

Addition of Grignard Reagents to Pyridazines

V. Addition of *tert*-Butylmagnesium Chloride to 3-Methoxy-6-methylpyridazine and 3-Chloro-6-methylpyridazine

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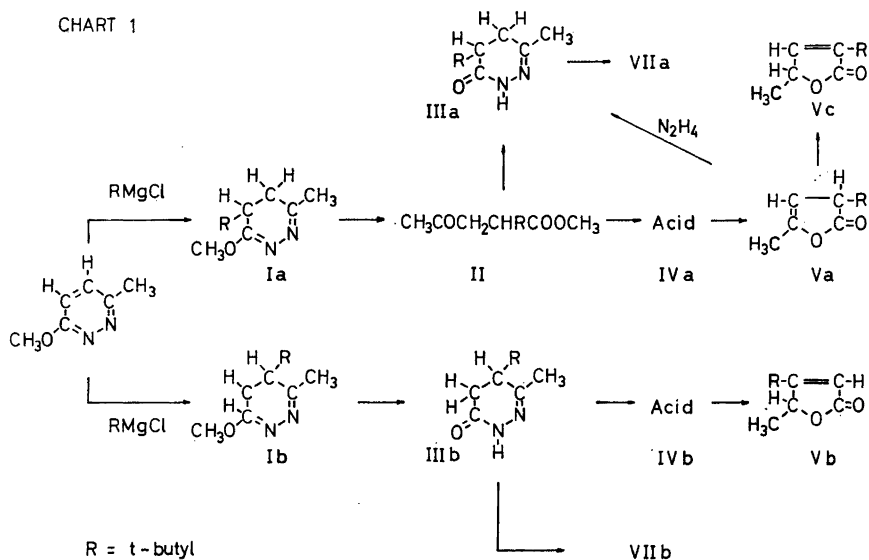
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A mixture of 5- and 4-*t*-butyl-3-methoxy-6-methyldihydropyridazines resulted from the addition of *t*-butylmagnesium chloride to 3-methoxy-6-methylpyridazine, and was characterized by the formation of methyl α -*t*-butyl-levulinate and 4-*t*-butyl-1,4,5,6-tetrahydro-6-oxo-3-methylpyridazine, respectively, upon acid hydrolysis. α -*t*-Butyl- γ -methyl- $\Delta(\beta,\gamma)$ -butenolide was prepared from the levulinic ester *via* the acid and subsequently isomerized to the corresponding $\Delta(\alpha,\beta)$ -butenolide. NMR and IR analyses of the two butenolides proved the position of the *t*-butyl group. The isomeric 4- and 5-*t*-butyl-6-chloro-3-methylpyridazines were prepared from the above pyridazinone and ester, respectively, and converted into the corresponding methoxy compounds.

Reaction of the Grignard reagent with 3-chloro-6-methylpyridazine gave a mixture of the two isomeric dihydropyridazines, which were oxidized with chloranil to the corresponding pyridazines, which were separated and dehalogenated. NMR analyses confirmed the structures given.

The reaction of Grignard reagents with unsymmetrically 3,6-disubstituted pyridazines has been shown to involve conjugate addition, yielding both 4- and 5-alkylated dihydropyridazines.¹ The reaction has now been extended to 3-chloro-6-methylpyridazine and 3-methoxy-6-methylpyridazine. Some reactions of the dihydropyridazines thus obtained have been studied as outlined in the Charts 1 and 2.

The dihydropyridazines, (Ia) and (Ib), were not isolated as such, but the composition of the crude reaction product was investigated by NMR although the ratio could not be established; absence of resonance signals from vinylic protons and N—H suggested the formulations (Ia) and (Ib), *cf.* Ref. 2. Further evidence for the structures was provided by acid hydrolysis to give the ester (II) and the pyridazinone (IIIb). The hydrolysis products were identified by



their conversion into the butenolides (Va), (Vc), and (Vb) *via* the acids, (IVa) and (IVb), see Chart 1.

Treatment of the $\Delta(\beta,\gamma)$ -butenolide (Va) with aqueous hydrazine gave, as expected,³ the pyridazinone (IIIa). On treatment with triethylamine it undergoes the expected isomerization to the butenolide (Vc),⁴ whereas the reverse reaction was not observed. The infra-red spectrum of (Va) exhibited

Table 1. Proton magnetic resonance parameters for butenolides.

	(Va)	(Vb)	(Vc)
<i>α-Hydrogen:</i>			
Chemical shift, δ ppm	2.97	5.83	none
Coupling constant, cps	2.4	1.5	—
Multiplicity	8	2	—
<i>β-Hydrogen:</i>			
Chemical shift, δ ppm	5.18	none	6.93
Coupling constant, cps	2.4 and 1.5	—	1.6
Multiplicity	8	—	2
<i>γ-Hydrogen:</i>			
Chemical shift, δ ppm	none	5.05	4.91
Coupling constant, cps	—	1.5 and 6.9	1.6 and 6.8
Multiplicity	—	8	8
<i>γ-Methyl:</i>			
Chemical shift, δ ppm	2.00	1.54	1.39
Coupling constant, cps	1.5 and 2.4	6.9	6.8
Multiplicity	4	2	2

C=O and C=C absorption bands at 1790 cm^{-1} and 1685 cm^{-1} , respectively, in accordance with reported spectra of $\Delta(\beta,\gamma)$ -butenolides,^{5,6} but in contrast to those of (Vc) and (Vb) (both 1745 cm^{-1} , conjugated C=O, *cf.* values reported for $\Delta(\alpha,\beta)$ -butenolides^{5,7}). A vinylic proton (δ 5.18 ppm) in the NMR spectrum (Table 1) of (Va) further supported its structure as α -*t*-butyl- γ -methyl- $\Delta(\beta,\gamma)$ -butenolide. Likewise, the NMR-spectra of (Vb) and (Vc) (Table 1) are in agreement with the proposed structures. It may be noted that the coupling constant between the γ hydrogen and the vinylic hydrogens of (Vb) and (Vc) are identical, thus rendering the two spectra virtually identical. As expected, however, the vinylic proton of (Vc) appears at lower field than that of (Vb). The NMR-data of the butenolides are in accordance with those previously reported for the corresponding phenyl-butenolides.¹

The levulinic ester (II) was converted into the pyridazinone (IIIa) by reaction with aqueous hydrazine. Bromination, dehydrobromination with sodium methoxide, and subsequent reaction with POCl_3 ¹ converted (IIIa) into (VIIa) (Charts 1 and 2). The isomeric chloropyridazine (VIIb) was prepared by an analogous series of reactions.

An attempt to prepare the pyridazines (IXa) and (IXb) by dehydrogenation⁸ of the mixture of the dihydropyridazines, (Ia) and (Ib), was unsuccessful.

The reaction of 3-chloro-6-methylpyridazine with the Grignard reagent gave a 1:1 mixture of the two isomeric 1,4-dihydropyridazines, (VI), as determined by NMR analysis, details of which are to be published later. As in the case of the corresponding methoxy compounds, *vide supra*, substitution with

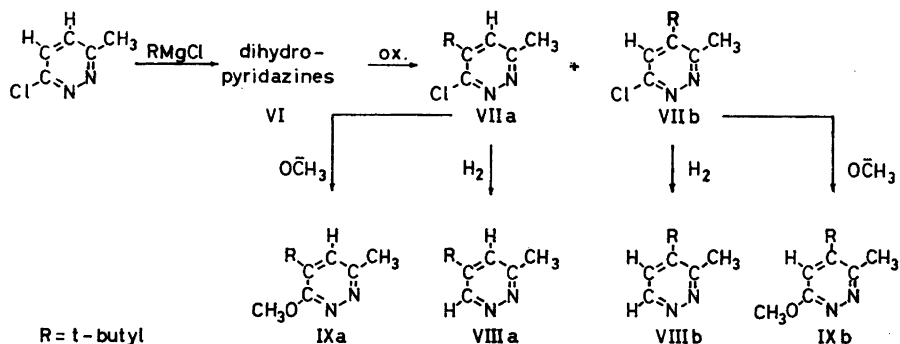


CHART 2

bromine and subsequent dehydrobromination was unsatisfactory, a mixture of the four pyridazines (VIIa) and (b); (IXa) and (b) being obtained in low yield. Dehydrogenation with chloranil, however, gave in one step a 60% yield of a mixture of the two pyridazines, (VIIa) and (VIIb). A similar dehydrogenation of the dihydropyridazines, (Ia) and (Ib), gave only a 30% yield of a mixture of (IXa) and (IXb). By chromatography, the mixture of (VIIa) and (VIIb) was separated into its components which were shown to be identical with the chloropyridazines prepared above. The structures were further verified by hydrogenolysis to give the halogen-free products, (VIIIa) and

Table 2. Proton magnetic resonance parameters for pyridazine derivatives.

Compound	Chemical shift (δ)						Coupling constants (cps)	
	δ_4	δ_5	δ_6	δ_{CH_2}	$\delta_{\text{C}(\text{CH}_2)_2}$	δ_{OCH_3}	J_{46}	J_{56}
(VIIa)	7.26	—	—	2.67	1.49	—	—	—
(VIIb)	—	7.29	—	2.89	1.42	—	—	—
(VIIIa)	7.29	—	9.15	2.73	1.36	—	2.4	—
(VIIIb)	—	7.30	8.89	2.95	1.42	—	—	5.4
(IXa)	6.98	—	—	2.50	1.40	4.06	—	—
(IXb)	—	6.73	—	2.74	1.37	4.01	—	—

NMR spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as an internal reference.

(VIIIb). NMR analyses of the latter (Table 2) showed that the coupling constant of the two aromatic protons were 2.4 cps (*meta* coupling, *cf.* Refs. 9, 10), and 5.4 cps (*ortho* coupling, *cf.* Refs. 9, 10), respectively. Again, the structures ascribed to the isomers, (VIIa) and (VIIb), were in accordance with their relative reactivity towards sodium methoxide. For (VIIb), the methoxylation was complete within 5 h whereas 216 h were required to complete the reaction for the more hindered chlorine of (VIIa).

EXPERIMENTAL

For preparative work thin-layer chromatography was carried out on 1 mm layers of PF₂₅₄ (Merck). The compounds were detected in UV light.

Dihydropyridazines (Ia and Ib). To a solution of *t*-butylmagnesium chloride (200 ml, 0.3 mole, prepared according to Organic Syntheses,¹¹ stored in tightly stoppered bottles, and titrated with hydrochloric acid before use), was added, with stirring, 3-methoxy-6-methylpyridazine¹² (12.4 g) in ether (10 ml). Each drop of the pyridazine produced a red colour, which disappeared within few seconds. The resulting solution was yellow. After further stirring (*ca.* 10 min), the Grignard complex was decomposed with methanol (10 ml) in ether (90 ml) with vigorous stirring. The resulting suspension was filtered, and the magnesium complexes were thoroughly washed with ether (*ca.* 200 ml). The combined, light-yellow filtrates were concentrated *in vacuo* at room temperature and gave a yellow oil (17.3 g consisting of a mixture of (Ia) and (Ib)).

Products of hydrolysis. 4-t-Butyl-1,4,5,6-tetrahydro-6-oxo-3-methylpyridazine (IIIb) and methyl α -t-butyl-levulinate (II). The above dihydropyridazines were dissolved in hydrochloric acid (18 ml of conc. hydrochloric acid and 82 ml of water) and refluxed for 10 min. Then the solution was cooled, and *ca.* 100 ml of petroleum ether was added. A colourless crystalline product immediately separated. The suspension was filtered, washed with petroleum ether, and air-dried. The yield of the pyridazinone (IIIb) was 3.8 g, m.p. 150–152°. A sample was recrystallized from ligroin-toluene for analyses, see Table 3. A yellow oil, 8.3 g, was obtained by removing the solvent *in vacuo* from the petroleum ether phase of the filtrates (above). Distillation of the oil gave the ester (II). Yield: 6.1 g, *cf.* Table 3.

α -t-Butyl-levulinic acid (IVa) was obtained by saponification of the ester (II, 6.1 g) in ethanolic sodium hydroxide. The solution was acidified with hydrochloric acid and extracted with ether. Yield: 4.9 g. Recrystallization from benzene/toluene gave 4.2 g of (IVa), m.p. 128–130°.

α -t-Butyl- γ -methyl- Δ (β,γ)-butenolide (Va). 7.1 g of the crude acid (IVa) was refluxed in acetic anhydride (20 ml) for 1 h. The reaction mixture was distilled (Podbielniak-

Table 3. Analyses.^a

Compound	m.p. ^b	Formula	C		H		N	
			found	calc.	found	calc.	found	calc.
(II)	b.p. 68–78°/1.2 mm	C ₁₀ H ₁₃ O ₃	64.50	64.40	9.70	9.76	16.85	16.65
(IIIa)	111.5–112.5°	C ₉ H ₁₆ N ₂ O	64.60	64.21	9.64	9.63	16.78	16.65
(IIIb)	154.5–155.5°	C ₉ H ₁₆ N ₂ O	64.60	64.21	9.84	9.63		
(IVa)	128–130°	C ₉ H ₁₆ O ₃	62.90	62.72	9.51	9.40		
(IVb)	113–115°	C ₉ H ₁₆ O ₃	63.00	62.72	9.48	9.40		
(Va)	b.p. 80.5°/10 mm	C ₉ H ₁₄ O ₂	69.80	70.10	9.55	9.15		
(Vb)	b.p. 125°/8 mm	C ₉ H ₁₄ O ₂	69.63	70.10	8.84	9.15		
(Vc)	31–32°	C ₉ H ₁₄ O ₂	69.85	70.10	9.19	9.15		
(VIIa)	61.5–62.5°	C ₉ H ₁₃ N ₂ Cl	58.78	58.54	7.01	7.10	15.01	15.16
(VIIb)	43–43.5°	C ₉ H ₁₃ N ₂ Cl	58.55	58.54	7.20	7.10	15.50	15.16
(VIIIa)	70–70.5°	C ₉ H ₁₄ N ₂	71.80	71.96	9.17	9.39		
(VIIIb), picrate	158.5–159.5	C ₁₅ H ₁₇ N ₅ O ₇	47.50	47.51	4.68	4.52		
(IXa)	47.75–48.75°	C ₁₀ H ₁₆ N ₂ O	66.60	66.66	8.92	8.95		
(IXb)	34–35°	C ₁₀ H ₁₆ N ₂ O	66.85	66.66	9.10	8.95		

^a Analyses were 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.

column), and the fraction, boiling at 80.5°/10 mm was collected. Yield, 4.0 g (63 %) of the butenolide (Va).

α-t-Butyl-γ-methyl-Δ(α,β)-butenolide (Vc). 2.5 g of the butenolide (above) was heated for 3 h at 100° with ca. 10 drops of triethylamine. Fractionation (Vigreux column, 106–110°/10 mm) gave 0.8 g (27 %) of the crude butenolide (Vc). Recrystallization from petroleum ether at –70° gave a sample for analyses (Table 3).

β-t-Butyl-levulinic acid (IVb). The tetrahydropyridazinone (IIIb), (9.9 g), was dissolved in warm 48 % hydrobromic acid (40 ml) and refluxed for 72 h. Water was added and the solution extracted 3 times with chloroform. Dilute potassium hydroxide was added to the organic layer and the unreacted pyridazinone was thoroughly extracted. The chloroform phase was dried with magnesium sulfate, and the solvent was evaporated *in vacuo*. 5.0 g of (IIIb) was recovered (51 %). The aqueous phase, containing the levulinic acid (IVb), was acidified and extracted 3 times with chloroform. The combined chloroform phases were dried and the solvent evaporated *in vacuo*. Yield, 2.7 g (27 %) of the levulinic acid (IVb). A sample was recrystallized from aqueous ethanol and subsequently from ligroin/toluene (5:3) for analysis, see Table 3.

β-t-Butyl-γ-methyl-Δ(α,β)-butenolide, (Vb). 2.7 g of the crude acid, (IVb), was refluxed in acetic anhydride (27 ml) for 96 h. The solution was evaporated *in vacuo* and the residue was distilled (Vigreux column). The fraction boiling at 125°/8 mm was purified by thin-layer-chromatography. (Eluent: petroleum ether:ether, 3:1).

5-t-Butyl-1,4,5,6-tetrahydro-6-oxo-methylpyridazine (IIIa). Methyl *α-t*-butyllevulinate (II), (49.8 g, b.p. 100–110°/12 mm) was refluxed with a solution of hydrazine (23 g of an 80 % hydrate in ethanol, 140 ml) for 45 h. The solvent was removed *in vacuo* and the light tan product was triturated with a mixture of water and petroleum ether (1:1). The colourless crystalline product was filtered off and washed with petroleum ether to give 43.7 g of crude (IIIa) (98 %, m.p. 94–100°). Recrystallization from aqueous ethanol gave 30 g (67 %), m.p. 108–109.5°. A sample was recrystallized from ligroin (b.p. 110–140°) for analysis, Table 3.

The same compound was obtained by treating the butenolide (Va) (above) with hydrazine hydrate. 0.51 g of (Va) (b.p. 80.5°/10) was refluxed with a solution of hydrazine (0.21 g of an 80 % hydrate in ethanol, 5 ml) for 24 h. The product was extracted with chloroform. Recrystallization from ligroin (60–80°) gave a colourless, crystalline product, identical with (IIIa) (no depression on admixture with the analytical sample).

5-t-Butyl-6-chloro-3-methylpyridazine (VIIa). The tetrahydropyridazinone (IIIa) (30 g) was dissolved in acetic acid (125 ml), and bromine (32 g) was added rapidly with stirring, the temperature being kept between 80–100°. Hydrogen bromide was evolved. After the addition, ether (300 ml) was added. The mixture was kept at 0° for 20 h, filtered, washed with ether and air-dried to give a bromopyridazinone (36.3 g), which was dissolved in a solution of sodium methoxide (20 g of Na in 350 ml of methanol) and refluxed for 1.5 h. The solvent was removed *in vacuo* and the residue was treated with water and extracted 3 times with chloroform. The extracts were dried, and the chloroform removed *in vacuo*, to give the crude pyridazinone (23 g). The product was refluxed in POCl₃ (240 ml) for 2 1/4 h, slowly poured onto ice, neutralized with ammonia and extracted 3 times with chloroform. The solvent was removed *in vacuo*, and the residue was distilled (Vigreux column). Yield: 18.3 g, b.p. 150–155°/10 mm of a yellow, crystalline product which was crystallized from ligroin (80–110°) at –70° to give 9.2 g of a product with m.p. 54–59°. A sample was recrystallized from aqueous ethanol to give colourless needles for analysis, see Table 3.

4-t-Butyl-6-chloro-3-methylpyridazine (VIIb). The tetrahydropyridazinone (IIIb) (3.46 g) was dissolved in acetic acid (15 ml), and bromine (3.9 g) was added rapidly with stirring, the temperature being kept between 100–110°. Hydrogen bromide was evolved. The solution was cooled to 0°, ether (10 ml) was added, the precipitate filtered, washed with ether and air dried to give 3.4 g of the crude bromopyridazinone. This was, in turn, refluxed with POCl₃ (50 ml) for 3 3/4 h, slowly poured onto ice, neutralized with ammonia, and extracted 3 times with chloroform. The solvent was removed *in vacuo*, and the residue (3.26 g) was recrystallized from petroleum ether to give a colourless crystalline product, m.p. 43–44.5° (no depression on admixture with the analytical sample below).

4-t-Butyl-6-chloro-3-methylpyridazine (VIIb) and 5-t-butyl-6-chloro-3-methylpyridazine (VIIa) via the dihydropyridazines (VI). To a solution of *t*-butylmagnesium chloride (120 ml) was added, with stirring, 3-chloro-6-methylpyridazine¹² (12 g). After completed addition, the solution was allowed to stand for 3/4 h at room temperature with stirring. The mixture of the dihydropyridazines (VI) was isolated as described above for (Ia) and (Ib), yield 17.1 g of a yellow (sometimes red) oil, which occasionally crystallized.

To a refluxing solution of chloranil (25 g) in benzene (450 ml) was rapidly added the crude above dihydropyridazines (VI) (17.1 g) in 10 ml of benzene. An additional 30 ml of benzene was used for washing. The solution turned black at once. The reaction mixture was allowed to cool for 1/2 h with stirring. Hydrochloric acid (500 ml, 6 N) was added, and the aqueous phase was neutralized with conc. ammonia at ca. 20° and extracted 3 times with chloroform. The organic phase was dried, and the chloroform removed *in vacuo* to give a black oil. Repeated distillation gave a light yellow, semicrystalline compound, b.p. 102–115°/0.85 mm. Yield: 9.42 g, 56 % total from 3-chloro-6-methylpyridazine. NMR-data showed a 45:55 content of the two chloropyridazines (VIIa) and (VIIb), which were separated by column chromatography (Merck silica gel 0.05–0.2 mm. Eluent: benzene:acetone, 8:1), and recrystallized from petroleum ether. (VIIa) gave no depression on admixture with the analytical sample (above). For (VIIb): see Table 3.

4-t-Butyl-6-methoxy-3-methylpyridazine (IXb) and 5-t-butyl-6-methoxy-3-methylpyridazine (IXa) via dihydropyridazines. Freshly prepared dihydropyridazines, (Ia) and (Ib) (4.16 g), in benzene (100 ml) were oxidized as above. Repeated distillation gave a yellow oil, b.p. 120–130°/10–12 mm. Yield: 1.35 g, 32 %. NMR showed a 1:1 ratio of the two methoxypyridazines, (IXa) and (IXb), respectively.

4-t-Butyl-6-methoxy-3-methylpyridazine (IXb). *4-t*-butyl-6-chloro-3-methylpyridazine (VIIb) (1.0 g) was refluxed for 5 h in a methanolic sodium methoxide solution (1/2 g of sodium in 100 ml of methanol). Water (10 ml) was added, and the pyridazine was extracted with ether (30 ml). The organic phase was treated with charcoal and magnesium sulfate, and the ether removed *in vacuo*. Yield of the crude product, 1.0 g. Recrystallization from petroleum ether gave a colourless, crystalline product for analysis, see Table 3.

5-t-Butyl-6-methoxy-3-methylpyridazine (IXa). *5-t*-Butyl-6-chloro-3-methylpyridazine (VIIa) (2.0 g) was refluxed for 216 h in a sodium methoxide solution (1 g of sodium in 40 ml of methanol). Isolation as described above for (IXb). Yield of the crude product: 1.7 g. A sample was purified by thin-layer chromatography (eluent: benzene:ether, 1:3), and recrystallization from petroleum ether to give a colourless, crystalline product for analysis, see Table 3.

4-t-Butyl-3-methylpyridazine (VIIIb). 4-t-Butyl-6-chloro-3-methylpyridazine (VIIb) (400 mg) was dissolved in 3 ml of 1 N methanolic potassium hydroxide and 20 ml of methanol.¹³ 20 ml of a Raney nickel suspension (prepared according to Organic Syntheses¹⁴) and 5 ml of methanol (used for washing) were added, and the hydrogenolysis was carried out at atmospheric pressure for 9 h. The catalyst was filtered off with magnesium sulfate as filter aid, and the solvent was removed *in vacuo*. The residue was extracted with dry ether and the ethereal solution filtered and evaporated to give 336 mg of a red oil. 200 mg of this was purified by thin-layer chromatography (eluent: ether) and isolated as the picrate for analysis, see Table 3.

5-t-Butyl-3-methylpyridazine (VIIIa). 5-t-Butyl-6-chloro-3-methylpyridazine (VIIa) (200 mg) was hydrogenolyzed in the same fashion. 1.5 ml of 1 N methanolic potassium hydroxide and 10 ml of a Raney nickel suspension were used. Hydrogenation: 12 1/4 h. The product was isolated and purified by thin-layer chromatography as above (eluent: benzene:ether, 1:3). Recrystallization from petroleum ether gave a colourless, crystalline product for analysis, see Table 3.

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