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Quaternization Reactions

II. Pyridazines

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The quaternization products from the reaction in acetonitrile between methyl iodide and about sixty pyridazines have been investigated. The quaternization of a pyridazine gave in most cases a mixture of isomers, and the mixture was analyzed using NMR-spectroscopy; the criteria on which the assignments of the signals to the isomers rest are discussed; in some cases other methods, such as polarography and chemical degradation, were used to establish the site of the quaternization. The composition of the quaternization mixture is determined mainly by steric and inductive effects.

In the first part of this series [1] a condensation reaction was described which started with a quaternization of a nitrogen atom adjacent to a methyl group. In an investigation of the scope of this reaction the quaternization of diazines was studied; it was found that in most cases a mixture of both of the quaternary isomers was formed. Below is discussed the quaternization of about sixty pyridazines. The quaternization of pyridazines has been investigated by Duffin and Kendall [2] who used chemical means to determine the site of the quaternization, and, most recently, by Bale, Simmonds, and Trager [3] who investigated the quaternization products of 3- and 4-methylpyridazine by NMR-spectroscopy. The quaternization of 3-methyl-6-chloropyridazine with methyl iodide has been mentioned by Basu and Rose.[4]

ANALYSIS OF THE REACTION MIXTURES

The composition of the reaction mixture was determined by NMR-spectroscopy; for the assignment of the signals to the components and the determination of their structure, the following methods were used.

A. In pyridazines having a methyl group placed adjacent to a nitrogen atom, the position of the N-methyl group of the quaternized pyridazine can be deduced from the NMR-spectrum. The signals from a methyl group at C-3 is dependent on the position of the positive charge, and in a mixture of

the two possible isomers two signals from the methyl group are found. The signal at lowest field is caused by the isomer with the positive charge located adjacent to the methyl group. The positive charge at the nitrogen atom induces on the methyl group a deshielding effect which diminishes with the distance between the groups.

This assignment is substantiated by the following observation. When the NMR-spectrum of the mixture of isomers is recorded in deuterium oxide as a solvent, the lower field signal disappears on addition of traces of potassium carbonate (in some cases sodium hydrogen carbonate was found preferable). A methyl group adjacent to the positive charge is acidic enough to allow its protons to exchange rapidly with deuterium under slightly alkaline conditions, whereas a methyl group in other positions is not. By applying this observation to the quaternization products of the α, β and γ-picolines, it was found that the 2-methyl group in 1,2-dimethylpyridinium iodide exchanged its protons with deuterium in deuterium oxide containing potassium carbonate, although the reaction was slower than in the case of 2,3-dimethylpyridazinium iodide. 1,3- and 1,4-Dimethylpyridinium iodide did not exchange its protons in the weakly alkaline solution, but the 4-methyl group of 1,4-dimethylpyridinium iodide exchanged its protons with deuterium on addition of NaOD, whereas 1,3-dimethylpyridinium iodide did not. Methyl groups bonded to the quaternized nitrogen atom have not been observed to exchange protons under these conditions neither in pyridines or pyridazines, nor on exocyclic nitrogen atoms as in 3-dimethylamino-6-trimethylammonium-pyridazine iodide. Further support for the location of the N-methyl group can be found in the long-range coupling between the N-2-methyl and the C-3-methyl groups. These couple through five bonds with the coupling constant varying from 0 to 0.6 cps; in no cases long-range coupling was observed between the methyl groups at C-3 and N-1. In 2,3,5-trimethyl-6-methoxypyridazinium iodide the methyl group at C-5 couples with the proton at C-4 and, through seven bonds, with the methyl group at N-2, with similar coupling constant. In this case the coupling constant for the coupling between the methyl groups at C-3 and N-2 is somewhat smaller. Similar results are found in the phthalazine and cinnoline series. In the latter a long-range coupling, through seven bonds, between the methyl groups at C-4 and N-1 is observed in 1,4-dimethylcinnolinium iodide; no coupling was detected between the methyl groups in 2,4-dimethylcinnolinium iodide. It thus seems that long-range coupling between the methyl groups at carbon and nitrogen occurs only when there are five or seven bonds between the protons. From the integrated signals of the N-methyl and the C-methyl protons the relative amounts of the two isomers are determined.

B. In pyridazines having a phenyl group adjacent to a nitrogen atom, the structure of the quaternized isomers can likewise be inferred from the NMR-spectrum. It has been shown [5] that the signal from a phenyl group in the 3-position of a pyridazine differs according to whether the phenyl group is coplanar with the pyridazine ring or not. A phenyl group at C-3 is forced out of the plane of the pyridazine ring by a substituent in the 4-position. It has now been found that an alkyl group substituted on the nitrogen atom adjacent to the phenyl group has a similar effect.

C. Pyridazines possessing a methoxy group adjacent to a nitrogen atom easily lose the methoxy group with the formation of an N-alkylated pyridazone when quaternization occurs adjacent to the methoxy group. The rate of the cleavage is dependent on the structure of the pyridazine. The NMR-signal of the N-methyl group in the pyridazone is shifted upfield compared with the signal from the N-methyl group of the quaternary compound.

D. On quaternization with methyl iodide of pyridazines having a chlorine atom adjacent to a nitrogen atom, the chlorine of one of the isomers is substituted with iodine. The positive charge on nitrogen activates the adjacent chlorine for the substitution reaction. Basu and Rose [4] made a similar observation in the quaternization of 3-methyl-6-chloropyridazine but isolated apparently only the iodine-containing product. The assignment of the signals from the N-methyl groups to the two isomers may be disputable but a choice can be made with certainty by using polarography. Carbon-iodine bonds of pyridazines and phthalazines are reduced at less negative potentials than the heterocyclic nucleus, whereas the carbon-chlorine bond is reduced at about the same or at a more negative potential than that of the nucleus.[6] A polarographic analysis of the quaternization reaction mixture thus shows the relative concentrations of the iodo- and chloro-pyridazinium compounds. A further confirmation of the assignment can be obtained by using deuterated dimethyl sulfoxide as a solvent for the NMR-measurement. On heating the solution of the quaternization mixture the iodine containing isomer is transformed to the pyridazone; the signal from the N-methyl group is therefore shifted upfield.

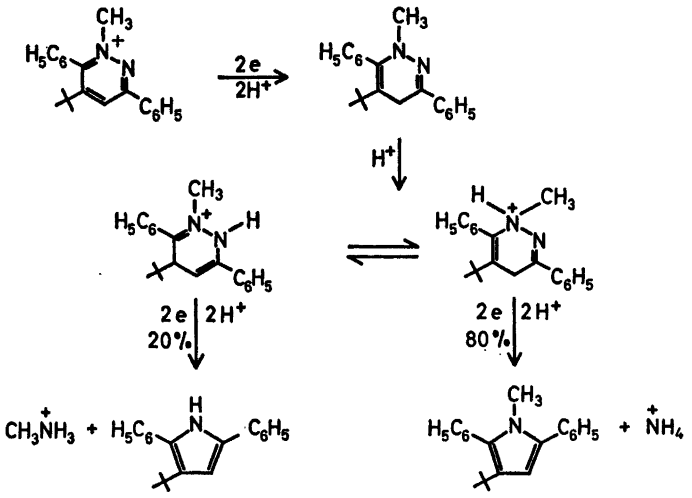
E. In some cases the signals from the 4- and 5-protons are of diagnostic value. In the quaternization of 3,6-bis-(dimethylamino)-pyridazine (LX) with alkyl iodides the signals from the 4- and 5-protons coalesce in one of the isomers and form a well separated AB-system in the other. (LX) can form two isomers on quaternization only if the quaternization takes place partly at a ring-nitrogen and partly at an exocyclic nitrogen atom. One would expect that a greater difference between the protons 4 and 5 would be found in the exocyclicly quaternized isomers than in the other one. In the quaternization of (LX) with methyl iodide, this assumption can easily be verified. The exocyclicly quaternized isomer should give two well-separated N-methyl signals with the relative intensities 3:2 (low field signal:high field signal), whereas the other isomer should give three signals with intensities 1:2:2. The spectrum obtained is in accordance with the assumption.

Again, the reaction between (LX) and ethyl or isopropyl iodide gives two isomers one of which contains a single signal from the 4- and 5-protons, and the other a well-separated AB-system; the latter signal was assigned to the isomer quaternized at the exocyclic nitrogen atom.

F. The position of the quaternization of pyridazines substituted in the 6-position with a methylamino group can be assigned from the NMR-spectrum in trifluoroacetic acid. The quaternization takes place in the nucleus and no methylation at the exocyclic nitrogen has been observed. When the positive charge is adjacent to the methylamino group a coupling with $J_{H,CH_3} = 5$ cps between the methyl group and the proton in the methylamino group is observed, whereas no coupling has been detected when the positive charge is at the more remote nitrogen atom. The reason might be that the adjacent positive

charge weakens the basicity of the exocyclic nitrogen and thus retards the protonation-deprotonation of the secondary amine, so the exchange of the N-H proton becomes slow measured on the NMR-time scale. In the quaternized isomer and the unquaternized compounds the exchange is rapid, resulting in an internal decoupling; in $CDCl_3$ the exchange reaction of the unquaternized compound is slow, and coupling occurs with a coupling constant of 5 cps. The chemical shifts of the signals from the methylamino group further confirm this assignment. The methyl group in the methylamino group adjacent to the positive charge gives a signal at a lower field (about 0.2 ppm) than the methyl group in the other isomer.

G. In some cases, especially when only one isomer is detectable, the structure of the product must be proved in other ways. Sometimes a preparative reduction at controlled potential furnishes a reduction product with a structure which is easier to determine than that of the quaternized compound. Thus, it has been shown that 1-methyl-3,6-diphenylpyridazinium iodide is reduced, at a potential corresponding to the first wave, to 1,4-dihydro-1-methyl-3,6-diphenylpyridazine.[6] The quaternization product from 4-t-butyl-3,6-diphenylpyridazine was shown to be 5-t-butyl-1-methyl-3,6-diphenylpyridazinium iodide from the following reduction scheme:

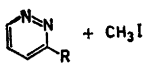


The structure of the dihydropyridazine, obtained by reduction in an acetate buffer, was determined by NMR-spectroscopy. Besides the signals from the phenylgroups three singlets were found in the spectrum ($CDCl_3$) at $\delta = 3.10$, 2.94, and 0.89 with the relative intensities 2:3:9. These signals were assigned to the methylene group, the N-methyl group, and the t-butyl group, respectively.

RESULTS

The reaction mixture from the quaternization of 50 mg of each compound was, after evaporation of the solvent, dissolved in a suitable solvent, mostly trifluoroacetic acid and the solution analyzed by means of NMR-spectroscopy by measuring the integrals of the relevant signals. The uncertainty of a determination is estimated to be in the order of 2—3 %; the reproducibility is mostly better than 2 %. In cases, however, where the difference in chemical shift between the relevant signals is small, the uncertainty may be greater. When only one signal from a N-methyl group is detected, the possibility still exists that two isomers are present, the signals happening to coalesce. The signals from the 4 and/or 5 protons may indicate the presence of two isomers but the limit for the detection of an isomer is higher for a signal from a single proton than from that of a methyl group.

Table 1. Composition of the quaternization mixture from reaction between methyl iodide and 3-R-substituted pyridazines determined by means of NMR-spectroscopy. The chemical shifts of the relevant NMR-signals are expressed in ppm (δ-units). Solvent: Trifluoroacetic acid.

		Quat. at N(1)			Quat. at N(2)		
		$N(1)-CH_3$		R	$N(2)-CH_3$		R
	R	δ	%	δ	δ	%	δ
I	H	4.81	(50)		4.81	(50)	
II	CH_3	4.70	72	2.91	4.65	28	3.06
III	C_6H_5	4.83	97		4.63	3	
IV	CH_2OH	4.78	82	5.35	4.67	18	5.51
V	CH_2OAc	4.81	88	5.70	4.81	12	5.92
				2.40			2.43
VI	$CONH_2$	4.95	>98				
VII	$COOCH_3$	4.93	>98	4.31			

In Table 1 are presented the results from the quaternization of monosubstituted pyridazines, including the chemical shifts of the signals in the NMR-spectrum of the two isomers and their relative concentration in the quaternization mixture. In Tables 2, 3, 4, and 5 are compiled the corresponding results from the quaternization of 3-methyl-, 3-phenyl-, 3-(4′-R′-phenyl)-, and 3-halo-pyridazines, respectively.

The quaternization at a ring nitrogen atom seems to be an irreversible reaction under the conditions employed and the composition of the reaction mixture thus kinetically controlled; the only exception hitherto found is the reaction between 2-methyl-benztriazole and methyl iodide which takes place under forced conditions and yields 1,3-dimethylbenztriazolium iodide. In the

Table 2. Composition of the quaternization mixture from reaction between methyl iodide and 3-methyl-5-R-6-X-pyridazines determined by means of NMR-spectroscopy. The chemical shifts of the relevant NMR-signals are expressed in ppm (δ-units).

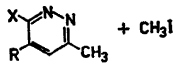
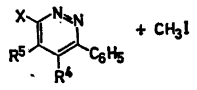
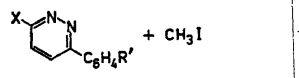
 + CH_3I			Quat. at N(1)				Quat. at N(2)					
			N(1)-CH_3		C(3)CH_3	X	N(2)-CH_3		C(3)CH_3	R	X	
	R	X	δ	%	δ	δ	δ	%	δ	δ	δ	Solv.
II	H	H	4.70	72	2.91		4.65	28	3.06			TFA
VIII	H	CH_3	4.60	(50)	2.83	3.03	4.60	(50)	3.03		2.83	TFA
IX	H	C_6H_5	4.55	8	2.95		4.72	92	3.08			TFA
X	H	t-C_4H_9		< 2			4.62	>98	3.05		1.51	TFA
XI	H	Cl	4.85	21	2.83		4.63	79	3.10			TFA
XII	H	Br	4.75	23	2.95		4.67	77	3.09			TFA
XIII	H	I	3.62	30	2.28		4.47	70	2.90			DMSO
XIV	H	OCH_3					4.50	>98	2.97		4.20	TFA
XV	H	SCH_3	4.42	12	2.75	2.95	4.53	88	2.95		2.68	TFA
XVI	H	NH_2	4.18	45	2.58		4.33	55	2.83			TFA
XVII	H	$NHCH_3$	4.19	12	2.57	3.28	4.34	88	2.78		3.05	TFA
XVIII	H	$N(CH_3)_2$					4.36	>98	2.77		3.27	TFA
XIX	H	NHAc	4.65	11	2.80	2.65	4.55	89	3.02		2.53	TFA
XX	H	$N(CH_3)Ac$	4.34	5	2.92	2.58	4.62	95	3.07		2.58	TFA
						3.75					3.75	
XXI	C_6H_5	Cl	4.78	16	2.95		4.63	84	3.10			TFA
XXII	CH_3	OCH_3					4.44	>98	2.90	2.53	4.23	TFA
XXIII	C_6H_5	OCH_3					4.48	>98	2.96		4.25	TFA

Table 3. Composition of the quaternization mixture from reaction between methyl iodide and 3-phenyl-4-R^4-5-R^5-6-X-pyridazines determined by means of NMR-spectroscopy. The chemical shifts of the relevant NMR-signals are expressed in ppm (δ-units).



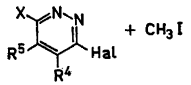
				Quat. at N(1)			Quat. at N(2)					
				$N(1)$-CH_3		X	$N(2)$-CH_3		X	R^4	R^5	
	R^4	R^5	X	δ	%	δ	δ	%	δ	δ	δ	Solv.
III	H	H	H	4.83	97		4.63	3				TFA
IX	H	H	CH_3	4.72	92	3.08	4.55	8	2.95			TFA
XXIV	H	H	C_6H_5	4.66	(50)		4.66	(50)				TFA
XXV	H	H	Cl	3.77	83		4.45	17				DMSO
XXVI	H	H	Br	5.00	84		4.61	16				TFA
XXVII	H	H	I	3.77	88		4.40	12				DMSO
XXVIII	H	H	OCH_3	4.33	22		4.46	78	4.28			TFA
XXIX	H	H	NH_2	4.08	92		4.14	8				DMSO
XXX	H	H	$NHCH_3$	4.32	58	3.35	4.32	42	3.15			TFA
XXXI	H	H	$N(CH_3)_2$	4.31	3	3.46	4.31	97	3.33			TFA
XXXII	H	H	NHAc	4.81	50	2.72	4.55	50	2.63			TFA
XXXIII	H	H	$N(CH_3)Ac$	4.72	34	2.66	4.62	66	2.68			
						3.85			3.85			
XXXIV	H	H	$N(C_4H_9)_2$				4.30	>98				TFA
XXXV	H	H	$CH{:}CHC_6H_5$	4.81	76		4.61	24				TFA
XXXVI	t-C_4H_9	H	C_6H_5				4.35	>98		1.42		TFA
XXXVII	C_6H_5	H	C_6H_5				4.61	>98				TFA
XXXVIII	H	t-C_4H_9	OCH_3				4.38	>98	4.32		1.55	TFA
XXXIX	t-C_4H_9	H	OCH_3				4.26	>98	4.13	1.32		TFA

Table 4. Composition of the quaternization mixture from reaction between methy iodide and 3-(4′-R′-C_6H_4)-6-X-pyridazines determined by means of NMR-spectroscopy. The chemical shifts of the relevant NMR-signals are expressed in ppm (δ units).



			Quat. at N(1)				Quat. at N(2)				
			$N(1)\text{-}CH_3$		X	R′	$N(2)\text{-}CH_3$		X	R′	
	R′	X	δ	%	δ	δ	δ	%	δ	δ	Solv.
XL	OCH_3	Cl	3.75	78		3.83	4.48	22		3.93	DMSO
XLI	OCH_3	OCH_3	4.37	30		4.05	4.50	70	4.28	4.05	TFA
XLII	OCH_3	$NHCH_3$	4.33	59	3.38	4.10	4.36	41	3.17	4.10	TFA
XLIII	OCH_3	$N(CH_3)_2$	4.35	3	3.48	4.07	4.35	97	3.35	4.07	TFA
XLIV	OCH_3	$N(CH_3)Ac$	4.67	38	{2.63 / 3.84}	4.06	4.63	62	{2.67 / 3.84}	4.06	TFA
XLV	CH_3	OCH_3	4.37	28		2.46	4.48	72	4.28	2.53	TFA

Table 5. Composition of the quaternization mixture from reaction between methyl iodide and 3-halo-4-R^4-5-R^5-6-X-pyridazines determined by means of NMR-spectroscopy. The chemical shifts of the relevant NMR-signals are expressed in ppm (δ-units).



					Quat. at N(1)			Quat at. N(2)					
					N(1)-CH_3		X	N(2)-CH_3		X	R^4	R^5	
	Halo	R^4	R^5	X	δ	%	δ	δ	%	δ	δ	δ	Solv.
XI	Cl	H	H	CH_3	4.63	79	3.10	4.85	21	2.83			TFA
XLVI	Cl	H	H	C_2H_5	4.67	64	{3.39 1.57}	4.88	36	{3.17 1.47}			TFA
XXV	Cl	H	H	C_6H_5	4.45	17		3.77	83				DMSO
XL	Cl	H	H	$C_6H_4OCH_3$	4.48	22	3.83	3.75	78			3.83	DMSO
XLVII	Cl	H	H	Cl	4.12	(50)		4.12	(50)				DMSO
XLVIII	Cl	H	H	OCH_3	4.60	11	4.23	4.75	89	4.18			TFA
IL	Cl	H	H	NH_2	3.94	69		3.42	31				DMSO
L	Cl	H	H	$NHCH_3$	4.22	33	3.35	4.67	67	3.08			TFA
LI	Cl	H	H	$N(CH_3)_2$				4.65	>98	3.26			TFA
LII	Cl	H	H	NHAc	4.40	19	2.42	3.61	81	2.08			DMSO
LIII	Cl	H	H	$N(CH_3)Ac$	4.75	42	{2.66 3.80}	4.90	58	{2.64 3.75}			TFA
XXI	Cl	C_6H_5	H	CH_3	4.63	84	3.10	4.78	16	2.95			TFA
LIV	Cl	H	CH_3	$N(CH_3)_2$				4.63	>98	3.28		2.63	TFA
LV	Cl	CH_3	H	$N(CH_3)_2$				4.72	>98	3.23	2.63		TFA
XII	Br	H	H	CH_3	4.67	77	3.09	4.85	23	2.95			TFA
XXVI	Br	H	H	C_6H_5	4.61	16		5.00	84				TFA
LVI	Br	H	H	NH_2	3.94	62		3.73	38				DMSO
LVII	Br	H	H	$NHCH_3$	4.21	32	3.34	4.65	68	3.10			TFA
LVIII	Br	H	H	$N(CH_3)_2$				4.67	>98	3.29			TFA
XIII	I	H	H	CH_3	4.47	70	2.90	3.62	30	2.28			DMSO
XXVII	I	H	H	C_6H_5	4.40	12		3.77	88				DMSO
LIX	I	H	H	$N(CH_3)_2$				4.65	>98	3.27			TFA

quaternization with methyl iodide of an exocyclic nitrogen atom as in 3,6-bis(dimethylamino)pyridazine the quaternized product may lose methyl iodide on moderate heating.

The composition of the quaternization mixture is not much dependent on the nature of the solvent or the reaction temperature. No differences in the relative amounts of the two isomers in the quaternization of 3-methyl-6-chloropyridazine were found when benzene or acetonitrile were used as solvents, and reaction temperatures at 30° or 80° produced no detectable difference in the composition of the quaternization mixture. The result obtained in benzene [3] in the quaternization of 3-methyl pyridazine agrees with that obtained in acetonitrile.

The signals from the 4- and 5-protons sometimes coalesce in unsymmetrical 3,6-disubstituted pyridazines; this happens in some of the quaternary compounds too, also in cases where the parent pyridazine gives two signals from the 4- and 5-protons.

3-Chloropyridazines yield on quaternization with methyl iodide an iodopyridazinium compound (method D) as mentioned above. In order to avoid this it was attempted to quaternize with methyl chloride but the rate of the quaternization with this reagent was slower than the rate of the self-quaternization, and from 3-chloro-6-methylpyridazine only 8-chloro-6,7-dihydro-3-methyldipyridazinopyrrole was obtained.[1]

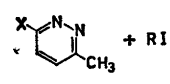
DISCUSSION

Several factors, such as steric, inductive, and mesomeric effects, influence the composition of the quaternization mixture. Of these the inductive and the steric effect seem the most important. The steric hindrance from a substituent affects only the reaction at the adjacent nitrogen atom, whereas the ponderal effect may influence the reaction at both nitrogen atoms. However, it is difficult at this stage to estimate the size of the ponderal effect, and the assumption will be made that the ponderal effect from a substituent in the pyridazine ring will be approximately equal on the two competing quaternization reactions. The inductive effect of a substituent mainly influences the adjacent nitrogen atom, and to a much lesser degree the one farther away. Also the mesomeric effect of a substituent in the 3 or 6 position influences mainly the reaction at the adjacent nitrogen atom.

The quaternization reaction of pyridazines is irreversible, the relative amounts of the two isomers are equal to the relative magnitude of the rate constants of the two reactions. If the considerations made above are sufficiently well-founded, the rate of the quaternization at a nitrogen atom in a pyridazine should, to a first approximation, be dependent only on the adjacent substituent.

By applying this assumption it should be possible to assign a certain factor to each substituent which for a 3-monosubstituted pyridazine expresses the ratio of the rate constants, k_S and k_H, of the reaction between methyl iodide and N-2, respectively N-1; $K_S^{Me} = k_S/k_H$. As the composition of the quaternization mixture is kinetically controlled, the substituent factor is directly

Table 6. The composition of the quaternization mixture from reaction between 3-methyl-6-X-pyridazines and different alkyliodides RI.

			Quat. at N(1)		Quat. at N(2)		
			C(3)-CH_3		C(3)-CH_3		
	X	R	δ	%	δ	%	Solv.
II	H	CH_3	2.91	72	3.06	28	TFA
—	H	C_2H_5	2.92	80	3.10	20	TFA
—	H	i-C_3H_7	2.91	90	3.13	10	TFA
IX	C_6H_5	CH_3	2.95	8	3.08	92	TFA
—	C_6H_5	C_2H_5	2.98	7	3.13	93	TFA
XI	Cl	CH_3	2.83	21	3.10	79	TFA
—	Cl	C_2H_5	2.96	31	3.13	69	TFA
—	Cl	i-C_3H_7	2.93	51	3.15	49	TFA
XIII	I	CH_3	2.28	30	2.90	70	DMSO
—	I	C_2H_5	2.80	51	2.95	49	DMSO
—	I	i-C_3H_7	2.80	64	2.97	36	DMSO
XVI	NH_2	CH_3	2.58	45	2.83	55	TFA
—	NH_2	C_2H_5	2.58	44	2.85	56	TFA
—	NH_2	i-C_3H_7	2.62	45	2.88	55	TFA

expressed in the composition of the quaternization mixture from a 3-substituted pyridazine. The substituent factor could also be obtained from the quaternization of a 3-S′-6-S″- substituted pyridazine, if K_S^{Me}, of one of the substituents were known. From a knowledge of the substituent factors the composition of the reaction mixture between methyl iodide and a disubstituted pyridazine could be calculated. If only one of the substituent factors were known, it should be possible from a measurement of the rate of the reaction to assign the site of the quaternization.

If the above mentioned assumption is correct, it would be expected that the relative amounts of quaternization products formed in an equimolar mixture of pyridine and a 2-substituted pyridine would approximate the relative amounts of the isomers formed on quaternization of a 3-substituted pyridazine. From the rates of quaternization of α-picoline and pyridine [7] the calculated relative amounts of quaternization products would be 32:68. 3-Methylpyridazine quaternizes 28 % at N-2 and 72 % at N-1.

In Table 7 are given K_S^{Me} values for a number of substituents from the quaternization of pyridazines with methyl iodide. In Table 7 is also compared the calculated percentage of the isomer quaternized at N-1 of 3-S′-6-S″-substituted pyridazines with the observed values. The percentage is calculated as 100 $K_{S''}^{Me}/(K_{S'}^{Me} + K_{S''}^{Me})$.

From Table 7 it is seen that a reasonably good agreement is found between the calculated and experimental data which suggests that the above mentioned assumptions are sufficiently well met to encourage further investigations along

Table 7. "Substituent factors" from the reaction between methyl iodide and some pyridazines together with calculated and experimental values for the percentage quaternized at N(1) in the reaction between methyl iodide and a 3-X-6-Y-pyridazine.

Y		CH_3		C_6H_5		Cl	
X	S_X^{Me}	Calc.	Found	Calc.	Found	Calc.	Found
H	1.00	28	28	3	3		
CH_3	0.38	—	—	6	8	21	21
C_6H_5	0.025	94	92	—	—	80	82
$C_6H_4OCH_3$	0.025	94	92	—	—	80	83
Cl	0.10	79	79	20	17	—	—
Br	0.105	77	77	19	16	—	—
I	0.16	70	70	13	12	—	—
OCH_3	0.01	99	> 98	72	78	91	87
NH_2	0.30	56	55	92	92	25	31
$NHCH_3$	0.04	90	88	38	42	71	67
$N(CH_3)_2$	0.001	> 99	> 98	97	97	> 99	> 98
NHAc	0.027	93	89	48	50	21	19

these lines. Not all the substituents represented in Tables 1 to 5 are included in Table 7; excluded are those which are represented only once, and for which no cross-checking has yet been possible.

Quaternization with methyl iodide of 3-chloro-6-methyl-pyridazine yields — within the uncertainty of the analysis — the same proportions of the two isomers in benzene solution at 80° and in acetonitrile at room temperature. The composition of the mixture is partly determined by steric factors as it changes with the size of the attacking reagent, (Table 6). The insensitivity of the composition of the quaternization mixture to the change in solvent means that the differences in solvation are of minor importance for the reaction, although the two solvents are widely different with respect to dielectric constant and solvation power towards ions. A change in the effective size of a substituent would heavily influence the composition of the reaction mixture.

The effective volume of a substituent may not be constant. A phenyl group in the 3 (6) position of a pyridazine is coplanar with the pyridazine ring, unless a substituent in the 4 (5) position forces it out of coplanarity. The steric hindrance imposed on the quaternization at N-2 (N-1) is quite different from a phenyl group coplanar with the pyridazine ring and one at a right angle to the pyridazine ring; in the latter case it is much smaller. This explains the striking difference between the quaternization of 3,6-diphenylpyridazine and 3,4,6-triphenylpyridazine or 3,6-diphenyl-4-t-butylpyridazine; in the last two cases the phenyl group at C-3 is not coplanar with the pyridazine ring, and the quaternization takes place exclusively at N-2.

The inductive effect is an important, sometimes deciding factor, as in the quaternization of, *e.g.*, 3-methyl-6-methoxy-pyridazine where only the isomer quaternized at N-2 has been detected. An illustrating example is 3-methyl-6-

chloro- and 3-methyl-6-iodopyridazine. The former quaternizes 21 % at N-1, whereas the latter gives 30 % at N-1. Here the greater volume of the iodine is not sufficient to counterbalance the less inductive effect of iodine compared to that of chlorine. The steric effect is accentuated further when the size of the attacking reagent is increased as seen in Table 6.

The influence of a substituent in the 4 or 5 position is difficult to predict on the basis of the present experimental data. The influence ranges from negligible (4-methylpyridazine)[3] through moderate (3-chloro-4-phenyl-6-methylpyridazine) to deciding (3,6-diphenyl-4-t-butylpyridazine).

The magnitude of K_S depends on steric and polar factors which may be expressed in an equation similar to that used by Taft.[8] When more data are available it is hoped that the relative importance of the steric and polar effects may be put on a quantitative basis using a method analogous to Taft's. The quaternization of pyridazines (and their benzoderivatives) is a suitable system for such measurements; the conditions for the two competing reactions are identical, and a good method for analyzing the reaction mixture and thus for obtaining the relative rate constants is available; the reaction is not sensitive towards changes in solvent, so solvation is not likely to be a complicating factor. Furthermore, K_S has generally different values for different quaternizing reagents. By varying the attacking reagents in the quaternization of a series of pyridazines a number of equations for similar reactions under similar conditions can be obtained; for a given substituent the terms expressing its inductive and mesomeric effect are approximately constant, and the variation in K_S is mainly dependent on the steric interactions between the substituent and the reagent. The relative importance of the steric and polar factors may thus be estimated. By applying reasonable values for the volume of the substituents and the reagents, for the ponderal and polar effect of the substituents, it might be possible to get a set of self-consistent values for the terms in the equations. Further work for obtaining the necessary data is in progress.

EXPERIMENTAL

The NMR-spectra were recorded at 60 Mc/s on a Varian Associates A-60 spectrometer. The temperature of the solutions were 33° ± 2°. Tetramethylsilane (TMS) was used as internal standard, and the chemical shifts are expressed in ppm (δ-units) from TMS taken as 0.00.

The pyridazines were prepared according to known methods.[2,9-12] Samples of several pyridazines were obtained from Dr. I. Crossland, Technical University of Copenhagen. The following compounds were prepared from the appropriate halogen compound by reaction with excess of aqueous ammonia or amine at 100°.

3-Methyl-6-methylaminopyridazine, m.p. 162°. (Found: C 58.55; H 7.54. Calc. for $C_6H_9N_3$: C 58.52; H 7.37). Acetate, m.p. 72—74°.

3-Phenyl-6-aminopyridazine, m.p. 165—167°. (Found: C 70.44; H 5.12. Calc. for $C_{10}H_9N_3$: C 70.16; H 5.30).

3-Phenyl-6-dibutylaminopyridazine, m.p. 46°. (Found: C 76.10; H 9.00. Calc. for $C_{18}H_{25}N_3$: C 76.28; H 8.89).

3-Phenyl-6-methylaminopyridazine, m.p. 162—164°. (Found: C 70.76; H 5.99. Calc. for $C_{11}H_{11}N_3$: 71.33; H 5.99). Acetate, m.p. 118°. (Found: C 68.89; H 5.88. Calc. for $C_{13}H_{13}N_3O$: C 68.70; H 5.77).

3-(4'-Methoxyphenyl)-6-methylaminopyridazine, m.p. 143—145°. (Found: C 66.27; H 6.08. Calc. for $C_{12}H_{13}N_3O$: C 66.96; H 6.09).

3-(4'-Methoxyphenyl)-6-dimethylaminopyridazine, m.p. 134°. (Found: C 67.86; H 6.68. Calc. for $C_{13}H_{25}N_{13}O$: C 68.10; H 6.59).

3-Chloro-6-acetaminopyridazine, m.p. 268—271°. (Found: C 42.30; H 3.51. Calc. for $C_6H_6ClN_3O$: C 42.00; H 3.52).

3-Chloro-6-methylaminopyridazine, m.p. 214—216°. (Found: C 41.22; H 4.41. Calc. for $C_5H_6ClN_3$: C 41.83; H 4.21). Acetate, m.p. 121—123°. (Found: C 45.25; H 4.33. Calc. for $C_7H_8ClN_3O$: C 45.29; H 4.35).

3-Bromo-6-dimethylaminopyridazine, m.p. 118°. (Found: C 36.15; H 4.00. Calc. for $C_6H_8BrN_3$: C 35.66; H 3.99).

3-Phenyl-6-bromopyridazine was prepared by reaction between 3-phenylpyridazone-6 and phosphoryl bromide, analogously to the preparation of the chloropyridazines; m.p. 166—168°. (Found: C 51.05; H 3.14. Calc. for $C_{10}H_7BrN_3$: C 51.09; H 3.00).

Procedure: 50 mg of the pyridazine was dissolved in 5 ml acetonitrile and 0.5 ml of methyl iodide added. The mixture was kept at 50° for 16 h in a closed vessel. The solvent was evaporated *in vacuo*, and the residue kept in a desiccator until it was dissolved in 0.5 ml of either trifluoroacetic acid (TFA) or deuterated dimethylsulfoxide (DMSO) and introduced into the NMR-spectrometer.

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REFERENCES

1. Lund, H. and Gruhn, S. *Acta Chem. Scand.* **20** (1966) 2637.
2. Duffin, G. F. and Kendall, J. D. *J. Chem. Soc.* **1959** 3789.
3. Bale, M. S., Simmonds, A. B. and Trager, W. F. *J. Chem. Soc. (B)* **1966** 876.
4. Basu, N. K. and Rose, F. L. *J. Chem. Soc.* **1963** 5660.
5. Crossland, I. *Acta Chem. Scand.* **20** (1966) 258.
6. Lund, H. Lecture. *4th Intern. Congr.* Polarography, Praha, July 1966.
7. Brown, H. C. and Cahn, A. *J. Am. Chem. Soc.* **77** (1955) 1715.
8. Taft, R. W. In Newman, M. S. *Steric Effects in Organic Chemistry*, Wiley, New York 1956, p. 559 ff.
9. Levisalles, J. *Bull. Soc. Chim. France* **1957** 1009.
10. Overend, W. G. and Wiggins, L. F. *J. Chem. Soc.* **1947** 239.
11. Steck, E. A. and Brandage, R. P. *J. Am. Chem. Soc.* **81** (1959) 6511.
12. Druey, J., Meyer, K. and Eichenberger, K. *Helv. Chim. Acta* **37** (1954) 121.

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