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The Addition of Grignard Reagents to Pyridazines

IV. *t*-Butylmagnesium Chloride and 3-Methoxy-6-phenylpyridazine

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A mixture of 4- and 5-*t*-butyl-3-methoxy-6-phenyldihydropyridazines is obtained by the reaction. The products were not separated, but the mixture was characterized by the formation of methyl α-*t*-butyl-β-benzoylpropionate and 4-*t*-butyl-1,4,5,6-tetrahydro-6-oxo-3-phenylpyridazine, respectively, upon acid hydrolysis. The yields of these compounds indicated a preferential formation of the 4-*t*-butyl isomer in the addition reaction. A reaction mechanism is suggested. The position of the *t*-butyl group in the methyl α-*t*-butyl-β-benzoylpropionate was ascertained by NMR analysis of the corresponding butenolide. Bromination of the dihydro compounds in cold hydrochloric acid gave the bromo compounds, mainly 5-bromo-4-*t*-butyl-4,5-dihydro-3-methoxy-6-phenylpyridazine. The latter compound gave 4-*t*-butyl-3-methoxy-6-phenylpyridazine by elimination of hydrogen bromide in sodium methoxide and 5-*t*-butyl-1,6-dihydro-6-oxo-3-phenylpyridazine by elimination of methyl bromide at 130°.

An improved synthesis of 3-methoxy-6-phenylpyridazine is given.

The reaction of Grignard reagents with symmetrically 3,6-disubstituted pyridazines has been shown to involve conjugate addition.[1-3] The reaction products were the 4- (or 5-) alkylated dihydropyridazines, which may be aromatized to the corresponding pyridazines.[4] If the two substituents of the 3,6-disubstituted pyridazines differ, the addition reaction must be expected to give two products (*cf.* above). The ratio of the amount of the latter products formed by the reaction may offer evidence as to the reaction mechanism involved (*cf.* below).

The reactions involved are illustrated in charts 1 and 2. Details for the preparation of the starting material (3-methoxy-6-phenylpyridazine [5]) is given (see Experimental). The dihydropyridazines (Ia and b) were not isolated as such, but the identity of the individual dihydropyridazines was established by hydrolysis in hydrochloric acid. The position of the *t*-butyl group, introduced by the Grignard reaction, apparently exerts a pronounced effect on the course of the hydrolysis: When the *t*-butyl group is adjacent to the methoxy group the dihydropyridazine (Ia) reacts as an imino ester and gives the corre-

sponding methyl ester (II), whereas the isomeric dihydropyridazine (Ib) gives the oxopyridazine (IIIb). The yield of the two products, 0.058 mole and 0.024 mole, respectively, from 0.10 mole of 3-methoxy-6-phenylpyridazine, represents a total yield of 82 %. The favored formation of (Ia) over (Ib) may either be due to the steric effect of the phenyl group or the reaction may be

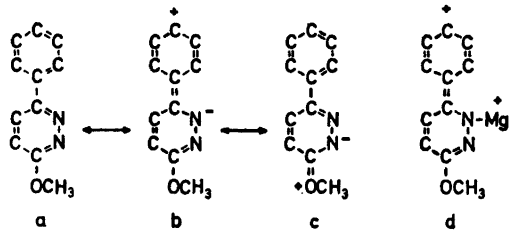

Fig. 1

controlled by the electronic requirements of the reagent. Considering the latter case it may be suggested that the initial reaction involves formation of a complex [6] between the electrophilic magnesium of the Grignard reagent and one of the nitrogen atoms of the pyridazine nucleus, the anionic alkyl subsequently attacking the carbon *para* to the nitrogen involved in complex formation (now the most electronegative of the two nitrogen atoms on account of the magnesium). If the resonance form (b) (see Fig. 1) of 3-methoxy-6-phenylpyridazine (a) is of more importance than (c), more of the magnesium complex (d) (corresponding to (b)) than the isomeric complex (corresponding to (c)) is formed (*cf.* the pK_a values of 2-phenylpyridine 4.55 [7] and of 2-methoxypyridine 3.28 [8]). Consequently the dihydropyridazine (Ia) (chart 1) is the major product; the ratio between the two isomers (Ia to Ib) is approximately 2:1, *cf.* above.

The position of the *t*-butyl group in the two series of compounds (a and b on the charts) is indicated by the formation of the acid (IVa) from benzene and *t*-butylsuccinic anhydride. If the reaction is analogous to the reaction

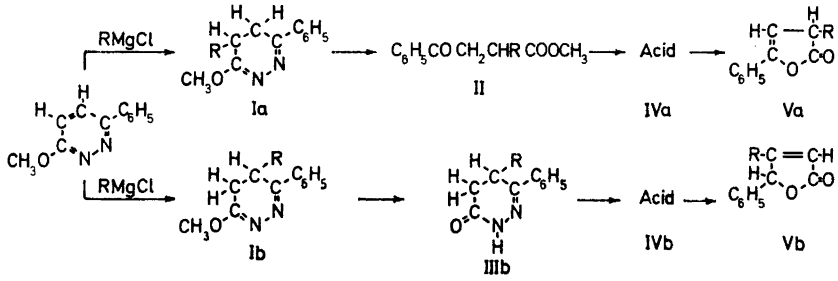

Chart 1

Table 1.

Butenolide	Va (R = H)	Va (R = *t*-but.)	Vb (R = *t*-but.)
α-Hydrogen:			
Chemical shift, δ ppm	3.33	3.18	5.92 or 6.02
Coupling constant cps	2.5	2.8	1.6
Multiplicity	2 (2 protons)	2	2
β-Hydrogen:			
Chemical shift, δ ppm	5.73	5.87	none
Coupling constant cps	2.5	2.8	—
Multiplicity	3	2	—
γ-Hydrogen:			
Chemical shift, δ ppm	none	none	5.92 or 6.02
Coupling constant cps	—	—	1.6
Multiplicity	—	—	2
IR C=O adsorption, cm^{-1} (in KBr)	1790, 1805	1796	1738—1760

between benzene and methylsuccinic anhydride [9] the alkyl must be α to the carboxyl group as in (IVa), *cf.* the isomeric acid (IVb). This result was confirmed by converting the two isomeric acids into the butenolides (Va) and (Vb) and comparing their NMR spectra with that of the authentic γ-phenyl-$\Delta(\beta,\gamma)$-butenolide (Va, R = H).[11] The structure of the latter compound is discussed

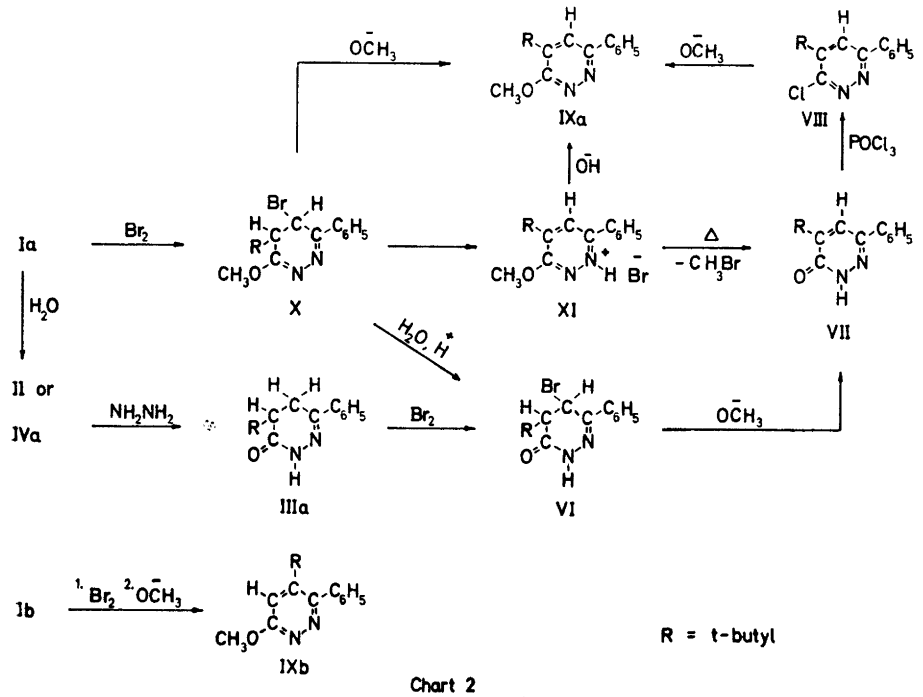

Chart 2

at length by Thiele and Sulzberger [12] and their results are in accordance with the NMR spectrum, see Table 1 (solvent deuterochloroform).

Only the structures (Va) and (Vb) are consistent with the data given in Table 1. It is interesting to observe the formation of (Vb). None of the isomeric $\Delta(\beta,\gamma)$-butenolides could be isolated, and the formation of (Vb) was much slower (reflux for one hour in acetic anhydride) than the formation of (Va) (reflux for a few seconds in acetic anhydride).

The ester (II) may be converted to the pyridazine (IXa) *via* the intermediates (IIIa), (VI), (VII), and (VIII) (see chart 2) in analogy with the synthesis of 3-methoxy-6-phenylpyridazine. An acetic acid solution of the intermediate (VI) does not eliminate hydrogen bromide spontaneously as the corresponding compound without the *t*-butyl group.

An attempt to prepare the pyridazine (IXb) by an analogous series of reactions was not successful because the pyridazinone (IIIb) could not be brominated by the procedure employed for the bromination of the isomeric pyridazinone (IIIa). In the latter reaction (formation of (VI)) the bromine is shown (see below) to substitute the hydrogen activated by the C=N group. Apparently, this also applies to (IIIb) where substitution at the most activated site is sterically hindered by the *t*-butyl group.

The mixture of the dihydropyridazines (Ia) and (Ib) may be brominated in aqueous hydrochloric acid. However, only (X) could be isolated, the presence of its isomer in the (b) series only being indicated by the formation of some of the pyridazine (IXb) by dehydrobromination of the mixture with sodium methoxide. The isomer (IXa) may be prepared in reasonable yield by the procedure.

The position of the bromine in the brominated dihydropyridazine (X) and its product of hydrolysis (VI) is shown by NMR analysis. The spectrum of (X) is characterized by the 9 protons of the *t*-butyl group (δ = 0.92 ppm), 3 protons of the methoxy group (δ = 4.05), 5 protons of the phenyl group (δ = 7.3 to 8.1) and finally by two doublets (δ = 2.65 and 5.13, J = 1.0 cps) attributed to the protons at C_4 and C_5, respectively. The alternative structure with two protons on the same carbon would not be expected to give the large chemical shift observed. The same conclusion as to the position of the bromine is shown by NMR analysis of the product of hydrolysis (VI): *t*-Butyl δ = 1.05; phenyl δ = 7.3 to 7.9; N—H δ = 10.0, broad; C_4H δ = 5.32, doublet, J = 1.5 cps; C_5H δ = 2.92, quartet. The latter resonance may be interpreted as a doublet with a spacing of 1.5 cps (coupling with C_4H) further split by a weak coupling (J = 0.6 cps) through the amide system [13] to the NH.

The bromodihydropyridazine (X) eliminates hydrogen bromide to give (XI), the hydrobromide of (IXa). When either of the two products (X) or (XI) are heated to *ca.* 130° methyl bromide is eliminated and the pyridazone (VII) is obtained in good yield. The methyl bromide is identified by its IR spectrum (vapor phase). It is reasonable to assume that the salt (XI) is an intermediate in the reaction (X) → (VII) + CH_3Br because the methoxypyridazine hydrobromide (XI) may be regarded as an (unsaturated) iminoester hydrobromide and must consequently give the amide and alkyl halide upon pyrolysis.[14]

The preparation of α- and β-*t*-butyl-β-benzoylpropionic acids (IVa and b) *via* the pyridazines seems to be the synthesis of choice, see Experimental. The following reactions were tested, but none of the acids expected were obtained:

The alkylation of ethyl *t*-butylcyanoacetate [15] with phenacyl bromide and subsequent hydrolysis and decarboxylation. — The aldol condensation of trimethylacetaldehyde [16] with acetophenone and subsequent conjugate addition of hydrogen cyanide.[17] — The alkylation of the sodium salt of acetophenone ($NaNH_2$) and of ethyl β-benzoylacetate with ethyl α-bromo-β,β,β-trimethylpropionate and subsequent hydrolysis. — The conjugate addition of *t*-butylmagnesium chloride to the ethylene glycol ketal of *sec*-butyl β-benzoylacrylate and subsequent hydrolysis.

EXPERIMENTAL

1,4,5,6-Tetrahydro-6-oxo-3-phenylpyridazine.[5] β-Benzoylpropionic acid [18] (158.5 g, 0.892 mole) was dissolved in a solution of hydrazine hydrate (62.5 g, 80 %, 1.00 mole) in 500 ml of water and heated for 2 h on the steam bath. When cold the white precipitate was filtered with suction and the product washed with cold water. Yield 149 g, 96 %.

1,6-Dihydro-6-oxo-3-phenylpyridazine, hydrobromide. In a 1-l three-necked flask, fitted with a dropping funnel, a stirrer and a reflux condenser arranged to permit removal of hydrogen bromide, was placed the pyridazinone (above, 149 g) and acetic acid (400 ml). The mixture was heated to 70° and bromine (43.7 ml, 0.856 mole) was added to the clear solution with stirring over a period of about 1 h, the rate of the addition being adjusted so as to maintain a temperature of 70 to 80°. Before all of the bromine was added the hydrobromide began to precipitate and hydrogen bromide was liberated. To the warm reaction mixture ether (200 ml) was added as fast as the capacity of the reflux condenser permitted. The white precipitate was filtered and washed thoroughly with ether (*ca.* 500 ml). Yield 204 g.

3-Chloro-6-phenylpyridazine.[5] The hydrobromide (above, 204 g) and phosphorus oxychloride (400 ml) was heated for 1 h on the steam bath and then refluxed for 1 h more. The resulting dark solution was poured onto ice with stirring and the acids were partly neutralized by adding aqueous ammonia (400 ml of a 25 % solution). The temperature was kept below 0° by the addition of ice (about 4 kg). The light brown precipitate was filtered and washed with *ca.* 2 l of water, stirred with water, filtered and washed with water. Yield 158 g.

3-Methoxy-6-phenylpyridazine.[5] To a solution of sodium methoxide, prepared from sodium (23 g, one mole) and dry methanol (1 l), was added 3-chloro-6-phenylpyridazine (158 g) and the mixture was heated in a flask fitted with a reflux condenser and a drying tube and kept at reflux temperature for 20 h. Water (1000 ml) was added to the resulting hot suspension of sodium chloride in methanol. After cooling the precipitate was filtered, washed thoroughly with water, stirred with water, filtered and washed with water. The dry, light brown product weighed 142 g (0.76 mole, m.p. 116—118°). The product was dissolved in 500 ml of toluene, treated with Norite, filtered hot, cooled with stirring, kept at 0° for 20 h, filtered, washed first with 100 ml of a 1:1 mixture of petroleum ether and toluene and finally with several 100 ml portions of petroleum ether. The dry, light tan, shining crystals weighed 126 g (0.68 mole, m.p. 116—118°, yield from β-benzoylpropionic acid 76 %).

Addition of Grignard reagent. To a stirred suspension of 3-methoxy-6-phenylpyridazine (18.6 g, 0.1 mole) in ether (200 ml) was added a solution of the *t*-butylmagnesium chloride (155 ml, 0.2 mole, prepared according to *Organic Syntheses*,[19] stored in tightly stoppered bottles and titrated with normal hydrochloric acid before use). The addition may be carried out rapidly (*ca.* 5 min). The ether refluxed and the reaction mixture turned brownish-yellow and became nearly homogeneous. After further stirring (*ca.* 5 min) the Grignard complex was decomposed with methanol [4] (40 ml) in ether (100 ml) with vigorous stirring.

The resulting suspension was filtered and the magnesium complexes were thoroughly washed with ether (*ca.* 200 ml). The combined yellow filtrates were concentrated *in vacuo* and gave a yellow oil (24.4 g, quantitative yield of the dihydropyridazines (Ia) and (Ib)).

Products of hydrolysis. 4-t-Butyl-1,4,6-tetrahydro-6-oxo-3-phenylpyridazine (IIIb) and methyl α-t-butyl-β-benzoylpropionate (II). The dihydropyridazines (above) were dissolved in hydrochloric acid (150 ml of concentrated hydrochloric acid and *ca.* 150 g of ice). A small piece of solid carbon dioxide was added to remove oxygen, and the solution was allowed to stand for 48 h at room temperature. The resulting suspension was filtered, washed thoroughly with water and dried *in vacuo*. The light tan product (20.1 g) was partly dissolved by heating it with ligroin (100 ml, b.p. 110—140°), the lumps being crushed with a spatula to ensure dissolution of all of the ester. The crystalline product was filtered from the ligroin at 0° and washed on the filter with petroleum ether (50 ml). The yield of the pyridazinone (IIIb) was 5.5 g, m.p. 186—191°. It was recrystallyzed from ethanol for analysis, see Table 2. The ester (II) crystallized from the combined filtrates by cooling to −80°, yield 12.6 g, m.p. 39—41°; recrystallization from petroleum ether for analysis. Further 1.8 g of the slightly yellow ester was obtained from the mother liquors by evaporating the solvents, total yield 14.4 g = 0.058 mole ester and 0.024 mole of the pyridazinone (IIIb) or 82 % from the 3-methoxy-6-phenylpyridazine.

α-t-Butyl-β-benzoylpropionic acid (IVa) and α-t-butyl-γ-phenyl-Δ(β,γ)-butenolide (Va). The ester (II, 10.1 g) was saponified for 2 h in an ethanolic sodium hydroxide solution (4.0 g of NaOH, 50 ml of water and 25 ml of ethanol). The solution was extracted with ether, heated to reflux, cooled and acidified with hydrochloric acid. The white, crystalline acid was filtered and washed with water to give 8.7 g (91 %, m.p. 120—131°). A sample was recrystallized from aqueous ethanol and finally from ligroin for analysis.

The acid (IVa) (Above; 6.0 g) was heated to the boiling point in acetic anhydride [20] (10 ml) and immediately cooled and poured with stirring into water (70 ml). A white, crystalline product separated immediately. The suspension was stirred for 1 h, filtered, washed thoroughly with water and air dried. The butenolide (5.3 g, 96 %, m.p. 68—70°) was recrystallized from ligroin (25 ml, 80/110°) at −80° and washed with cold petroleum ether to give a pure sample (4.5 g, 81 %) for analysis (Va, Table 2) and NMR spectrum (Table 1).

The acid (IVa) was also prepared from *t*-butylsuccinic anhydride [3] and benzene by a Friedel-Crafts synthesis according to the corresponding *Organic Syntheses* preparation [18] of β-benzoylpropionic acid. The product was distilled (140—160°/0.5), recrystallized from ethanol-water and from ligroin to give (IVa), mixed melting point and IR spectrum as above.

β-t-Butyl-β-benzoylpropionic acid (IVb) and β-t-butyl-γ-phenyl-Δ(α,β)-butenolide (Vb). The pyridazinone (IIIb, 0.5 g) was dissolved in warm hydrobromic acid conc. (2 ml) and refluxed for 3 h. The suspension was cooled and the acid filtered, dissolved in dilute sodium hydroxide, decolorized with Norite and liberated with hydrochloric acid. An analytical sample was obtained by recrystallization from aqueous ethanol and from ligroin, see Table 2.

The acid (IVb, above, 6.0 g) was refluxed in acetic anhydride (10 ml). NMR analysis of a sample taken after 5 min indicated the presence of considerable amounts of the acid (IVb). The conversion was complete after reflux for 1 h. The product was distilled *in vacuo* (4.2 g, b.p. 150—152°/0.6) and crystallyzed from ligroin 110/140 to give 3.7 g of an analytical sample (Table 2) for NMR analysis (Table 1).

4-t-Butyl-3-methoxy-6-phenylpyridazine (IX from ester (II) via (IIIa), (VI), (VII) and (VIII); see chart 2). Methyl α-*t*-butyl-β-benzoylpropionate (II, 39.6 g, 0.16 mole) was refluxed with a solution of hydrazine (10.0 g of an 80 % hydrate, 0.16 mole) in hydrochloric acid (60 ml of a 4 N solution) for 48 h. Crystallization started after *ca.* 5 h. After cooling the crystals were filtered and washed with aqueous ethanol (1:1) and dried. The yield of 5-*t*-butyl-1,4,5,6-tetrahydro-6-oxo-3-phenylpyridazine (IIIa) was 34.7 g (0.151 mole, 94 %, m.p. 161—163°). A sample for analysis was prepared by recrystallization from ethanol, see Table 2. The pyridazinone (34.7 g; IIIa) was dissolved in acetic acid (50 ml) and bromine (7.7 ml, 0.15 mole) was added with stirring, the temperature being kept between 90 and 100°. Hydrogen bromide was evolved. After the addition water was added and the crystals were filtered, washed with water and aqueous ethanol (50 ml, 1:1) and dried to give the bromopyridazinone (VI) (36.0 g, 77 %). A sample was recrystallized from ethanol for analysis and NMR spectra, see Table 2.

Table 2.

Compound	m.p.	Fomula	C found	C calc.	H found	H calc.	N found	N calc.	hal. found	hal. calc.
II	38–39°	$C_{15}H_{20}O_3$	72.50	72.50	8.02	8.10				
IIIa	161–162°	$C_{14}H_{18}N_2O$	73.20	73.01	7.72	7.89	12.20	12.16		
IIIb	192–193°	$C_{14}H_{18}N_2O$	73.25	73.01	7.57	7.89	12.03	12.16		
IVa	130–131°	$C_{14}H_{18}O_3$	71.65	71.77	7.51	7.77				
IVb	124–125°	$C_{14}H_{18}O_3$	71.50	71.77	7.62	7.77				
Va	69–70°	$C_{14}H_{16}O_2$	77.60	77.72	7.43	7.48				
Vb	101–102°	$C_{14}H_{16}O_2$	77.70	77.72	7.23	7.48				
VI	decomp.	$C_{14}H_{17}BrN_2O$	54.40	54.36	5.77	5.56	8.97	9.01	25.87	25.83
VII	183–184°	$C_{14}H_{16}N_2O$	73.50	73.62	7.12	7.10	12.42	12.27		
VIII	74–75°	$C_{14}H_{15}ClN_2$	68.08	68.12	6.02	6.14	11.15	11.33	14.20	14.33
IXa	75–76°	$C_{15}H_{18}N_2O$	74.15	74.35	7.50	7.50	11.67	11.56		
IXb	69–70°	$C_{15}H_{18}N_2O$	73.90	74.35	7.71	7.50	11.61	11.56		
X	decomp.	$C_{15}H_{19}BrN_2O$	55.50	55.74	5.98	5.94	8.72	8.67	24.88	24.71
XI	decomp.	$C_{15}H_{19}BrN_2O$	55.92	55.74	6.08	5.94	8.62	8.67	24.90	24.71

Analyses are by Mr. Preben Hansen, The Chemical Laboratory of the University of Copenhagen.

The bromopyridazinone (VI) (36.0 g, above) was dissolved in a solution of sodium methoxide (2.8 g of Na in 100 ml of methanol) at reflux temperature and subsequently cooled to 15°, diluted with water (100 ml) and filtered. The crystals were washed with aqueous methanol (1:1) and dried to give the pyridazinone (VII) (30.3 g, 88 % from the bromopyridazinone; m.p. 180–183°). A sample was recrystallized first from ligroin and then from ethanol for analysis, see Table 2.

The pyridazone (VII, above; 30.3 g) was refluxed in $POCl_3$ (169 ml) for 7 h, poured onto ice, neutralized with ammonia and extracted with chloroform. The organic phase was treated with Norite and dried with magnesium sulfate, the chloroform removed *in vacuo* and the residue treated with petroleum ether and cooled to induce crystallization. The crystals were filtered and washed with petroleum ether to give the nearly pure chloropyridazine (VIII) (18.2 g, 55 % from the pyridazone, m.p. 60–61°). A sample was recrystallized from petroleum ether for analysis, see Table 2.

The chloropyridazine (VIII, 18.2 g, above) was refluxed for 5 h in sodium methoxide (4.0 g of sodium in 100 ml of methanol). Water was added and the pyridazine extracted twice with chloroform, the organic phase treated with Norite and magnesium sulfate and the chloroform removed *in vacuo*. The resulting oil was treated with petroleum ether and cooled to 0°. The crystals were filtered and washed with cold petroleum ether. The methoxypyridazine (IXa) (11.1 g, 63 % from the chloropyridazine, m.p. 73–75°) did not depress the melting point of an analytical sample (see Table 2; *cf.* below); however, it did contain a trace of halogen. More of the methoxypyridazine (6.4 g, m.p. 69–73°) was obtained by evaporating the petroleum ether from the filtrates, thus rendering the yield nearly quantitative.

4-t-Butyl-5-bromo-3-methoxy-6-phenyl-4,5-dihydropyridazine (*X*); *preparation.* To an etheral solution of the dihydropyridazines (filtrate from the magnesium complexes, *cf.* above, prepared from 18.6 g (0.10 mole) of the 3-methoxy-6-phenylpyridazine) was added cold hydrochloric acid (50 ml of hydrochloric acid conc. and ice in excess to ensure low temperatures during the subsequent reactions) and the dihydropyridazines were extracted by thorough shaking. The aqueous phase containing the dihydropyridazines was cooled by adding more ice and then bromine (6.5 ml, 0.13 mole) was poured into the solution, the flask was stoppered and the mixture shaken thoroughly. The brominated products were extracted twice with chloroform, the combined chloroform phases were shaken vigorously for 1 min with cold aqueous ammonia (100 ml of 28 % ammonia and ice in excess) and finally dried with magnesium sulfate. All the manipulations were carried out without interruptions. The chloroform was removed *in vacuo* and the light tan crystalline product (28.5 g) was recrystalllized from ethanol (100 ml) to give yellow

crystals (17.6 g, 0.054 mole or 54 % from the pyridazine employed). A sample was recrystallized from ligroin (110—140°) and from ethanol for analysis (see Table 2) and NMR spectra. The product generally melted at 134—136° with decomposition and evolution of vapours, *cf.* below. Fast heating resulted in higher decomposition temperatures, *ca.* 150°.

Reactions of (X). Elimination of hydrogen bromide. The bromodihydropyridazine (X, above, 4.2 g) was dissolved in ethanol (42 ml) at reflux temperature and allowed to stand at room temperature. After two days crystals had separated. The crystals did not dissolve again when the ethanol was heated to reflux temperature. After 4 days more the crystals were filtered to give 1.2 g of the salt (XI). A sample was recrystallized from ethanol for analysis, see Table 2. The product was treated with hot chloroform and the remanence (1.2 g) dissolved in chloroform (10 ml) and water (10 ml) by stirring the mixture for 2 h. The organic layer was evaporated *in vacuo* and the residue was dissolved in warm petroleum ether, filtered and cooled. The white crystals which separated were filtered, washed with cold petroleum ether and dried to give the pyridazine (IX, 0.4 g, m.p. 74—76°, no depression on admixture of analytical sample).

Elimination of hydrogen bromide from (X): Sodium methoxide. The bromodihydropyridazine (X, above, 14.8 g) was refluxed in a solution of sodium methoxide (2.5 g of sodium in 100 ml of methanol) for 24 h, diluted with water (100 ml) and extracted 3 times with chloroform. The extracts were dried with magnesium sulfate and the chloroform removed *in vacuo*. The light yellow, oily crystals (11.1 g) were recrystallized from petroleum ether (50 ml) at −80° to give (IXa) (8.6 g, 78 % from the bromodihydropyridazine, m.p. 74—76°). A sample was recrystallized from ethanol-water for analysis, see Table 2.

Pyrolysis of X. Elimination of methyl bromide. The bromodihydropyridazine (X, above, 815 mg, 2.52 mmole) was placed in a small ampoule adapted to collect the methyl bromide in a receiver cooled to −80°. The pyridazine was heated to 130° (bath temperature). The bath was removed when the reaction became too vigorous. The product was finally heated to 142° for a few minutes and the methyl bromide immediately weighed (190 mg); the ampoule was estimated to contain further 33 mg of the (gaseous) bromide (difference weighing after flushing the ampoule with air and estimating the total volume; total yield of methyl bromide 223 mg, 2.35 mmoles, 93 %). The residue from the pyrolysis (573 mg, 2.51 mmoles, m.p. 160—182°) was recrystallized from aqueous ethanol (10 ml of ethanol and 5 ml of water) to give the pyridazone (VII) (412 mg, 1.81 mmoles, 72 %, m.p. 183—184°).

Hydrolysis of (X). The bromodihydropyridazine (X, above, 5.0 g) was dissolved in concentrated hydrochloric acid (20 ml) and allowed to stand for 6 days at room temperature. Water was added and the crystals filtered and recrystallized from ligroin (110—140°) and washed with petroleum ether to give (VI) (3.5 g, 72 %, decomposition points between 130 and 150° depending on heating velocity) identified by the IR spectrum.

5-t-Butyl-3-methoxy-6-phenylpyridazine (IX b). To the ethanolic mother liquor (100 ml) from the recrystallization of the dihydrobromopyridazine (X, above) was added sodium ethoxide (from 2.3 g of sodium) and the dark solution was refluxed for 16 h. Addition of water and extraction with chloroform gave a brown oil (9.0 g) which was distilled through a short Vigreux column. The yellow oil (6.8 g, b.p. 150—160°/0.5—0.7 mm) consisting of a mixture of the two pyridazines (IX a and b) and some unidentified impurities was chromatographied on a silica gel column (0.8 g on 100 g of silica gel Merck 0.05—0.2 mm eluated with benzene-ether 6:4). Fractions containing pure (IX a) and practically pure (IX b) were obtained. The pyridazine (IX b) was recrystallized from petroleum ether for analysis, see Table 2.

NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal zero of reference. The authors wish to thank professor Børge Bak for providing the spectra. IR spectra were taken by cand. pharm I. G. Krogh Andersen on an Infracord model 137 and on a Perkin-Elmer Spectrograph model 421.

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