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Quaternization Reactions

V. Quaternization of 1,3,4-Thiadiazoles

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A series of 2,5-disubstituted 1,3,4-thiadiazoles has been quaternized with methyl iodide. The influence of alkyl substituents on product distribution is smaller in the thiadiazole series than in the pyridazine series. The difference in geometry of the 5- and 6-membered rings may be responsible for the observed difference between the two series.

Certain diazaheteroaromatic compounds, such as pyridazines, their benzoderivatives, and 1,3,4-thiadiazoles, are well suited for the study of steric influence on the quaternization reaction, as they are planar molecules and possess two reaction centres which are symmetrically situated with respect to the ring. Each half of the ring may be considered independently, and the reaction rate at one nitrogen atom may to a first approximation be assumed to be dependent only on the adjacent substituent.

The quaternization of some pyridazines,[1,2] cinnolines,[3,4] and naphthyridines[5] has been investigated by this method and the results compared to the kinetic results from the quaternization of pyridines. In the present investigation, 1,3,4-thiadiazoles have been quaternized with methyl iodide; kinetic results from quaternization of thiazoles are of interest in this connection.[6,7]

RESULTS AND DISCUSSION

The quaternization of the 1,3,4-thiadiazoles was performed under conditions where the reaction is practically irreversible and the product distribution thus kinetically controlled; the thiadiazoles were quaternized at 50° for 20 h, and as treatment of 3-ethyl-2,5-dimethyl-1,3,4-thiadiazolium iodide with methyliodide at 80° for 10 days did not produce any detectable amount of the 2,3,5-trimethyl derivative, the loss of an alkyl group from a quaternized ring nitrogen is too slow to influence the product distribution even at the higher temperature.

In Table 1 is given the product distribution of the quaternization with methyl iodide of some 2,5-unsymmetrically substituted 1,3,4-thiadiazoles, where the alkyl substituents are methyl groups in which some of the hydrogen atoms are replaced by methyl groups.

Table 1. Product distribution in the quaternization of some 1,3,4-thiadiazoles with methyl iodide in acetonitrile at 50°C.

R-2	R-5	% quat. at N-3	% quat. at N-4	log k_{N3}/k_{N4}
H	CH_3	55	45	+0.09
CH_3	CH_3	(50)	(50)	0
CH_3CH_2	CH_3	43.5	56.5	−0.11
$(CH_3)_2CH$	CH_3	26	74	−0.45
$(CH_3)_3C$	CH_3	2.5	97.5	−1.60
$(CH_3)_2CH$	C_2H_5	38	62	−0.21
$(CH_3)_3C$	C_2H_5	4.5	95.5	−1.33
$(CH_3)_3C$	$CH(CH_3)_2$	8.5	91.5	−1.03

The product distribution of the quaternization of some unsymmetrically substituted 1,3,4-thiadiazoles, in which R-2 is ethyl, propyl, isobutyl, neopentyl, or benzyl and R-5 is methyl, ethyl, or isopropyl, is given in Table 2.

Table 2. Product distribution in the quaternization of some 1,3,4-thiadiazoles with methyl iodide in acetonitrile at 50°C.

R-2	R-5	% quat. at N-3	% quat. at N-4	log k_{N3}/k_{N4}
HCH_2CH_2	CH_3	43.5	56.5	−0.11
$CH_3CH_2CH_2$	CH_3	42	58	−0.14
$(CH_3)_2CHCH_2$	CH_3	39	61	−0.19
$(CH_3)_3CCH_2$	CH_3	33	67	−0.30
$C_6H_5CH_2$	CH_3	40	60	−0.18
$CH_3CH_2CH_2$	C_2H_5	47	53	−0.05
$(CH_3)_2CHCH_2$	C_2H_5	45.5	54.5	−0.08
$(CH_3)_3CCH_2$	C_2H_5	43.5	56.5	−0.11
$C_6H_5CH_2$	C_2H_5	48	52	−0.04
$CH_3CH_2CH_2$	$CH(CH_3)_2$	57	43	0.12
$(CH_3)_2CHCH_2$	$CH(CH_3)_2$	57	43	0.12
$(CH_3)_3CCH_2$	$CH(CH_3)_2$	56	44	0.10

In Table 3 are given the results from quaternization of some 1,3,4-thiadiazoles containing other substituents than alkyl groups.

Table 3. Product distribution in the quaternization of some derivatives of amino-1,3,4-thiadiazoles with methyl iodide in acetonitrile.

R-2	R-5	% quat. at N-3	% quat. at N-4
H	NH_2	27	73
CH_3	NH_2	24	76
H	$NHCOCH_3$	68	32
CH_3	$NHCOCH_3$	63	37

5-Amino-2-methyl-1,3,4-thiadiazole has been reported[8] to quaternize with ethyl iodide at N-3; the assignment was made on the ground that the product has an active methyl group. The results with methyl iodide show that the major product is 5-amino-2,4-dimethyl-1,3,4-thiadiazolium iodide and suggest that ethyl iodide also would quaternize at the nitrogen adjacent to the amino group. This emphasizes that assignment of products in the quaternization of diazaheterocyclic compounds, based solely upon chemical data, must be treated with care.

Compared to the results obtained in the pyridazine series, the effect of the *ortho*-substituents in 1,3,4-thiadiazoles is smaller. As for the pyridazines, the main influence of the substituents is assumed to be of steric origin, including steric hindrance of the attack of the reagent on the reaction site, steric strain in the transition state, steric control of the reacting conformation, steric hindrance of solvation, and steric inhibition of resonance.

From a statistical investigation of equilibrium and rate constants of *ortho*-substituted aromatic compounds, it has been concluded[9,10] that in the majority of cases the influence of *ortho*-substituents could be expressed in terms of inductive and resonance effects and that it was not necessary to include steric effects, except for very bulky groups, such as the *tert*-butyl group.

The equilibrium constants involving proton transfer to monosubstituted benzenes or heteroaromatic compounds are not likely to be dependent on steric hindrance; the rate constants considered[9,10] are for reactions which take place at an atom outside the ring and which in most cases allow an attack of the reagent perpendicular to the plane of the ring, as only one *ortho*-substituent is present. Neither the equilibrium constants nor the rate constants considered would thus be expected to show serious complications due to steric hindrance.

The direction of the attack of the reagent and thus the geometry of the transition state is important for the discussion of steric effects; the addition of the bulky *tert*-butylmagnesium chloride to unsymmetrically substituted pyridazines[11] is much less dependent on the size of the substituents than the quaternization reaction; in the former case, the reagent attacks nearly perpendicular to the plane of the pyridazine ring, whereas the quaternizing reagent attacks along a path which deviates only slightly from a line passing through the centre of the ring and the nitrogen atom; the attacking reagent and the *ortho*-substituents is thus situated in the same plane (or nearly so) which makes the steric strain in the transition state important.

The influence of an alkyl group on the rate of quaternization at an adjacent centre is very nearly the same in the 1,3,4-thiadiazole and the thiazole series,[6,7] but it is smaller than in the pyridine or pyridazine series.

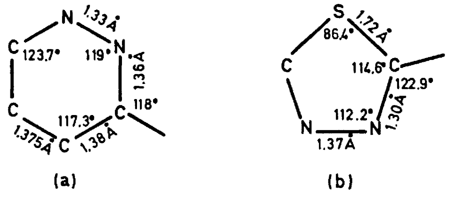


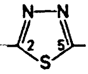
Fig. 1. Molecular shape of pyridazine[12] (a) and 1,3,4-thiadiazole[13] (b).

In Fig. 1 the geometry of the pyridazine and the 1,3,4-thiadiazole rings are shown. For the steric strain in the transition state of the quaternization reaction, the angles N2-C3-subst. and N3-C2-subst. of the pyridazine, resp. 1,3,4-thiadiazole ring are important; the greater the angle, the further removed from the reaction centre is the substituent and thus the smaller is its steric influence. The steric influence of an *ortho*-substituent in a five-membered ring would thus be expected to be smaller than in a six-membered ring which is in accordance with the experimental results.

EXPERIMENTAL

Materials. The 1,3,4-thiadiazoles were obtained by treatment of the appropriate diacylhydrazines with recrystallized P_2S_5. The NMR-spectra are given in Table 4. Before quaternization the material was purified by preparative GLC on a column of 20 % SE 30 on Chromosorb W.

Table 4. Chemical shifts in the NMR-spectra of 2,5-dialkyl-1,3,4-thiadiazoles.

R-2	R-5	C (2) 2^2	C (1) 2^1		C (1) 5^1	C (2) 5^2	C (3) 5^3	Solvent
CH_3	CH_3		2.72		2.72			$CDCl_3$
CH_3	C_2H_5		2.72		3.08	1.39		none
CH_3	$CH(CH_3)_2$		2.70		3.37	1.34		»
CH_3	$C(CH_3)_2$		2.70			1.41		»
CH_3	$CH_2CH_2CH_3$		2.69		3.02	1.78	0.96	»
CH_3	$CH_2CH(CH_3)_2$		2.70		2.92	1.99	0.95	»
CH_3	$CH_2C(CH_3)_3$		2.75		2.97		1.02	»
CH_3	$CH_2C_6H_5$		2.62		4.32	7.25		$CDCl_3$
C_2H_5	$CH(CH_3)_2$	1.36	3.07		3.27	1.38		none
C_2H_5	$C(CH_3)_3$	1.40	3.11			1.48		»
C_2H_5	$CH_2CH_2CH_3$	1.40	3.10		3.02	1.81	1.02	$CDCl_3$
C_2H_5	$CH_2CH(CH_3)_2$	1.40	3.12		2.95	2.08	1.01	none
C_2H_5	$CH_2C(CH_3)_3$	1.41	3.11		2.96		1.03	»
C_2H_5	$CH_2C_6H_5$	1.31	3.00		4.32	7.27		$CDCl_3$
$CH(CH_3)_2$	$C(CH_3)_3$	1.43	3.42			1.48		none
$CH(CH_3)_2$	$CH_2CH_2CH_3$	1.37	3.38		3.02	1.79	0.98	»
$CH(CH_3)_2$	$CH_2CH(CH_3)_3$	1.42	3.41		2.93	2.0	1.01	»
$CH(CH_3)_2$	$CH_2C(CH_3)_3$	1.46	3.41		2.95		1.02	»

The *quaternization* was made by treating a solution (1 %) of the thiadiazole in acetonitrile with a ten-fold excess of methyl iodide at 50°C for 20 h in a closed vessel. After removal of the solvent and excess methyl iodide, the residue was dissolved in deuterated chloroform and the NMR-spectra recorded.

The *analysis* of the reaction mixture was performed with a Varian A 60 NMR-spectrophotometer as described previously.[1,2] The reproducibility of the determinations was generally better than 2 % and often better than 1 % when the intensity of two singlets were compared; the results from the quaternizations with ethyl iodide and isopropyl iodide were less reproducible (within 5 %). The results given are the average of at least 3 quaternizations.

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