

Addition of Grignard Reagents to Pyridazines

IX. Addition of *t*-Butylmagnesium Chloride to Alkyl-, Aryl-, and Chloro-Pyridazines

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Addition of *t*-butylmagnesium chloride to 3,6-dimethyl-, 3,6-di-*t*-butyl-, 3,6-diphenyl-, and 3,6-dichloropyridazine in all cases gives the corresponding 4-*t*-butyl-3,6-di-substituted-1,4-dihydropyridazines. Again, pyridazines unsymmetrically substituted in 3- and 6-position with methyl, *t*-butyl, phenyl, or chlorine, are alkylated in the 4- or 5-position to a mixture of the two possible 1,4-dihydropyridazines in ratios apparently determined by the steric requirements of the substituents in 3- and 6-position. The unstable dihydropyridazines are identified by NMR spectroscopy.

Dehydrogenation of the dihydropyridazines affords the corresponding pyridazines except in cases where two *t*-butyl groups are positioned *ortho* to each other. Thus, the attempted thermal elimination of hydrogen bromide from 3,5,6-tri-*t*-butyl-4-bromo-4,5-dihydropyridazine, obtained by bromination of the corresponding dihydropyridazine, gives 3,6-di-*t*-butylpyridazine and *t*-butyl bromide.

The addition of *t*-butylmagnesium chloride to pyridazines, carrying a methoxy group in 3- or 6-position (I; R³ or R⁶=methoxy) has previously been shown to give the corresponding 4- or 5-*t*-butyl-4,5-dihydropyridazines.¹⁻³ As an extension of this work, it is now shown that compounds of type I (Chart 1), carrying alkyl, aryl, or chloro substituents at the 3- and 6-positions, give exclusively the corresponding 4- or 5-*t*-butyl-3,6-disubstituted 1,4- (or 2,5-) dihydropyridazines, II and III. In most cases, oxidation of the dihydropyridazines leads to the pyridazines, IV and V.

The additions are carried out conventionally, with excess Grignard reagent. The adducts are decomposed with methanol to give the crude dihydropyridazines (see Experimental). Identification of the individual dihydropyridazines is based either on NMR spectroscopy (Table 2) and (or) by identification of the corresponding aromatized products. The relative amounts of

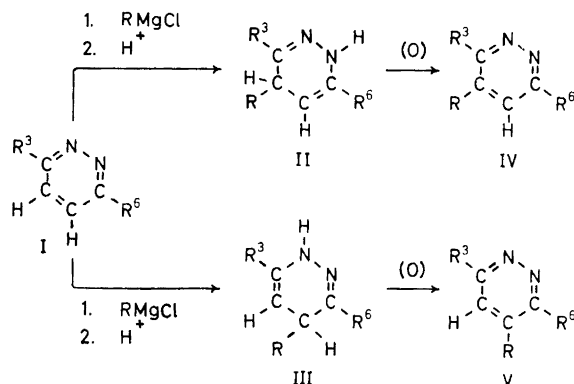


Table 1.

Compound	R^3	R^6	Grignard add.		Quaternization	
			C^4 %	C^5 %	N^1 %	N^2 %
Ie	CH_3	C_6H_5	90	10	2	98
If	CH_3	Cl	50	50	21	79
Ig	CH_3	C_6H_5	75	25	8	92
Ih	Cl	C_6H_5	66	34	17	83
Ii	C_6H_5	C_6H_5	25	75	—	—
Ij ³	CH_3	OCH_3	50	50	—	> 98
Ik ⁴	OCH_3	C_6H_5	66	34	78	22

Relative yields of the two dihydropyridazines (C^4 : addition to C^4 , (II) in chart 1; C^5 : addition to C^5 , III in Chart 1), obtained from 3,6-disubstituted pyridazines (I), as compared to the relative yields of the N^1 - and N^2 -methylated products obtained from the same pyridazines (I) with methyl iodide.⁹

the isomeric dihydropyridazines formed (Table 1) were in all cases determined from the NMR spectra of the crude products.

Identification. The necessary NMR data for the identification of the five pairs of isomeric dihydropyridazines (II and III, e to i, Chart 1) may be obtained from the spectra of 4-*t*-butyl-3,6-dimethyl-1,4-dihydropyridazine (IIb) and 4-*t*-butyl-1,4-dihydro-3,6-diphenylpyridazine (IIa) (see Table 2).

The former reveals the presence of an $\text{N}-\text{H}$ proton removable by D_2O exchange. A vinylic proton, H^5 , provides further evidence of the 1,4-dihydro structure and appears as a multiple with 11 peaks, each separated by 1.2 cps, indicating coupling to methyl at 6-position ($J=1.2$ cps), H^4 ($J=6.0$ cps), and the $\text{N}-\text{H}$ ($J=2.4$ cps). The two latter coupling constants are in agreement with values recently reported by Sauer *et al.* for analogous 1,4-dihydropyridazines.⁴ Exchange with deuterium oxide simplifies the spectrum: the vinylic

Table 2. NMR data.^a

No.	Compound, Chart 1		Chemical shifts, δ -values and spin patterns ^b				Coupling constants ^c				
	R ^s	R ^s	R ^s	R ^s	NH	H ⁴	H ⁵	J _{15 or 24}	J ₄₅	J	
IIa	C ₆ H ₅	C ₆ H ₅	0.84 s	7.18 to m	7.98	<7.98	3.63 db	5.00 q	2.7	6.6	
IIb	CH ₃	CH ₃	0.90 s	2.06 s	1.84 br	6.77 br	2.58 db	4.28 m	2.4	6.0	1.2 ^d 0.7 ^e
IIc	Cl	Cl	0.97 s	—	—	7.08 br	3.04 db	5.69 q	2.6	6.0	
IId	C ₄ H ₉	C ₄ H ₉	0.84 s	1.15 or s	1.21 s	7.03 br	2.82 db	4.32 q	2.8	6.9	
IIe	CH ₃	C ₄ H ₉	0.88 s	2.04 s	1.15 s	6.84 br	2.59 db	4.30 q	2.5	6.0	
IIIe	CH ₃	C ₄ H ₉	0.85 s	1.88 db	1.22 s	6.84 br	4.32 m	2.89 db	—	6.6	
IIIf	CH ₃	Cl	0.92 s	2.06 s	—	7.04 s	2.73 db	4.58 q	2.4	6.4	
IIIIf	CH ₃	Cl	0.94 s	1.85 br	—	7.04 m	4.32 m	2.90 db	2.4	5.6	1.4 ^f 0.5 ^g
IIIg	CH ₃	C ₆ H ₅	0.98 s	2.13 s	7.36 (NH hidden)	7.62 (NH hidden)	2.78 db	4.81 q	2.6	6.0	
IIIIg	CH ₃	C ₇ H ₅	0.78 s	1.84 br	7.20 (NH hidden)	7.82 (NH hidden)	4.48 m	3.42 db	2.4	6.0	
IIIf	Cl	C ₆ H ₅	1.06 s	—	7.37 m	7.62 (NH hidden)	3.12 db	4.82 q	2.6	5.8	
IIIIf	Cl	C ₆ H ₅	0.81 s	—	7.29 m	7.92 (NH hidden)	4.85 q	3.59 db	2.6	6.4	
IIIf	C ₄ H ₉	C ₆ H ₅	0.93 s	1.27 s	? (hidden)	—	3.13 q	4.86 q	2.8	7.0	
IIIIf	C ₄ H ₉	C ₆ H ₅	0.79 s	1.18 s	7.19 (NH hidden)	7.92 (NH hidden)	4.57 q	3.47 db	2.6	6.2	
VII	Chart 2		1.17 or s	1.23 or s	1.23 s	5.97 br	2.54 q	4.16 q	1.6	3.7	
VIII	IIa, R=H		—	7.28 to	8.28 ca.	7.61 (hidden)	3.37 db	4.95 sext.	2.2	4.0	

^a Spectra are taken on a Varian A-60 spectrometer.^b δ -values are in ppm relative to tetramethylsilane, solvent deuteriochloroform.^c s=singlet, db=doublet, q=quartet, sext.=sextet, m=multiplet and br=broad.^d Coupling constants are given in cps and are taken directly from the observed splittings (first order).
^e H⁵ to CH₃, ^f H⁴ to CH₃, ^g H⁴ to CH₃, ^h H⁵ to CH₃.

2 protons

multiplet collapses into two quartets, and the broad signal at $\delta=1.85$, assigned to the methyl at position 6, is seen to split up into a quartet with a spacing of 0.7 cps, indicating coupling ($J=0.7$ cps) to H^4 in addition to the expected coupling with the vinylic proton. The signals at $\delta=2.58$ are accordingly relatively broad.

The second product (IIa) shows the presence of a vinylic proton H^5 , coupled to the neighbouring H^4 and to the N—H as above. This again suggests a 1,4-dihydropyridazine structure. The signals due to the aromatic protons are split into two groups, the most deshielded of which corresponds to two protons, at δ 7.66 to 7.98 ppm (the two *o*-protons of the 3-phenyl group; integration indicates the presence also of the N—H), and to eight protons, between δ 7.18 ppm and 7.61 ppm (the remaining aromatic protons). This splitting pattern indicates the presence of the grouping $C_6H_5-C=N$.

The other dihydropyridazines listed in Table 2 (c to i) all exhibit spectral characteristics similar to those of the two compounds discussed above, indicating their contents of the same structural features.

Addition of the Grignard reagent to 3,6-dichloropyridazine¹ and to 3,6-di-*t*-butylpyridazine gives products characterized by chemical shifts and coupling constants similar to those of the other dihydropyridazines. Consequently, an alternative structure previously suggested for compound IIc by one of the authors is obviously in error.¹

Addition to the unsymmetrically 3,6-disubstituted pyridazines produces the two possible, isomeric 4-substituted 1,4-dihydropyridazines, II and III, indicated in Chart 1 and listed in Table 2. Identification of the individual products (see below) and determination of the relative yields of II and III (presented in Table 1) may in many cases be derived directly from the NMR spectra of the crude products. In several cases, the pure dihydropyridazines could not be isolated, due to their unstable character.

The two dihydropyridazines derived from 3-methyl-6-*t*-butylpyridazine (IIe and IIIe) can be identified from the NMR spectrum of the crude product by the characteristic splitting arising from coupling between the methyl group and the vinylic proton in (IIIe); (IIe) does not show this splitting, *cf.* (IIa). The isometric pairs of products obtained from 3-methyl-6-chloropyridazine and 3-methyl-6-phenylpyridazine (IIf and IIIf, IIg and IIIg, respectively) may be similarly distinguished. The identity of (IIg) is further confirmed by the observed splitting of the phenylic protons in (IVg), the corresponding dehydrogenation product.⁵

The structures assigned to the products obtained from 3-chloro-6-phenylpyridazine are based on dehydrogenation and subsequent methoxylation to authentic pyridazines.⁶ The isomer (IIIh) could not be isolated, and the data for this compound are derived from the NMR spectrum of the crude reaction mixture.

The addition product from 3-*t*-butyl-6-phenylpyridazine consists mainly of the isomer (IIIi), identified by dehydrogenation with bromine to give a fair yield of (Vi). The NMR spectrum of the latter shows a sharp resonance of the phenyl protons indicating the presence of a substituent *ortho* to the phenyl group.⁵

A diphenyldihydropyridazine (VIII, prepared according to Alder and Niclas,⁴ who suggested its structure to be 4,5-dihydro-3,6-diphenylpyridazine) is included in Table 2. Again, NMR-evidence favours a 1,4-dihydropyridazine structure, but a peak at δ 2.6 ppm suggests the presence of some (*ca.* 15 %) of the corresponding 4,5-dihydroisomer in the deuteriochloroform solution. Addition of trifluoroacetic acid converts the mixture into 4,5-dihydro-3,6-diphenylpyridazine, characterized by a multiplet at δ 7.63 to 8.26 ppm, and a sharp peak at δ 3.5 ppm, in the ratio 10 to 4. Neutralization of the acid solution with aqueous ammonia reverses the reaction.

Chemical properties. Aromatization of the dihydropyridazines (II) and (III) was accomplished for 10 of the 14 dihydropyridazines studied, the dehydrogenation involving oxidation with either chloranil,³ or hydrogen peroxide,⁷ or bromination and subsequent dehydrobromination.² Thus, 4-*t*-butyl-1,4-dihydro-3,6-diphenylpyridazine (IIa) is readily brominated and dehydrobrominated with sodium methoxide to give 4-*t*-butyl-3,6-diphenylpyridazine (IVa). 3,4,6-Tri-*t*-butyl-1,4-dihydropyridazine (IIId) is again readily brominated to 3,4,6-tri-*t*-butyl-5-bromo-4,5-dihydropyridazine (VI, see Chart 2), the structure being based on the chemical shifts of the doublets of the two ring protons: H⁴ 2.84 ppm, and H⁵ 4.82; $J_{4,5}$ =1.3 cps. However, attempted elimination of hydrogen bromide with sodium methoxide did not lead to 3,4,6-tri-*t*-butylpyridazine as expected, 3,6-di-*t*-butylpyridazine (Id) being the only product isolated. Again, pyrolysis of the bromodihydropyridazine resulted in the formation of (Id); the *t*-butyl bromide eliminated during the reaction could be collected in good yield. The apparent resistance to the formation of an aromatized pyridazine ring carrying two *ortho* positioned *t*-butyl groups is likewise illustrated by the failing attempts to aromatize the dihydropyridazines (IIIe) and (IIIi).

Oxidation of the three pairs dihydropyridazines (II and III, f, g, and h) all give the expected aromatized 4-*t*-butylpyridazines.^{3,6}

Generally, the dihydropyridazines are not stable, and several of them could not be isolated in analytically pure condition. Samples dissolved in deuteriochloroform are slowly oxidized to the corresponding aromatized products. A special case is 3,4,6-tri-*t*-butyl-1,4-dihydropyridazine (IIId) undergoing a very ready reaction with oxygen to a peroxide, (VII), of un-

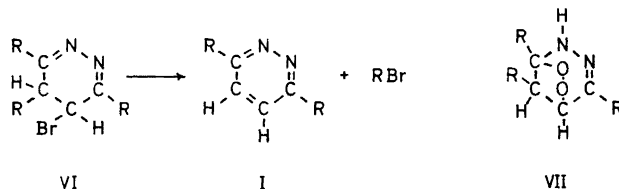


Chart 2. R=(CH₃)₃C.

proven structure, though NMR-data support the structure (VII), Chart 2. The peroxide liberates iodine from hydroiodic acid.

The relative yields of isomeric dihydropyridazines are presented in Table 1. They seem to reflect the size of the substituents at positions 3 and 6, since the main product consists of that isomer which is formed by attack of the Grignard alkyl group at the position farthest removed from the most bulky of the two substituents. This further suggests that the rate limiting step does not involve the formation of a complex between magnesium and the nitrogen of the pyridazine. The electrophilic magnesium probably coordinates at the less hindered nitrogen atom (*e.g.* N¹ in 3-*t*-butyl-6-methylpyridazine, in analogy with quaternization reactions studied by Lund and Lunde⁹), but does not polarize the nucleus effectively enough so as to direct the nucleophilic reagent to the sterically hindered 4-position (in analogy with the alkylation of quaternized pyridazines with the same Grignard reagent.¹⁰)

However, the size of the substituents in the 3- and 6-positions has a greater effect on the course of the quaternization reaction than on that of the Grignard reaction. Thus, 3-methyl-6-*t*-butylpyridazine shows no detectable quaternization at N¹ with methyl iodide in acetonitrile (less than 2 % according to NMR analysis⁹) whereas the reaction with *t*-butylmagnesium chloride gives approximately 10 % attack at the hindered 5-position. Considering the size of the reagents (methyl *versus t*-butyl) this result is surprising but may be explained by the effect of the coordinating magnesium (*cf.* above) or by assuming that the transition state leading to the less rigid dihydropyridazine ring system is not affected by steric requirements of the reagent to the same extent as that leading to the quaternized product.

Table 3. Analyses^a

Compound	m.p. ^b	Formula	% C		% H		% N	
			found	calc.	found	calc.	found	calc.
(Id)	177–177.5°	C ₁₂ H ₂₀ N ₂	74.90	74.95	10.56	10.48	14.66	14.57
(Ie)	47–49°	C ₉ H ₁₄ N ₂	72.14	71.96	9.44	9.39	18.68	18.65
(Ii)	99–99.5°	C ₁₄ H ₁₆ N ₂	78.79	79.21	7.90	7.60	13.31	13.20
(IIa)	95–96°	C ₂₀ H ₂₂ N ₂	82.80	82.72	7.71	7.64	9.64	9.65
(IIe)	125–126°	C ₁₈ H ₂₄ N ₂	74.75	74.94	11.54	11.61	13.30	13.45
(IIg)	91–93°	C ₁₅ H ₂₀ N ₂	79.17	78.90	8.84	8.39	12.44	12.76
(IIIh)	—	C ₁₄ H ₁₇ N ₂ Cl	67.50	67.60	7.04	6.89	11.02	11.26
(IIIe)	92–93°	C ₁₃ H ₂₄ N ₂	74.68	74.94	11.51	11.16	13.32	13.45
(IIIf)	59–61°	C ₉ H ₁₅ N ₂ Cl	57.80	57.91	7.98	8.10	14.90	15.01
(IIIg)	112–114°	C ₁₅ H ₂₀ N ₂	78.80	78.90	8.83	8.39	12.25	12.76
(IVa)	104–105°	C ₂₀ H ₂₀ N ₂	83.10	83.30	6.92	6.99	9.76	9.71
(IVe)	57–58°	C ₁₃ H ₂₂ N ₂	75.40	75.66	10.75	10.75	13.73	13.57
(IVg)	71–72°	C ₁₅ H ₁₈ N ₂	79.80	79.61	8.11	8.02	12.42	12.38
(Vg)	123–124°	C ₁₅ H ₁₈ N ₂	79.55	79.61	8.13	8.02	12.28	12.38
(Vi)	112–113°	C ₁₈ H ₂₄ N ₂	80.59	80.55	9.11	9.01	10.41	10.44
(VI)	87–88°	C ₁₆ H ₂₂ N ₂ Br	58.65	58.35	9.07	8.88	8.56	8.51
(VII)	120–121°	C ₁₆ H ₃₀ N ₂ O ₂	68.20	68.10	10.67	10.62	10.04	10.08

^a Performed by Mr. Preben Hansen, The Chemical Laboratory of the University of Copenhagen, and by Mr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, West Germany.

^b All melting points are uncorrected.

EXPERIMENTAL

Preparative thin-layer chromatography was carried out on 1 mm layers of PF₂₇₄ (Merck). The compounds were detected in UV light. For analytical data, see Table 3.

Starting materials. The compounds Ic,¹² If,¹³ and Ih⁶ were synthesized according to the literature. The compounds Ib, Id, Ie, Ig, and Ii were prepared by the general method of Levisalles.¹¹ Thus ethyl γ,γ,γ -trimethylacetoacetate (57 g), *t*-butylglyoxal (38 g), and hydrazine hydrate gave 63.2 g crude product, which upon recrystallization from ligroin-toluene 1:1, afforded 3,6-di-*t*-butylpyridazine (24.7 (24.7 g, 39 %, colourless needles, m.p. 175–176.5°). Repeated crystallization for analysis, see Table 3, compound Id. Compounds Ie and Ii were obtained in yields of 32 % and 20 %, respectively.

Details for the preparation of 3,6-diphenylpyridazine (Ia)¹⁶ are not given in the literature. *cis*-Dibenzoyl ethylene^{15,16} (12.2 g) was dissolved in acetic acid (130 ml) at 65°, and aqueous hydrazine hydrate (4.0 g, 80 %) was added at once with stirring. The reaction mixture was heated for 3 h at 80° and kept at 0° overnight. Filtration and washing with ether gave 10 g (84 %) of crystalline material, m.p. 220–222.5° consisting of (Ia). Recrystallization from acetic acid (200 ml), and washing of the colourless crystals with ether, gave 9.2 g (77 %) of a product with m.p. 220–222°.

*Reaction of pyridazines with *t*-butylmagnesium chloride. General procedure.* The pyridazine was dissolved in dry ether, and *t*-butylmagnesium chloride was added in excess. Apparently the reaction was over when the immediately formed red colour had vanished or changed to yellow. Generally, the reaction mixture was refluxed, and in most cases extended reaction times had no effect on the yield. Only if one of the substituents was chloro, the resulting dihydropyridazine magnesium adducts were labile and had to be kept cold and worked up immediately. The reactions of chloropyridazines were shown to be very fast: Both 3,6-dichloropyridazine and 3-chloro-6-methylpyridazine (molarity: 0.01) react with *t*-butylmagnesium chloride (molarity: 0.66) with an approximate half life of 4×10^{-4} sec.¹⁷

The reaction mixture was decomposed by adding methanol (10 % in ether) to the chilled reaction mixture. The suspension was filtered and the magnesium complexes were thoroughly washed with ether. The combined filtrates were concentrated *in vacuo* and at room temperature to give the crude product, which was subjected immediately to NMR analysis. In most cases the stability of the dihydropyridazines permitted isolation (chromatography, recrystallization) of the pure compounds for analysis (including NMR). All compounds were labile and had to be stored *in vacuo*.

3,6-Diphenylpyridazine (Ia) is only slightly soluble in ether but may be dissolved directly in the Grignard reagent. After 3 h at room temperature the reaction product could be isolated as described above.

4-t-Butyl-3,6-diphenylpyridazine (IVa). The crude dihydropyridazine (IIa, prepared as above from 4.6 g 3,6-diphenylpyridazine and 40 ml 1.4 N *t*-butylmagnesium chloride) was dissolved in chloroform, and bromine (3.4 g) was added with stirring, the temperature being kept between 15 and 20°. The solution was allowed to stand for 0.5 h at room temperature. Unreacted bromine was removed with dilute ammonia. The organic phase was dried and the chloroform removed *in vacuo*. The residue was refluxed with excess sodium methoxide for 0.5 h. Water was added and the aqueous layer was separated and extracted with chloroform. The combined chloroform extracts were dried, the chloroform evaporated *in vacuo* to give 6.55 g of the crude product. Trituration and thorough washing with petroleum ether afforded 3.6 g of a light yellow compound, m.p. 98–101°. This was dissolved in ethanol, and a residue consisting of 200 mg of 3,6-diphenylpyridazine was removed at 0°. Addition of water (10 ml) gave 4-*t*-butyl-3,6-diphenylpyridazine (IV; 2.6 g, 47 %, m.p. 104–105°; see Table 3). Further 0.7 g could be obtained from the filtrate, m.p. 98–101°.

*4-t-Butyl-3,6-dichloro-1,4-dihydropyridazine (IIc)*¹ was prepared from 3,6-dichloropyridazine (10 g) and *t*-butylmagnesium chloride (100 ml, 1.25 N) to give 11.3 g (82 % crude product).

*3,4,6-Tri-*t*-butyl-1,4-dihydropyridazine (IIId)* was prepared from 3,6-di-*t*-butylpyridazine (2.02 g) and *t*-butylmagnesium chloride (100 ml, 1.5 N) to give 2.49 g of a yellow oil (94 %, crude product).

Peroxide of 3,4,6-tri-*t*-butyl-1,4-dihydropyridazine (VII). The formation of crystals in the oil (IIId, above) was occasionally observed. The peroxide could be induced to

crystallize from petroleum ether at -70° and further purified by chromatography (eluent, benzene-ether, 3:1) and recrystallized from petroleum ether to give colourless crystals, see Table 3.

5-Bromo-3,4,6-tri-*t*-butyl-4,5-dihydropyridazine (VI) was prepared from 3,4,6-tri-*t*-butyl-1,4-dihydropyridazine (IIId, 2.49 g) and bromine (4 g) at 25° , as described above, to give 3.05 g (94.5 %) of a yellow, crystalline compound, m.p. $74.5-78.5^{\circ}$. A sample was further purified by recrystallization from petroleum ether and by thin-layer chromatography (eluent, benzene-ether, 1:1), see Table 3.

Pyrolysis of 5-bromo-3,4,6-tri-*t*-butyl-4,5-dihydropyridazine (100 mg) was carried out in a small ampoule adapted to collect possible pyrolysis products in a receiver cooled to -70° . About 20° above the melting point, a vigorous gas evolution took place. The warm melt recrystallized and was shown to be 3,6-di-*t*-butylpyridazine. The distillate consisted of *t*-butyl bromide (NMR, IR, and gas chromatographic analysis).

The bromodihydropyridazine was refluxed with excess sodium methoxide in methanol for 5 min; only the starting material (VI) was isolated. The refluxing was extended to 3.5 h; only 3,6-di-*t*-butylpyridazine was isolated.

Chloranil oxidation of the dihydropyridazine (IIId) gave exclusively 3,6-di-*t*-butylpyridazine (Id).

4,6-Di-*t*-butyl-1,4-dihydro-3-methylpyridazine (IIe), was prepared from 3-*t*-butyl-6-methylpyridazine (Ie, 1.0 g) and *t*-butylmagnesium chloride (30 ml, 1.5 N) to give 1.35 g (97 %) of colourless crystals. Recrystallization from petroleum ether, see Table 3.

5,6-Di-*t*-butyl-2,5-dihydro-3-methylpyridazine (IIIe) was isolated by extracting a freshly prepared sample of the dihydropyridazines (IIe and IIIe, above) with cold petroleum ether. The combined extracts were concentrated *in vacuo* and the residue purified by thin-layer chromatography (eluent, benzene-ether 1:3). Recrystallization from petroleum ether gave a sample, kept cold *in vacuo* for analysis, see Table 3.

4,6-Di-*t*-butyl-3-methylpyridazine (IVe) was obtained from the above mixture of the dihydropyridazines (6.5 g) by oxidation with chloranil (7.5 g). The crude product was distilled, yield 3.5 g (49 %), b.p. $145-150^{\circ}/14$ mm. Recrystallization from petroleum ether gave 2.0 g (31 %) of colourless crystals, m.p. $55.5-57.5^{\circ}$. The same product is obtained by bromination and dehydrobromination of (IIe); yield 24 %.

4-*t*-Butyl-6-chloro-1,4-dihydro-3-methylpyridazine (IIIf) and 5-*t*-butyl-6-chloro-2,5-dihydro-3-methylpyridazine (IIIIf). A mixture of the two dihydropyridazines was prepared from 3-chloro-6-methylpyridazine (700 mg) and *t*-butylmagnesium chloride (7 ml, 1.4 N) to give 945 mg (93 %, crude product). Separation of the two pyridazines was attempted by thin-layer chromatography (eluent, benzene-ether, 9:1). Only 5-*t*-butyl-6-chloro-2,5-dihydro-3-methylpyridazine could be isolated. The very labile compound was dissolved in cold petroleum ether, filtered, concentrated, and kept *in vacuo* for analysis, see Table 3.

4- and 5-*t*-Butyl-3-methyl-6-phenylpyridazine (IVg and Vg). A mixture of the dihydropyridazines (IIg and IIIg) was prepared from 3-methyl-6-phenylpyridazine (8.5 g) and *t*-butylmagnesium chloride (100 ml, 1.5 N) to give 10.1 g (90 %) crude product. Oxidation with chloranil (12.5 g) and distillation gave a light brown crystalline product, 3.34 g, b.p. $150-160^{\circ}/0.7$ mm. The two pyridazines were separated by thin-layer chromatography (eluent, benzene-ether 3:2). Recrystallization for analysis from petroleum ether at -70° , see Table 3.

4-*t*-Butyl-1,4-dihydro-3-methyl-6-phenylpyridazine (IIg) and 5-*t*-butyl-2,5-dihydro-3-methyl-6-phenylpyridazine (IIIg), prepared as above, could be separated by thin-layer chromatography (eluent, benzene-ether, 2:1) and recrystallized from petroleum ether at 0° for analysis, see Table 3. The compounds were unstable and were stored cold *in vacuo*.

4- and 5-*t*-Butyl-3-chloro-6-phenylpyridazine (IVh and Vh). A mixture of the dihydropyridazines (IIh and IIIh) was prepared from 3-chloro-6-phenylpyridazine (2 g) and *t*-butylmagnesium chloride (60 ml, 1.4 N) to give 2.36 g (90 %) crude product. Bromination (2.0 g at 50 to 55°) and subsequent dehydrobromination with conc. ammonia gave 2.50 g crude product. Repeated chromatography and recrystallizations from petroleum ether only gave a homogeneous sample of the isomer (IVh), m.p. $58-59^{\circ}$ (authentic sample: m.p. $61-62^{\circ}$, cf. 72° erroneously stated in Ref. 6). The other isomer, (Vh), m.p. $104-105^{\circ}$, was pure according to NMR analysis but contained, however, ca. 30 % of the 3-bromo derivative. Both isomers were methoxylated to the known 4- and 5-*t*-butyl-3-methoxy-6-phenylpyridazines by reflux in methanolic sodium methoxide.⁶

4-*t*-butyl-3-chloro-1,4-dihydro-6-phenylpyridazine (IIh) (very unstable) was isolated from the mixture of the two dihydropyridazines (IIh and IIIh, above) by thin-layer chromatography (eluent, petroleum ether with 5% ethyl acetate) and kept cold and *in vacuo* before analysis. The isomer (IIIh) could not be isolated by the technique used.

3,5-Di-*t*-butyl-6-phenylpyridazine (Vi). A mixture of 3,5-di-*t*-butyl-2,5-dihydro-6-phenylpyridazine (IIIi) and 3,4-di-*t*-butyl-1,4-dihydro-6-phenylpyridazine (IIi) was prepared from 3-*t*-butyl-6-phenylpyridazine (0.5 g) and *t*-butylmagnesium chloride (10 ml, 1.5 N). Yield: 0.64 g of a light yellow, crystalline compound. NMR analysis indicated the presence of both dihydropyridazines. The crude mixture was brominated with 0.4 g of bromine, yield 0.75 g. NMR analysis indicated the presence of two bromo-dihydropyridazines. Dehydrobromination with sodium methoxide (0.3 g sodium in 10 ml of methanol) and reflux for 15 min gave 0.57 g of impure 3,5-di-*t*-butyl-6-phenylpyridazine. Purification by thin-layer chromatography (eluent, benzene-ether, 12:5) and recrystallization from petroleum ether gave pure (Vi), see Table 3. None of the isomeric 3,4-di-*t*-butyl-6-phenylpyridazine could be isolated.

REFERENCES

1. Crossland, I. *Acta Chem. Scand.* **16** (1962) 1877.
2. Christensen, A. and Crossland, I. *Acta Chem. Scand.* **17** (1963) 1276.
3. Avellén, L., Crossland, I. and Lund, K. *Acta Chem. Scand.* **21** (1967) 2104.
4. Sauer, J., Mielert, A., Lang, D. and Peter, D. *Chem. Ber.* **98** (1965) 1435.
5. Crossland, I. *Acta Chem. Scand.* **20** (1966) 258.
6. Crossland, I. and Rasmussen, L. K. *Acta Chem. Scand.* **19** (1965) 1652.
7. Alder, K. and Niklas, H. *Ann.* **585** (1954) 81.
8. Holm, T. *Acta Chem. Scand.* **19** (1965) 1819.
9. Lund, H. and Lunde, P. *Acta Chem. Scand.* **21** (1967) 1067.
10. Crossland, I. and Kelstrup, E. *Acta Chem. Scand.* **22** (1968) 1669.
11. Levisalles, J. and Baranger, P. *Compt. Rend.* **242** (1956) 1336.
12. Mizsoni, R. H. and Spoerri, P. E. *J. Am. Chem. Soc.* **73** (1951) 1873.
13. Overend, W. G. and Wiggins, L. F. *J. Chem. Soc.* **1947** 239.
14. Conant, J. B. and Lutz, R. E. *J. Am. Chem. Soc.* **45** (1923) 1304.
15. Paal, C. and Schulze, H. *Ber.* **35** (1902) 168.
16. Paal, C. and Schulze, H. *Ber.* **33** (1900) 3795.
17. Holm, T. *Private communication.*

Received November 19, 1968