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# The Addition of Grignard Reagents to Pyridazines

## II. The Preparation of 4-Alkylated 3,6-Dimethoxypyridazines

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The applicability of the reaction between 3,6-dimethoxypyridazine and various Grignard reagents to yield 4-substituted 4,5-dihydro-3,6-dimethoxypyridazines is demonstrated. Bromination and subsequent dehydrobromination of the dihydro compounds is shown to afford the otherwise rather inaccessible 4-alkylated and 4-arylated 3,6-dimethoxy pyridazines. The use of methanol for the decomposition of some Grignard addition complexes is illustrated; the modification proves to be essential for the preparation of 4-ethyl-3,6-dimethoxypyridazine.

In a preceding paper[1] the reaction between *tert*-butylmagnesium chloride and 3,6-dimethoxypyridazine was shown to involve a 1,4-addition to the heterocyclic nucleus, thus yielding 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxypyridazine (I, R = *tert*-butyl). The reaction has now been applied to other Grignard reagents; furthermore the dihydro compounds obtained (I) have been dehydrogenated to yield the corresponding aromatic derivatives (IV).

### RESULTS AND DISCUSSION

*Dihydropyridazines.* The preparation of various 4-alkylated and 4-arylated dihydropyridazine derivatives was attempted by using the method previously described for the preparation of 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxpyridazine (I, R = $(CH_3)_3C$). Only the phenyl and the isopropyl groups could, however, be introduced by this method. The addition of ethylmagnesium bromide and methylmagnesium iodide to 3,6-dimethoxypyridazine only resulted in the formation of tarry products besides some of the starting material. This seems to be in accordance with the instability of the products obtained by the reaction of 3,6-dichloropyridazine and the latter two Grignard reagents [1].

The introduction of the ethyl group may, however, be accomplished by a slight modification of the procedure. Instead of using aqueous acid such as a 20 % ammonium chloride for the decomposition of the Grignard-pyridazine complex, dry methanol was employed. This modification offers an advantage

over the standard procedure, both on account of its simplicity (see *Experimental*) and because the reaction mixture remains anhydrous. The decomposition probably takes place according to the following equation:

$$2\ RMgX + 2\ CH_3OH \rightarrow 2\ RH + (CH_3O)_2Mg + MgX_2$$

Here R may stand either for the alkyl group of the Grignard reagent or for the anion of the reaction complex. The magnesium methanolate removes any water present. The reaction products were isolated from the filtrate.

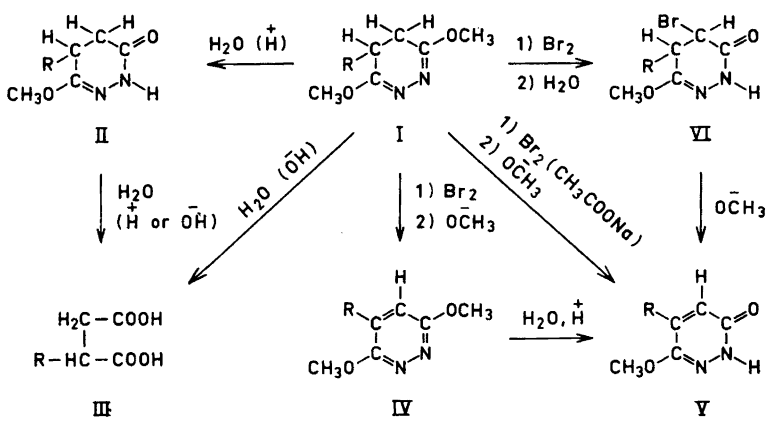
In contrast to the other Grignard reagents investigated, methylmagnesium halides apparently do not react with 3,6-dimethoxypyridazine (the chloride and iodide was tested). Hardly any heat of reaction was observed when the reagents were mixed, and most of the 3,6-dimethoxypyridazine was recovered after the decomposition of the Grignard-pyridazine complex with methanol.

The structure of the dihydro compounds (I) is probably analogous to that of 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxypyridazine [1] as indicated by the isolation of the pyridazones (II) and the substituted succinic acids (III) after hydrolysis. Evidence as for the structures may also be gained from the NMR spectra *. The spectrum of 4,5-dihydro-3,6-dimethoxy-4-phenylpyridazine (I, R = $C_6H_5$) dissolved in carbon tetrachloride revealed three groups of peaks: one group between $\delta$ 6.95 and 7.25 attributed to the five protons of the phenyl group, a second group consisting partly of two closely spaced peaks of high intensity at $\delta$ 3.71 and 3.73 (the six protons of two methoxy groups) and partly of a few small peaks in part hidden by the two larger peaks attributed to the proton at the 4-position of the ring. Finally a third group of peaks between $\delta$ 2.45 and 2.68 were attributed to the two protons at the 5-position of the pyridazine ring.

The hydrogen ratio determined by the integral curve is 5.2 : 7.0 : 1.9 as compared to the theoretical values 5 : 7 : 2. This interpretation is in accordance with the NMR spectrum of the structurally similar 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxypyridazine given in a preceding paper [1].

*Dehydrogenation.* Dihydropyridazines have by other workers been dehydrogenated by the action of platinum in the presence of a hydrogen acceptor (cyclohexene [2]) and by the action of bromine (in acetic acid [3-4] or in ethyl acetate [5]) and subsequent dehydrobromination. The former method, effective in the dehydrogenation of 4,5-dihydro-3,6-dimethylpyridazine, proved to be ineffective in the case of 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxypyridazine (I, R = *tert*-butyl) [1], and the latter method, by which 6-phenyl- and 6-methyl-2,3,4,5-tetrahydro-3-oxopyridazine may be converted in high yields into the corresponding 6-substituted 2,3-dihydro-3-oxopyridazines fails when applied to the pyridazinones (II). Apparently, the replacement of a methyl by a methoxy group renders the dihydropyridazine derivatives less susceptible to dehydrogenation. The resistance towards oxidation may also be illustrated by the many unsuccessful attemps to oxidize 4,5-dihydro-3,6-dimethoxy-4-phenylpyridazine (I, R = $C_6H_5$) with various oxidizing agents (see *Experimental*).

* The spectrum was taken in a Varian A-60 spectrometer at 60 Mc/sec using tetramethylsilane as an internal zero of reference.




The only effective oxidizing agent among those tested was bromine. The reaction I → IV takes place in two steps, first a bromination followed by a dehydrobromination brought about by sodium methoxide. In neutral solution (*e.g.* chloroform) 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxypyridazine was only partially brominated (as indicated by the fact that the reaction mixture assumes the colour of the bromine before the equivalent amount is added), but bases such as sodium acetate or pyridine apparently promoted the reaction. When sodium acetate was used (procedure *a*) large amounts of the oxo compounds (*e.g.* 1,6-dihydro-3-methoxy-6-oxo-4-phenylpyridazine (V, R = phenyl) from 4-phenyl-3,6-dimethoxy-4,5-dihydropyridazine) were formed, probably the acetic acid liberated from the acetate by the hydrogen bromide »hydrolyzed» the methoxy groups. No oxo compounds were isolated when pyridine (procedure *b*) was used as the base and the yield of the 4-substituted 3,6-dimethoxypyridazines was improved.

The only reaction product containing bromine isolated from the bromination of the dihydropyridazine (I, R = *tert*-butyl), has been formulated as (VI) on the basis of its analysis and on its conversion to the pyridazone (V) by the action of sodium methoxide. None of the bromine compounds constituting intermediate steps to the dimethoxypyridazines (IV) have been isolated but they must, however, simply be derived from (I) by monosubstitution of bromine at the 4- or 5-position. The bond between the bromine and the pyridazine nucleus in the latter compounds must be essentially covalent (*cf.* the ionic structure of the bromination product of 2,3,4,5-tetrahydro-6-methyl-3-oxopyridazine proposed by Overend and Wiggens [3]) because the bromination product of, *e.g.*, 4,5-dihydro-3,6-dimethoxy-4-phenylpyridazine does not react immediately with a cold solution of sodium methoxide in methanol. The reaction starts when the components are heated to reflux as indicated by the evolution of heat and the rapid precipitation of sodium bromide.

From the 4-substituted 3,6-dimethoxypyridazines the corresponding pyridazones (V) are obtained; the indicated position of the substituent R in the latter compounds has not been verified.

*Table 1.*

| Compound | Substituent | m.p. °C | b.p. °C/mm | Formula | C found | C calc.. | H found | H calc. | N found | N calc. | Br found | Br calc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $C_6H_5$ | 93 —94 | | $C_{12}H_{14}N_2O_2$ | 65.90 | 66.01 | 6.32 | 6.46 | 12.72 | 12.83 | | |
| II | $(CH_3)_2CH$ | 116 —117 | | $C_8H_{14}N_2O_2$ | 56.40 | 56.45 | 8.20 | 8.29 | 16.53 | 16.46 | | |
| II | $C_6H_5$ | 197 —198 | | $C_{11}H_{12}N_2O_2$ | 64.20 | 64.71 | 5.60 | 5.93 | 13.68 | 13.73 | | |
| IV | $C_2H_5$ | 28 —29 | 70/10 | $C_8H_{12}N_2O_2$ | 56.02 | 57.14 | 7.10 | 7.20 | 17.06 | 16.65 | | |
| IV | $(CH_3)_2CH$ | | 72—74/0.6 | $C_9H_{14}N_2O_2$ | 59.65 | 59.34 | 7.42 | 7.76 | 15.68 | 15.37 | | |
| IV | $(CH_3)_3C$ | | 74/0.5 | $C_{10}H_{16}N_2O_2$ | 61.40 | 61.16 | 8.10 | 8.26 | 15.62 | 14.27 | | |
| IV | $C_6H_5$ | 69 — 70 | *ca.* 140/0.4 | $C_{12}H_{12}N_2O_2$ | 66.30 | 66.65 | 5.77 | 5.59 | 12.92 | 12.96 | | |
| V | $(CH_3)_2CH$ | 128 —129 | | $C_8H_{12}N_2O_2$ | 56.80 | 57.14 | 7.20 | 7.20 | 16.74 | 16.65 | | |
| V | $(CH_3)_3C$ | 140 —141 | | $C_9H_{14}N_2O_2$ | 59.45 | 59.34 | 7.61 | 7.76 | 15.51 | 15.37 | | |
| V | $C_6H_5$ | 214 —215 | | $C_{11}H_{10}N_2O_2$ | 65.56 | 65.33 | 5.01 | 4.98 | 13.89 | 13.86 | | |
| VI | $(CH_3)_3C$ | 169.5—171 | | $C_9H_{15}BrN_2O_2$ | 40.90 | 41.05 | 5.56 | 5.75 | 10.77 | 10.63 | 30.41 | 30.40 |

Analyses by P. Hansen, The Chemical Laboratory of the University of Copenhagen.

## EXPERIMENTAL

Analyses: see Table 1.

*4,5-Dihydro-3,6-dimethoxy-4-phenylpyridazine* (I, R = $C_6H_5$). To a stirred solution of phenylmagnesium bromide, prepared from magnesium (12 g, 0.50 mole) and bromobenzene (78.5 g, 0.50 mole) in 200 ml of ether, was added 3,6-dimethoxyridazine[6] (30 g, 0.21 mole) portionwise. A considerable amount of heat was liberated as indicated by lively reflux of the ether. The addition was stopped when it was unable to cause any further reflux. The magnesium complex was decomposed by the addition of a 20 % aqueous solution of ammonium chloride. A sticky precipitate formed and rendered mechanical stirring very difficult. The ether was decanted and the precipitate thoroughly extracted with ether. The combined extracts were dried over magnesium sulfate and the ether removed *in vacuo*. The residue was distilled through a 20 cm Vigreux column and the fraction 125—150°/0.5 mm collected. This product, which crystallized spontaneously, amounted to 25 g. It was contaminated with 3,6-dimethoxypyridazine and diphenyl. An analytical sample was obtained by several recrystallizations from a 1:1 mixture of benzene and ligroin (b.p. 80—110°).

*Products of hydrolysis. 1,4,5,6-Tetrahydro-3-methoxy-6-oxo-4-(or 5-)phenylpyridazine* (II, R = $C_6H_5$) was obtained by hydrolysis of the dihydro compound in 4 N hydrochloric acid at 0° for 20 h; recrystallization from benzene.

*Phenylsuccinic acid* (III, R = $C_6H_5$) was obtained from the dihydro compound by reflux in 2 N aqueous sodium hydroxide. After recrystallization from 4 N hydrochloric acid the sample gave no depression of the melting point on admixture of an authentic sample, prepared according to Lapworth and Baker [11] kindly supplied by Dr. Munch-Petersen.

*Oxidations.* The dihydropyridazine (I, R = $C_6H_5$) (1 g) was added to a solution of potassium permanganate (1 g) in acetone (150 ml) and acetic anhydride (1 ml)[7]. Apparently only hydrolysis to (II, R = $C_6H_5$) took place. Also the following two oxidizing agents proved ineffective: hydrogen peroxide and sodium hydroxide in ethanol[8] and lead dioxide in acetic acid [8].

*Bromination and dehydrobromination. 3,6-Dimethoxy-4-phenylpyridazine* (IV, R = $C_6H_5$) and *1,6-dihydro-3-methoxy-6-oxo-4-phenylpyridazine* (V, R = $C_6H_5$). *Method a.* The dihydropyridazine (I, R = $C_6H_5$; 20 g = 0.092 mole) was dissolved in chloroform (200 ml) and pulverized anhydrous sodium acetate (16 g, 0.2 mole) was added. To this mixture bromine (16 g, 0.10 mole) in chloroform (20 ml) was added with stirring. The salts were removed by filtration, the chloroform evaporated *in vacuo* and the residue slowly added to a boiling solution of sodium (*ca.* 7 g, 0.3 g-atom) in methanol. The reaction was exothermic and sodium bromide precipitated. The solution was refluxed 10 min more, excess methanol evaporated *in vacuo* and sufficient ether and water added to form two phases. The aqueous layer was separated and extracted with ether. The combined ether extracts were dried over magnesium sulfate, the ether evaporated *in vacuo* and the residue recrystallized from aqueous acetone (7 ml of acetone + 3 ml of water) using decolourizing carbon. The yield was 2 g (*ca.* 10 %), m.p. 65—67°. Repeated crystallizations from the same solvent and from ligroin (b.p. 80—100°) yielded white crystals of 3,6-dimethoxy-4-phenylpyridazine (IV, R = $C_6H_5$).

The aqueous phase was acidified and *ca.* 10 g of a crystalline product precipitated. Repeated crystallization from aqueous ethanol (1:1) including treatment with decolourizing carbon yielded white crystals of 1,6-dihydro-3-methoxy-6-oxo-4-phenylpyridazine (V, R = $C_6H_5$), m.p. 214°—215°.

The latter product was also obtained by hydrolysis of the corresponding dimethoxy compound. The 3,6-dimethoxy-4-phenylpyridazine was dissolved in 2 N hydrochloric acid and refluxed for one hour. White crystals separated. The reaction mixture was cooled to 0° and filtered and the crystals recrystallized twice from ethanol, m.p. 214—215°, no depression on admixture of the above product (V, R = $C_6H_5$).

*Method b* involved the bromination of the dihydro compound in a mixture of pyridine and chloroform. The crude dihydro compound may be used directly: Phenylmagnesium bromide in excess and 3,6-dimethoxypyridazine (14 g, 0.10 mole) yielded 19.1 g of a light brown, crystalline product. Methanol was used for the decomposition of the Grignard

complex, see "4-ethyl-3,6-dimethoxypyridazine", below. The product thus obtained was dissolved in a mixture of chloroform (50 ml) and dry pyridine (35 ml). The solution was cooled in ice and bromine (13 g, 0.081 mole) dissolved in chloroform (20 ml) was added with vigorous stirring. The temperature was kept below 10°. The reaction mixture was washed three times with ice water and dried over magnesium sulfate. The chloroform was removed *in vacuo* and the residue poured into a solution of sodium methoxide (from 5 g sodium, 0.22 g-atom) in methanol (100 ml). No reaction took place until the temperature was raised to the boiling point of the solution. The spontaneous reaction was very vigorous. The reaction mixture was refluxed for 15 min and allowed to stand at room temperature overnight. The sodium bromide was filtered and washed with methanol, most of the solvent was removed *in vacuo* and enough ether and water was added to give two phases. The aqueous layer was extracted three times with ether, the combined extracts dried over magnesium sulfate and concentrated *in vacuo*. The oily residue (17.9 g) crystallized slowly. Recrystallization from aqueous acetone (50 ml of acetone to 25 ml of water) afforded 9.9 g of light brown crystals, m.p. 65–67°. Two additional crystallizations, one from ligroin (b.p. 80–110°) and one from aqueous acetone yielded 7.5 g (0.035 mole, 35 %) of 3,6-dimethoxy-4-phenylpyridazine (IV), m.p. 69–70°. The mother-liquors from the crystallizations contained considerable amounts of the pyridazine (IV) besides some of the starting material.

*4-*tert*-Butyl-3,6-dimethoxypyridazine* (*IV*, *R* = $(CH_3)_3C$). *Method a:* The dihydropyridazine (I) (10.3 g) yielded 4.6 g (44 %) of the 4-*tert*-butyl-3,6-dimethoxypyridazine. This sample was redistilled for analysis, b.p. 74°/0.5 mm. A gaschromatographic analysis indicated the presence of ca. 2 % impurities; as in the case of the corresponding dihydropyridazine (I)[1] the nitrogen content (as determined by the Dumas method) was much *higher* than the calculated value.

*Method (b)*. The overall yield of (IV) from 3,6-dimethoxypyridazine (35 g, 0.25 mole) was 67 % (33.1 g, 0.169 mole) of a slightly yellow oil; according to the gaschromatographic analysis the sample was practically pure.

*4-*tert*-Butyl-3-methoxy-6-oxo-1,6-dihydropyridazine* (*V*, *R* = $(CH_3)_3C$) was obtained from the dimethoxy compound (IV) (above) by refluxing in 2 N hydrochloric acid for 0.5 h. The white crystals were recrystallized three times from aqueous ethanol (3 ml of ethanol to 6 ml of water) and once from ligroin (b.p. 110–140°) m.p. 140–141°; no depression was encountered on admixture of the product prepared below.

The same compound could be obtained by treating 4-*tert*-butyl-4,5-dihydro-3,6-dimethoxypyridazine (I, R = $(CH_3)_3C$; 10 g) dissolved in chloroform (30 ml) with bromine (5 g). The reaction mixture was concentrated *in vacuo* and dissolved in petroleum ether. After 10 days at 0° 7.0 g of a crystalline product had separated. The product was recrystallized once from ligroin (b.p. 100–140°) and twice from aqueous ethanol (50 %); m.p. 97–137°. A sample recrystallized four times from ligroin yielded the bromo compound, m.p. 169.5–171° (VI, R = $(CH_3)_3C$); hydrolysis of a methoxy group must have taken place. Another sample was refluxed for 5 h with sodium ethoxide in ethanol, water and ether added until two phases separated, and the aqueous layer acidified to yield a brown precipitate. This product was treated with decolourizing carbon and recrystallized three times from aqueous ethanol (3 ml of ethanol to 6 ml of water) and once from ligroin, m.p. 140–141° (V, R = $(CH_3)_3C$).

*4-Isopropyl-3,6-dimethoxypyridazine* (*IV*, *R* = $(CH_3)_2CH$) was prepared from 3,6-dimethoxypyridazine and isopropylmagnesium bromide according to the procedure employed for the preparation of the corresponding *tert*-butyl compound; the bromination was carried out using the sodium acetate method *a*. The dihydro compound prepared (I, R = $(CH_3)_2CH$) did not give correct analysis but was identified by hydrolysis to (II, R = $(CH_3)_2CH$) and to isopropylsuccinic acid (III, R = $(CH_3)_2CH$).

*4-Ethyl-3,6-dimethoxypyridazine* (*IV*, *R* = $C_2H_5$). From the reaction between ethylmagnesium bromide and 3,6-dimethoxypyridazine none of the expected dihydro compound (I, R = $C_2H_5$) was obtained when aqueous ammonium chloride was used for the decomposition of the Grignard complex (*cf.* the preparation of 4,5-dihydro-3,6-dimethoxy-4-phenylpyridazine, above). However, the following modification proved to be favourable: A solution of ethylmagnesium bromide was prepared (approximate concentration 1.5 M as determined by titration with N hydrochloric acid). To the solution of ethylmagnesium bromide (60 ml, *ca.* 0.09 mole) was added ether (50 ml) and then portionwise 3,6-dimethoxypyridazine (7.0 g, 0.050 mole). After the addition the solution was brown. A mixture

of methanol (20 ml) and ether (20 ml) was slowly added with cooling in ice water. The sticky precipitate formed crystallized on thorough mixing with the ether-methanol. The precipitate was removed by filtration and extracted with ether. The combined filtrates were concentrated *in vacuo* and yielded a brown oil. The crude dihydropyridazine was dissolved in chloroform (10 ml) and dry pyridine (10 ml) and subsequently brominated at *ca.* 10° by the slow addition of a solution of bromine (6 g, 0.038 mole) in chloroform (10 ml). The reaction mixture was washed three times with ice water, concentrated *in vacuo* and poured slowly into a hot solution of sodium methoxide (prepared from 3 g, 0,13 mole, of sodium) in methanol. Sodium bromide was removed by filtration and enough ether and water added to give two phases. These were separated and the aqueous layer extracted with ether. The combined ether extracts were concentrated *in vacuo* and the dark brown residue distilled, b.p. 67°/0.3 mm. The yellow oil (4.3 g) crystallized; before analysis a sample was recrystallized four times from petroleum ether at −80°; m.p. 28−29°. As the elemental analysis was somewhat erroneous the purity was checked by gas-chromatography. The presence of *ca.* 10 % of 3,6-dimethoxypyridazine was indicated. This may in part account for the too low value of »C, found». Gaschromatographic analysis of the crude product indicated a 96 % content of 4-ethyl-3,6-dimethoxypyridazine. Overall yield: 4.1 g or 49 %.

The compound (IV, R = $C_2H_5$) was identified through its conversion into 4-ethyl-1,6-dihydro-3-hydroxy-6-oxopyridazine on hydrolysis for 24 hours in N hydrochloric acid. After recrystallization from water the melting point was 226−229°. An authentic specimen, m.p. 228−230°, was kindly supplied by Dr. Regitze Rosenørn of this laboratory. It had been prepared from ethylmaleic anhydride [9] and hydrazine by the method of Mizzoni and Spoerri [10]. The two products were found to be identical on the basis of mixed melting point and infrared spectra.

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