Conversion of 4-Amino-4*H*-1,2,4-triazole to 1,3-Bis(1*H*-azol-1-yl)-2-aryl-2-propanols and 1-Phenacyl-4-[(benzoyl or 4-toluenesulfonyl)-imino]-(1*H*-1,2,4-triazolium) Ylides [1]

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Dedicated to the memory of Dr. Roland K. Robins

A series of 1,3-bis(1*H*-azol-1-yl)-2-aryl-2-propanols **17** were synthesized in an one-pot procedure by reacting 1-aryl-2-(1*H*-1,2,4-triazol-1-yl)- or 1-aryl-2-(1*H*-imidazol-1-yl)ethanones with dimethylsulfoxonium methide in the presence of either 1,2,4-triazole or imidazole. The aromatic groups in **17** were either 4-bromo-, 4-chloro-, 2,4-dichloro- or 2,4-difluorophenyl. 4-Amino-4*H*-1,2,4-triazole was acylated with either benzoyl or 4-toluenesulfonyl chloride to afford [4-(benzoyl or 4-toluenesulfonyl)amino]-4*H*-1,2,4-triazole. Subsequent alkylations with 4-bromo- or 4-chlorophenacyl bromide produced 1-(4-bromo- or 4-chlorophenacyl)-4-[(benzoyl- or 4-toluenesulfonyl)amino]-1*H*-1,2,4-triazolium bromides. Neutralizations of these salts provided the corresponding ylides.

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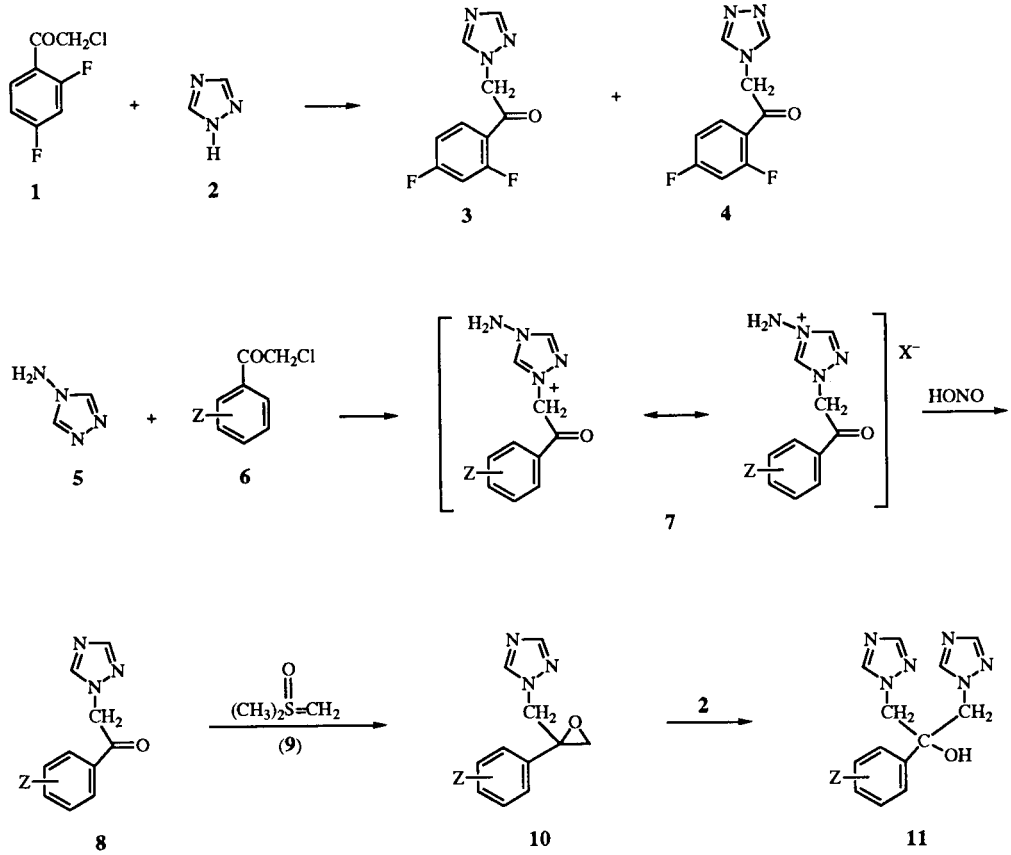
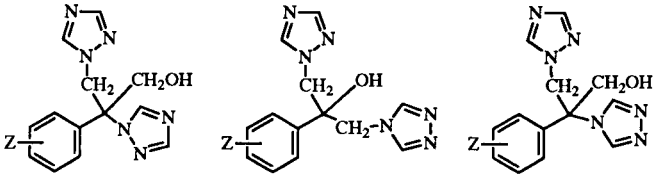
Imidazole or 1,2,4-triazole are the heterocyclic rings of choice and are essential structural features of many of the potent azole fungicides [2,3]. Among a plethora of such highly active compounds stands out fluconazole [1,3-bis-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-2-propanol, **11d**] which was introduced in 1990 as one of the most effective water-soluble oral antifungal agents [2-4]. This paper presents the synthesis of some new 1,3-bis(1*H*-azol-1-yl)-2-aryl-2-propanols **17**, as well as their ^1H and ^{13}C nuclear magnetic resonance (nmr) spectra.



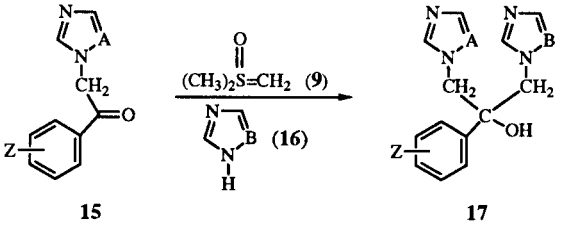
1,3-Bis(1*H*-azol-1-yl)-2-aryl-2-propanols **17**.

Several routes have been developed for the synthesis of 1,3-(1*H*-imidazol-1-yl or 1*H*-1,2,4-triazol-1-yl)-2-haloaryl-2-propanols **17**. To prepare symmetrical members, one approach is to add an aromatic Grignard reagent to 1,3-dichloroacetone to produce a 1,3-dichloro-2-aryl-2-propanol. Displacement of the chloro groups by either imidazole or 1,2,4-triazole leads to **17**. This sequence can be reversed by reacting 1,3-dichloroacetone, first with an azole to form the 1,3-bis(*N*-azolyl)acetone, then with an organometallic reagent to produce **17** (A = B = CH or N) [5a], [5c]. By far the most versatile approach, particularly for the synthesis of unsymmetrical examples of **17**, consists of reacting 1-aryl-2-(1*H*-imidazol-1-yl or 1*H*-1,2,4-triazol-1-yl)ethanones with **9**, (generated, *in situ*, from trimethylsulfoxonium iodide and a base) to form 1-(1*H*-imidazol-1-yl or 1*H*-1,2,4-triazol-1-yl)-2-aryl-2,3-epoxypropanes **10**. Ring opening of such epoxides by either imidazole or 1,2,4-triazole furnishes **17** [5a], [5d].

The synthesis of fluconazole is chosen to illustrate some of the problems associated with earlier processes. The apparent straight-forward displacement of 2-chloro-2′,4′-difluoroacetophenone (**1**) by 1,2,4-triazole (**2**) provides 1-(2,4-difluorophenacyl)-1*H*-1,2,4-triazole (**3**) in only 40% yield, after an extensive work-up [5a]. Theoretically, among the byproducts could be some of the isomeric 4-(2,4-difluorophenacyl)-4*H*-1,2,4-triazole (**4**), but this problem of competing *N*-4 alkylation is never mentioned [5]. However, the problem of preparing 1-alkyl-1*H*-1,2,4-triazoles in high yield has been solved.



12 **13** **14**



15 **17**

where Z is as follows: **a** = 4-Br
b = 4-Cl
c = 2,4-Cl_2
d = 2,4-F_2

Three groups have published recently elegant syntheses of 1-phenacyl-1*H*-1,2,4-triazoles **8** [6-8] which begins with the quaternization of commercially available 4-amino-4*H*-1,2,4-triazole (**5**) [9] with phenacyl halides **6** to form pure **7** [6-8]. Diazotization of **7** (with the loss of nitrous oxide) readily provides **8**, also in excellent yield [6-8]. We have found that **3** can be made in excellent yield in this way. In general, phenacyl halides work extremely well. But, for reasons not yet understood, quaternization of **5** with 1,3-dichloroacetone produces intractable mixtures, even under mild conditions, containing little or no analogous quaternary ammonium salts. Selected proton and carbon-13 nmr data of **7** and **8** are assembled in Table 1.

The conversion of **8** to 1,3-bis-(1*H*-1,2,4-triazol-1-yl)-2-aryl-2-propanols (**11**) was initially accomplished in two steps [5a]. Reaction of **8** with **9** leads to an epoxide **10**, which can be isolated, but tends to be contaminated with starting material and other compounds (nmr) and is relatively difficult to purify. Even, when **10** is reacted immediately with **2**, the yield of **11** is only moderate [5a], [5c]. While ring-opening is expected to take place at the least hindered site of **10** to form **11**, one cannot rule out that **2** may attack the tertiary carbon of **10** to give some **12**. Furthermore, the tautomers of **2**, and the ambident nature of the anion of **2**, suggests that *N*-4 can also attack **10** to create two more isomers, namely, **13** and **14**. Some recently published ring openings of unsymmetrical oxiranes by **2** support regiospecific ring attack at the least hindered site by either *N*-1 (or *N*-2), rather than *N*-4 [10]. One can surmise that in **2** the proximity of the *vicinal* ring nitrogens (*N*-1, *N*-2) impart enhanced nucleophilicity, due to the "α-effect" [11] to these neighboring nitrogens, rather than for isolated *N*-4.

The convenient one-pot method for reacting **3** with trimethylsulfoxonium iodide, powdered (85%) potassium hydroxide pellets and **2** in hot *t*-butyl alcohol lends itself to a facile synthesis of fluconazole (**11d**, 38%), which represents a better yield than the one reported [5c]. Such a procedure obviates the problem of isolating and purifying the rather labile intermediate epoxide **10d** [5a]. This one-pot procedure was extended to the synthesis of the new 4-bromo analog **11a** (64%) and to several known ones, **11b**, **11c**.

To prepare unsymmetrical 1-(1*H*-1,2,4-triazol-1-yl)-2-aryl-3-(1*H*-imidazol-1-yl)-2-propanols, we chose to commence with pure 1-phenacyl-1*H*-1,2,4-triazoles **15** (A = N) in a reaction with **9** in the presence of imidazole **16** (B = CH). As expected, the intermediate epoxide opens regioselectively to provide pure **17a-d** (A = N, B = CH) which in keeping with a number of recently published ring opening of unsymmetrical epoxides with imidazole to furnish only one alcohol [10d], [12]. Only one of the four of such "mixed" azolyl alcohols **17c** (A = N, B = CH) had been

Table 1

Selected Proton and Carbon-13 Chemical Shifts for **7** and **8**

Compound	Solvent [a]	Z	X	Proton NMR Signals				Carbon-13 NMR Signals			
				CH_2	H-3	H-5	NH_2	CH_2	C-3	C-5	C=O
7a	D	4-Br [b]	Br	6.32 (s)	10.24 (s)	9.38 (s)	7.23 (s)	58.4	145.1	144.0	189.9
7b	D	4-Cl	Br	6.36 (s)	10.30 (s)	9.36 (s)	[d]	58.5	145.0	143.9	189.6
7c	D	2,4-Cl_2 [c]	Cl	6.26 (s)	10.43 (s)	9.36 (s)	7.26 (s)	59.9	144.9	143.7	190.5
7d	D	2,4-F_2	Cl	6.18 (d) [J = 2.7 Hz]	10.44 (s)	9.39 (s)	7.31 (s)	60.5	144.7	143.6	187.1
8a	D	4-Br	–	5.99 (s)	8.51 (s)	8.12 (s)	–	55.1	151.2	145.5	191.9
8b	C	4-Cl	–	5.68 (s)	8.27 (s)	8.03 (s)	–	55.1	151.2	145.5	191.6
8c	C	2,4-Cl_2 [c]	–	5.62 (s)	7.99 (s)	8.24 (s)	–	57.9	152.1	144.7	192.3
8d	C	2,4-F_2	–	5.60 (d) [J = 3.3 Hz]	8.04 (s)	8.22 (s)	–	58.4	152.0	144.9	187.7

[a] Solvent C is deuteriochloroforml; Solvent D is deuteriodimethyl sulfoxide. [b] Reported in ref [6], mp 221°. [c] Mp for **7c** in ref [7] is 214-215° and for **8c** is 115-116°. [d] Proton signal for NH_2 is buried amongst aromatic proton signals.

Table 2

Carbon-13 Chemical Shifts of 1,3-Bis(azolyl)-2-aryl-2-propanols

Solvent [a]	Structure **17** A	B	Z	Mp (°C)	lit Mp (°C)	CH_2 (A)	CH_2 (B)	C-OH	Azole Ring A 2	3	4	5	Azole Ring B 2	3	4	5
C	N	N	4-Br	147-150	–	55.9	55.9	75.8	–	152.1	–	144.8	–	152.1	–	144.8
D	N	N	4-Br	147-150	–	56.1	56.1	74.6	–	150.8	–	145.1	–	150.8	–	145.1
C	N	N	4-Cl [b]	103-104	153-155	56.0	56.0	75.7	–	152.1	–	144.8	–	152.1	–	144.8
C	N	N	2,4-Cl_2 [b]	183-187	183-186	53.5	53.5	76.7	–	151.7	–	144.6	–	151.7	–	144.6
C	N	N	2,4-F_2 [c]	135-136	138-140	54.9	54.9	75.3	–	151.9	–	144.6	–	151.9	–	144.6
C	CH	N	4-Br	158-159	–	54.2	56.2	75.1	138.2	–	127.7	120.7	–	151.4	–	144.7
C	CH	N	4-Cl	139-140	–	54.4	56.4	75.4	138.3	–	128.1	120.5	–	151.7	–	144.7
C	CH	N	2,4-Cl_2 [b]	170-171	169-170	53.2	51.8	77.1	138.2	–	128.8	120.3	–	152.1	–	144.2
C	CH	N	2,4-F_2	147-148	–	53.4	55.0	75.4	138.2	–	128.5	120.3	–	151.8	–	144.4
D	CH	CH	4-Br	123-126	–	54.0	54.0	75.0	137.8	–	127.4	120.2	137.8	–	127.4	120.2
D	CH	CH	4-Cl	123-130	–	54.1	54.1	75.4	138.1	–	127.7	120.6	138.1	–	127.7	120.6
C	CH	CH	2,4-Cl_2 [b]	165-168	160-175	52.1	52.1	76.6	138.2	–	128.2	120.1	138.2	–	128.2	120.1
C	CH	CH	2,4-F_2	133-136	–	53.6	53.6	75.4	138.2	–	128.3	120.1	138.2	–	128.3	120.1

[a] Solvent C is deuteriochloroform; Solvent D is deuteriodimethyl sulfoxide. [b] Reported in ref [5c]. [c] Reported in ref [5a].

Table 3

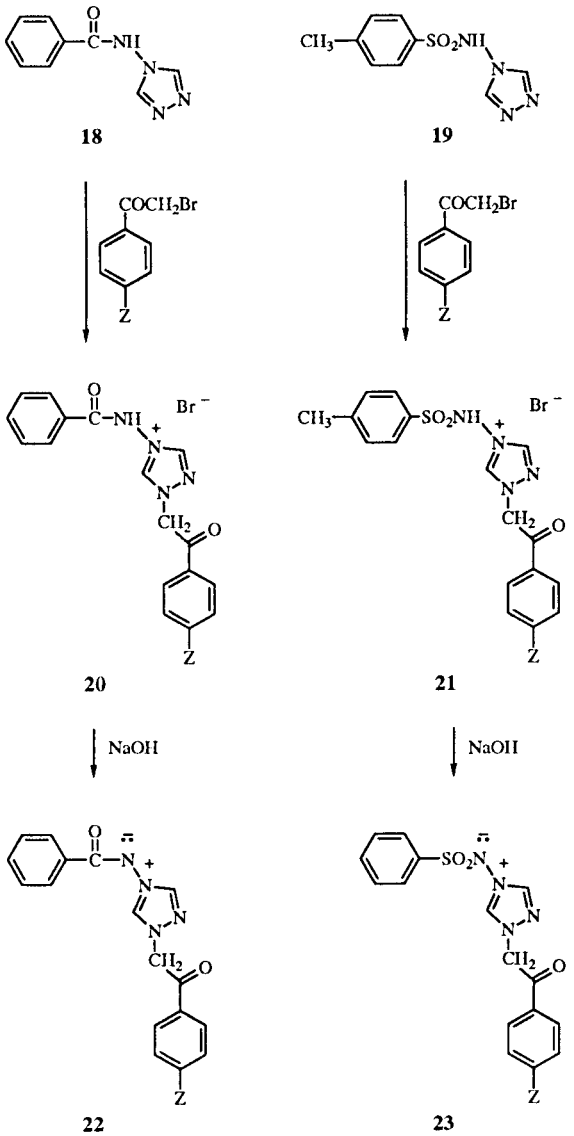
Selected Proton NMR Chemical Shifts of **17**

Solvent [a]	Structure **17** A	B	Z	Methylene Protons CH*H'* (A)	CH*H'* (A)	CH*H'* (B)	CH*H'* (B)	Azole Ring A 2	3	4	5	2	3	4	5
C	N	N	4-Br	4.40	4.51	4.40	4.51	–	7.96	–	7.87	–	7.96	–	7.87
D	N	N	4-Cl	4.42	4.52	4.42	4.52	–	7.97	–	7.89	–	7.97	–	7.89
C	N	N	2,4-Cl_2	4.58	5.07	4.58	5.07	–	8.09	–	7.84	–	8.09	–	7.84
C	N	N	2,4-F_2	4.46	4.75	4.46	4.75	–	8.06	–	7.85	–	8.06	–	7.85
C	CH	N	4-Br	4.22	4.29	4.37	4.45	7.22	–	6.73	6.61	–	7.90	–	7.81
C	CH	N	4-Cl	4.24	4.30	4.39	4.45	7.22	–	6.72	6.61	–	7.89	–	7.81
C	CH	N	2,4-Cl_2	4.41	4.70	4.44	5.26	7.37	–	6.85	6.84	–	7.96	–	7.80
D	CH	N	2,4-F_2	4.31	4.50	4.50	4.72	7.38	–	6.72	6.34	–	8.31	–	7.82
D	CH	CH	4-Br	3.68	3.81	3.68	3.81	6.76	–	6.24	6.22	6.76	–	6.24	6.22
D	CH	CH	4-Cl	4.20	4.45	4.20	4.45	7.30	–	6.83	6.71	7.30	–	6.83	6.71
C	CH	CH	2,4-Cl_2	4.30	4.85	4.30	4.85	7.32	–	6.88	6.87	7.32		6.88	6.87
C	CH	CH	2,4-F_2	4.21	4.46	4.21	4.46	7.28	–	6.85	6.84	7.28	–	6.85	6.84

described before [5c]. This one-pot procedure is equally applicable to the synthesis of four 1,3-bis(1*H*-imidazol-1-yl)-2-aryl-2-propanols **17a-d** (A = B = CH), one of which had been described before, namely **17c**, [5c]. Starting from the requisite *N*-phenacylimidazoles, the reaction with **9** and imidazole **16** (B = CH) produces such compounds.

Selected nmr data of these azolyl alcohols **17** are listed in Tables 2 and 3. The expected chemical shifts are in accord with published parameters for such azole derivatives [13]. As expected, methylene protons attached to the 1,2,4-triazole ring are somewhat more deshielded to those adjacent to the imidazole ring of **17**. The triazole system is more electronegative (compared to imidazole). These *N*-methylene proton resonances appeared as AB quartets,

with a geminal coupling constant of 14.1 ±0.3 Hz.



4-*N*-Acylimino-1-alkyl-1*H*-1,2,4-triazolium Ylides.

Alkylations and acylations of 4-amino-4*H*-1,2,4-triazole (**5**) are well documented in the literature. Furthermore, the chemistry, and in particular the photochemistry, of such products has been examined in some detail [6], [14]. It has been reported that 4-acylamino-1-alkyl-1*H*-1,2,4-triazolium salts are conveniently prepared by acylating the 4-amino group of **5** first, followed by alkylation of *N*-1 of these 4*H*-substituted 1,2,4-triazoles. However, the reverse procedure, namely quaternization of *N*-1 of **5** first, followed by acylation of the 4-amino group is very much in vogue [14b], [14f], [14g]. We chose to acylate the 4-amino group of **5** first with either benzoyl or 4-toluenesulfonyl chloride to obtain **18** and **19**. Alkylation of **18** and **19** with 4-chloro- or 4-bromophenacyl bromide yielded salts **20** and **21**, respectively. Neutralization of these salts gave rise to stable ylides **22** and **23**. Proton chemical shifts of such triazolium salts have been reported [14b], [14c], [14h]. Salts and ylides of type **20-23** have chemical shifts for H-3 and H-5 of the triazolium ring between 8.8-9.8 and 9.7-10.8 ppm, respectively [14c]. These shifts can vary as much as 0.5 ppm upon change of solvents (water, deuterium oxide, deuteriochloroform and deuteriodimethyl sulfoxide). Furthermore, it was reported that salts like **20, 21** exchange H-5 readily in deuterium oxide, while the same H-D exchange takes place in the ylides provided that sodium deuteroxide is added [14c]. Typical carbon-13 chemical shifts of unsymmetrical triazolium rings are not in the literature and we report those for **20-23** in Table 4. However, due to the proximity of the chemical shifts for C-3 and C-5 (as little as 0.3 ppm), unequivocal assignments could not be made with any degree of certainty.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra (at 300 and 75.4 MHz, respectively) were recorded in deuteriochloroform (solvent C) or in deuteriodimethyl sulfoxide (solvent D) on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are designated as singlets (s), doublets (d), triplets (t),

Table 4

Selected ^{13}C Chemical Shifts of 1,2,4-Triazolium Salts **20** and **21**, and Ylides **22** and **23** in Deuteriodimethyl Sulfixide

4-Subsitutent in Triazolium Ring	Z	Anion for Salt	Triazolium Ring C-3 and C-5	CH_2	Phenacyl C=O	Benzoyl C=O	CH_3
C_6H_5CONH	Cl	Br^-	145.7, 145.3	59.1	189.3	166.0	–
C_6H_5CON	Cl	–	143.0, 141.3	57.9	190.3	167.8	–
C_6H_5CONH	Br	Br^-	145.7, 145.4	59.1	189.6	165.9	–
C_6H_5CON	Br	–	143.1, 141.5	57.9	190.5	167.7	–
$4\text{-}CH_3C_6H_4SO_2NH$	Cl	Br^-	144.9, 144.1	58.5	189.5	–	21.0
$4\text{-}CH_3C_6H_4SO_2N$	Cl	–	145.2, 143.5	58.1	189.8	–	20.8
$4\text{-}CH_3C_6H_4SO_2NH$	Br	Br^-	144.8, 144.3	58.8	189.7	–	21.2
$4\text{-}CH_3C_6H_4SO_2N$	Br	–	145.2, 143.5	58.0	190.0	–	20.8

multiplets (m), and if broad, by br. A number of nmr parameters are compiled in Tables 1-4. Electron impact (EI) or chemical ionization (CI) mass spectra were obtained on a Finnigan mass spectrometer, Model 4510, at 70 eV, ionization temperature, 120-140°. Ions less than 5% of the base peak, and ions below m/z 50, are not reported, unless deemed important. Ions bearing halo groups are recorded in sets with their respective intensities bracketed together.

Research chemicals and solvents were purchased from Aldrich Chemical Co., Milwaukee, WI, unless specified otherwise, and were used as supplied. Pyridine, *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide were stored over 4Å molecular sieves, once the container had been opened. Petroleum ether refers to that fraction boiling between 30-60°. Evaporation or removal of solvents, *in vacuo*, was carried out by means of a rotary flash evaporator at the water pump (20-30 torr) at about 40°. Thin layer chromatograms (tlc) were developed on Aldrich silica gel coated polyester plates containing a 254 nm fluorescent indicator. Column chromatography was performed on silica gel (grade 60, 230-400 mesh). Elemental analyses were carried out by Midwest Microlab, Indianapolis, IN.

1-(2,4-Difluorophenacyl)-4-amino-(1*H*-1,2,4-triazolium) Chloride (**7d**).

Of the three solvents reported for the alkylation of **5**, to prepare **7**, namely, acetonitrile, 2-propanol and DMF [6-8], we found that the reaction proceeds best in acetonitrile.

A solution of 2-chloro-2',4'-difluoroacetophenone (**6d**, 5.54 g, 0.029 mole) and **5** (2.56 g, 0.031 mole) in acetonitrile (50 ml) was refluxed for 16 hours. Upon cooling, the colorless salt **7d** (7.0 g, 88%) was collected, washed with acetonitrile (20 ml), and dried, *in vacuo*, mp 193-194°.

Anal. Calcd. for $C_{10}H_9F_2ClN_4O$: C, 43.73; H, 3.22; N, 20.40. Found: C, 43.78; H, 3.22; N, 20.34.

1-(2,4-Difluorophenacyl)-1*H*-1,2,4-triazole (**8d**).

To a vigorously stirred ice-cold aqueous suspension of **7d** [7.0 g, (0.025 mole) in 40 ml] was added concentrated hydrochloric acid (4.25 ml, 0.51 mole). A solution of sodium nitrite (1.85 g, 0.027 mole) in water (10 ml) was added dropwise, with vigorous stirring, at a rate to prevent excessive foaming (30 minutes). The mixture was permitted to come to room temperature and was stirred for another 15 minutes. Upon neutralization with concentrated ammonium hydroxide, colorless **8d** (4.17 g, 73%) was filtered, washed with water and dried, mp 105-106°, lit [5a] mp 103-105°.

1-(4-Bromophenacyl)-1*H*-1,2,4-triazole (**8a**).

This ketone was obtained after diazotization of **7a** [8a] (7.60 g, 0.021 mole), as described above. Ketone **8a** (4.86 g, 87%) was recrystallized from ethanol, mp 175-176°; lit [8a] mp 165-166°; ms: (EI) m/z (relative intensity) 267, 265 (M^+, 2.3, 2.1), 185, 183 (100, 97), 157, 155 (22, 20), 76 (17), 75 (13), 51 (5.9).

Anal. Calcd. for $C_{10}H_8BrN_3O$: C, 45.14; H, 3.03; N, 15.79. Found: C, 44.99; H, 2.85; N, 15.70.

1-(4-Chlorophenacyl)-4-amino-1*H*-1,2,4-triazolium Bromide (**7b**).

A stirred mixture of 2-bromo-4'-chloroacetophenone (11.68 g, 0.050 mole) and **5** (4.41 g, 0.053 mole) in 2-propanol (250 ml) was heated under reflux (24 hours). Upon cooling, the colorless salt (13.35 g, 84%) was filtered, washed with cold 2-propanol and dried, mp 204-206°. Recrystallization from ethanol raised the mp to 206-208°. After this work had been completed, the same salt was reported, without a mp [8a].

Anal. Calcd. for $C_{10}H_{10}BrClN_4O$: C, 37.82; H, 3.17; N, 17.64. Found: C, 37.69; H, 2.99; N, 17.62.

1-(4-Chlorophenacyl)-1*H*-1,2,4-triazole (**8b**).

A solution of **7b** (6.66 g, 0.021 mole) in 50 ml of water containing 3.05 ml of concentrated hydrochloric acid was diazotized by the dropwise addition of sodium nitrite (1.52 g, 0.022 mole) in a saturated aqueous solution (15 ml) at 0-5°. The reaction mixture was then allowed to warm to room temperature (1 hour) and was then neutralized by the addition of ammonium hydroxide solution (*p*H 7). The product (3.77 g, 81%) was filtered and recrystallized from ethanol, mp 150-151°. This ketone was also reported, after we had completed this work, mp 143-145° [8a]; ms: (CI, methane at 0.2 torr, ionization temperature, 327°) m/z (relative intensity) 252, 250 [$(M + C_2H_5)^+$, 3.7, 27], 224, 222 [$(M + 1)^+$, 30, 100], 223 (21), 139 (10).

Anal. Calcd. for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.14; H, 3.56; N, 19.07.

General Procedure for the Synthesis of 1,3-Bis(1*H*-azol-1-yl)-2-aryl-2-propanols **11** and **17**.

The *N*-phenacylazole (1 mmole) was reacted (18-48 hours) with the requisite azole, (1.1 mmoles), in the presence of trimethylsulfoxonium iodide (1.25 mmoles), and powdered potassium hydroxide pellets (85%, 2.5 mmoles), dissolved in boiling *t*-butyl alcohol (approximately 5-10 ml). Workup consisted of evaporating the reaction mixture, *in vacuo*, dilution with water (10-20 ml) and extraction with methylene chloride (4 x 5-10 ml). The extract was dried (magnesium sulfate) and the solvent removed, *in vacuo*. Frequently, trituration with ether gave rise to the majority of the pure product, which could then be recrystallized, if necessary. Alternatively, the crude product was purified by means of column chromatography. Details of several preparations are provided.

1,3-Bis(1*H*-1,2,4-triazol-1-yl)-2-(4-chlorophenyl)-2-propanol (**11b**).

A mixture of **7b** [8a, 14a] (1.11 g, 0.005 mole), **2** (0.38 g, 0.006 mole), trimethylsulfoxonium iodide (1.31 g, 0.007 mole) and powdered 85% potassium hydroxide (0.70 g, 0.013 mole) in *t*-butyl alcohol (50 ml) was refluxed for 48 hours. Solvents were removed, *in vacuo*, the residue suspended in water (50 ml) and extracted with methylene chloride (4 x 25 ml). The organic phase was dried (magnesium sulfate) and evaporated, *in vacuo*, to provide a yellow oil which solidified upon trituration with ether. Recrystallization from ethyl acetate provided **11b** (0.76 g, 50%), mp 103-104°. This compound had been reported from an initial reaction of 1,3-dichloroacetone with 4-chlorophenylmagnesium iodide to give 1,3-dichloro-2-(4-chlorophenyl)-2-propanol (85%), followed by displacement by **2** (using sodium hydride in DMF at 100° for 6 hours) to give **11b**, (50%), mp 153-155° [5c].

Anal. Calcd. for $C_{13}H_{13}ClN_6O \cdot H_2O$: C, 48.38; H, 4.69; N, 26.04. Found: C, 48.40; H, 4.59; N, 25.45.

1,3-Bis(1*H*-1,2,4-triazol-1-yl)-2-(4-bromophenyl)-2-propanol (**11a**).

A mixture of **8a** (4.17 g, 0.016 mole), **2** (1.38 g, 0.020 mole), trimethylsulfoxonium iodide (4.95 g, 0.023 mole) and powdered 85% potassium hydroxide (2.95 g, 0.05 mole) in *t*-butyl alcohol (50 ml) was refluxed for 24 hours. Solvents were evaporated, *in vacuo*, and the residue suspended in water (100 ml) and extracted with methylene chloride (4 x 25 ml). The organic phase was dried

(magnesium sulfate), evaporated, *in vacuo*, to furnish a yellow oil which solidified under ether. This brown solid was filtered to give **11a** (4.0 g, 64%). Chromatographed on silica gel, the major fraction being eluted by methylene chloride-ethanol (7:3) to give **11a**, mp 147-150°; R_f = 0.62 (methylene chloride-ethanol, 9:1); ms: (EI) m/z (relative intensity) 351, 349 [$(M + 1)^+$, 13, 11], 282, 280 (8.8, 11), 268, 266 (44, 44), 264, 262 (6.1, 5.7), 226, 224 (11, 8.9), 199, 197 (8.6, 8.9), 185, 183 (12, 18), 171, 169 (35, 36), 157, 155 (12, 12), 132 (9.4), 125 (54), 118 (13), 117 (6.5), 102 (11), 91 (8.0), 90 (29), 89 (18), 83 (56), 82 (100), 77 (13), 76 (15), 75 (18), 70 (19), 65 (7.2), 63 (9.0), 56.3 (13), 55 (51), 51 (10), 50 (14).

Anal. Calcd. for $C_{13}H_{13}BrN_6O \cdot 0.5H_2O$: C, 43.59; H, 3.94; N, 23.46. Found: C, 43.73; H, 3.90; N, 22.96.

1-(1*H*-Imidazol-1-yl)-2-(4-bromophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**17a**, A = N, B = CH).

1-(1*H*-Imidazol-1-yl)-2-(4-bromophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**17a**, A = N, B = CH).

A mixture of **8a** (2.7 g, 0.01 mole), imidazole (0.76 g, 0.011 mole), trimethylsulfoxonium iodide (2.58 g, 0.013 mole) and powdered 85% potassium hydroxide (1.64 g, 0.029 mole) in *t*-butyl alcohol (40 ml) was refluxed for 24 hours. The solvent was removed, *in vacuo*, the residue suspended in water (50 ml) and extracted with methylene chloride (4 x 25 ml). After workup, according to the general procedure, there was obtained an oil which was solidified (ether) and was recrystallized from ethyl acetate to afford a yellow solid (2.46 g, 71%), mp 158-159°; ms: (EI) m/z (relative intensity) 350, 348 [$(M + 1)^+$, 23, 21], 268, 266 (17, 17), 185, 183 (8.3, 8.7), 171, 169 (18, 18), 157, 155 (7.7, 7.3), 118 (6.0), 90 (13), 89 (7.9), 83 (14), 82 (100), 81 (39), 77 (7.7), 76 (7.8), 75 (7.9), 69 (5.3), 55 (17), 54 (30), 51 (8.0).

Anal. Calcd. for $C_{14}H_{14}BrN_5O$: C, 48.29; H, 4.05; N, 20.11. Found: C, 48.48; H, 4.08; N, 19.64.

1-(1*H*-Imidazol-1-yl)-2-(4-chlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**17b**, A = N, B = CH).

A mixture of **8b** (2.21 g, 0.01 mole), imidazole (0.76 g, 0.011 mole), trimethylsulfoxonium iodide (2.58 g, 0.013 mole) and powdered 85% potassium hydroxide (1.40 g, 0.025 mole) were reacted, and worked up, as described in the general method. There was isolated a pale yellow solid (1.30 g, 43%), mp 139-140° (from ethyl acetate); ms: (EI) m/z (relative intensity) 305, 303 (M^+, 0.7, 0.4), 224 (5.9), 222 (18), 139 (6.2), 127 (5.5), 125 (17), 111 (5.7), 83 (7.0), 82 (58), 81 (19), 55 (9.1), 54 (11).

Anal. Calcd. for $C_{14}H_{14}ClN_5O$: C, 55.36; H, 4.65; N, 23.06. Found: C, 55.29; H, 4.72; N, 22.82.

1-(1*H*-Imidazol-1-yl)-2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**17c**, A = N, B = CH).

From **8c** [7,8a] (2.0 g, 0.008 mole), imidazole (0.59 g, 0.009 mole), trimethylsulfoxonium iodide (2.02 g, 0.01 mole) and powdered 85% potassium hydroxide (1.1 g, 0.02 mole) in boiling *t*-butyl alcohol for 48 hours, there was obtained a yellow solid (0.75 g, 29%), mp 170-171° (from ethyl acetate). This compound had been reported by Worthington (in unspecified overall yield) from **10c** and imidazole, sodium hydride in DMF at 80° (2 hours), mp 169-170° [5c].

1-(1*H*-Imidazol-1-yl)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**17d**, A = N, B = CH).

When **8d** (2.0 g, 0.009 mole), imidazole (0.67 g, 0.010 mole), trimethylsulfoxonium iodide (2.36 g, 0.012 mole) and powdered 85% potassium hydroxide (1.26 g, 0.022 mole) were reacted (24 hours) in refluxing *t*-butyl alcohol (25 ml), the product was isolated as a pale yellow solid (1.72 g, 63%), mp 147-148° (from ethyl acetate); ms: (EI) m/z (relative intensity) 305 (M^+, 2.6), 224 (20), 223 (5.8), 141 (9.5), 127 (19), 83 (6.0), 82 (55), 81 (20), 55 (10), 54 (10).

Anal. Calcd. for $C_{14}H_{13}F_2N_5O$: C, 55.08; H, 4.29; N, 22.94. Found: C, 55.01; H, 4.18; N, 22.92.

1,3-Bis(1*H*-imidazol-1-yl)-2-(4-bromophenyl)-2-propanol (**17a**, A = B = CH).

Following the general procedure, 1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)ethanone **15a** (A = CH) [15] (2.0 g, 0.0076 mole), imidazole (0.56 g, 0.0083 mole), trimethylsulfoxonium iodide (2.08 g, 0.0093 mole) and powdered 85% potassium hydroxide (1.24 g, 0.019 mole) were reacted in refluxing *t*-butyl alcohol (50 ml) for 18 hours. The product (2.22 g, 85%) melted between 123-126°.

Anal. Calcd. for $C_{15}H_{15}BrN_4O \cdot H_2O$: C, 49.33; H, 4.69; N, 15.34. Found: C, 49.00; H, 4.58; N, 15.02.

1,3-Bis(1*H*-imidazol-1-yl)-2-(4-chlorophenyl)-2-propanol (**17b**, A = B = CH).

1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**15b**, A = CH) [15], (2.0 g, 0.0091 mole) was treated with imidazole (0.68 g, 0.010 mole), trimethylsulfoxonium iodide (2.49 g, 0.011 mole) and powdered 85% potassium hydroxide (1.49 g, 0.022 mole) in 50 ml of boiling *t*-butyl alcohol (24 hours) to afford the product (1.76 g), mp 123-130°.

Anal. Calcd. for $C_{15}H_{15}Cl_2N_4O \cdot 1.5H_2O$: C, 54.63; H, 5.49; N, 16.99. Found: C, 54.61; H, 5.23; N, 16.82.

1,3-Bis(1*H*-imidazol-1-yl)-2-(2,4-dichlorophenyl)-2-propanol (**17c**, A = B = CH).

From 1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone nitrate [16] (2.0 g, 0.006 mole), trimethylsulfoxonium iodide (1.7 g, 0.0084 mole), imidazole (0.48 g, 0.007 mole) and powdered 85% potassium hydroxide (1.3 g, 0.024 mole) yielded a crude product which was chromatographed on silica gel. The major fraction (1.1 g, 53%) was eluted by methylene chloride-methanol (7:3), mp 165-168°; [R_f = 0.37, methylene chloride-methanol (9:1)]. This compound had been synthesized from 1,3-dichloro-2-(2,4-dichlorophenyl)-2-propanol and imidazole, mp 160-175° [5c].

1,3-Bis(1*H*-imidazol-1-yl)-2-(2,4-difluorophenyl)-2-propanol (**17d**, A = B = CH).

From 1-(2,4-difluorophenyl)-2-(1*H*-imidazol-1-yl)ethanone [15] (**15d**, A = CH, 3.0 g, 0.014 mole), trimethylsulfoxonium iodide (3.6 g, 0.018 mole), imidazole (1.0 g, 0.015 mole) and powdered potassium hydroxide (85%, 2.2 g, 0.039 mole) in boiling *t*-butyl alcohol (50 ml, 48 hours). There was isolated a solid which was recrystallized from ethyl acetate and weighed 2.4 g (59%), mp 145-146°; ms: (EI) m/z (relative intensity) 305 [$(M + 1)^+$, 12], 304 (M^+, 17), 224 (14), 223 (100), 141 (24), 127 (27), 113 (7.0), 82 (47), 81 (45), 69 (9.3), 68 (6.4), 55 (7.2), 54 (29), 52 (5.1).

Anal. Calcd. for $C_{15}H_{14}F_2N_4O$: C, 59.21; H, 4.64; N, 18.41. Found: C, 59.15; H, 4.68; N, 17.97.

4-Benzamido-4*H*-1,2,4-triazole (**18**).

A suspension of 4-amino-4*H*-1,2,4-triazole (**5**, 4.2 g, 0.05 mole) and benzoyl chloride (7.0 g, 0.05 mole) in dry pyridine (100 ml)

was refluxed (24 hours). Solvents were removed, *in vacuo*, to provide a cream-colored solid which was dissolved in hot water (100 ml), neutralized with sodium bicarbonate until no further effervescence was observed. On cooling, a white precipitate was obtained which was filtered and washed with water to give **18** (6.5 g, 69%), mp 236-237°, recrystallized from ethanol, mp 242-243°, lit [14a] mp 248°; ^{13}C nmr (solvent D): 127.7, 128.8, 130.5, 132.8 (phenyl C's), 143.8 (C-3, C-5 of triazole), 165.7 (C=O).

4-(4-Toluenesulfonamido)-4*H*-1,2,4-triazole (**19**).

A mixture of **5** (2.1 g, 0.025 mole) and 4-toluenesulfonyl chloride (4.8 g, 0.025 mole) in pyridine (50 ml) was refluxed for 6 days. The mixture was cooled and the solvent was removed, *in vacuo*. Upon cooling, the mixture was diluted with water (25 ml) and the light brown solid, filtered, washed with water, dried and recrystallized from ethanol to produce **19** (4.4 g, 74%), mp 218-219°, lit [14c] mp 222°; ^{13}C nmr (solvent D): 21.1 (CH_3), 127.7, 130.3, 132.5, 145.3 (phenyl C's), 142.7 (C-3, C-5 of triazole). This compound had been made previously (60%) in nitromethane at 60° (6 hours) and had to be separated from accompanying *N,N*-disulfonamide [14c].

1-(4-Bromophenacyl)-4-benzamido-1*H*-1,2,4-triazolium Bromide (**20a**).

A stirred mixture of **18** (0.5 g, 0.0027 mole) 4-bromophenacyl bromide (0.74 g, 0.0027 mole) was boiled in 2-propanol (30 ml) for 4 hours. The colorless solid (0.90 g, 73%) was filtered, washed with ether, mp 238-240° (from ethanol).

Anal. Calcd. for $C_{17}H_{14}Br_2N_4O_2$: C, 43.80; H, 3.03; N, 12.02. Found: C, 43.93; H, 3.07; N, 12.10.

1-(4-Chlorophenacyl)-4-benzamido-1*H*-1,2,4-triazolium Bromide (**20b**).

Similarly (to preparation of **20a**), a mixture of **18** (1.97 g, 0.011 mole) and 4-chlorophenacyl bromide (2.33 g, 0.010 mole) was boiled in 2-propanol (50 ml, 4 hours). The product weighed 2.3 g (55%), mp 236-237° (from ethanol).

Anal. Calcd. for $C_{17}H_{14}BrClN_4O_2$: C, 48.42; H, 3.35; N, 13.29. Found: C, 48.27; H, 3.01; N, 13.22.

1-(4-Bromophenacyl)-4-toluenesulfonamido-1*H*-1,2,4-triazolium Bromide (**21a**).

A mixture of **19** (0.5 g, 0.0021 mole) and 4-bromophenacyl bromide (0.58 g, 0.0021 mole) was refluxed in 2-propanol (30 ml) for 4 hours. On cooling, the light brown crystals (0.43 g, 40%), were filtered, washed with ether, dried and recrystallized from ethanol, mp 200-201°.

Anal. Calcd. for $C_{17}H_{16}Br_2N_4O_3S$: C, 39.56; H, 3.12; N, 10.85. Found: C, 39.72; H, 3.31; N, 10.64.

1-(4-Chlorophenacyl)-4-toluenesulfonamido-1*H*-1,2,4-triazolium Bromide (**21b**).

A mixture of **19** (0.5 g, 0.0021 mole) and 4-chlorophenacyl bromide (0.49 g, 0.021 mole) in 2-propanol (25 ml) was refluxed for 5 hours. On cooling, the colorless salt (0.34 g, 34%) was isolated, mp 216-218° (from ethanol).

Anal. Calcd. for $C_{17}H_{16}BrClN_4O_3S$: C, 43.28; H, 3.42; N, 11.88. Found: C, 43.35; H, 3.53; N, 11.90.

1-(4-Bromophenacyl)-4-benzoylimino-1*H*-1,2,4-triazolium Ylide (**22a**).

Neutralization of **20a** was affected by adding 0.23 g (0.0005 mole) to a hot sodium hydroxide solution (0.0005 mole in 10 ml of water). On cooling, the light brown solid was isolated and was recrystallized from ethanol to provide **22a** (0.17 g, 89%), mp 210-211°; ms: (EI) m/z (relative intensity) 386, 384 (M^+, 16, 13), 309, 307 (5.1, 5.3), 225, 223 (23, 22), 187 (15), 186 (6.9), 185 (95), 184 (8.2), 183 (100), 169 (5.5), 162 (5.9), 161 (54), 157 (29), 155 (30), 147 (20), 119 (34), 118 (22), 116 (8.5), 106 (5.1), 105 (50), 104 (6.7), 93 (6.5), 91 (28), 90 (11), 89 (24), 77 (51), 76 (28), 75 (11), 65 (5.1), 64 (16), 63 (18), 62 (7.6), 55 (9.2), 52 (5.6), 51 (58).

Anal. Calcd. for $C_{17}H_{13}BrN_4O_2 \cdot 0.5H_2O$: C, 51.79; H, 3.58; N, 14.21. Found: C, 52.06; H, 3.31; N, 14.13.

1-(4-Chlorophenacyl)-4-benzoylimino-1*H*-1,2,4-triazolium Ylide (**22b**).

Neutralization of **20b** (1.0 g, 0.0024 mole) by hot sodium hydroxide solution (0.04 mole) in water (60 ml) afforded **22b** (0.73 g, 89%), which was recrystallized from ethanol, mp 207-208°; ms: (EI) m/z (relative intensity) 342, 340 (M^+, 5.0, 22), 263 (12), 187 (21), 179 (13), 161 (36), 147 (40), 141 (16), 141 (18), 139 (100), 125 (13), 119 (27), 118 (15), 113 (10), 111 (37), 105 (43), 91 (12), 89 (10), 77 (50), 75 (22), 64 (12), 63 (8.8), 55 (5.2), 51 (32).

Anal. Calcd. for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44. Found: C, 59.49; H, 3.83; N, 16.20.

1-(4-Bromophenacyl)-4-(toluenesulfonyl)imino-1*H*-1,2,4-triazolium Ylide (**23a**).

After **21a** (0.2 g, 0.00039 mole) was added to hot sodium hydroxide solution (0.00039 mole in 5 ml of water), there was obtained impure **23a** (0.17 g), mp 203-205°, which was recrystallized from ethanol, mp 229-230°; ms: (EI) m/z (relative intensity) 278 (10), 264 (5.0), 262 (5.3), 239 (9.8), 238 (14), 186 (5.1), 185 (61), 184 (6.2), 183 (54), 171 (8.4), 157 (22), 156 (9.6), 155 (71), 139 (20), 123 (5.1), 108 (9.7), 107 (11), 92 (11), 91 (100), 90 (6.7), 89 (12), 77 (7.1), 76 (14), 75 (14), 74 (5.4), 65 (36), 63 (12), 51 (22).

Anal. Calcd. for $C_{17}H_{15}BrN_4O_3S \cdot 0.5H_2O$: C, 45.96; H, 3.63; N, 12.61. Found: C, 46.42; H, 3.45; N, 12.46.

1-(4-Chlorophenacyl)-4-(toluenesulfonyl)imino-1*H*-1,2,4-triazolium Ylide (**23b**).

Neutralization of **21b** (0.24 g, 0.0005 mole) was achieved by adding the salt to hot sodium hydroxide solution (0.0005 mole in 5 ml of water). The solid so obtained (0.17 g, 87%), mp 210-212° was recrystallized from ethanol, mp 226-227°; ms: (EI) m/z (relative intensity) 393 [$(M + 1)^+$, 1.5], 279 (7.1), 250 (8.1), 239 (25), 224 (22), 223 (8.3), 222 (67), 219 (7.2), 212 (7.4), 200 (6.3), 180 (13), 174 (8.0), 173 (12), 172 (100), 171 (6.4), 159 (5.2), 158 (7.0), 157 (68), 156 (9.2), 155 (23), 153 (5.8), 139 (36), 125 (26), 123 (5.1), 113 (8.5), 98 (8.8), 93 (11), 85 (60), 84 (5.8), 70 (54), 65 (5.5), 59 (10), 57 (13), 56 (6.5).

Anal. Calcd. for $C_{17}H_{15}ClN_4O_3S$: C, 52.24; H, 3.87; N, 14.33. Found: C, 52.14; H, 3.87; N, 14.34.

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