 2925, 1596, 1588, 1495, 1482, 1220, 760 cm^{-1}; MS for $C_{14}H_{20}N_4O_2$ *m/z* (relative intensity) 276 (M^+, 3), 261 (3), 219 (29), 190 (100), 127 (63), 113 (18), 94 (35), 77 (26). Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.80; H, 7.27; N, 20.47.

1-Methyl-5-(1-phenylethyl)-1*H*-tetrazole (2i). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **2i** (189 mg, 72%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.84 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 3.72 (s, 3 H, NCH_3), 4.24 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 7.14–7.17 (m, 2 H, arom), 7.26–7.36 (m, 3 H, arom); IR (neat) 3470, 2983, 1603, 1585, 1514, 1494, 1460, 1099, 1062, 755 cm^{-1}; MS for $C_{10}H_{12}N_4$ *m/z* (relative intensity) 188 (M^+, 13), 159 (9), 145 (7), 132 (12), 105 (100), 91 (11). Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.69; H, 6.38; N, 29.79.

1-Methyl-α,β-diphenyl-1*H*-tetrazole-5-ethanol (2j). The oily solid was recrystallized from CH_2Cl_2/hexanes to yield **2j** (174 mg, 44%, 9:1 mixture of diastereomers) as a white solid: mp 194–200 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 0.2 H, CH_3), 3.69 (s, 2.8 H, CH_3), 4.23 (d, 0.1 H, PhCH), 4.28 (d, 0.9 H, J = 8.5 Hz, PhCH), 5.45 (d, 0.9 H, J = 8.6 Hz, PhCHOH), 5.65 (d, 0.1 H, PhCHOH), 6.87–6.90 (m, 2 H, arom), 7.09–7.12 (m, 2 H, arom), 7.18–7.26 (m, 6 H, arom); ^{13}C NMR ($CDCl_3$) ppm 155.6 (s), 139.9 (s), 134.7 (s), 128.9 (d), 128.6 (d), 128.2 (d), 128.1 (d), 128.0 (d), 126.6 (d), 50.8 (d), 33.5 (q); IR (mineral oil mull) 3270, 2924, 1601, 1584, 1518, 1495, 1487, 1465, 1055, 710 cm^{-1}; MS for $C_{16}H_{16}N_4O$ *m/z* (relative intensity) 280 (M^+, 1), 174 (100), 131 (27), 117 (24). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.34; H, 5.70; N, 19.91.

α-(1,1-Dimethylethyl)-1-methyl-β-phenyl-1*H*-tetrazole-5-ethanol (2l). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **2l** (259 mg, 45%) as a white solid: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9 H, CH_3), 3.87 (s, 3 H, NCH_3), 3.96 (d, 1 H, J = 4.4 Hz, PhCH), 4.35 (d, 1 H, J = 4.4 Hz, CHOH), 7.23–7.35 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) ppm 155.6 (s), 137.2 (s), 128.8 (d), 128.2 (d), 127.7 (d), 82.5 (d), 42.2 (d), 36.0 (d), 33.2 (d), 26.6 (q); IR (mineral oil mull) 3471, 3394, 2923, 1603, 1515, 1497, 1478, 1350, 1048, 736, 697 cm^{-1}; MS for $C_{14}H_{20}N_4O$ *m/z* (relative intensity) 245 (2), 203 (61), 174 (100), 160 (14), 131 (31), 117 (30). Anal. Calcd for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.59; H, 7.67; N, 21.39.

2,5-Diethyl-2*H*-tetrazole (4a). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4a** (217 mg, 48%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 3 H, J = 7.7 Hz, CH_2CH_3), 1.62 (t, 3 H, J = 7.4 Hz, NCH_2CH_3), 2.90 (q, 2 H, J = 7.7 Hz, CH_2CH_3), 4.60 (q, 2 H, J = 7.4 Hz, NCH_2CH_3); IR (neat) 3490, 2982, 1502, 1453, 1184, 1066, 977 cm^{-1}; MS for $C_5H_{10}N_4$ *m/z* (relative intensity) 126 (M^+, 25), 112 (18), 101 (58), 83 (100), 56 (72), 43 (66). Anal. Calcd for $C_5H_{10}N_4$: C, 47.60; H, 7.99. Found: C, 47.71; H, 7.97.

5-Ethyl-α-phenyl-2*H*-tetrazole-2-ethanol (4b). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4b**

(380 mg, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, J = 7.6 Hz, CH_2CH_3), 2.93 (q, 2 H, J = 7.7 Hz, CH_2CH_3), 3.08 (d, 1 H, OH), 4.78 (d, 2 H, J = 7.1 Hz, $CHCH_2$), 5.28–5.35 (m, 1 H, OHCH), 7.36–7.46 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) ppm 167.9 (s), 139.3 (s), 128.8 (d), 128.6 (d), 125.8 (d), 72.3 (d), 59.5 (t), 18.9 (t), 12.2 (q); IR (neat) 3382, 2980, 1707, 1603, 1587, 1501, 1454, 1439, 1403, 1065, 750, 701 cm^{-1}; MS for $C_{11}H_{14}N_4O$ m/z (relative intensity) 208 (1), 189 (1), 175 (1), 164 (9), 146 (7), 112 (100), 107 (62), 83 (52). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.47; N, 25.67. Found: C, 60.67; H, 6.43; N, 25.35. Corrected for 0.63% H_2O, found by Karl Fisher analysis.

1-[[5-Ethyl-2*H*-tetrazol-2-yl]methyl]cyclohexanol (4c). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4c** (478 mg, 50%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.25–1.70 (m, 10 H, CH_2), 1.38 (t, 3 H, J = 7.7 Hz, CH_3), 2.93 (q, 2 H, J = 7.7 Hz, CH_2CH_3), 4.59 (s, 2 H, NCH_2); ^{13}C NMR ($CDCl_3$) ppm 167.9 (s), 71.1 (s), 61.9 (t), 35.0 (t), 25.4 (t), 21.6 (t), 19.0 (t), 12.3 (q); IR (neat) 3411, 2935, 1698, 1501, 1458, 1448, 1193, 1174 cm^{-1}; MS for $C_{10}H_{18}N_4O$ m/z (relative intensity) 210 (M^+, 2), 192 (10), 179 (19), 112 (100), 99 (75). Anal. Calcd for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 57.12; H, 8.63; N, 26.35.

α-(1,1-Dimethylethyl)-5-ethyl-2*H*-tetrazole-2-ethanol (4d). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4d** (474 mg, 66%) as a white solid: mp 60–61 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H, CH_3), 1.38 (t, 3 H, J = 7.6 Hz, CH_2CH_3), 2.92 (q, 2 H, J = 7.6 Hz, CH_2CH_3), 3.83–3.89 (m, 1 H, CHOH), 4.44–4.52 (m, 1 H, NCH_2), 4.74–4.79 (m, 1 H, NCH_2); ^{13}C NMR ($CDCl_3$) ppm 167.9 (s), 77.3 (d), 55.4 (t), 34.3 (s), 25.6 (q), 19.0 (t), 12.3 (t); IR (mineral oil mull) 3310, 2953, 1503, 1480, 1439, 1431, 1411, 1082 cm^{-1}; MS for $C_9H_{18}N_4O$ m/z (relative intensity) 199 (1), 183 (1), 170 (1), 141 (16), 112 (11), 99 (14), 83 (100). Anal. Calcd for $C_9H_{18}N_4O$: C, 54.52; H, 9.15; N, 28.26. Found: C, 54.47; H, 9.50; N, 28.20.

2-Ethyl-5-(phenoxymethyl)-2*H*-tetrazole (4e) and 2-Ethyl-5-(1-phenoxyethyl)-2*H*-tetrazole (4e'). The oil was chromatographed eluting with 10% EtOAc/hexanes. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield **4e'** (137 mg, 24%) as a pale yellow oil and **4e** (337 mg, 64%) as a pale yellow oil. Physical data for **4e'**: ^{1}H NMR ($CDCl_3$) δ 1.62 (t, 3 H, J = 7.4 Hz, CH_2CH_3), 1.80 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 4.62 (q, 2 H, J = 7.4 Hz, CH_2CH_3), 5.70 (q, 1 H, J = 6.6 Hz, $CHCH_3$), 6.91–7.01 (m, 3 H, arom), 7.22–7.28 (m, 2 H, arom); IR (neat) 2989, 1599, 1587, 1494, 1456, 1232, 1064, 755 cm^{-1}; MS for $C_{11}H_{14}N_4O$ m/z (relative intensity) 218 (M^+, 5), 162 (2), 133 (7), 125 (7), 121 (6), 105 (7), 97 (8), 77 (14), 69 (16), 41 (100). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.47; N, 25.67. Found: C, 60.52; H, 6.58; N, 25.44. Physical data for **4e**: ^{1}H NMR ($CDCl_3$) δ 1.66 (t, 3 H, J = 7.4 Hz, CH_2CH_3), 4.67 (q, 2 H, J = 7.4 Hz, CH_2CH_3), 5.33 (s, 2 H, OCH_2), 6.97–7.06 (m, 3 H, arom), 7.26–7.34 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 162.5 (s), 158.0 (s), 129.5 (d), 121.6 (d), 114.8 (d), 60.7 (t), 48.6 (t), 14.5 (q); IR (neat) 2989, 2943, 1600, 1588, 1496, 1461, 1239, 1037, 756 cm^{-1}; MS for $C_{10}H_{12}N_4O$ m/z (relative intensity) 204 (M^+, 100), 161 (2), 133 (5), 119 (94), 107 (8), 91 (40), 83 (43), 77 (94), 65 (56). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.97; H, 6.05; N, 27.21.

5-(Phenoxymethyl)-α-phenyl-2*H*-tetrazole-2-ethanol (4f). The yellow solid was chromatographed eluting with 20% EtOAc/hexanes to yield **4f** (348 mg, 78%) as a white solid: mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 4.77–4.90 (m, 2 H, NCH_2), 5.33 (t, 1 H, CHOH), 5.35 (s, 2 H, OCH_2), 6.98–7.05 (m, 3 H, arom), 7.29–7.43 (m, 7 H, arom); ^{13}C NMR ($CDCl_3$) ppm 162.5 (s), 157.7 (s), 138.9 (s), 129.4 (s), 128.7 (s), 128.6 (s), 126.7 (d), 125.7 (d), 121.5 (d), 114.7 (d), 72.1 (d), 60.4 (t), 59.6 (t); IR (mineral oil mull) 3437, 2925, 1601, 1587, 1522, 1496, 1484, 1365, 1245 cm^{-1}; MS for $C_{16}H_{16}N_4O_2$ m/z (relative intensity) 296 (M^+, 68), 190 (19), 107 (100), 94 (73), 79 (61), 77 (59). Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.70; H, 5.53; N, 18.84.

1-[[5-(Phenoxymethyl)-2*H*-tetrazol-2-yl]methyl]cyclohexanol (4g). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4g** (534 mg, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.25–1.70 (m, 10 H, CH_2), 2.44 (s, 1 H, OH), 4.55 (s, 2 H, NCH_2), 5.36 (s, 2 H, OCH_2), 6.98–7.04 (m, 3 H, arom), 7.26–7.33 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 162.5 (s), 157.7 (s), 129.4 (d), 121.6 (d), 114.9 (d), 71.1 (s), 62.3 (t), 60.6 (t), 34.9 (t), 25.2 (t), 21.5 (t); IR (neat) 3429, 2936, 1600, 1588, 1496, 1459, 1449, 1241, 1220, 1037, 755 cm^{-1}; MS for $C_{15}N_{20}N_4O_2$ m/z (relative intensity) 288 (M^+, 40), 190 (30), 119 (14), 99 (97), 94 (100). Anal. Calcd for $C_{15}N_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.24; H, 6.97; N, 19.43.

α-(1,1-Dimethylethyl)-5-(phenoxymethyl)-2*H*-tetrazole-2-ethanol (4h). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4h** (681 mg, 95%) as a colorless oil which solidified after several days: mp 53–56 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H, CH_3), 2.35 (bs, 1 H, OH), 3.89–3.93 (m, 1 H, CHOH), 4.54–4.62 (m, 1 H, NCH_2), 4.77–4.82 (m, 1 H, NCH_2), 5.34 (s, 2 H, $PhOCH_2$), 6.97–7.05 (m, 3 H, arom), 7.26–7.34 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 162.4 (s), 157.7 (s), 129.3 (d), 121.5 (s), 114.6 (d), 77.1 (d), 60.4 (t), 55.6 (t), 34.2 (s), 25.4 (q); IR (neat) 3425, 2960, 1600, 1588, 1496, 1461, 1366, 1241, 1219, 1037, 754 cm^{-1}; MS for $C_{14}H_{20}N_4O_2$ m/z (relative intensity) 276 (M^+, 59), 261 (4), 219 (23), 177 (17), 119 (37), 94 (74), 69 (100), 57 (49), 43 (99). Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.77; H, 7.24; N, 20.23.

2-Methyl-5-(1-phenylethyl)-2*H*-tetrazole (4i). The oil was chromatographed eluting with 9/1 hexanes/EtOAc to yield **4i** (153 mg, 54%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.75 (d, 3 H, J = 7.2 Hz, $CHCH_3$), 4.29 (s, 3 H, NCH_3), 4.44 (q, 1 H, J = 7.3 Hz, $CHCH_3$), 7.20–7.36 (m, 5 H, arom); IR (neat) 2978, 1604, 1494, 1453, 1055, 1028, 755, 730 cm^{-1}; MS for $C_{10}H_{12}N_4$ m/z (relative intensity) 188 (M^+, 6), 160 (16), 117 (8), 105 (100). Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.66; H, 6.49; N, 29.58.

2-Methyl-α,β-diphenyl-2*H*-tetrazole-5-ethanol (4j). The oil was chromatographed eluting with 20% EtOAc/hexanes to yield **4j** (221 mg, 56%) as a white solid: mp 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 4.24 (s, 3 H, CH_3), 4.59 (d, 1 H, J = 7.3 Hz, PhCH), 5.53 (d, 1 H, PhCHOH), 7.20–7.43 (m, 10 H, arom); ^{13}C NMR ($CDCl_3$) ppm 166.6 (s), 141.0 (s), 137.0 (s), 129.4 (d), 128.6 (d), 128.2 (d), 127.9 (d), 127.7 (d), 126.8 (d), 76.2 (d), 51.6 (d), 34.9 (q); IR (mineral oil mull) 3363, 2924, 1658, 1603, 1586, 1497, 1487, 1450, 1424, 1402, 1389, 1041, 1033, 745 cm^{-1}; MS for $C_{16}H_{16}N_4O$ m/z (relative intensity) 235 (1), 174 (100), 146 (11), 116 (16), 103 (24), 77 (20). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.84; H, 5.58; N, 20.12. Corrected for 5.65% H_2O, found by Karl Fisher analysis.

1-[(2-Methyl-2*H*-tetrazol-5-yl)phenylmethyl]cyclohexanol (4k). The white solid was recrystallized from CH_2Cl_2/hexanes to yield **4k** (443 mg, 56%) as a white solid: mp 113–115 °C; ^{1}H NMR ($CDCl_3$) δ 1.15–1.70 (m, 10 H, CH_2), 3.05 (bs, 1 H, OH), 4.33 (s, 3 H, CH_3), 4.38 (s, 1 H, PhCH), 7.22–7.33 (m, 3 H, arom), 7.48–7.51 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 166.8 (s), 137.0 (s), 129.9 (d), 128.0 (d), 127.0 (d), 72.9 (s), 52.8 (d), 39.3 (q), 37.1 (t), 35.2 (t), 25.4 (t), 21.8 (t), 21.6 (t); IR (mineral oil mull) 3495, 2921, 1599, 1493, 1483, 1446, 1414, 1392, 986, 746 cm^{-1}; MS for $C_{15}H_{20}N_4O$ m/z (relative intensity) 272 (M^+, 1), 229 (1), 187 (1), 174 (100), 103 (18). Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 65.97; H, 7.51; N, 20.59.

α-(1,1-Dimethylethyl)-2-methyl-β-phenyl-2*H*-tetrazole-5-ethanol (4l). The oil was chromatographed eluting with CH_2Cl_2 to yield **4l** (331 mg, 44%) as a white solid: mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 9 H, CH_3), 2.48 (bs, 1 H, OH), 4.17 (d, 1 H, J = 6.0 Hz, CHOH), 4.29 (s, 3 H, NCH_3), 4.54 (d, 1 H, J = 6.6 Hz, PhCH), 7.25–7.33 (m, 3 H, arom), 7.51–7.54 (m, 2 H, arom); ^{13}C NMR ($CDCl_3$) ppm 168.5 (s), 138.2 (s), 129.5 (d), 128.4 (d), 127.2 (d), 79.6 (d), 45.4 (d), 39.1 (q), 35.5 (s), 26.4 (q); IR (mineral oil mull) 3470, 2956, 2926, 1624, 1480, 1451, 1384, 1357, 1086, 1080, 753 cm^{-1}; MS for $C_{14}H_{20}N_4O$ m/z (relative intensity) 245 (2), 203 (9), 174 (100), 146 (16), 116 (23), 103 (31). Anal. Calcd for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.80; H, 7.82; N, 21.65.

5-Ethyl-α-phenyl-1*H*-tetrazole-1-ethanol (5). Tetrazole **1a** (500 mg, 4.5 mmol) was added to a flame-dried, round-bottom flask and dissolved in Et_2O (38 mL). The solution was cooled to −78 °C, and t-BuLi (2.9 mL, 1.7 M in pentane) was added dropwise. The reaction was stirred at −78 °C for 30 min. Benzaldehyde (0.51 mL, 5.0 mmol) was added, and the reaction was allowed to warm to 20 °C. Et_2O (190 mL) was added. The organic layer was then washed with 15% HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and H_2O (40 mL). The organic portion was dried, filtered, and concentrated in vacuo to yield a yellow

oil. The oil was chromatographed eluting with 40% EtOAc/hexanes. Material was rechromatographed eluting with 2% CH_3OH/CH_2Cl_2. Fractions homogenous by TLC were combined and concentrated in vacuo to yield **5** (168 mg, 17%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 7.6 Hz, CH_2CH_3), 2.66–2.86 (m, 2 H, CH_2CH_3), 3.00 (d, 1 H, OH), 4.31–4.39 (m, 1 H, CH_2), 4.44–4.50 (m, 1 H, CH_2), 5.24–5.30 (m, 1 H, CHOH), 7.36–7.42 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) ppm 156.9 (s), 139.8 (s), 128.9 (d), 128.7 (d), 125.8 (d), 72.7 (d), 54.0 (t), 16.8 (t), 11.2 (q); IR (neat) 3347, 2985, 2943, 1586, 1522, 1495, 1455, 1424, 1065, 702 cm^{-1}; MS for $C_{11}H_{14}N_4O$ m/z (relative intensity) 218 (M^+, 1), 175 (3), 146 (2), 112 (100), 107 (58), 79 (51), 77 (38), 56 (52). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.47; N, 25.67. Found: C, 60.66; H, 6.50; N, 25.58. Corrected for 0.99% H_2O, found by Karl Fisher analysis.

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