

The Addition of Grignard Reagents to Pyridazines

VI. The Reaction of *tert*-Butylmagnesium Chloride with 3,6-Disubstituted-1-methylpyridazinium Iodides

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The reaction of 3-phenyl-1-methylpyridazinium iodide, 3-phenyl-1,6-dimethylpyridazinium iodide, and 3,6-diphenyl-1-methylpyridazinium iodide with *tert*-butylmagnesium chloride is shown to give the corresponding 4-*tert*-butyl-1,4-dihydropyridazines. The positions *ortho* to the quaternized nitrogen are also attacked by the Grignard reagent to give small amounts of the 2-*tert*-butyl-1,2-dihydropyridazines and 6-*tert*-butyl-1,6-dihydropyridazines. The formation of 2,5-diphenyl-3-*tert*-butyl-1-methylpyrrole, 2,5-diphenyl-3-*tert*-butylpyrrole, and 3-phenyl-4-*tert*-butyl-1,6-dimethyl-1,4,5,6-tetrahydropyridazine is observed.

The addition of Grignard reagents to 3,6-disubstituted pyridazines has been shown to yield 4- and 5-substituted 1,4- or 4,5-dihydropyridazines.¹ The quaternization of one of the nitrogen atoms might be expected to have a pronounced effect on the course of the reaction, and this has been confirmed by the present work.

The reaction of three 1-methylpyridazinium iodides (Ia, Ib, and Ic, see Chart 1) with the Grignard reagent is carried out by dissolving the pyridazinium salt in *ca.* three fold excess of *tert*-butylmagnesium chloride in ether and decomposing the reaction mixture with methanol. The main products of the reaction are the corresponding 4-*tert*-butyl-1-methyl-1,4-dihydropyridazines IIa, IIb, and IIc. Smaller amounts of the 2-*tert*-butyl-1,2-dihydropyridazines IVb and IVc and the 6-*tert*-butyl-1,6-dihydropyridazines IIIa and IIIb are isolated. A 1,4,5,6-tetrahydropyridazine V and two pyrroles² VI and VII are also formed. A list of the reaction products from each of the methiodides is given in Table 1 (see also Chart 1) together with the yields (both absolute and relative).

The balance of isolated products from Ia and Ic amounts to 80–85 %. NMR spectra of the crude products show both that no appreciable amounts of unidentified compounds are present, and that the relative yields are nearly

the same as those determined after chromatography. However, in the case of Ib the yield of the products after chromatography is only *ca.* 60 % and the yield of the crude product *ca.* 80 % from methiodide. According to NMR analysis the product distribution in the latter is about the same as that determined after chromatography.

From the above it may be concluded that the relative yields given in Table 1 correspond reasonably well with the actual product distribution.

Identification. The structures of the compounds listed in Table 2 are based on the NMR data given and on the analytical data of Table 1.

The dihydropyridazine IVc may be identified directly from the NMR data. The structure proposed is the only one which would be expected to show virtually identical vinyl protons in the NMR spectrum.

The structures given for IIb and IIIb are consistent with the NMR data (the coupling constants of the methyl groups) and are further supported by the structure given for IVb, which in turn is derived by comparison with IVc.

The dihydropyridazines IIa and IIIa are identified by comparison of their NMR spectra with those of IIb and IIIb.

A reasonable alternative to the structure given for IIc is 3,6-diphenyl-4-*tert*-butyl-1-methyl-1,6-dihydropyridazine. However, comparison of the spectrum of IIc with those of IIb and IIIb supports the structure proposed.

CHART I

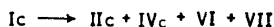
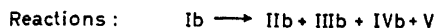
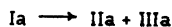
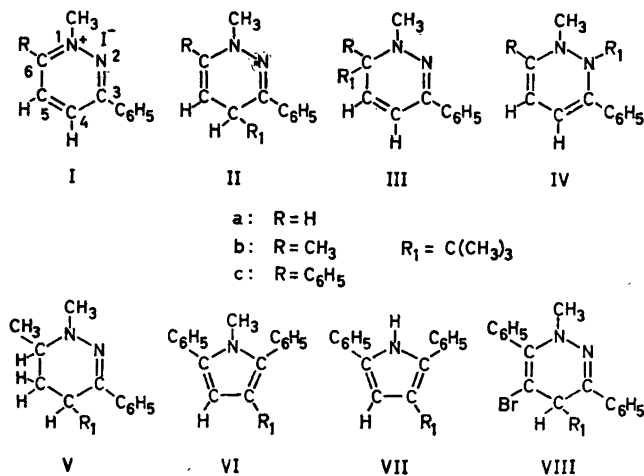


Table 1.^a

Compound	Yield ^b abs. %	Yield ^c rel. %	M.P. unccr.	Formula	% C ^d		% H		% N	
					found	calc.	found	calc.	found	calc.
IIa	53 — 58	71	37 — 38°	C ₁₅ H ₂₀ N ₂	78.80	78.90	8.79	8.83	12.30	12.27
IIIa	21 — 24	29	oil	C ₁₅ H ₂₀ N ₂	78.07	78.90	8.62	8.83	12.00	12.27
IIIb	48 — 53	84	62 — 63°	C ₁₆ H ₂₂ N ₂	78.40	79.29	8.93	9.15	11.46	11.56
IIIb	6 — 6.5	10	74 — 76°	C ₁₆ H ₂₂ N ₂	78.95	79.29	9.21	9.15	11.22	11.56
IVb	1.5	2.5	34 — 35°	C ₁₆ H ₂₂ N ₂	78.67	79.29	8.94	9.15	11.58	11.56
V	2.0	3.5	oil	C ₁₆ H ₂₄ N ₂	78.60	78.63	9.98	9.90	11.24	11.46
V, picrate	—	—	154 — 155°	C ₂₂ H ₂₇ N ₃ O ₇	55.62	55.80	5.80	5.75	14.76	14.79
Ic	—	—	203 — 205°	C ₁₇ H ₁₅ N ₂	54.20	54.58	4.06	4.04	7.30	7.49
IIc	70 — 80	87	58 — 60°	C ₂₁ H ₂₇ N ₂	82.32	82.85	7.91	7.95	9.13	9.20
IVc	3 — 3.5	4	78 — 79°	C ₂₁ H ₂₇ N ₂	82.12	82.85	8.05	7.95	9.11	9.20
VI	4.5 — 5.5	7	85 — 86°	C ₂₁ H ₂₃ N ₂	—	—	—	—	—	—
VII	1.5 — 2.0	2	92 — 93°	C ₂₀ H ₂₁ N	—	—	—	—	—	—
VIII ^e	—	—	125 — 126°	C ₂₁ H ₂₃ N ₃ Br	65.65	65.81	6.11	6.05	7.40	7.31
IX ^f	—	—	—	C ₂₁ H ₂₄ N ₃ Br ₂	32.60	32.17	3.11	3.09	3.74	3.57

^a The microanalyses are made by Mr. Preben Hansen, The Chemical Laboratory of the University of Copenhagen. The authors acknowledge the prompt analyses on the unstable compounds.

^b Yield from methiodide. These figures are taken as the mean from several experiments.

^c Basis is the sum of reaction products = 100 %.

^d The values found for carbon are somewhat low.

^e Bromine, found 20.78 %. Calc. 20.85 %.

^f Bromine, found 60.15 %. Calc. 61.17 %.

Table 2. NMR data.^a

Compound	δ in ppm ^b	J in cps	(s)=singlet,	(d)=doublet,	(t)=triplet,	(m)=multiplet
IIa	δ \sum H 2 7.90-7.66(m)	7.49-7.24(m)	6.38(d)	4.79(quartet)	3.49(d)	3.30(s) 0.77(s)
	J	3	1	1	1	3
IIIa	δ \sum H 2 7.80-7.55(m)	7.49-7.22(m)	6.58(d)	7.1 and 6.0 5.65(quartet)	3.80(d)	3.44(s) 0.90(s)
	J	3	1	1	1	3
IIIb	δ \sum H 2 7.90-7.62(m)	7.45-7.14(m)	4.49(two quartets)	9.8 and 6.5 3.42(d)	6.5	3.30(s) 1.94(broad)
	J	3	1	1	1	3
IIIb	δ \sum H 2 7.73-7.50(m)	7.40-7.17(m)	6.45(d)	$J_{HH}=6.1, J_{CH_3}=1.2$ 5.34(d)	6.1	1.46(s) 0.96(s)
	J	3	1	3	3	3
IVb	δ \sum H 5 7.68-7.12(m)	6.00(two quartets)	9.8	5.38(two quartets)	2.67(s)	1.87(t) 1.00(s)
	J	1	1	1	3	3
V	δ \sum H 2 7.72-7.48(m)	$J_{HH}=5.2, J_{CH_3}=1.0$ 7.32-7.07(m)	3.36(m)	2.99(s)	$J_{HH}=5.2, J_{CH_3}=1.1$ 2.58-1.64(m)	1.1 0.93(d)
	J	3	1	3	3	3
V, picrate	δ \sum H 1 10.17(s)	8.90(s)	$J_{CH_3}=6.8$ 7.95-7.74(m)	ABC-system	ABC-system	6.8 3.25(s)
	J	2	2	1	1	3
IIc	δ \sum H 2 7.95-7.68(m)	7.49-7.20(m)	4.62(d)	3.61(d)	$J_{CH_3}=7.0$ 3.19(s)	3.00-2.42(m) 1.21(d)
	J	8	1	1	3	3
IVc	δ \sum H 10 7.85-7.13(m)	6.19(s)	2.60(s)	1.07(s)	0.85(s)	7.0
	J	2	3	9	9	9
VIII	δ \sum H 2 8.00-7.77(m)	7.60-7.22(m)	4.04(s)	3.16(s)	0.97(s)	
	J	8	1	3	9	

^a The NMR spectra were recorded on a Varian A-60 spectrometer.^b The compounds were dissolved in deuteriochloroform 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.

The structure ascribed to V is based on decoupling of the methyl group at C(6) and the proton at C(6) and on the splitting of the phenyl protons. All the dihydropyridazines containing the grouping $C_6H_5-C=N$ show this splitting. In the picrate of V the doublet of the C-methyl group may be observed.

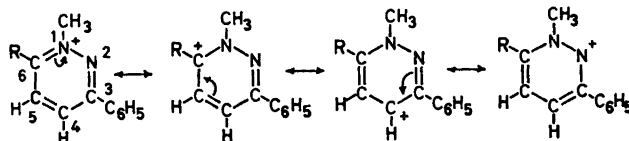
Chemical properties of the dihydropyridazines. The reaction products II, III, and IV are all very unstable compounds even in the crystalline state and at -20° if oxygen is present. The stability at low temperatures *in vacuo* was not investigated.

None of the compounds IIa, IIb, or IIc react with nucleophiles such as *tert*-butylmagnesium chloride or lithium aluminium hydride in ether or sodium borohydride in methanol, but they do react with electrophiles such as halogens and nitrous acid (and oxygen) to give mixtures of products.

Only in the case of addition of bromine to the dihydropyridazine IIc it was possible to isolate a reasonably pure reaction product IX (see Table 1). Quantitative bromination³ and elementary analysis indicates the consumption of six equivalents of bromine per mole of IIc. Treatment of IX with methanolic sodium methoxide gives VIII, the 5-bromo derivative of IIc. The structure given for VIII is not conclusive. It is based on a comparison with IIc.

DISCUSSION

The ground state of the methiodides I can be regarded as a resonance hybrid of the following structures:



The formation of II, III, and IV may be rationalized as involving the addition of the nucleophilic Grignard reagent to one of the electron deficient positions indicated by the structures above. Attack at a position *meta* to the quaternized nitrogen would give rise to charge separation in the transition state. The preferential attack at the 4- or 5-positions of the pyridazine nucleus is in accord with previous findings.^{1,10} However, in the case of quaternized N-heteroaromatic compounds 1,2-addition seems to be the rule.⁴⁻⁷ In the few instances where 1,4-additions have been observed,⁷⁻⁹ this orientation of attack is accounted for by considering the stabilizing effect of condensed rings present.

The decrease in the yield of III in the series IIIa, IIIb, and IIIc (relative yields 29 %, 10 %, and 0 %, respectively, see Table 1) may be ascribed to steric factors.

Only few reactions involving N-alkylation by Grignard reagents have formerly been described.^{7,9}

The tetrahydropyridazine V is not formed by reduction of the dihydropyridazine IIb with Grignard reagent. Neither *tert*-butylmagnesium chloride, lithium aluminium hydride in ether (reflux), nor sodium borohydride in methanol (reflux) reduce IIb.

EXPERIMENTAL

See Table 1 for melting points and analytical data.

3-Phenylpyridazine was prepared from 3-phenyl-6-chloropyridazine¹⁰ by catalytic dehalogenation with Raney-Ni. 3-Phenyl-6-chloropyridazine (30 g, 0.158 mole) and potassium hydroxide (9 g, 0.161 mole) were dissolved in ethanol (*ca.* 250 ml). Raney-Ni suspension (*ca.* 10 g) was added and hydrogen passed in at atmospheric pressure. The dehalogenation could be followed by thin layer chromatography and had to be stopped at about 70–80 % conversion because of formation of by-products interfering with the isolation. The dehalogenation lasted *ca.* 35 h, the reaction mixture was then filtered, the solvents removed *in vacuo*, and the residue dissolved in warm toluene. Cooling and subsequent addition of petroleum ether gave impure 3-phenylpyridazine, which could be recrystallized from either water or ligroin. Yield 9.4 g, 38 %, m.p. 98°–100° (102–3°¹¹).

Starting materials. 3-Phenyl-1-methylpyridazinium iodide¹³ (Ia) was prepared from 3-phenylpyridazine (above) and 3-phenyl-1,6-dimethylpyridazinium iodide¹³ (Ib) from 3-phenyl-6-methylpyridazine (preparation analogous to the method of Levisalles¹²).

3,6-Diphenyl-1-methylpyridazinium iodide (Ic) was prepared from 3,6-diphenylpyridazine^{14,15} (8 g, 35 mmoles) and methyl iodide (46 g, 322 mmoles) by refluxing overnight in acetonitrile (*ca.* 150 ml). The solvent was removed *in vacuo* and the residue recrystallized from ethanol to give the methiodide (12 g, 90 %), m.p. see Table 1.

tert-Butylmagnesium chloride was prepared from commercial magnesium turnings according to *Organic Syntheses*¹⁶ and titrated for total base before use.

Reactions of methiodides with tert-butylmagnesium chloride. General procedure. In a 250 ml three necked flask provided with reflux condenser, polyethylene stopper, separatory funnel, and magnetic stirrer finely pulverized methiodide (2 mmoles) is placed. Dry nitrogen is led through the system, 50 ml of dry ether is added, and stirring started. The Grignard reagent (6 mmoles) is then added all at once. Stirring is continued for half an hour, the reaction mixture then chilled in an ice bath, and decomposed with methanol (0.36 ml) in dry ether (50 ml). It is important that the excess of methanol does not exceed 50 % (based on moles of Grignard reagent employed). The hydrolysis mixture is repeatedly filtered with suction, until the filtrate is clear, and the residue on the filter is thoroughly washed with ether. The filtrate is concentrated *in vacuo* and the resulting oil immediately chromatographed on a silica gel column, Merck Kieselgel 0.05–0.20 mm (see below). The procedure outlined so far may be adopted to a 10 g scale.

Work-up of the crude products. The procedures given here are outlined on the basis of many experiments. Where indications seem unnecessarily laborious, they are as a rule justified because neglecting them leads to lower yields or even complete destruction of the products.

3-Phenyl-1-methylpyridazinium iodide (Ia). 10.0 g of methiodide is used. The crude product is chromatographed on a column (250 g of silica gel deactivated with 25 ml of water), elution being carried out for 2–3 h with petroleum ether:benzene 1:1. The fractions containing 3-phenyl-4-*tert*-butyl-1-methyl-1,4-dihydropyridazine (IIa) and 3-phenyl-6-*tert*-butyl-1-methyl-1,6-dihydropyridazine (IIIa) are combined and concentrated *in vacuo* to give an oil (6.05 g, 78 % from methiodide). NMR data showed the distribution to be 4.30 g of IIa and 1.75 g of IIIa, or 71 % and 29 %, respectively. Continued chromatography gave no pure compounds. Separation of the dihydropyridazines IIa and IIIa can be accomplished with difficulty using silica gel deactivated with 5 % water and petroleum ether:benzene 1:2. IIa is recrystallized from petroleum ether at –70° to –80° until the m.p. is 37–38° (see Table 1). IIIa does not crystallize from petroleum ether at –70° to –80° even after repeated purifications by chromatography on silica gel.

3-Phenyl-1,6-dimethylpyridazinium iodide (Ib). 10.0 g of methiodide is processed in order to get reasonable amounts of the minor reaction products mentioned below. The crude product is chromatographed on a column (250 g of silica gel deactivated with 12.5

ml of water), elution being carried out in *ca.* 3 h with petroleum ether containing 9 % ether to give three eluates. The first contains nearly pure 3-phenyl-2-*tert*-butyl-1,6-dimethyl-1,2-dihydropyridazine (IVb), the second a mixture of 3-phenyl-4-*tert*-butyl-1,6-dimethyl-1,4-dihydropyridazine (IIb) and 3-phenyl-6-*tert*-butyl-1,6-dimethyl-1,6-dihydropyridazine (IIIb), and the third nearly pure 3-phenyl-4-*tert*-butyl-1,6-dimethyl-1,4,5,6-tetrahydropyridazine (V).

The first eluate is concentrated *in vacuo*, the resulting yellow oil chromatographed on a column (70 g silica gel deactivated with 3.5 ml water) with petroleum ether containing 9 % ether. The dihydropyridazine IVb is obtained as a pure yellow oil (120 mg, 1.6 % from methiodide). Crystallization from petroleum ether at -70° to -80° gives yellow crystals, see Table 1.

The second eluate gives, after concentration *in vacuo*, a nearly colourless oil (4.35 g, 56 % from methiodide). NMR data showed the distribution to be *ca.* 3.86 g of IIb and 0.490 g of IIIb, or 89 % and 11 %, respectively. From this mixture IIb can be recovered in pure form by three recrystallizations from petroleum ether at -70° to -80° , see Table 1. IIIb can be isolated in very small yield by chromatography on silica gel, see Table 1.

After concentration *in vacuo* the third eluate gives the tetrahydropyridazine V as a practically pure oil (140 mg, 1.8 % from methiodide), which could not be crystallized even after several purifications on silica gel. The picrate of V is obtained, when V is allowed to react with excess picric acid in ethanol at room temperature, and is recrystallized from ethanol, see Table 1.

3,6-Diphenyl-1-methylpyridazinium iodide (Ic). 10.0 g of methiodide is processed in order to get reasonable amounts of the minor reaction products mentioned below. The crude product is chromatographed on a column (250 g silica gel), elution being carried out as rapidly as possible with petroleum ether containing 7 % benzene. A yellow eluate is collected and concentrated *in vacuo* to give an oil identified as 3,6-diphenyl-2-*tert*-butyl-1-methyl-1,2-dihydropyridazine (IVc, 257 mg, 3.2 % from methiodide). After crystallization from petroleum ether at -70° to -80° yellow crystals are obtained, see Table 1.

The column is then eluted with petroleum ether containing 15 % benzene giving an eluate containing 2,5-diphenyl-1-methyl-3-*tert*-butylpyrrole (VI, 384 mg, 5.0 % based on methiodide). Concentration *in vacuo* and recrystallization from methanol gives VI, m.p. $85-86^{\circ}$ ($85-86^{\circ}$ ²). NMR data are consistent with those reported by Lund.²

The column is then eluted with pure benzene, and all fractions containing both 3,6-diphenyl-4-*tert*-butyl-1-methyl-1,4-dihydropyridazine (IIc) and 2,5-diphenyl-3-*tert*-butylpyrrole (VII) are collected, concentrated *in vacuo*, and the oil is kept overnight at -20° . Chromatography on a new column (250 g silica gel) with petroleum ether:benzene 1:1 gives two eluates, one containing both the dihydropyridazine IIc and the pyrrole VII, the other containing only the dihydropyridazine IIc. The former eluate is concentrated *in vacuo* and the resulting oil chromatographed on a new column (100 g silica gel). This time the separation is complete, giving (after concentration *in vacuo*) the pyrrole (VII, 131 mg, 1.8 % from methiodide), which after recrystallization from petroleum ether at -70° to -80° gives colourless crystals, m.p. $92-93^{\circ}$ ($89-90^{\circ}$ ²). NMR data are consistent with those reported by Lund.²

The eluates containing the dihydropyridazine IIc are combined and concentrated *in vacuo* to give IIc as a nearly colourless oil. A yield of *ca.* 75 % has been obtained in other experiments. Crystallization followed by recrystallization from petroleum ether at -70° to -80° gives colourless crystals, see Table 1.

Bromination of the dihydropyridazine IIc. A solution of IIc in carbon tetrachloride is cooled in an ice bath and bromine (*ca.* 5 moles per mole of IIc) dissolved in carbon tetrachloride is added rapidly. A dark red oil separates and slowly solidifies. The supernatant is decanted, the residue washed with carbon tetrachloride and subsequently triturated with chloroform to give orange crystals (IX, see Table 1). IX is treated with excess of methanolic sodium methoxide at room temperature, the methanol removed *in vacuo*, water added, and the products extracted with chloroform. Drying with magnesium sulfate and concentration *in vacuo* followed by chromatography on silica gel give, as the main product, 3,6-diphenyl-4-*tert*-butyl-5-bromo-1-methyl-1,4-dihydropyridazine (VIII), see Table 1.

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