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The Addition of Grignard Reagents to Pyridazines

VIII. Chemically Nonequivalent Methylene Protons in 4,5-Dihydropyridazine Derivatives

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The addition of various Grignard reagents to 3,6-*bis*-dimethylamino-1-methylpyridazinium iodide is shown to give the corresponding 4-substituted-4,5-dihydropyridazinium iodides. The structures of these unknown compounds are established by chemical means and by NMR spectroscopy.

In deuterium oxide the methylene protons at C_5 in the 4,5-dihydropyridazinium iodides exchange with deuterium in a highly stereoselective manner and with retention of configuration. This phenomenon is discussed and an explanation based on conformational and electronic factors is suggested.

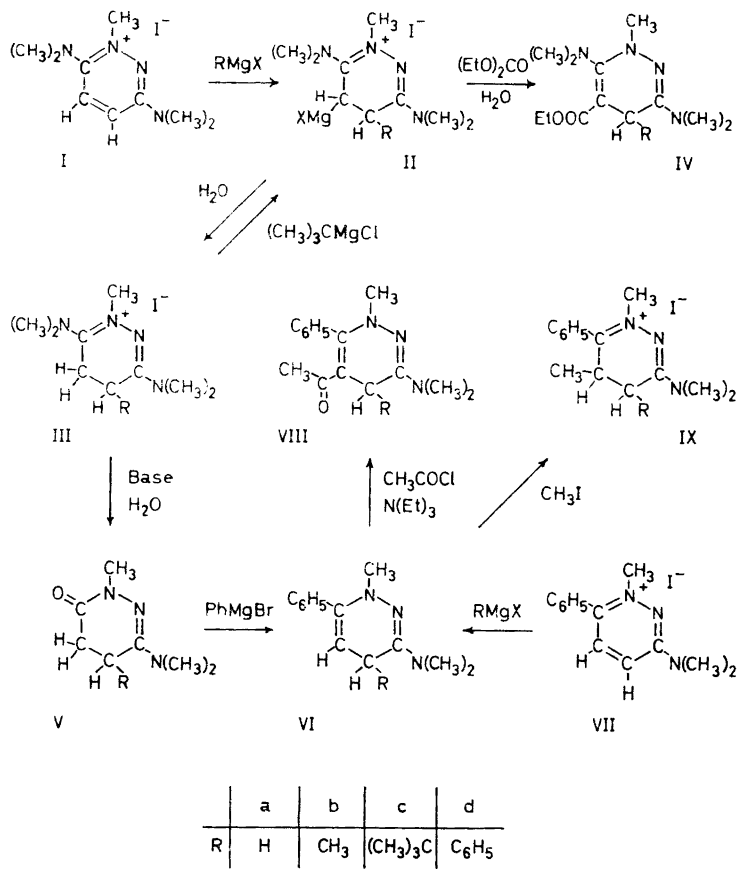
The addition of *t*-butylmagnesium chloride to 1-methyl-3,6-disubstituted-pyridazinium iodides has been shown to yield 1-methyl-3,6-disubstituted-4-*t*-butyl-1,4-dihydropyridazines as the main products in the three cases studied.[1]

The present work includes investigation of the addition of "HMgBr",[2] methylmagnesium iodide, *t*-butylmagnesium chloride, and phenylmagnesium bromide to 1-methyl-3,6-*bis*-dimethylaminopyridazinium iodide (I, see Chart I), structural elucidation of the resulting dihydropyridazinium iodides IIIa, IIIb, IIIc, and IIId, and an investigation of the deuterium exchange of these salts in various solvents.

The addition of Grignard reagents to the methiodide I was carried out by suspending the methiodide in an ethereal solution containing about six equivalents of the Grignard reagent and refluxing the reaction mixture for 2 h. Decomposition with water gave the corresponding 4-substituted-4,5-dihydropyridazinium salts IIIb, IIIc, and IIId. The addition of "HMgBr" to the methiodide I was carried out in a somewhat different way (see Experimental).

The product distribution in the crude oils were investigated by NMR. Only in the case of *t*-butylmagnesium chloride were significant amounts (25—30 %) of byproducts observed, but all attempts to isolate or identify other compounds than the 4,5-dihydropyridazinium iodide IIIc failed.

CHART I



	a	b	c	d
R	H	CH_3	$(CH_3)_3C$	C_6H_5

The structure elucidation followed two paths (see Chart I). The first was the transformation of the suggested intermediate C-magnesium compounds IIb, IIc, and IId into the 4-substituted-5-ethoxycarbonyl-1,4-dihydropyridazines IVb, IVc, and IVd. The analogous ethoxycarbonyl compound IVa was not formed when the 4,5-dihydropyridazinium salt IIIa was dissolved in an ethereal solution of *t*-butylmagnesium chloride and this solution allowed to react with a great excess of diethyl carbonate (*cf.* Experimental). Instead, the ethoxycarbonyl-1,4-dihydropyridazine IVc was isolated in small yield. No satisfactory explanation of this unexpected result can be offered at present.

The second path was somewhat more troublesome. The 4-substituted 4,5-dihydropyridazinium salts IIIa, IIIb, IIIc, and IIId could all be transformed into the corresponding pyridazinones Va, Vb, Vc, and Vd on treatment

with base (see Experimental for details). The pyridazinones Vc and Vd reacted with phenylmagnesium bromide to give the very unstable 4-substituted-1,4-dihydropyridazines VIc and VId, which, in turn, were synthesized from 6-phenyl-3-dimethylamino-1-methylpyridazinium iodide [3] by addition of *t*-butylmagnesium chloride and phenylmagnesium bromide, respectively (*cf.* earlier work [1]). As the dihydropyridazines VIc and VId were too unstable for convenient purification they were characterized by the derivatives VIIIc, VIIId, and IXc (see Chart I).

The reactions of the ene-hydrazine VI with methyl iodide and acetyl chloride are in accordance with the analogous reactions of enamines with alkyl halides and acid chlorides.

The derivatives VIIIc, VIIId, and IXc were synthesized both from the pyridazinones Vc and Vd and from the methiodide VII, and the three pairs of compounds were shown to be identical on the basis of mixed melting points and IR spectra.

The deuterium exchange reactions of the salts IIIa, IIIb, IIIc, and IIId will be discussed later.

Identification. The purpose of the chemical transformations outlined in Chart I was to prove the structure of the salts IIIa, IIIb, IIIc, and IIId, all of which must contain a dihydropyridazine ring according to the analytical data of Table 1, the NMR spectra of Table 2, and the chemical evidence presented. The structures of the suggested intermediates IIa, IIb, IIc, and IId are discussed in a later section.

The iodide IIIa. The NMR spectrum of IIIa in deuterium oxide solution showed a nearly symmetrical A_2B_2-like pattern for the ring protons. This is only compatible with the 4,5-dihydropyridazinium structure shown in Chart I.

The iodide IIIb. The structure of the 4-methyl-5-ethoxycarbonyl-1,4-dihydropyridazine IVb was determined by NMR data, the vicinal coupling of the methyl group being of particular significance. Therefore the methyl group in the salt IIIb must be situated at C^4. The vicinal coupling of the C-methyl group of IIIb eliminates all possibilities other than the 4-methyl-4,5-dihydropyridazinium structure given.

The iodides IIIc and IIId. The dihydropyridazines VIc and VId were prepared from the methiodide VII [3] and were characterized by their NMR spectra and the elementary analyses of the derivatives VIIIc, VIIId, and IXc.

The substituent R must be placed at C^4 in VIc and VId according to the spectra and therefore R must also be placed at C^4 in the corresponding salts, IIIc and IIId.

Both a 1,4- and 1,6-dihydropyridazine structure may be suggested for VIc and VId, although the 1,4-structure is by far the most probable by comparison with earlier work;[1] this point is not very important in the present context.

N—H protons in dihydropyridazines are known to absorb at low field ($\delta > 6.50$ ppm) in the NMR spectrum.[4,5] From the NMR spectra of the salts IIIc and IIId the presence of such protons therefore can be excluded. Besides, no vinylic protons appear in the spectra.

This leaves but two possible structures for IIIc and IIId: The 4,5- or 5,6-dihydropyridazinium compound. The latter possibility may be rejected on the basis of chemical evidence and NMR data. Therefore, the salts IIIc and IIId must be formulated as 4-substituted-4,5-dihydropyridazinium iodides as shown.

The pyridazinones Va, Vb, Vc, and Vd. No N—H, O—H, or vinylic protons appear in the NMR spectra of these compounds. In all four cases the IR spectra show a strong absorption in the region 1640—1654 cm^{-1}, which may be attributed to the carbonyl group.[6a] These facts are only compatible with the structure shown in Chart I.

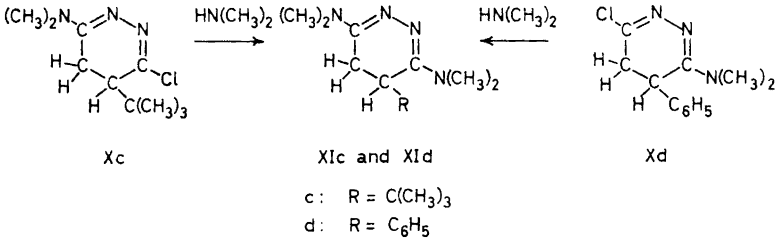
The ethoxycarbonyl compounds IVb, IVc, and IVd. The structure of IVb has been discussed *(vide supra)*. The similar formulation of IVc and IVd shown in Chart I cannot be proved rigorously, but the physical properties (including the NMR spectra) of the three compounds are very similar.

The acetyl dihydropyridazines VIIIc and VIIId. In VIIIc and VIIId the substituent R must be placed at C^4. The IR spectra show strong absorptions at 1580 cm^{-1} (VIIIc) and 1572 cm^{-1} (VIIId) indicating conjugated β-amino-α,β-unsaturated carbonyl systems [6b] and therefore support the structures given.

The iodide IXc. The vicinal coupling of the methyl group in the NMR spectrum of IXc reduces the number of possible isomers to a 4,5- or 5,6-dihydropyridazine system. Comparison with the salts IIIa, IIIb, IIIc, and IIId and with the structure of the starting material VIc strongly supports the formulation of Chart I.

The compounds XIc and XId (see Chart II) are assumed to have the same 4,5-dihydropyridazine structure as the known starting materials Xc and Xd.[4]

CHART II



Xc XIc and XId Xd

c: R = $C(CH_3)_3$
d: R = C_6H_5

The mechanism of the Grignard reaction. In earlier work on the addition of *t*-butylmagnesium chloride to pyridazinium salts [1] the formation of the dihydropyridazines isolated apparently involved a nucleophilic attack at one of the electron deficient positions in the ring followed by an electron shift giving a 1,2-, a 1,4-, or a 1,6-addition, respectively. In all cases investigated predominant 1,4-addition was observed (this case is outlined in Chart III, A).

Table 1.

Compound	Yield	M.P.	Formula	% C [a]		% H		% N		% I	
	%	uncorr.		found	calc.	found	calc.	found	calc.	found	calc.
I	66	178–80°	$C_9H_{17}N_4I$	35.20	35.08	5.62	5.56	18.08	18.18	41.38	41.18
IIIa	<10	151–52°	$C_9H_{19}N_4I$	34.55	34.85	6.25	6.18	18.30	18.07	40.72	40.88
IIIb	80.5	138–39°	$C_{10}H_{21}N_4I$	37.11	37.05	6.64	6.53	17.22	17.28	38.90	39.15
IIIc	42–47	152–54°	$C_{13}H_{27}N_4I$	42.88	42.61	7.49	7.43	15.05	15.30	34.90	34.64
IIId	79	161–63°	$C_{15}H_{23}N_4I$	46.45	46.65	6.06	6.00	14.27	14.50	32.69	32.86
IVb	—	oil	$C_{13}H_{24}N_4O_2$	58.00	58.18	9.04	9.02	20.67	20.88	—	—
IVc	30–40	oil	$C_{16}H_{30}N_4O_2$	61.51	61.90	9.72	9.74	18.02	18.05	—	—
IVd	34	97–8°	$C_{18}H_{26}N_4O_2$	65.10	65.43	8.06	7.93	16.80	16.96	—	—
Va	—	oil	$C_7H_{13}N_3O$	54.55	54.17	8.70	8.44	27.20	27.08	—	—
Vb	—	oil	$C_8H_{15}N_3O$	56.56	56.78	8.98	8.94	24.54	24.83	—	—
Vc, picr.	—	182–84°	$C_{17}H_{24}N_6O_8$	46.32	46.36	5.65	5.49	19.15	19.08	—	—
Vd	68–69	93– 4°	$C_{13}H_{17}N_3O$	67.20	67.50	7.47	7.41	18.22	18.17	—	—
VII	86.5	—	$C_{13}H_{16}N_3I$	45.67	45.75	4.79	4.73	12.27	12.32	37.50	37.19
VIIIc	—	127–28°	$C_{19}H_{27}N_3O$	72.12	72.80	8.68	8.68	13.35	13.41	—	—
VIIId	—	156–57°	$C_{21}H_{23}N_3O$	75.80	75.64	7.06	6.95	12.55	12.60	—	—
IXc	—	158–59°	$C_{18}H_{28}N_3I$	52.05	52.30	6.82	6.83	10.08	10.16	30.55	30.70
XIc	—	79–86°	$C_{12}H_{24}N_4$	63.90	64.24	10.73	10.78	24.96	24.98	—	—
XId	—	175°d.	$C_{14}H_{20}N_4$	69.00	68.82	8.36	8.25	23.08	22.93	—	—

[a] The microanalyses are by Mr. Preben Hansen, The Chemical Laboratory of the University of Copenhagen. The author acknowledges the prompt analyses on the unstable compounds.

Table 2. NMR data.[a] Compounds I to IX.

Compound		δ in ppm [b]	J in cps	(s)=singlet,	(d)=doublet,	(t)=triplet,	(m)=multiplet	
I	δ	8.11(d)	7.92(d)	4.18(s)	3.31(s)	3.18(s)		
	$\sum$H	1	1	3	6	6		
	J	10.1	10.1					
IIIa	δ	3.60(s)	3.38(s)	3.14−2.88(m)	3.00(s)			
	$\sum$H	3	6	4	6			
	J			A_2B_2 system				
IIIb	δ	3.68(s)	3.41(s)	3.56−2.99(m)	3.03(s)	1.17(d)		
	$\sum$H	3	6	3	6	3		
	J			$ABCX_3$ system		7.0		
IIIc	δ	3.64(s)	3.44(s)	3.22(broad)	3.06(s)	1.00(s)		
	$\sum$H	3	6	3	6	9		
	J			ABC system				
*IIId[c,e]	δ	7.54−7.05(m)	4.79(quartet)	3.68(s)	3.51(m)	3.34(m)	3.14(s)	3.01(s)
	$\sum$H	5	1	3	1	1	6	6
	J		$J_{13}=6.53$			$J_{12}=-16.26$		
			$J_{23}=2.33$		$J_{13}=6.53$	$J_{23}=2.33$		
IVb	δ	4.09(quartet)	3.83(quartet)	3.25(s)	2.88(s)	2.76(broad)	1.25(t)	0.80(d)
	$\sum$H	2	1	3	6	6	3	3
	J	7.0	7.0				7.0	7.0
IVc [d]	δ	4.12(quartet)	3.88(s)	3.17(s)	2.92(s)	3.06−2.59(broad)	1.25(t)	0.85(s)
	$\sum$H	2	1	3	6	6	3	9
	J	7.0					7.0	
IVd	δ	7.23(broad)	5.18(s)	4.24(quartet)	3.21(s)	2.96(s)	2.73(s)	1.33(t)
	$\sum$H	5	1	2	3	6	6	3
	J			7.0				7.0
Va	δ	3.26(s)	2.90(s)	2.82−2.22(m)				
	$\sum$H	3	6	4				
	J			A_2B_2 system				
Vb	δ	3.22(s)	3.30−2.04(m)				2.89(s)	1.13(d)
	$\sum$H	3	3				6	3
	J		$J_{12}=-16$, $J_{13}=5.8$, $J_{23}=1.7$	(calc. as an ABX system)				7.1
Vc	δ	3.20(s)	3.00−2.39(m)	2.91(s)	1.00(s)			
	$\sum$H	3	3	6	9			
	J		ABC system					

Table 2. Continued.

*Vd [c,e]	δ	7.49–7.04(m)	4.09(quartet)	3.34(s)	2.86(m)	2.88(s)	2.64(m)
	$\sum$H	5	1	3	1	6	1
	J		$J_{13}=7.58$		$J_{12}=-16.33$		$J_{12}=-16.33$
			$J_{23}=1.86$		$J_{13}=7.58$		$J_{23}=1.86$
VIc	δ	7.46–7.15(broad)	4.39(d)	3.20(d)	2.97(s)	2.75(s)	0.98(s)
	$\sum$H	5	1	1	3	6	9
	J		6.5	6.5			
VId	δ	7.38–7.05(m)	4.61(d)	4.38(d)	3.06(s)	2.71(s)	
	$\sum$H	10	1	1	3	6	
	J		5.9	5.9			
VII	δ	8.29(d)	8.05(d)	7.86–7.50(broad)	4.36(s)	3.33(s)	
	$\sum$H	1	1	5	3	6	
	J	9.2	9.2				
VIIIc	δ	7.42(broad)	4.38(s)	3.09(s)	3.00(s)	1.41(s)	0.91(s)
	$\sum$H	5	1	3	6	3	9
VIIId	δ	7.54–6.80(m)	5.53(s)	3.16(s)	2.98(s)	1.43(s)	
	$\sum$H	10	1	3	6	3	
IXc	δ	7.70(s)	3.95–3.24(m)	3.88(s)	3.46(s)	3.29(s)	1.27(d) 1.15(s)
	$\sum$H	5	2	3	3	3	3 9
	J		ABX_3 system				7.4

[a] Most of the NMR spectra were recorded on a Varian A-60 spectrometer. The NMR spectra of the compounds marked with an asterisk were recorded on a Varian A-100 spectrometer.

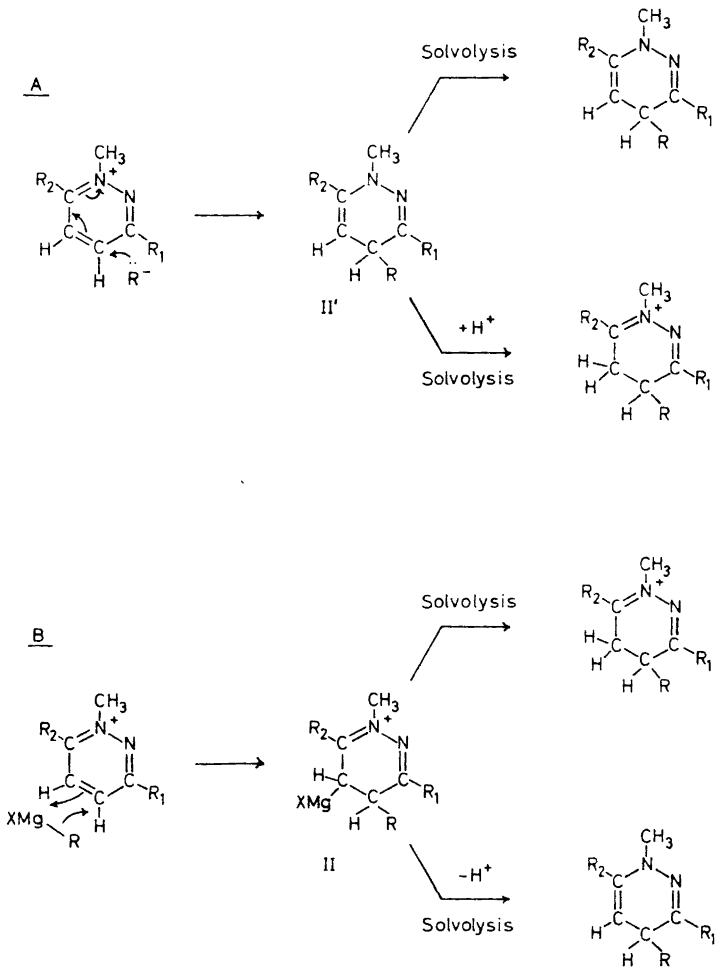
[b] The compounds were dissolved in deuterochloroform with tetramethylsilane as an internal standard. No precautions were taken to keep operating conditions constant, so the δ-values given are only correct within ± 0.10 ppm.

[c] The δ- and the J-values were calculated using EDB (J. S. Martins (Univ. of Alberta) version (TWOSUM) of NMREN/NMRIT by R. C. Ferguson and D. W. Martin *J. Chem. Phys.* **41** (1964) 2087).

[d] The odd appearance of the dimethylamino peak at 3.06–2.59 δ may be due to steric hindrance. At 100° in pyridine two sharp dimethylamino peaks are obtained.

[e] The numbering of the ring protons is defined in Chart IV.

CHART III



The addition of Grignard reagents to 1-methyl-3,6-*bis*-dimethylamino-pyridazinium iodide (I) seems to follow a somewhat different reaction path. The structure of the salts IIIa, IIIb, IIIc, and IIId, and the formation of the ethoxycarbonyl compounds IVb, IVc, and IVd, strongly suggest that the Grignard reagents add to the C^4-C^5 double bond to give the intermediate C-magnesium compounds IIa, IIb, IIc, and IId (see Chart III, B), which may react with electrophiles as normal Grignard reagents.

However, the 4-substituted-1-methyl-3,6-*bis*-dimethylamino-1,4-dihydro-pyridazine II′ (see Chart III, A) might be an alternative intermediate in the addition of Grignard reagents to the methiodide I. On hydrolysis, the com-

pound II′ might be basic enough to add hydrogen iodide to form the observed products IIIa, IIIb, IIIc, and IIId (see Chart III, A). This possibility is considered highly unlikely, however, because of the formation of the ethoxycarbonyl compounds IVb, IVc, and IVd by reaction of the intermediate with diethyl carbonate.

On the other hand it cannot at present be excluded that the Grignard reactions investigated earlier [1] involve addition to the C^4—C^5 double bond in the pyridazinium salts as outlined in Chart III, B. In principle, the 4,5-dihydropyridazinium salts formed by methanolysis [1] might deprotonate immediately.

The two mechanisms may in all cases be distinguished from each other by NMR spectra of the Grignard reaction solutions. If the intermediate were of the 1,4-dihydropyridazine type (II′) a vinylic proton should appear in the spectra. If a C-magnesium compound (II) was formed, one would expect a doublet at relatively high field due to the shielded proton at C^5. However, satisfactory NMR techniques have not been developed as yet.

Low temperature NMR experiments on the iodides IIIb, IIIc, and IIId. In these salts, strong conjugation between the dimethylamino group at C^6 and the positively charged nitrogen atom in the ring might be expected. As information concerning this effect is of importance in the conformational analysis (see next section) NMR spectra of the compounds IIIb, IIIc, and IIId were obtained at decreasing temperatures. If the conjugation was of significance, then the dimethylamino group at C^6 should be subjected to restricted rotation and, accordingly, the two N-methyl groups should be magnetically nonequivalent at low temperatures.

As a matter of fact, a splitting into a doublet of the dimethylamino group at highest field in the spectra of all three salts was observed, but this splitting is attributed to the dimethylamino group at C^3 for the following reasons:

The coalesce temperatures in deuterochloroform for the salts IIIb, IIIc, and IIId were −41°, −2°, and −35°, respectively. If the restricted rotation observed resulted from the conjugative effect mentioned above very similar coalesce temperatures would be expected. The observed values indicate that steric factors are operative. Consequently, it may be concluded that the splitting is to be attributed to the dimethylamino group at C^3. Furthermore, consideration of inductive and — if existing — conjugative effects suggests that the dimethylamino group at C^6 is the one at low field in the spectra.

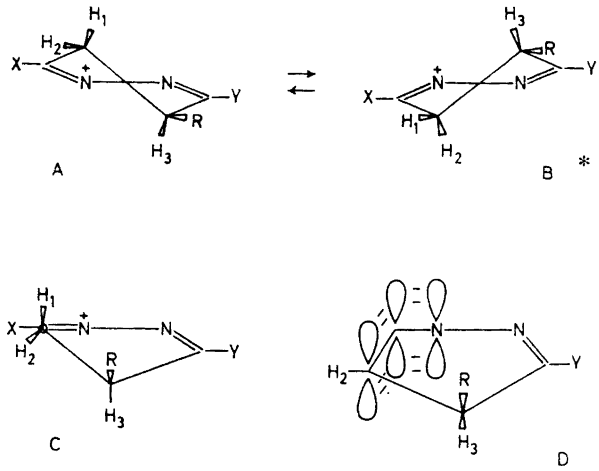
The splitting of the C^3 dimethylamino group in the NMR spectrum of the salt IXc also supports the interpretation given.

As the C^6 dimethylamino group at low field in the NMR spectra of the salts IIIb, IIIc, and IIId do not show any splitting down to −55° to −60°, it may be concluded that the conjugation mentioned above is of small importance or perhaps nonexistent.

Conformational analysis. If the conclusion of the preceding section is accepted the 1,3-cyclohexadiene system may be selected as a basis for the discussion. By optical rotary dispersion [7] and microwave [8] methods this system has been shown to exist in a slightly twisted conformation, the dihedral angle between the two double bonds being approximately 17.5° [8] in good agreement with the Dreiding model.[7]

It may now be assumed that the 4,5-dihydropyridazine system exists in a very similar conformation and that semiquantitative conclusions concerning angles and bond lengths in the 4,5-dihydropyridazine ring may be drawn from the Dreiding model of 1,3-cyclohexadiene. The carbon-carbon double bond length is 1.33 Å and the carbon-nitrogen double bond length is 1.29 Å estimated from the covalent radii.[9] Although this difference is small, other factors may be at work, and the validity of the assumption is not easy to assess.

CHART IV



If the assumption is accepted, then 4,5-dihydropyridazines must exist in an equilibrium of two equally populated conformations (A and B in Chart IV, X=Y and R=H). When X≠Y and more significantly R≠H the two conformations A and B will no longer be equally populated.

In order to obtain information about the conformational population of 4- or 5-substituted-4,5-dihydropyridazines the relevant NMR data of the known compounds Xc and Xd,[4] the model compounds XIc and XId (see Chart II), and the salt IIId are presented in Table 3.

The compounds XIc and XId were synthesized as models for the salts IIIc and IIId, respectively, for reasons which will become clear in the discussion in Table 3.

In conformation A (see Chart IV) the following coupling constants are expected: $J_{12} \sim -16$ cps, $J_{13} \sim 9-10$ cps, and $J_{23} \sim 2$ cps. In conformation B one would expect $J_{12} \sim -16$ cps, $J_{13} \sim J_{23} \sim 2$ cps. These expectations are based on an inspection of the Karplus curves (see, *e.g.*, Bible [10]). The Karplus curves may not apply to 4,5-dihydropyridazines in the quantitative sense,

* The positions of H_3 and R are to be exchanged.

Table 3. NMR data.[a] Compounds X and XI.

Compound	δ_3[b]	δ_4	δ_6	δ_{H_1}[b]	δ_{H_2}	δ_{H_3}	J_{12}[c]	J_{13}	J_{23}
Xc	—	—	—	—	—	—	−16.50	9.15	1.08
Xd	—	—	—	—	—	—	−17.33	8.40	1.13
XIc	2.96[d]	0.94	2.96[d]	2.14	2.76	2.56	−16.15	7.96	1.40
XId	2.74[e]	7.40−7.04	2.86[e]	2.57	2.70	3.88	−15.51	7.54	1.82
IIId	3.01	7.54−7.05	3.14	3.51	3.34	4.79	−16.26	6.53	2.33

[a] The NMR spectra were recorded on a Varian A-100 spectrometer. The compounds were dissolved in deuterochloroform with tetramethylsilane as an internal standard. No precautions taken to keep operating conditions constant, so the δ-values given are only correct within ± 0.10 ppm.

[b] δ_n means the δ-value (if any) for the substituent in position n. The numbering of the ring protons is defined in Chart IV.

[c] The J-values given for the compounds XIc, XId, and IIId have been calculated using EDB (see note c in Table 2). Those for the compounds Xc and Xd are due to Kofod.[4]

[d] The two dimethylamino peaks are exactly coincident in deuterochloroform.

[e] The assignment is arbitrary.

but the following qualitative conclusion must be correct: If $J_{13} \gg J_{23}$ then conformation A is the most important, if $J_{13} \sim J_{23}$ then conformation B is the predominant one.

Inspection of Table 3 shows, that in all cases $J_{13} \gg J_{23}$, the least convincing example being the salt IIId. The low value for J_{13} in this salt may be ascribed to the electronegativity of the positively charged nitrogen atom. It may be argued that for reasons mentioned later (see the last section) and outlined in Chart IV, H^1 should be more affected than H^2 by the positive charge. Similar argumentation has been applied to cyclohexane systems with electronegative substituents.[11] Comparison of the salt IIId with the model compound XId supports the argument given (see Table 3). Furthermore NMR spectra of IIId recorded at −80° in methylene chloride show no splitting besides that of the dimethylamino group at position 3 (*vide supra*) indicating that only conformation A exists in significant amounts in solution.

The conclusion is, that the compounds IIId, XIc, and XId in solution exist predominantly or perhaps completely in formation A with the substituent R placed equatorially.

Deuterium exchange. Considerations concerning the mechanism of the Grignard reactions (*vide supra*) initiated an investigation of the deuterium exchange of the salts IIIa, IIIb, IIIc, and IIId and later of the dihydropyridazines XIc and XId. Several solvents were used, but only the most quantitative data (deuterium oxide as solvent) are presented in tabular form (Table 4).

In preliminary experiments, deuterochloroform solutions of the above mentioned compounds were shaken with deuterium oxide. One proton was exchanged in IIIc and IIId, but none were exchanged in IIIa, IIIb, XIc, and XId. When the deuterochloroform solutions of IIIb, IIIc, IIId, XIc, and XId were shaken with a dilute solution of sodium carbonate in deuterium oxide, two protons were exchanged in IIId (one proton very quickly, the

other much slower), one proton was exchanged in IIIb and IIIc and none in XIc and XId.

When XIc was dissolved in tetradeuteromethanol, one proton exchanged within few minutes. No further exchange took place.

In tetradeuteromethanol solution one proton in compound XId was exchanged within 10—15 min. The benzylic proton was also exchanged, but this took hours even at 65°. The last ring proton did exchange but more slowly than the benzylic proton.

More quantitative data were obtained, when the deuterium exchanges were carried out in deuterium oxide as solvent (see Table 4). The dihydropyridazine XId had to be excluded because of low solubility in water.

With the salts IIIa, IIIb, IIIc, and IIId the exchanges in the heterogeneous deuterium oxide-deuterochloroform system were much faster than in deuterium oxide solution. The reason for this difference is obscure. Exactly the opposite order seems to apply to the dihydropyridazines XIc and XId.

Table 4. Deuterium exchange data.

Compound	N_1 [a]	N_2 [a]	T_{D_2O} min [b] H_1 [c]	H_2 [c]	$T_{CO_3^{2-}}$ min [b] H_1 [c]	H_2 [c]
IIIa	0	2	∞	∞	4	4
IIIb	0	1	∞	∞	<7	∞
IIIc	1	0	<10	∞	Small	∞
IIId	1	1	*ca.* 90	∞	<6	*ca.* 70
XIc	1	0	< 7	∞	Small	∞

[a] N_1 means the number of protons exchanged when the compound is dissolved in D_2O. N_2 means the number of protons *further* exchanged when a small amount of sodium carbonate is added to the solution. The amount of sodium carbonate used was not determined, so the T-values (see next note) cannot be compared in the vertical sense.

[b] T_{D_2O} and $T_{CO_3^{2-}}$ mean the half-exchange-time for the proton designated (numbering according to Chart IV) in D_2O and D_2O+sodium carbonate, respectively.

[c] It has been shown exactly which proton exchanges the faster only in the case of IIId and XIc. For the compounds IIIa, IIIb, and IIIc reasonable suggestions have been given. See the text for discussion.

The numbering of the ring protons is that of Chart IV, in which A represents the most stable conformation with X=Y=dimethylamino.

Apparently (*vide infra*) only the methylene protons at C^5 were exchanged (XId did not quite conform to this generalization, *vide supra*). Therefore, from the data outlined above (especially Table 4) it must be quite clear that the methylene protons, which are diastereotopic,[12] exchange at very different rates and therefore are of widely different chemical reactivity. Only few examples of this phenomenon seem to be known,[13–16] most of which involve different rates of deuterium exchange for diastereotopic methylene protons in sulfoxides. It may be stressed that although many instances of magnetically nonequivalent, diastereotopic methylene protons are known, to the author's knowledge only the five examples cited give evidence of chemically nonequivalent protons.

DISCUSSION

From the very definition of the concept of diastereotopic groups[12] it follows that such groups *in principle* must have different properties in all respects. Therefore the chemical nonequivalence observed (see the preceding section) is not unexpected. However, three points may be emphasized.

1) It is possible to measure the difference in chemical reactivity of the diastereotopic protons quantitatively.

2) It may be decided exactly *which* proton exchanges most rapidly.

3) The origins to the nonequivalence may be suggested.

Ad 1: The data of Table 4 are admittedly very inaccurate. The disappearance of the protons was followed by NMR, but the necessary integrations were complicated by the unfavourable positions of the methylene protons in the spectra. Furthermore, in the presence of sodium carbonate the formation of pyridazinones from the salts IIIa, IIIb, IIIc, and IIId interfered with the integrations.

Ad 2: The question of which proton exchanges the faster may be settled for the salt IIId and the dihydropyridazines XIc and XId if the conclusion drawn in the section "Conformational analysis" (*vide supra*) is accepted. Using the numbering of Chart IV, it may be stated that H^1 in all three cases is exchanged more rapidly than H^2. The criteria for this assignment are as follows.

In the NMR spectrum of the salt IIId dissolved in deuterium oxide the absorption of H^1 ($J_{13}=6.53$ cps) slowly disappears (see Table 4) and simultaneously the quartet of the benzylic proton is transformed into a doublet with a spacing of about 2 cps. If sodium carbonate is added the absorption of H^2 slowly vanishes and the doublet at low field gradually collapses into a singlet.

In the NMR spectrum of the dihydropyridazine XIc dissolved in deuterium oxide the absorption of H^1 ($J_{13}=7.96$ cps) rapidly disappears. Addition of sodium carbonate produces no further changes in the spectrum.

In the case of the dihydropyridazine XId dissolved in tetradeuteromethanol the decline of H^1 cannot be followed because of the unfavourable chemical shift of H^1. But the quartet of the benzylic proton collapses into a broad singlet ($J_{23}=1.82$ cps) indicating the disapperance of H^1.

It is now assumed that the deuterium exchanges of the salts IIIb and IIIc are analogous, that is, only the methylene protons are exchanged, and H^1 more rapidly than H^2.

The salt IIIa is a special case because the conformations A and B (see Chart IV) probably are very close to equally populated and therefore no exchange rate difference for H^1 and H^2 is observed (see Table 4).

Ad 3: The difference in exchange rates of the diastereotopic methylene protons H^1 and H^2 can only be understood if the exchange reactions are 100 % stereoselective and occur with retention of configuration. This remarkably high stereoselectivity may be due simply to H^1 and H^2 being diastereotopic. Another explanation might be an unequal population of the two possible conformations A and B (Chart IV). The relative importance of these two effects has been discussed [17–19] in relation to the many examples of magnetically nonequivalent diastereotopic protons in the literature. The contribution of the

two effects have been calculated in some cases,[19] but the current conclusion is, that although the intrinsic asymmetry [18] in many cases is of little importance, the contributions of this effect may occasionally be quite significant.[19]

The relationship between magnetic and chemical nonequivalence may be complicated, so the above discussion cannot be applied to the present problem directly. However, it is difficult to accept that intrinsic asymmetry could be responsible for the great chemical nonequivalence observed.

If the 4,5-dihydropyridazine ring is viewed along the $C^5—C^6$ bond (Fig. C in Chart IV) the vertical projection of the $C^5—H^1$ bond is seen to be nearly parallel to the atomic *p*-orbitals at C^6 and at $N^1{}_+$. This follows from an inspection of the Dreiding model of 1,3-cyclohexadiene. Therefore, if H^1 is removed and $C^5{}_-$ becomes planar (or nearly so) extensive overlap of the atomic *p*-orbitals at C^5, C^6, and $N^1{}_+$ might be possible. This possibility of overlap constitutes the driving force of the exchange.

This model applies to the salts IIIb, IIIc, and IIId, but the case of the dihydropyridazines XIc and XId may, in fact, be quite similar.

However, the high retention of configuration is not very easy to explain. Deuterium exchange reactions are often found to proceed with high retention,[20] but preferably in media of low dielectricity constants. But the exchange reactions of the salts IIIb, IIIc, and IIId follow the same pattern in the heterogeneous deuterium oxide-deuterochloroform system as in deuterium oxide solution.

It may be argued that the probable transition state (Fig. D in Chart IV) is dissymmetric, but this fact alone could hardly account for the high retention observed.

The 4,5-dihydropyridazines XIc and XId give rise to separate problems. First of all, deuterium exchange would not be expected to take place under the experimental conditions used. Even if the model presented in Chart IV is applicable the driving force should be much smaller than in those cases with a positive charge at N^1. Secondly, one would expect rather similar driving forces in the exchanges of H^1 and H^3. Although in XId the benzylic proton does exchange in tetradeuteromethanol, the exchange is very slow compared with that of H^1 and the phenyl group may be in part responsible. Anyhow, H^3 in XIc does not exchange at all neither in tetradeuteromethanol nor in deuterium oxide.

To sum up the simple model suggested in Chart IV for the exchange mechanism does account for the driving force of the reaction and for the stereoselectivity. However, no convincing answers to the questions concerning the retention of configuration observed can be given at present.

EXPERIMENTAL

(See Table 1 for melting points and analytical data).

3,6-bis-*Dimethylamino-pyridazine* may be synthesized from 3,6-dichloropyridazine according to Druey *et al.*[21] or Steck.[22]

A better procedure than those mentioned was to dissolve 3,6-dichloropyridazine (101.5 g, 0.68 mole) in abs. ethanol (about 400 ml). Aqueous dimethylamine (153 g of a 60 % solution, 2.04 moles) was added and the reaction mixture refluxed for 1 1/2 h. The solvents were removed *in vacuo* and the residue was dissolved in abs. ethanol (about 400 ml). Aqueous dimethylamine (306 g of a 60 % solution, 4.08 moles) was added, the

reaction mixture was transferred to an autoclave and heated for 19 h at 120°. Most of the solvents were then removed *in vacuo*, water was added and the aqueous phase extracted thoroughly with chloroform. The chloroform phase was dried, filtered and evaporated in *vacuo*. The finely divided residue was triturated with toluene: ligroin 1:1 and then air dried. Yield 100 g (88.5 % from 3,6-dichloropyridazine) of a product with m.p. 135—138° (lit. 140—42°[21]), which was pure enough for most purposes.

3,6-bis-*Dimethylamino-1-methylpyridazinium iodide (I).* The reaction of 3,6-*bis*-dimethylaminopyridazine with methyl iodide has been mentioned in the literature,[3,23] and shown to give a mixture of the exo- and the endo-quaternized products,[3] mostly the former.

The ring quaternized product was obtained by heating 3,6-*bis*-dimethylaminopyridazine (30 g, 0.181 mole) with methyl iodide (30 ml, 0.481 mole) in acetonitrile (40—50 ml) in a sealed glass tube at 120° for 4 h. The product was taken up in chloroform, and the chloroform solution filtered and evaporated *in vacuo*. The finely divided residue was triturated with ethyl acetate several times until the ethyl acetate used became only weakly coloured. One recrystallization from acetonitrile yielded 38.5 g (69.1 %) of essentially pure methiodide (I), m.p. 178—80° (accompanied by destruction, not well defined).

Addition of t-*butylmagnesium chloride, phenylmagnesium bromide, and methylmagnesium iodide to 3,6*-bis-*dimethylamino-1-methylpyridazinium iodide (I). General procedure.* In a 500 ml three-necked flask provided with reflux condenser, polyethylene stopper, separatory funnel, and magnetic stirrer was placed finely pulverized methiodide (I) (5.0 g, 16.2 mmoles). Dry nitrogen was let through the system, 70—80 ml of dry ether was added, and stirring started. Grignard reagent (about 100 mmoles) was then added all at once and the stirred reaction mixture refluxed for 2 h. The flask was then chilled in an ice bath and chipped ice added slowly to the solution. The addition of ice was stopped precisely at the point, when the suspended magnesium salts flocked together and formed a tough jelly. The ether was removed *in vacuo* and the jelly thoroughly extracted with chloroform. The chloroform was evaporated and the residual oil triturated with ethyl acetate, which was then removed *in vacuo* to eliminate the last traces of chloroform. In the case of addition of phenylmagnesium bromide the product oil was at this stage extracted three times with boiling ethyl acetate to remove impurities originating from the Grignard reagent.

The product oil was then induced to crystallize from ethyl acetate or ethyl acetate-acetone. Recrystallization from ethyl acetate-acetone.

3,6-bis-*Dimethylamino-1-methyl-4,5-dihydropyridazinium iodide (IIIa).* The reagent "HMgBr" was prepared as a dark grey powder according to Clapp and Woodward.[2]

To a suspension of methiodide (I) (about 800 mg, 2.6 mmoles) in 50 ml of ether was added "HMgBr"-powder (about 62.5 mmoles) and the stirred reaction mixture refluxed for 13—14 min. Work-up was analogous to that for the Grignard additions described above. The product oil was triturated with ethyl acetate:acetone 4:1 to give dark coloured crystals. Two recrystallizations from acetone yielded a nearly colourless product in very low yield. The quality of the "HMgBr" used was of paramount importance and the conditions of the reaction must be varied accordingly.

Purification of 3,6-bis-*dimethylamino-1-methyl-4,5-dihydropyridazinium iodide (IIIa) and of 4-phenyl-3,6*-bis-*dimethylamino-1-methyl-4,5-dihydropyridazinium iodide (IIId).* The recrystallized iodide IIId was contaminated with about 8 % of the corresponding bromide as shown by a preliminary elementary analysis. The bromide present was transformed into the iodide by treatment with potassium iodide in acetone containing a little water. The solution was stirred for 1 h and the solvents then removed *in vacuo*. Water was added and the aqueous phase was extracted with chloroform. The chloroform phase was dried, filtered and evaporated *in vacuo*, and the product oil crystallized from ethyl acetate. Recrystallization from ethyl acetate-acetone yielded the analytically pure iodide.

The bromide content in the recrystallized salt IIIa was not determined. The transformation into the pure iodide was carried out exactly as described for the salt IIId.

3,6-bis-*Dimethylamino-4-substituted-5-ethoxycarbonyl-1-methyl-1,4-dihydropyridazines (IVb, IVc, and IVd). General procedure.* The corresponding 3,6-*bis*-dimethylamino-4-substituted-1-methyl-4,5-dihydropyridazinium salt (IIIb, IIIc and IIId, respectively) (500 mg, 1.30—1.54 mmoles) was suspended in 50 ml ether and *t*-butylmagnesium chloride

(about 20 mmoles) added. The mixture was refluxed for 1 h, diethyl carbonate (about 80 mmoles) added and the reflux continued for 18—20 h. Work-up was analogous to that described above for the Grignard additions. Excess diethyl carbonate could be nearly completely removed by slight heating at about 1 mm.

The product was transferred to an aluminium oxide (Merck) column (100 g, neutral, deactivated with about 3.0 ml of water) and the column eluted with benzene:ethyl acetate 6:1. The ethoxycarbonyl compounds were obtained as nearly colourless oils. Only the phenylsubstituted compound slowly crystallized on standing.

2-Methyl-6-dimethylaminopyridazinone-3 (Va). 3,6-*bis*-Dimethylamino-1-methylpyridazinium iodide (I) (2.04 g, 66.1 mmoles) was suspended in 40—50 ml of ether and an ethereal suspension of lithium aluminium hydride (1.0 g, 26.4 mmoles) added. The reaction mixture was refluxed for 3 h, then chilled and hydrolyzed with chipped ice as described for the Grignard additions above. The ether was removed *in vacuo* and the residue thoroughly extracted with chloroform. The chloroform was removed *in vacuo*, the product oil transferred to an aluminium oxide column (60 g, basic, deactivated with 2.5 ml of water) and eluted with benzene:ethyl acetate 2:3. Pure fractions were selected and the solvents evaporated *in vacuo* to give a colourless oil. The yield was not determined.

2-Methyl-5-t-butyl-6-dimethylaminopyridazinone-3 (Vc). 3,6-*bis*-Dimethylamino-4-*t*-butyl-1-methyl-4,5-dihydropyridazinium iodide (IIIc) (507 mg, 1.39 mmoles) was dissolved in a mixture of 20 ml of methanol and 20 ml of water and aqueous sodium hydroxide (4.12 mmoles) added. The reaction mixture was refluxed for 15 min, then chilled and extracted with chloroform. The chloroform phase was dried, filtered and evaporated *in vacuo*. The yield was quantitative.

A picrate was easily formed with excess picric acid in ethanol.

2-Methyl-5-phenyl-6-dimethylaminopyridazinone-3 (Vd). 3,6-*bis*-Dimethylamino-4-phenyl-1-methyl-4,5-dihydropyridazinium iodide (IIId) (5.01 g, 13.0 mmoles) was dissolved in 100 ml of methanol and a methanolic solution of sodium methoxide (218 mmoles) added. The reaction mixture was stirred for 1 h at room temperature. Most of the solvent was removed *in vacuo*, water was added and the water phase extracted with chloroform. The chloroform phase was dried, filtered and evaporated *in vacuo* to give a dark red oil. This oil was transferred to an aluminium oxide column (60 g, neutral, deactivated with 1.8 ml of water) and eluted with benzene:ethyl acetate 1:1. The resulting red crystals were recrystallized from benzene-benzine (b.p. 60—80°) to give a nearly colourless product pure enough for most purposes. Yield 68 %.

2,5-Dimethyl-6-dimethylaminopyridazinone-3 (Vb). This compound was prepared analogous to the phenyl compound described above. Pure fractions from the column chromatography were selected and the solvents removed *in vacuo* to give a colourless oil. The yield was not determined.

3-Dimethylamino-6-phenyl-1-methylpyridazinium iodide (VII). The quaternization of 3-dimethylamino-6-phenylpyridazine [24] with methyl iodide in acetonitrile solution has been shown [3] to give 97 % of the title product and 3 % of the isomer. The latter is difficult to remove by recrystallization, but for the present purposes *(vide infra)* this is not necessary.

3-Dimethylamino-6-phenylpyridazine [24] (10.0 g, 50.3 mmoles) was dissolved in 100 ml of boiling benzene and methyl iodide (68.5 g, 0.481 mole) added. The reaction mixture was refluxed for 1 1/2 h. The methiodide precipitated as a heavy oil, but shaking the flask induced crystallization. Recrystallization from ethanol-ethyl acetate 1:1 gave a yellow orange product (14.8 g, 86.5 %).

3-Dimethylamino-6-phenyl-4-t-butyl-1-methyl-1,4-dihydropyridazine (VIc). From 2-methyl-5-t-butyl-6-dimethylaminopyridazinone-3 (Vc). The pyridazinone Vc was dissolved in great excess (10—12 equiv.) of phenylmagnesium bromide in ether. Dry benzene was added under simultaneous distillation of the reaction mixture until the boiling point had reached 75—80°. The reaction mixture was then refluxed for about 18 h and then hydrolyzed with a mixture of ice and concentrated hydrochloric acid. The acid solution was extracted with ether and the ether extracts discarded. The aqueous phase was then made basic with concentrated aqueous ammonia and extracted with chloroform. The chloroform phase was dried, filtered and concentrated *in vacuo* and the resulting oil rapidly transferred to an aluminium oxide column (60 g, neutral, deactivated with 3.2 ml of water) and eluted with benzene containing 7 % (by volume) ethyl acetate. As the product was unstable, all operations described so far must be carried out as rapidly as

possible. The elution of the column was best followed visually. A greenish coloured zone moved down the column. When this zone had been eluted, the fractions containing material absorbing in UV light were combined and the solvents removed *in vacuo*. The resulting green oil was essentially pure 1,4-dihydropyridazine VIc. The yield was estimated to be about 20 %.

From 3-dimethylamino-6-phenyl-1-methylpyridazinium iodide (VII). The methiodide VII (512 mg, 1.50 mmoles) was suspended in 50 ml of dry ether and *t*-butylmagnesium chloride (about 10 mmoles) added. The reaction mixture was stirred for 1 h at room temperature and then hydrolyzed with a mixture of ice and concentrated hydrochloric acid. The aqueous solution was made basic with concentrated aqueous ammonia and extracted with chloroform. The procedure from here on was exactly analogous to that described above. The yield was not determined.

3-Dimethylamino-6-phenyl-4-t-butyl-5-acetyl-1-methyl-1,4-dihydropyridazine (VIIIc). The dihydropyridazine VIc (420 mg, 1.55 mmoles) was dissolved in dry benzene, and benzene solutions of triethylamine (2.00 mmoles) and of acetyl chloride (redistilled, 1.98 mmoles) were added. The reaction mixture was stirred and refluxed for 2 h and subsequently thoroughly extracted with water. The benzene layer was separated and the aqueous phase extracted with chloroform. The combined organic layers were dried, filtered and evaporated *in vacuo*. The resulting oil was transferred to an aluminium oxide column (60 g, basic, deactivated with 3.0 ml of water) and eluted with benzene containing 15 % ethyl acetate (by volume). Pure fractions were selected and the solvents removed *in vacuo* to give yellow crystals. Recrystallization from water-ethanol. The yield was not determined.

3-Dimethylamino-6-phenyl-4-t-butyl-1,5-dimethyl-4,5-dihydropyridazinium iodide (IXc) The dihydropyridazine VIc was dissolved in acetonitrile and a great excess of methyl iodide added. The reaction mixture was refluxed for 2 h and then evaporated *in vacuo*. The resulting oil was triturated with ethyl acetate and subsequently recrystallized from ethyl acetate-acetone to give a nearly colourless product.

3-Dimethylamino-4,6-diphenyl-1-methyl-1,4-dihydropyridazine (VId). From 2-methyl-5-phenyl-6-dimethylaminopyridazinone-3 (Vd). The pyridazinone Vd (503 mg, 2.18 mmoles) was dissolved in phenylmagnesium bromide (about 10 mmoles) in ether. Dry benzene was added under simultaneous distillation of the reaction mixture until the boiling point had reached 75—80°. The solution was then refluxed for 2 h.

The rest of the procedure was analogous to that for the corresponding *t*-butyl compound (VIc). The fractions from the column chromatography were combined and the solvents removed to give a reddish coloured oil, which according to NMR was nearly pure. The yield was not determined.

From 3-dimethylamino-6-phenyl-1-methylpyridazinium iodide (VII). The procedure was analogous to that described for the corresponding *t*-butyl compound (VIc) except that about 20 mmoles phenylmagnesium bromide was used to about 500 mg methiodide. The yield was not determined.

3-Dimethylamino-4,6-diphenyl-5-acetyl-1-methyl-1,4-dihydropyridazine (VIIId). This compound was prepared analogously to the corresponding *t*-butyl compound (VIIIc) from the dihydropyridazine (VId). The product from the column chromatography was recrystallized from benzene-benzine (b.p. 60—80°) to give light yellow crystals.

3,6-bis-Dimethylamino-4-t-butyl-4,5-dihydropyridazine (XIc). Pure 3-chloro-6-dimethylamino-4-*t*-butyl-4,5-dihydropyridazine (Xc) [4] (2.83 g, 13.1 mmoles) and dimethylamine (redistilled, 7.49 g, 167 mmoles) dissolved in 20 ml of ethanol was heated in a closed steel tube at 120° for 20 h. The reaction mixture was chilled, taken up in chloroform, and the chloroform phase was extracted with water, then dried, filtered and evaporated *in vacuo* to give a semi-crystalline product, which was pressed hard between filter papers to remove adhering oil. The resultant light tan crystals were recrystallized from benzine (b.p. 60—80°) several times to give a colourless product. The m.p. was determined to 79—86°, but the analysis on the product was acceptable (see Table 1). The yield was not determined.

3,6-bis-Dimethylamino-4-phenyl-4,5-dihydropyridazine (XId). Pure 3-chloro-6-dimethylamino-5-phenyl-4,5-dihydropyridazine (Xd) [4] (2.67 g, 11.35 mmoles) and dimethylamine (redistilled, 7.49 g, 167 mmoles) dissolved in 20 ml of ethanol was treated

exactly as the corresponding *t*-butyl compound (Xc). The chloroform extract was evaporated *in vacuo* to give an oil, which on trituration with ethyl acetate crystallized to a slightly tan product. Recrystallization from acetone gave colourless crystals. The yield was not determined.

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