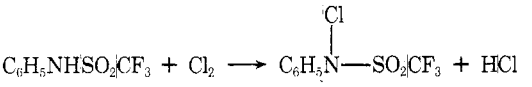
reacts at the acidic (1,1,1-trifluoromethanesulfonyl)amino site (pK_a = 4.45 for **1**)[1] as illustrated for the chlorination of



1. Attempts to isolate such an intermediate in this study were unsuccessful. Such intermediates have been isolated from numerous aryl-substituted *N*-phenylbenzenesulfonamides[7] and *N,N*-dichloroalkanesulfonamides have also been prepared.[8] The former compounds rearrange in glacial acetic acid to give ortho–para ring chlorination. In addition, further chlorination of the *N*-chloro-*N*-phenylbenzenesulfonamides with sodium hypochlorite in glacial acetic acid results in the formation of *N*-chloro-*N*-(2,4,-dichlorophenyl)benzene sulfonamide.[7] Therefore the directing group in the present study is probably an *N*-halogen-(1,1,1-trifluoromethanesulfonyl)amino moiety which is clearly an ortho–para directing group as indicated by the results shown in Tables I and II.

In the present study bromination of 1,1,1-trifluoro-*N*-phenylmethanesulfonamides was found to be much more selective (only 2,4-dibromination with 3 equiv of bromine) than was chlorination. Both bromination and chlorination of aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides result in higher overall yields when compared with the previous syntheses[2] and require less expensive starting materials. The halogenation technique also allowed syntheses of sulfonamides in cases where the corresponding di- or trihalogenated anilines were not commercially available. These anilines could have been prepared by conventional techniques but the subsequent sulfonylations would then have been low yield reactions as previously described.

Acknowledgments. The authors are indebted to Mr. P. B. Olson and coworkers for the elemental analyses. We wish to thank Dr. T. S. Reid and Dr. J. E. Robertson for their interest and encouragement.

Registry No.—Bromine, 7726-95-6; chlorine, 7782-50-5.

References and Notes

(1) R. D. Trepka, J. K. Harrington, J. E. Robertson, and J. T. Waddington, *J. Agr. Food Chem.*, **18**, 1176 (1970).
(2) R. D. Trepka, J. K. Harrington, J. W. McConville, K. T. McGurran, A. Mendel, D. R. Pauly, J. E. Robertson, and J. T. Waddington, *J. Agr. Food Chem.*, **22**, 1111 (1974).
(3) R. L. Shriner, M. T. Goebel, and C. S. Marvel, *J. Amer. Chem. Soc.*, **54**, 2470 (1932).
(4) A. G. Kostova, R. Kh. Gershman, and V. T. Akin'shina, *Zh. Obshch. Khim.*, **29**, 2012 (1959).
(5) L. Z. Gandel'sman, M. I. Dronkina, V. P. Nazaretyan, and L. M. Yagupol'skii, *Zh. Org. Khim.*, **8**, 1659 (1972).
(6) Nomenclature of the fluorinated compounds is according to *Chem. Abstr.* **7**, Subject Index, Part 1, Section IV (1972).
(7) F. D. Chattaway, *J. Chem. Soc.*, **85**, 1181 (1904).
(8) N. N. Melnikov, I. D. Sukhareva, and F. Ya. Kavenoki, *Zh. Prikl. Khim.*, **18**, 568 (1945).

On The Alkylation of Multisite Aromatic Heterocycles. 1,2,3,4-Thiatriazoles

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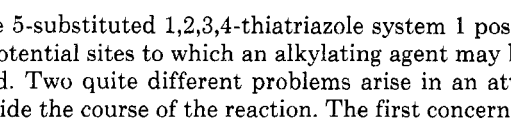
5-Substituted 1,2,3,4-thiatriazoles are alkylated with triethyloxonium tetrafluoroborate to give a single product. The location of the ethyl group in the ring at position 3 has been accomplished by means of ^1H, ^{15}N, and ^{13}C nmr. CNDO calculations were performed to rationalize the exclusive alkylation of nitrogen β to sulfur. The theoretical and experimental results are in conflict, suggesting that the reaction is more complicated than it appears.

The 5-substituted 1,2,3,4-thiatriazole system **1** possesses five potential sites to which an alkylating agent may be delivered. Two quite different problems arise in an attempt to decide the course of the reaction. The first concerns substituent *vs.* ring attack. The second arises in the latter case and involves a decision as to which heteroatom of **1** has been alkylated. It is to these questions that we primarily address ourselves in the sequel.



1a, X = SCH_2CH_3 **2a**, X = SCH_2CH_3
b, X = SCH_3 **b**, X = SCH_3
c, X = C_6H_5 **c**, X = C_6H_5

Treatment of sodium 1,2,3,4-thiatriazole-5-thiolate (**1**, X = S^-) with diphenylmethyl, triphenylmethyl, and benzoyl chloride were formerly believed to yield 4-substituted 1,2,3,4-thiatriazoline-5-thiones.[2] In a recent paper these reactions were reexamined and evidence was presented that the products obtained in fact are all 5-substituted 1,2,3,4-thiatriazoles.[3] On the other hand it was reported by Neidlein and Tauber that alkylation of 5-arylamino-1,2,3,4-thiatriazoles (**1**, X = NHAr) with diazomethane leads to formation of 4-methyl-5-arylimino-1,2,3,4-thiatriazolines, while alkylation with dimethyl sulfate provides 5-*N*-aryl-*N*-methylamino-1,2,3,4-thiatriazoles.[4] These results prompted us to investigate the reaction of 5-mercapto-1,2,3,4,-thiatriazole (**1**, X = SH) with diazomethane and triethyloxonium tetrafluoroborate. Only the 5-alkylthio-1,2,3,4-thiatriazoles are formed.

By contrast the latter products, **1a** and **1b**, as well as 5-phenylthiatriazole (**1c**), can be alkylated with $Et_3O^+BF_4^-$ yielding crystalline salts. Under similar alkylating conditions, the alkoxy derivative (**1**, X = OC_2H_5) decomposes entirely to nitrogen, sulfur, and ethyl cyanate as previously described.[5] Apparently the electronegative ethoxy moiety reduces electron density in the ring sufficiently so that alkylation cannot compete with fragmentation.

The structures of the former salts are analyzed below on the basis of ^1H, ^{13}C, and ^{15}N nmr data.

S *vs.* N Alkylation. Upon treatment with triethyloxonium tetrafluoroborate the 5-ethyl- and 5-methylthio derivatives of **1** (**a, b**) lead to a single product salt in each case in 65 and 35% yields, respectively. The ^1H nmr values of starting thiatriazoles and the corresponding ethyl derivatives are given in Table I.

Ring alkylation is immediately suggested since the ethyl

Table I
^{1}H Nmr Values of Thiatriazoles and Thiatriazolium Salts

Compd	$-SCH_3$	$-SCH_2CH_3$	$-SCH_2CH_3$	$-NCH_2CH_3$	$-NCH_2CH_3$
1a		3.43[a]	1.57		
2a		3.57[b]	1.51	5.26	1.83
1b	2.88[a]				
2b	3.02[b]			5.38	1.86
2c				5.34[c]	1.94

[a] Solvent, CCl_4. [b] Solvent, d_6-acetone. [c] Solvent, $CD_3OD/CDCl_3$ (1:1).

groups delivered by the alkylating agent display δ values expected of *N*-ethyl salts[6] rather than *S*-ethyl salts.[7] Furthermore the new bands appearing in the nmr spectra of the alkylated alkylthio derivatives **2a** and **2b** are virtually superimposable with those of the phenyl system **2c**, a substance for which side-chain alkylation is not possible.

In all cases of alkylation, products are crystalline and stable up to 180–200° in the solid state. Although nothing has been reported regarding the cycloaddition behavior of *S*-alkyl thiephenium salts,[8] thiophene *S*-oxides dimerize spontaneously at ambient temperatures.[9] A cryoscopic molecular weight determination on the phenyl salt **2c** shows that the compound is monomeric. Solutions of the latter are stable (nmr) for periods of at least 1 year. Finally the ^{1}H nmr spectra of salts **2a–c** (Table I) do not accommodate the nonequivalence of alkyl substituents expected of dimers.

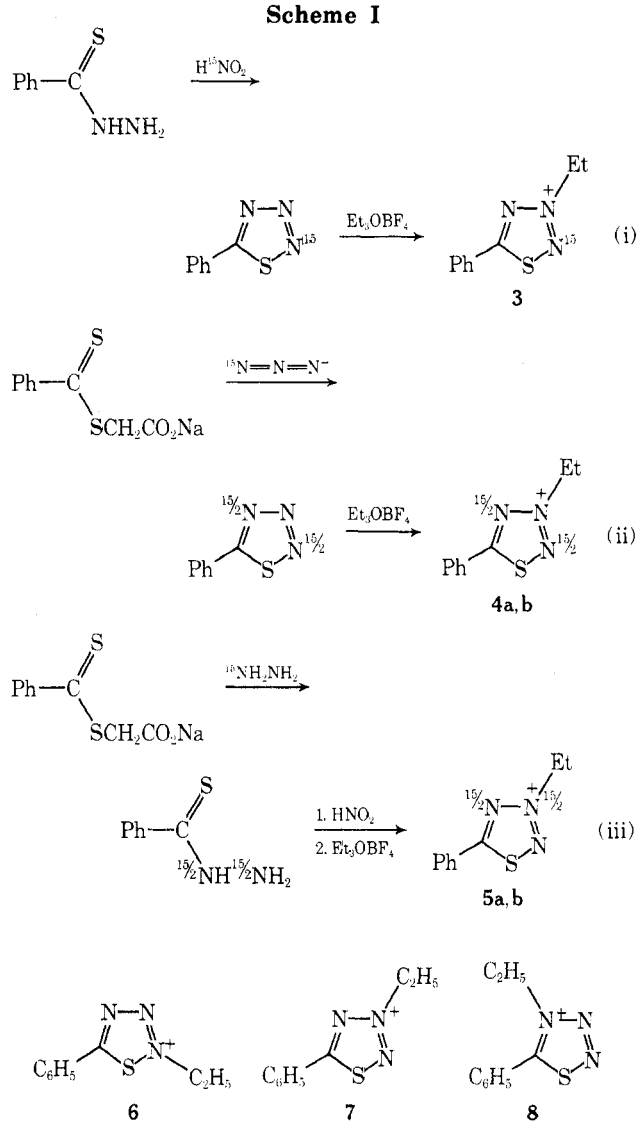
In sum, the proton nmr spectra, molecular weight measurement, and stability of thiatriazolium salts **2a, 2b,** and **2c** argue for N *vs.* S alkylation within the ring. In addition the near identity of chemical shifts and coupling constants for the ethyl groups suggests strongly that the position of alkylation is common to the three salts. In an attempt to define which of the three nitrogens has been ethylated, three isotopically distinct ^{15}N-labeled 5-phenyl-1,2,3,4-thiatriazoles have been prepared as outlined in the synthetic scheme (Scheme I). Each compound was subsequently alkylated with triethyloxonium tetrafluoroborate (**3, 4,** and **5**) and analyzed by ^{15}N and ^{13}C nmr spectroscopic data.

The three possible N-alkylation products are illustrated by structures **6, 7,** and 8 (*i.e.*, N-2, N-3, and N-4 alkylation, respectively). Both nitrogen chemical shifts and coupling constants (J_{NH}, J_{NC}) derived from the labeled substances **3, 4,** and **5** have been used to locate the alkylated nitrogen as N-3.

Alkylation Product 3 (^{15}N-2). In the ^{1}H nmr spectrum of salt **3** the methylene signal at δ 5.34 ppm is observed as a double quartet with $^3J_{HH}$ = 7.25 Hz and an additional splitting of 2.4 Hz. The methyl signal at δ 1.94 ppm is a clean triplet ($^3J_{HH}$ = 7.25 Hz) exhibiting a line width at half height of 0.2 Hz. The 2.4-Hz splitting of the methylene signal can be assigned to ^{15}N–H interaction by means of heterodecoupling. The corresponding ^{15}N-2 chemical shift is found to be -31 ± 2 ppm. No change in line width of the methyl signal was observed during the decoupling experiment.

Alkylation Product 4 (^{15}N-2 and ^{15}N-4). The ^{1}H nmr spectrum of **4a** and **4b** is very similar to that of **3** described above. The methyl signal is a sharp triplet with a line width of ~0.2 Hz, while the methylene signal again appears as a double quartet. The latter, however, evidences a line width somewhat larger than that found for compound **3.** Decoupling at the nitrogen frequency determined above for N-2 results in a quartet of triplets (see Figure 1). The outer lines are separated by 1.64 Hz. This spacing represents the coupling of the methylene protons to ^{15}N at position 4. Thus altering the nitrogen decoupling frequency produces another triplet structure in which the spacing of the outer lines is 2.4 Hz. The shift position of ^{15}N-4 is accordingly -73 ± 2 ppm.

Scheme I



Alkylation Product 5 (^{15}N-3 and ^{15}N-4). The low abundance of ^{15}N in sample **5** (30% total, 15% in **5a** and **5b,** respectively) limits the accuracy of the nmr measurement. Nonetheless, although the methylene signal is dominated by the methyl-induced quartet, satellites with a spacing of 1.7 Hz can be observed. The satellites disappear when the material is irradiated at −73 ppm, the shift frequency determined for ^{15}N-4. In the decoupled spectrum no evidence for an additional set of satellites was found. An upper limit of about 1.2 Hz is therefore placed on the magnitude of the coupling between CH_2 and ^{15}N at position 3. In contrast to the isotopic substitutions **3** and **4,** the methyl signal of **5** displays ^{15}N satellites with a spacing of 3.7 Hz. To erase the latter, irradiation at yet a third nitrogen frequency was necessary. The chemical shift of ^{15}N-3 is consequently established as -91 ± 2 ppm. Structure 7′ and Table II summarize the three nitrogen shift values for salt **2c** derived from the isotopic species **3, 4,** and **5.**

Further General Discussion of the Nmr Spectra of the Alkylation Products. Recently, nitrogen chemical shift data have been reported for a large number of five-membered heterocycles.[10] Among the molecules cited are

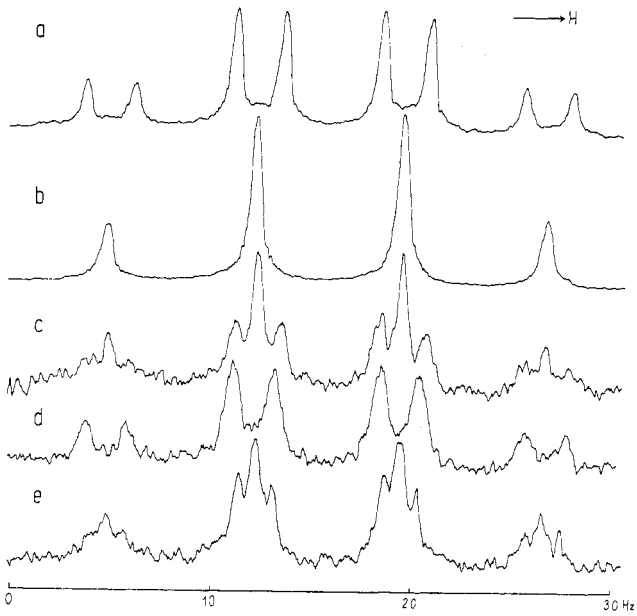
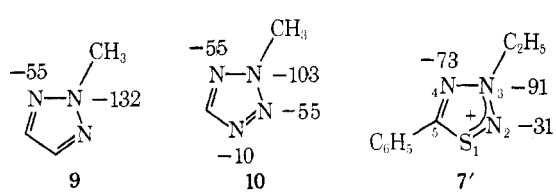


Figure 1. ^{1}H nmr spectra displaying the CH_2 group in the thiatriazolium salts **3** and **4** (a and b and c, d, and e, respectively) under ^{15}N selective decoupling. Spectra a and d show the undecoupled bands of **3** and **4** respectively. The decoupling rf field is present but offset sufficiently (15 kHz) so as not to influence the spectra. Curve b depicts the decoupling of ^{15}N-2 in compound **3** at a frequency of 10,137,040 ± 3 Hz. Spectrum c illustrates the result of irradiating salt **4** at 10,136,620 ± 5 Hz. At the latter frequency ^{15}N-4 is decoupled. The resulting spectrum is a superposition of equally intense spectra a and b. In e ^{15}N-2 (**4**) was irradiated at 10,137,040 ± 3 Hz leading to a combination pattern containing b and type a [J (^{15}N(**4**)–CH_2) = 1.64 Hz; *cf.* Table II].

2-methyl-1,2,3-triazole (**9**) and 2-methyl-1,2,3,4-tetrazole (**10**) (Chart I). No thiatriazoles were included in the work,

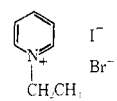
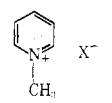
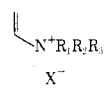
Chart I
^{14}N Chemical Shift for Triazole 9 (CH_3OH) and Tetrazole 10 (CH_3OH) and ^{15}N Shifts for Salt 7′ (3, 4, 5) ($CDCl_3/CD_3OD$ 1:1) in Parts per Million Upfield from CH_3NO_2



but based on a few selected examples the authors suggest that ring substitution of CH with S ought to have a minor influence on chemical shifts in the nitrogen nmr spectrum. In the present case the ring carries a positive charge which may well be located largely on sulfur.[11] Consequently a deshielding of N-2 relative to N-4 can be expected. Given these considerations the ^{14}N chemical shifts observed for compounds **9** and **10** may be seen as expectation values for salt **2c** to within 10–20 ppm. Furthermore it appears to be general that nitrogen atoms in five-ring aromatic heterocycles lacking σ lone-pair electrons are shielded to a greater extent than nitrogens bearing them. The former give rise to signals in the range −100 to −190 ppm while the latter are observed from 0 to −25 ppm for N–**N**–N and from −20 to −70 ppm for the N–**N**–C combination.[10] In view of this correlation, the ^{15}N chemical shift values determined for **2c** (*cf.* **7′** and Table II) can be consistently interpreted as an indication of alkylation at N-3.

The assignment is strengthened by evaluation of the heteronuclear coupling constants. Thus the ^{15}NH coupling constants for thiatriazolium salts can be profitably compared to literature data (Table II). These and other measurements[14] permit the generalization that $|^2J_{NH}| < |^3J_{NH}|$. Applied to compound **2c**, the latter suggests that a sizable nitrogen coupling to methyl should be observable when ^{15}N is bonded directly to CH_2CH_3. Table II illustrates that only ^{15}N-3 fulfills the necessary criterion. In agreement with previous work[15,16] the methylene group shows little or no nitrogen coupling (<1.2 Hz).

Table II
^{15}N Chemical Shifts and ^{15}NH Coupling Constants for Thiatriazolium Salt 7 and Related N-alkylated Heterocycles[a]

^{15}N position	$\delta(^{15}N)$,[b] ppm	$J(^{15}N-CH_2)$, Hz	$J(^{15}N-CH_3)$, Hz
2	−31 ± 2	2.43 ± 0.05	<0.2[c]
3	−91 ± 2	<1.20[c]	3.74 ± 0.1
4	−73 ± 2	1.64 ± 0.05	<0.2[c]
			3.4[a,d] 3.1[a,e]
			0.6–1.8[a,e]
		<Line width	2.8[a,f]

[a] Coupling constants for heterocycles other than **7** were measured as $J(^{14}NH)$ values and converted to $J(^{15}NH)$ by $J(^{14}NH) = 0.7129 \times J(^{15}NH)$; *cf.* M. Bose, N. Das, and N. Chatterje, *J. Mol. Spectros.*, **18**, 32 (1965). [b] Position relative to CH_3NO_2; $\delta(NH_4^+) = -360$ ppm. [c] Coupling not observed. The values listed represent the observable half-width limit. [d] Reference 14. [e] Reference 15. [f] M. Ueyama and K. Tori, *Org. Magn. Resonance*, **4**, 913 (1972).

Table III illustrates that the methylene group shows little or no nitrogen coupling (<1.2 Hz).

The noise decoupled natural abundance ^{13}C spectra of the phenylthiatriazole isotope **1c** and salt **2c** are recorded in Table III. The chemical shifts of the aromatic ring carbons are in agreement with the work of Ray, *et al.*[17] The meta carbons are unaffected by ion formation while C_1 experiences increased shielding. The ^{13}C response of C_{para} to alkylation may appear surprising, but the same effect has been recently established for a variety of phenyl-substituted five-membered-ring nitrogen heterocycles and their azolium salts.[18]

Of importance in confirming the site of alkylation is the ^{13}C shift position of NCH_2, a doublet at 61 ppm (J = 5 Hz). Data given by Bucci[19] shows that for the neutral NCH_2CH_3 moiety a chemical shift value of 50 ppm can ordinarily be expected. The increased electronegativity of N-3 in **7′**, by virtue of ring-supported positive charge, leads to a downfield shift bringing the value close to what is observed for ethoxy derivatives. The ^{13}C data is in accord with pmr chemical shifts (Table I) in ruling out S alkylation.

The splitting of the methylene carbon resonance in **3** by ~5 Hz corresponds to a ^{15}N–^{13}C coupling constant. The quantity is in the range found by Lichter and Roberts[14] for heteronuclear splittings of this type.

The total evidence, proton and ^{15}N and ^{13}C chemical shift data as well as spin–spin splitting constants (J_{NH} and J_{NC}), effectively eliminates sulfur alkylation and simultaneously fixes the site of ethylation for **2c** to be N-3.

Attempts were made to unambiguously synthesize 5-phenyl-3-ethyl-1,2,3,4-thiatriazolium tetrafluoroborate (**7**)

Table III
^{13}C Chemical Shifts for Phenylthiatriazole 1c and Thiatriazolium Salt 7[a]

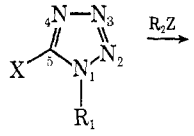
Compd	C_1	C_{ortho}	C_{meta}	C_{para}	C-5	CH_2	CH_3
1c	125.84	129.14	129.14	132.63	178.46		
2c	122.79	129.07	129.52	135.48	186.42	60.65	49.58
Δδ	-3.05	-0.07	0.38	2.85	7.96		

[a] Lines are measured relative to internal TMS. δ ($CDCl_3$) has been used as secondary standard. Positive δ values correspond to low field shifts.

by a nonalkylation route. Thus 2-ethylthiobenzoylhydrazine was treated with nitric acid in tetrafluoroboric acid, but only an unidentified sulfur-free compound was obtained. Apparently redox processes dominate the cyclization reaction.

Thermal Properties of Thiatriazolium Tetrafluoroborates. The alkyl N-3 assignment is consistent with the pronounced thermal stability of the salts. All 5-substituted thiatriazoles decompose spontaneously either at room temperature or upon slight warming with evolution of N_2, whereas the salts are unchanged up to 180–200°. Evidently alkylation at the 3 position effectively blocks the ability of the system to eject nitrogen under mild conditions. It must be pointed out, however, that this observation permits no *a priori* prediction concerning the thermal properties of thiatriazolium salts bearing a substituent at the 2 or 4 position.

Reactivity Considerations. The finding that the alkyl moiety is located on N-3 of the phenyl salt **2c** was unexpected. There are several reasons for believing *a priori* that N-4 might be the preferred nucleophilic center. The literature records a single example of thiatriazole ring alkylation. Diazomethane is reported to deliver methyl to the 4 position.[4] Similar results are available for other multisite heterocycles. A variety of papers argue that tetrazoles **11** are alkylated exclusively on N-4 to give **12**.[20,21a] In the case of 5-aminotetrazole (**11**, X = NH_2; R_1 = alkyl) the major product was assigned structure **12**, while the mesoionic derivative **13** (N-3 alkylation) was isolated in low yield.[22] A recent careful study shows that in least one case (**11**, X = C_6H_5), alkylation at N-3 (*i.e.*, **14**) competes favorably with reaction at N-4.[23]



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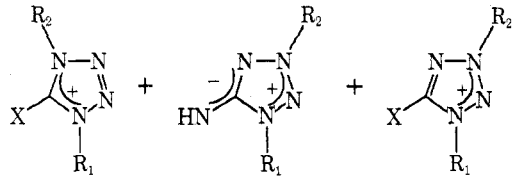
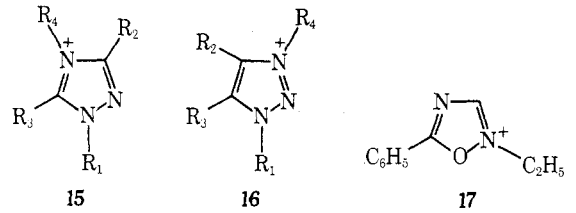
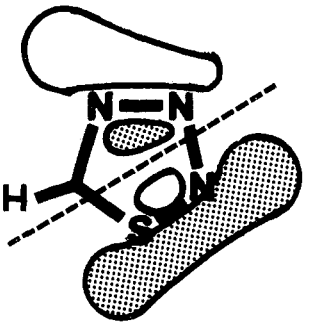


12 **13** **14**

1,2,4-Triazoles are reported to alkylate[21b] and protonate[24] at N-4 (*i.e.*, **15**), while the 1,2,3 isomers produce the



15 **16** **17**



18

X	Total charge distribution	Sigma framework charge distribution	Frontier orbital coefficients $\Sigma(c^f)^2$
S	+0.07	-0.15	0.27
N-2	-0.19	+0.05	0.29
N-3	+0.11	+0.03	0.14
N-4	-0.39	-0.02	0.30

Figure 2. CNDO calculated charge densities (total and σ) and highest occupied molecular orbital for thiatriazole. The relative areas correspond to the squares of the contributing atomic orbital coefficients.

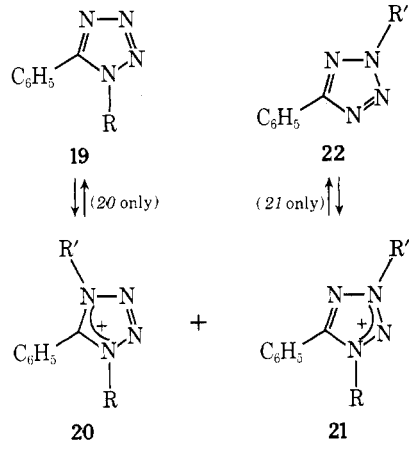
N-3 derivatives **16**.[25] A contrasting example is the N-2 alkylation product **17** from a 1,2,4-oxadiazole.[20b]

If the above examples were to be used as a guide to relative nitrogen nucleophilicity in five-membered heterocyclic rings of the type described, the following reactivity order is suggested: N-4 ≥ N-3 ≫ N-2.[26] This generalization should be regarded with caution. Only certain of the above citations provide definitive structural evidence as to the site of alkylation. Furthermore there is no uniformity with regard to ring substituents, the type of alkylating agent or the solvent employed. It is well known that these and other factors strongly influence the site of reactivity for related ambident systems.[27] An additional product controlling influence, kinetic *vs.* thermodynamic control, is discussed below.

In an attempt to derive a reactivity rationale for our assignment, SCF–MO–CNDO calculations[28] have been carried out for the unknown parent thiatriazole **18**. Total charge densities[29] and the frontier orbital electron distribution for the energy-geometry optimized heterocycle are given in Figure 2. These theoretical quantities have been used as indices of positional reactivity under conditions where the reaction is charge controlled or orbital controlled, respectively.[34,35] In the present case both criteria predict the reactivity order N-4 ≥ N-2 > N-3.

In sum general literature trends for poly nitrogen heterocycles suggest N-4 to be at least strongly competitive with N-3 as the favored nucleophilic center in thiatriazoles,

while our calculations indicate a clear preference for N-4 over N-3.[36] On the contrary the latter bears the alkyl moiety. There are several factors which permit partial reconciliation of the apparent disagreement. It is possible that the 4-ethyl salt **8** is generated in a kinetically controlled step followed by dealkylation and re-ethylation at N-3 to give the thermodynamically favored isomer **7**.[37] Similar heterocycles have been observed to undergo a thermodynamic equilibration of this type, but always in the presence of iodide ion, a powerful nucleophile.[23,33] In particular 1-alkyl-5-phenyltetrazoles **19** alkylate both at N-4 (**20**) and N-3 (**21**) under mild conditions. The system is ultimately converted through the less stable N-3 salt **20** to the energetically favored 1-alkyl-4-phenyltetrazole **22**.[23]



In the present case (**1c** → **7**) it seems unlikely that the tetrafluoroborate anion or possible traces of F^- have the capability to promote the required dealkylation. Furthermore the reaction has been monitored by nmr under ambient conditions during its early stages. The result does not support a multistep reaction scheme. The only new signals which appear in the spectrum of the freshly prepared solution are those arising from the 3-ethyl salt.[38]

A second explanation for the observed result may be steric in origin. Bulky substituents affect product distribution in the positional alkylation[40] and quaternization[33] of di-, tri-, and tetraaza heterocycles in a decided manner. Likewise 2-substituted 1,2,3-triazoles quaternize less readily than the 1-substituted isomer.[41]

It has not been demonstrated conclusively that the alkylthio derivatives **2a** and **2b** are ethylated at position 3. Based on the course of the reaction for phenylthiatriazole **1c** and the similar nmr spectra of salts **2** (Table I), it seems reasonable to assume that the side-chain sulfur cases possess structure **7**. If this hypothesis is valid and steric effects dominate electronic factors, both phenyl and *S*-alkyl are completely blocking reaction at position 4. Results reported for the phenyltetrazole **19** and the *s*-triazolo[4,3-*a*]pyridine[33] system make it unlikely that steric compression alone would direct the alkylating agent so specifically.

In conclusion, a conflict remains between the present result, literature precedent and the calculations. The general lack of reaction at N-2 for multisite heterocycles appears an even greater anomaly than the absence of observable competition between N-3 and N-4 for thiatriazoles **1**. The course of the thiatriazole alkylation clearly needs much closer attention.

Experimental Section

Nmr. ^1H spectra were obtained on a Varian HA-100 spectrometer by frequency sweep at 32°. The samples were prepared by dissolving 15 mg of the thiatriazolium compound in a 50:50 mixture of $CDCl_3$ and CD_3OD with TMS as internal reference. After several freeze–thaw cycles the degassed samples were sealed. ^{15}N decoupling was performed using a Schlumberger FSD 120 frequency synthesizer. The probe was modified for heterodecoupling according to McFarlane.[16] The chemical shift of ^{15}N was determined by comparison with the the decoupling frequency for ammonium nitrate.[42] The ^{13}C spectrum of compound **7** was obtained using the sample described above on a Varian XL-100 Fourier transform spectrometer: 100 *k* transients, pulse width 60 μsec over a range of 5000 Hz, aquisition time 0.4 sec, 4 K data points.

Alkylation of 1,2,3,4-Thiatriazole-5-thiol. A. Diazomethane (140 mmol, 2.5% ether solution) was added dropwise to 1,2,3,4-thiatriazole-5-thiol (11.9 g, 100 mmol) in dry diethyl ether (100 ml) at −20°. The resulting solution was stored overnight at 0° and then concentrated *in vacuo* without heating to ~50 ml. Concurrently 5-methylthio-1,2,3,4-thiatriazole, mp 32.0–34.0° (8.0 g, 60.1 mmol, 60%), precipitated from solution. The material was identified by comparison of its ir and nmr spectra with that of an authentic sample (mp 34.0–34.5°).[2a]

Evaporation of the mother liquor led to additional less pure product (mp 29.0–33.0°, 4.5 g, 33.8 mmol) corresponding to a total yield of 94%.

B. 1,2,3,4-Thiatriazole-5-thiol (1.00 g, 8.4 mmol) was neutralized with 0.6 ml of 50% aqueous sodium hydroxide (pH 9, phenolphthalein) and mixed with methylene chloride (10 ml) by stirring. Triethyloxonium tetrafluoroborate (1.60 g, 8.4 mmol) in methylene chloride (5 ml) was added at 0°. During addition sodium tetrafluoroborate precipitated. After filtration and drying ($MgSO_4$) the solution was evaporated to dryness and the remaining solid recrystallized from methanol (5 ml) (1.12 g, 8.4 mmol, 100%). The product was identified as above.

Alkylation of 5-Substituted 1,2,3,4-Thiatriazoles. The 5-substituted 1,2,3,4-thiatriazole (20 mmol) was dissolved in methylene chloride (10 ml) and a solution of triethyloxonium tetrafluoroborate (20 mmol) in methylene chloride (10 ml) was added dropwise over a short period of time. The system was surrounded with a water bath at ambient temperature. After standing overnight at room temperature the solvent was removed and the residue extracted several times with dry ether. The thiatriazolium salts thus obtained were recrystallized from absolute ethanol. Yields were from 50 to 70% after crystallization; for nmr shift values, see Table I.

With different 5 substituents the following analytical results were obtained: C_6H_5, mp 87.5–88.5° (Calcd for $C_9H_{10}N_3SBF_4$: C, 38.75; H, 3.87; N, 15.07. Found: C, 39.05; H, 3.69; N, 15.22.); CH_3S, mp 86.0–86.5° (Calcd for $C_4H_8N_3S_2BF_4$: C, 19.45; H, 3.47; N, 16.95. Found: C, 19.27; H, 3.28; N, 16.81.); C_2H_5S, mp 58.0–59.5° (Calcd for $C_5H_{10}N_3S_2BF_4$: C, 22.83; H, 3.83; N, 15.97. Found: C, 22.87; H, 3.83; N, 15.97.).

2-^{15}N-Labeled 5-Ethyl-3-phenyl-1,2,3,4-thiatriazolium Tetrafluoroborate (3). To 2-^{15}N-5-phenyl-1,2,3,4-thiatriazole (0.20 mmol) [prepared from thiobenzhydrazide and $Na^{15}NO_2$ (95% isotopically labeled) by the usual (see also below) procedure[43]] in methylene chloride (150 μl) was added triethyloxonium tetrafluoroborate (0.20 mmol) in methylene chloride (150 μl). After 24 hr at room temperature the solvent was removed *in vacuo* and the remaining solid or half-crystalline product washed a few times with dry ether. Recrystallization from absolute ethanol (300 μl) yielded ~25 mg of the crystalline title compound in 95% isotopic purity. Sometimes the material crystallized only after short boiling with ethanol. With the exception of J_{NH}, the ^1H nmr spectrum is identical with that of the unlabeled species.

Mixture of 3-^{15}N- and 4-^{15}N-Labeled 3-Ethyl-5-phenyl-1,2,3,4-thiatriazolium Tetrafluoroborate (5a,b). A. Preparation of the ^{15}N-Labeled Thiatriazole. To $^{15}NH_2NH_2$, H_2SO_4 (1.3 mmol) [prepared according to Bak, *et al.*,[44] from $^{15}NH_4Cl$ (30% isotopically labeled)] neutralized with 1 *N* NaOH (2.6 ml) and cooled in ice was slowly added a solution of carboxymethyl dithiobenzoate[45] (1.3 mmol) in 1 *N* NaOH (1.3 ml). After 1 hr at room temperature the mixture was extracted with a total of 15 ml of ether, washed with a small amount of water, dried over $MgSO_4$, and evaporated *in vacuo*. Thiobenzhydrazide thus formed was converted to the thiatriazole by the usual procedure.[43a]

B. The thiatriazole was alkylated with Et_3OBF_4 as described above for the 2-^{15}N-labeled product. The yield was ~20 mg of a crystalline mixture of the title compounds each 15% isotopically labeled. With the exception of J_{NH}, the ^1H nmr spectrum is identical with that of the unlabeled species.

Mixture of 2-^{15}N- and 4-^{15}N-Labeled 3-Ethyl-5-phenyl-1,2,3,4-thiatriazolium Tetrafluoroborate (4a,b). A. Preparation of $Na^{15}N_3$. The procedure used is a small-scale modification

of well-known methods.[46] A small test tube with a side arm containing solution A was closed by means of a rubber bulb and the side arm fitted with a plastic tube leading to solution C kept cooled in an ice bath. By means of a needle pierced through the rubber bulb, and reaching below the surface of solution A, nitrogen was swept through the system in a gentle stream during the whole procedure. From a syringe, fitted with a needle pierced through the rubber bulb, solution B was added slowly to solution A. After finishing addition the converted solution C was left covered overnight and the precipitate then isolated by means of centrifugation. The $Na^{15}N_3$ (95% isotopically pure at one nitrogen) thus formed was washed two times with small amounts of CH_3OH–Et_2O (1:1) and then with dry ether, yield 17 mg. Solutions: A, $Na^{15}NO_2$ (95% isotopically labeled) (60 mg), H_2O (200 μl), C_2H_5OH (25 μl); B, H_2O (200 μl), concentrated H_2SO_4 (25 μl), C_2H_5OH (25 μl); C, Na (25 mg) in CH_3OH (300 μl), NH_2NH_2, H_2O (50 μl), ether (500 μl).

B. Formation of the Thiatriazole. A solution of carboxymethyl dithiobenzoate[45] (5.0 mmol) in 1 *N* NaOH (5 ml) and water (1 ml) was prepared and washed with ether to remove impurities. Excess ether dissolved in the water phase was removed by bubbling a stream of nitrogen through the solution. To 0.6 ml of this solution was added the above prepared $Na^{15}N_3$ (17 mg). The resulting solution was left at room temperature for 4 hr. The thiatriazole was isolated by means of centrifugation and carefully washed with water, yield 15 mg.

C. The thiatriazole was alkylated with $Et_3OB_4^-$ as described above for the 2-^{15}N-labeled product. The yield was ~5 mg of a crystalline mixture of the title compounds each 47.5% isotopically labeled. With the exception of J_{NH}, the ^{1}H nmr spectrum is identical with that of the unlabeled species.

The Alkylation Process of 5-Phenyl-1,2,3,4-thiatriazole Followed by Means of Pmr Spectroscopy. Equivalent amounts of thiatriazole (32.0 mg) and $Et_3OB_4^-$ (37.6 mg) were dissolved in CD_2Cl_2 (0.5 ml) and the ^{1}H nmr signals recorded at given intervals during 22 hr, the time necessary for practical transformation. No signals besides those of the starting materials and the signals arising from 3-ethyl-5-phenyl-1,2,3,4-thiatriazolium tetrafluoroborate were observed.

Molecular Weight Determination. 3-Ethyl-5-phenyl-1,2,3,4-thiatriazolium tetrafluoroborate (1.427 g) was dissolved in water (86.3593 g) and the freezing point depression determined to 0.222° ± 0.005°. From these values a molecular weight of 277 ± 5 can be determined (calculated 279).

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Registry No.—**1a,** 52098-78-9; **1b,** 52098-77-8; **1c,** 34733-85-2; **2a,** 53336-74-6; **2b,** 53336-76-8; **2c,** 53336-78-0; triethyloxonium tetrafluoroborate 368-39-8.

References and Notes

(1) Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1971–1976.
(2) (a) E. Lieber, E. Oftedahl and C. N. R. Rao, *J. Org. Chem.*, **28,** 194 (1963); (b) E. Lieber, C. N. Pillai, J. Ramachandran, and R. D. Hites, *ibid.*, **22,** 1750 (1957).
(3) C. Christophersen and A. Holm, *Acta Chem. Scand.*, **25,** 2015 (1971).
(4) R. Neidlein and J. Tauber, *Arch. Pharm.*, **304,** 687 (1971).
(5) K. A. Jensen and A. Holm, *Acta Chem. Scand.*, **18,** 826 (1964).
(6) M. Begtrup, private communication.
(7) M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Amer. Chem. Soc.*, **88,** 5747 (1966).
(8) G. Brumlik, A. Kosak, and R. Pitcher, *J. Amer. Chem. Soc.*, **86,** 5360 (1964).
(9) J. L. Melles and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **72,** 491 (1953); W. Davies and F. C. James, *J. Chem. Soc.*, 15 (1954); W. J. Bailey and E. W. Cummins, *J. Amer. Chem. Soc.*, **76,** 1932 (1954); *cf.* C. D. Hurd, *Quart. Rep. Sulfur Chem.*, **4** (A), 90 (1969).
(10) M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron*, **28,** 637 (1972).
(11) CNDO calculations[12] have been performed on the three methyl salts of 1,2,3,4-thiatriazole corresponding to the isomeric species **6, 7,** and **8** (*i.e.*, NCH_3, **2, X** = H). In all cases the heteroatom bearing the burden of the charge is sulfur (+0.30 to +0.34). Nitrogen charges are either low and positive or negative (+0.23 to −0.33). Computed bond orders[13] likewise suggest salts of type **6–8** to possess a high degree of electron distribution of the type represented by structure **7′**.
(12) J. P. Snyder, unpublished results; *cf.* ref 28 for the parameterization.
(13) R. J. Boyd, *Can. J. Chem.*, **51,** 1151 (1973).
(14) R. L. Lichter and J. D. Roberts, *J. Amer. Chem. Soc.*, **93,** 5218 (1971).
(15) J. F. Biellmann and H. Callot, *Bull. Soc. Chim. Fr.*, 397 (1967).
(16) H. C. E. McFarlane and W. McFarlane, *Org. Magn. Resonance*, **4,** 161 (1972).
(17) G. J. Ray, R. J. Kurland, and A. K. Colter, *Tetrahedron*, **27,** 735 (1971).
(18) M. Begtrup, *Acta Chem. Scand.*, **27,** 3101 (1973); **B28,** 61 (1974).
(19) P. Bucci, *J. Amer. Chem. Soc.*, **90,** 252 (1968).
(20) (a) F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Amer. Chem. Soc.*, **73,** 4457 (1951); G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)*, 1355 (1955); R. M. Herbst and C. F. Froberger, *J. Org. Chem.*, **22,** 1050 (1957); R. M. Herbst and K. G. Stone, *ibid.*, **22,** 1139 (1957). (b) D. M. Zimmerman and R. A. Olofson, *Tetrahedron Lett.*, 3452 (1970).
(21) (a) G. F. Duffin, *Advan. Heterocycl. Chem.*, **3,** 37 (1964); (b) 35 (1964).
(22) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, **76,** 2894 (1954).
(23) T. Isida, S. Kozima, K. Nabika, and K. Sisido, *J. Org. Chem.*, **36,** 3807 (1971).
(24) G. B. Barlin and T. J. Batterham, *J. Chem. Soc., B,* 516 (1967).
(25) F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Justus Liebigs Ann. Chem.*, **515,** 119 (1935); R. H. Wiley and J. Moffat, *J. Amer. Chem. Soc.*, **77,** 1703 (1955); C. S. Rondestvedt and P. K. Chang, *ibid.*, **77,** 6532 (1955).
(26) To our knowledge there are no recorded cases of N-2 alkylation for 1,2,3,4-tetrazoles (**11**) or the isomeric thiazoles where R_1 is other than a proton. The oxadiazole precursor of **17** appears to represent an exception to the overall trend.
(27) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland,, *J. Amer. Chem. Soc.*, **77,** 6269 (1955). D. C. Nonhebel and H. D. Murdoch, *J. Chem. Soc.*, 2153 (1962). S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **86,** 1997 (1964); **87,** 3228 (1965). N. A. J. Rogers and A. Sattar, *Tetrahedron Lett.*, 1471 (1965). P. A. Chopard, R. F. Hudson, and G. Klopman, *J. Chem. Soc.*, 1379 (1965). J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N.Y., 1968, pp 298–302.
(28) R. J. Boyd and M. A. Whitehead, *J. Chem. Soc., Dalton Trans.*, 73 (1972); 78 (1972); 81 (1972).
(29) It is imperative to point out that the calculated total excess charges are due almost entirely to polarization of the π-electron framework, although the alkylation process surely engages primarily the σ-electron system. Preliminary calculations of the potential surface for protonation of thiatriazole **18** indicate that an electrophile prefers an in-plane attack.[12] This is in accord with the intuitive view of lone-pair N alkylation as well as *ab initio* calculations on related systems.[30] Calculated π-electron densities of polyaza heterocycles have been used previously to rationalize reactivity,[31] but predictions[32] have not always been rewarded by experimental verification.[33]
(30) R. Bonaccorsi, A. Pullman, E. Scrocco, and J. Tomasi, *Chem. Phys. Lett.*, **12,** 622 (1972); *Theoret. Chim. Acta (Berl.)*, **24,** 51 (1972).
(31) L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.*, **47,** 113 (1951); W. Woźnicki and B. Zurawski, *Acta Phys. Polonica.*, **31,** 95 (1967).
(32) K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, **31,** 265 (1966).
(33) W. W. Paudler and R. J. Brumbaugh, *J. Heterocycl. Chem.*, **5,** 29 (1968).
(34) G. Klopman and R. F. Hudson, *Theoret. Chim. Acta*, **8,** 165 (1967); G. Klopman, *J. Amer. Chem. Soc.*, **90,** 223 (1968).
(35) R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **2,** 36 (1973).
(36) Similar calculations for substituted thiatriazoles in several conformations (*i.e.*, **1,** X = C_6H_5, SCH_3, NH_2) lead to the same qualitative partial and total electron distribution as for the parent system.[12]
(37) A referee has suggested a 1,5-sigmatropic shift as a possible alternative rearrangement pathway.
(38) This finding furthermore rules out the formation of considerable quantities of other alkylated isomers lost during work-up (crystallized yields of **2** are 50–70%; see Experimental Section). Thiatriazoles **1** are labile in the presence of mineral or Lewis acids giving rise to such products as nitriles and disulfides.[39] The moderate, crystallized yields of **2** are thus attributed to acid-catalyzed (HCl, HF, BF_3) decomposition of starting thiatriazoles.
(39) A. Holm, unpublished results.
(40) F. L. Pyman, *J. Chem. Soc.*, **97,** 1814 (1910); K. v. Auwers and H. Hollman, *Chem. Ber.*, **59,** 601 (1926); R. A. Henry, *J. Amer. Chem. Soc.*, **73,** 4470 (1951); C. Pedersen, *Acta Chem. Scand.*, **13,** 888 (1959); C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30,** 1892 (1965).
(41) R. Gompper, *Chem. Ber.*, **90,** 382 (1957). M. Begtrup and P. A. Kristensen, *Acta Chem. Scand.*, **23,** 2733 (1969). M. Begtrup, *ibid.*, **25,** 249 (1971); M. Begtrup and K. V. Poulsen, *ibid.*, **25,** 2087 (1971).
(42) B. M. Schmidt, L. C. Brown, and D. Williams, *J. Mol. Spectrosc.*, **3,** 30 (1959).
(43) (a) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15,** 1104 (1961). (b) K. A. Jensen and A. Holm *Acta Chem. Scand.*, **23,** 2183 (1969).
(44) B. Bak, C. Hylling Christensen, D. Christensen, T. S. Hansen, E. J. Pedersen, and J. T. Nielsen, *Acta Chem. Scand.*, **19,** 2434 (1965).
(45) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15,** 1087 (1961).
(46) J. Thiele, *Chem. Ber.*, **41,** 2681 (1908); W. L. Semon and V. R. Damerelle, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N.Y., 1961, p 204.