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Quaternization Reactions

IV. Quaternization of 3,6-Dialkylpyridazines

HENNING LUND and VIGGO LUND

Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

A series of 3,6-dialkylpyridazines has been quaternized with methyl iodide and the product distribution analyzed by NMR-spectroscopy. The product distribution is kinetically controlled under the present reaction conditions, and it is independent of the nature of the solvent, except in ethers. The product distribution is only moderately dependent on the electrical properties of substituents, but much more on steric factors.

The alkylation of tertiary amines has been used in several cases [1–9] to throw light on the steric influence of substituents on reaction rates; the quaternization of some 3,6-disubstituted pyridazines [3] has previously been studied in this context; in the present investigation a series of unsymmetrically substituted 3,6-dialkylpyridazines has been included.

On quaternization of such pyridazines two products are obtained, one quaternized at N-1 (QN1) and one at N-2 (QN2), and the product distribution QN1/QN2 is the measured quantity. This is evaluated from the NMR-spectrum of the reaction mixture from which the reaction medium, usually acetonitrile, has been removed. The ratio QN1/QN2 is of interest if the reaction is kinetically controlled as QN1/QN2 then is equal to the ratio of the rate constants k_{N1}/k_{N2}, where k_{N1}, resp. k_{N2}, are the rate constants of the reaction at N1, resp. N2.

RESULTS AND DISCUSSION

The value of the data is critically dependent upon whether the reaction is kinetically or thermodynamically controlled. The previous data [3] suggested kinetic control and this has been confirmed in two ways.

A kinetic control requires that the reverse reaction is negligible under the employed reaction conditions. This was tested by treating 1-ethyl-3,6-dialkylpyridazinium iodides with a great excess of methyl iodide in acetonitrile under various conditions (Table 1).

Table 1. Reaction between 1-ethyl-3,6-dialkylpyridazinium iodide and methyl iodide in acetonitrile under various conditions.

R-3	R-6	Reaction time (days)	Temperature	Exchange %
CH_3	CH_3	7	110°	0
$C(CH_3)_3$	$C(CH_3)_3$	1	65°	0
»	»	4	65°	0
»	»	14	65°	15
»	»	5	80°	50

An attack of iodide on the quaternized compound would yield ethyl iodide and the pyridazine which would quaternize with the excess of methyl iodide. An exchange of the ethyl group with a methyl group would be easily detectable in the NMR-spectrum of the reaction mixture.

Whereas even forced conditions (110°, 7 days) failed to produce detectable products of the reverse reaction of 1-ethyl-3,6-dimethylpyridazinium iodide, prolonged heating at a more moderate temperature (65°, 14 days) of the sterically very crowded 1-ethyl-3,6-di-*tert*-butylpyridazinium iodide did, in fact, give some 1-methyl-3,6-di-*tert*-butylpyridazinium iodide. The rate of the reverse reaction was, however, far too small to influence the product distribution under the usually employed experimental conditions (50°C, 24 h).

Quaternization of 3-*tert*-butyl-6-dimethylaminopyridazine with methyl iodide in CD_3CN could be followed in the NMR-spectrometer. The results (Table 2) shows that the ratio between the two products quaternized at N-1

Table 2. Product distribution during reaction between methyl iodide and 3-*tert*-butyl-6-dimethylaminopyridazine in CD_3CN.

Reaction time	Temp.	% Reaction	k_{N1}/k_{N2}	% quat. at NMe_2
1 h 10′	35°	10	64/36	15
2 h 40′	35°	20	62.2/37.8	15
5 h 15′	35°	40	62.6/37.4	15
24 h	35°	90	61.5/38.5	15
4 days	35°	> 99	63/37	8
6 days	35°	> 99		5
2 days	60°	> 99	62.8/37.2	0

and N-2 was constant during the reaction; a certain amount of product quaternized at the dimethylamino group was formed during the reaction, but as this reaction is reversible under these conditions (*vide infra*), the exo-quaternized product disappeared at the end of the reaction.

3,6-Bis(dimethylamino)pyridazine with methyl iodide quaternizes at 35°C to the iodide of 3-dimethylamino-6-trimethylammonium pyridazine. Heating a solution of this compound in acetonitrile with equimolar amounts

of 3,6-dimethylpyridazine gives a mixture of 1,3,6-trimethylpyridazinium iodide and 1-methyl-3,6-bis(dimethylamino)pyridazinium iodide together with some of the unquaternized pyridazines. The amount of quaternized product is somewhat smaller than corresponding to the starting material. The exo-quaternized compound is attacked by iodide and some of the methyl iodide thus formed is lost, whereas the remaining part quaternizes the ring-nitrogens in the usual manner.

Influence of solvent. Solvation of reaction partners is one of the most important factors in reactions in solution. The influence of an *o*-substituent could conceivably work through a change in the solvation of the reaction centre.

Previously the quaternization of 3-chloro-6-methylpyridazine has been investigated in acetonitrile and benzene and no difference in product distribution was found. In order to test this apparent independence of solvent a pyridazine, 3-*tert*-butyl-6-dimethylaminopyridazine, having a polar group (dimethylamino) and a non-polar group (*tert*-butyl) near the two reaction centres was quaternized in different solvents with dielectric constants ranging from 1.9 to 35 and dipole moments from 0 to 3.9 Debye (Table 3).

Table 3. Product distribution in the reaction between methyl iodide and 3-*tert*-butyl-6-dimethylaminopyridazine in various solvents.

Solvent	% quat. at N-1	% quat. at N-2
Hexane	62.6	37.4
Benzene	62.8	37.2
Carbon tetrachloride	62	38
Acetone	62.8	37.2
Acetonitrile	63	37
Dimethoxyethane	79	21
Tetrahydrofuran	84	16

From Table 3 it is evident that most solvents, both polar and non-polar ones, do not influence the product distribution, that is, they influence the two rate constants in the same manner. Ethers, however, differ from most other solvents. This effect, albeit smaller, is also found in the quaternization of 3-methyl-6-isopropylpyridazine with methyl iodide in acetonitrile (QN-2/QN-1 = 81.5/18.5), tetrahydrofuran (QN-2/QN-1 = 85.5/14.5), and diethyl ether (QN-2/QN-1 = 85/15). The reason for this anomaly is not known; one could imagine that the methylating agent in ethers was an oxonium compound having other steric requirements than methyl iodide. Although it has previously been found that replacement of methyl iodide with a larger alkyl iodide (ethyl or isopropyl iodide) changed the product distribution in the same manner as ethers do, it has not been demonstrated that QN-2/QN-1 in the methylation reaction was dependent on the leaving group of the methylating reagent.

Electrical influence of substituents. In a previous investigation [3] it was concluded that the most important factor in determining the product distribu-

tion in quaternization of pyridazines was the steric influence of the substituents adjacent to the reaction centre. In order to test that, a few 4-substituted pyridazines, unsubstituted in the 3- and 6-positions, were quaternized with methyl iodide (Table 4).

Table 4. Product distribution in quaternization of various 4-substituted pyridazines with methyl iodide in acetonitrile.

R-4	% quat. at N-1	% quat. at N-2
CH_3	~50	~50
tert-C_4H_9	~50	~50
$N(CH_3)_2$	75	25

The results show that alkyl groups, in accordance with previous findings, did not have any detectable effect within the experimental error of the method; the dimethylamino group had, however, a noticeable effect. In a Hammett equation the observed difference in the rate of quaternization at the *meta* and *para* positions would correspond to a value of the reaction constant ϱ of approximately -0.2, assuming it valid to use σ_p^+ and σ_m^+; the validity of this assumption is questionable.

At present no quantitative correlation is attempted and we shall here only argue that the electrical influence of 4-substituents on the product distribution is small. The "normal" electrical effect of a substituent *ortho* to the reaction centre is better represented by σ_p than by σ_m, but the electrical effect of an *o*-substituent on reactions involving the lone pair electrons of the nitrogen atom in pyridine, quinoline, and isoquinoline is "abnormal" and is better represented by the σ_I- or σ_m-substituent constant than by σ_p.[10] In this connection it is of interest that it was found that 4-methylpyrimidine quaternized 80 % at N-1 and 20 % at N-3, whereas 3-methylpyridazine quaternizes 72 % at N-2.

A substituent in the 3- or 6-position is *ortho* and *meta* to the reaction centres, and if it is assumed that the "abnormal" behaviour in the pyridine and quinoline series also would be found in the pyridazine series for reactions involving the lone pair electrons, the electrical influence of a substituent in the 3- (or 6)-position would be proportional to $\sigma_m - \sigma_o$ which would be small. As the reaction constant for the quaternization of pyridazines is fairly small, it may be concluded that the electrical influence of substituents is small. Alkyl groups have, furthermore, only a small electrical effect, and in pyridazines substituted in both the 3- and 6-positions with alkyl groups the difference in electrical effect on the two reaction centres would be very small indeed.

The results from the quaternization of a series of 3,6-dialkylpyridazines are shown in Table 5. In Fig. 1 the abscissa is log k_{alkyl}/k_{Me} for pyridazines and the ordinate log k_{alkyl}/k_{Me} for 2-alkylated pyridines;[11] the plot shows that the effect exhibited by alkyl groups *ortho* to the nitrogen in pyridazines parallels that found in pyridines. The steric effect of a given alkyl group is, however, slightly smaller in the pyridazine series than in the pyridine series.

Table 5. Product distribution in reaction between methyl iodide and unsymmetrically substituted 3-R-6-R′-pyridazines in acetonitrile.

	R (3)	R′ (6)	% quat. at N-1	% quat. at N-2	log k_{N2}/k_{N1}
I	H	CH_3	28	72	0.41
II	CH_3	CH_3	(50)	(50)	0
III	C_2H_5	CH_3	65	35	−0.27
IV	$CH(CH_3)_2$	CH_3	81.5	18.5	−0.64
V	$C(CH_3)_3$	CH_3	> 99	< 1	(~ −2.6)[a]
VI	$CH(CH_3)_2$	C_2H_5	68	32	−0.33
VII	$C(CH_3)_3$	C_2H_5	> 99	< 1	
VIII	$C(CH_3)_3$	$CH(CH_3)_2$	~ 99	~ 1	~ −2

[a] Calculated.

In Fig. 1 the point indicating the *tert*-butyl group does not correspond to a measurement in the pyridazine series, but is calculated from the data of 3-isopropyl-6-*tert*-butylpyridazine and 3-methyl-6-isopropylpyridazine (Table 5) on the assumption that $Q_AN\text{-}1/Q_CN\text{-}2 = (Q_AN\text{-}1/Q_BN\text{-}2)\ (Q_BN\text{-}1/Q_CN\text{-}2)$ where Q_AN, Q_BN, and Q_CN are proportional to the rate of quaternization at a nitrogen *ortho* to a methyl, isopropyl, or *tert*-butyl group, respectively.

The geometry of the pyridine [12,13] and pyridazine [14] nuclei differs only slightly and whether these small differences could explain the results seems doubtful. It might rather be that the $N-N-CH_3$ ($-I$) angle in the transition state in pyridazines were smaller than 120° and that the higher double bond character of the N(2)−C(3) bond compared to the N(1)−N(2) bond was of importance in this connection.

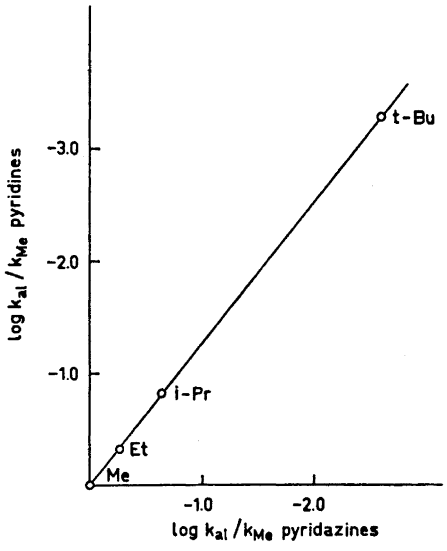

Fig. 1. Comparison of the influence of alkyl groups on the rate of quaternization at an adjacent ring nitrogen in the pyridazine and pyridine series. Abscissa: log $k_{6\text{-alkyl}}/k_{3\text{-methyl}}$ of pyridazines; ordinate: log $k_{2\text{-alkyl}}/k_{2\text{-methyl}}$ of pyridines.

The lower reaction rate of *o*-substituted pyridazines is caused by steric strain in the transition state, and in evaluating this strain all possible conformations must be considered; the great difference in steric influence between the *tert*-butyl group and the isopropyl group is due to the possibility of having a conformation of the isopropyl group in which a proton rather than a methyl group points towards the attacking reagent.

Table 6. Product distribution in quaternization of some 3,4,6-trisubstituted pyridazines with methyl iodide in acetonitrile.

	R-3	R′-4	R″ 5	R‴ 6	% quat. at N-1	% quat. at N-2
IX	CH_3	*tert*-C_4H_9	H	CH_3	67	33
X	CH_3	H	H	C_6H_5	8	92
XI	CH_3	*tert*-C_4H_9	H	C_6H_5	20	80
XII	CH_3	H	*tert*-C_4H_9	C_6H_5	62	38
XIII	C_6H_5	*tert*-C_4H_9	H	C_6H_5	5	95

In Table 6 are presented data showing an effect which may mainly be due to the different steric requirements of a phenyl group in two different positions with regard to the pyridazine ring. In one situation the angle between the planes of the phenyl and pyridazine rings in the most stable conformation is small, whereas in the other situation the angle between the planes is forced by an *ortho*-substituent in the pyridazine ring to be approximately 90°.

In the quaternization of 4-*tert*-butyl-6-methyl-3-phenylpyridazine (XII) the steric effect of a phenyl ring perpendicular to the pyridazine ring, the "thickness" of a phenyl ring, is compared to that of a methyl group. The observed effect of the phenyl ring may include a "buttressing effect" induced by the bulky *tert*-butyl group, which adds to the apparent "thickness" of the phenyl ring. The finding that the steric requirements of the phenyl group under these conditions is slightly smaller than that of a methyl group is in accordance with the generally accepted idea of the shape of a phenyl group.

The magnitude of the "buttressing effect" may be estimated from the quaternization of 4-*tert*-butyl-3,6-dimethylpyridazine (IX). This result suggests that in the absence of a "buttressing effect" the reaction mixture of XII would probably have the composition 75:25 rather than 62:38 found experimentally.

The quaternizing reagent also influences the product distribution (Table 7); going from methyl iodide through ethyl iodide to isopropyl iodide the percentage of the major compound has been found to increase. Although other than steric factors may operate and the change is not dramatic it is worth noting that the direction of the effect is that which would be expected from steric influence of the substituents. Such an influence would come more into play when a larger reagent attacks.

Other diazaheterocyclic systems, such as 1,3,4-thiadiazoles,[15] quinoxalines, and 1,8-naphthyridines [16] may be investigated similarly, and a more thorough

Table 7. Product distribution in quaternization of some 3,6-substituted pyridazines in acetonitrile with different alkyl iodides RI.

R'-3	R''-6	R	% quat. at N-1	% quat. at N-2	log k_{N1}/k_{N2}
CH_3	H	CH_3	72	28	0.41
CH_3	H	C_2H_5	80	20	0.60
CH_3	H	i-C_3H_7	90	10	0.95
CH_3	C_2H_5	CH_3	35	65	−0.27
CH_3	C_2H_5	C_2H_5	31	69	−0.35
CH_3	C_2H_5	i-C_3H_7	30	70	−0.37
CH_3	i-C_3H_7	CH_3	18.5	81.5	−0.64
CH_3	i-C_3H_7	C_2H_5	18	82	−0.66
CH_3	i-C_3H_7	i-C_3H_7	16	84	−0.72
t-C_4H_9	$N(CH_3)_2$	CH_3	63	37	0.23
t-C_4H_9	$N(CH_3)_2$	C_2H_5	70	30	0.37
t-C_4H_9	$N(CH_3)_2$	i-C_3H_7	80	20	0.60

discussion will be postponed until more results are available. A preliminary conclusion is, however, that a major influence of a substituent on the rate of the quaternization reaction in pyridazines is of steric origin, which may include 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.

EXPERIMENTAL

Materials. The dialkylpyridazines were made according to Levisalles and Baranger.[17] 3-*tert*-Butyl-6-isopropylpyridazine, m.p. 136–137°. (Found: C 74.31; H 10.15; N 15.61. Calc. for $C_{11}H_{18}N_2$: C 74.11; H 10.18; N 15.71.) 3-*tert*-Butyl-6-dimethylamine pyridazine was prepared from 3-*tert*-butyl-6-chloropyridazine and an alcoholic solution of dimethylamine at 80°C in a closed vessel. M.p. 95–97°. (Found: C 67.13; H 9.56; N 23.31. Calc. for $C_{10}H_{17}N_3$: C 67.00; H 9.56; N 23.44.) 4-*tert*-Butyl-3,6-diphenylpyridazine, 4-*tert*-butyl-3,6-dimethylpyridazine, 4- and 5-*tert*-butyl-3-methyl-6-phenylpyridazine were made by addition of *tert*-butylmagnesium chloride to the appropriate pyridazines and oxidizing the dihydro compounds according to Avellén and Crossland.[18]

Quaternization was performed in a closed vessel as previously described; reaction temperature 50°C, reaction time 24 h.

The analysis of the reaction mixture was performed with a Varian A 60 NMR-spectrophotometer as described previously.[3] 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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