The reaction between lithium alkyls and compounds of the α,β-unsaturated carbonyl type generally afford compounds formed by addition of the organometallic compound to the hetero double bond (1,2-addition). Apparently, this also applies to heterocyclic compounds containing the C=N bond, the organometallic alkyl group attacking the carbon adjacent to the nitrogen atom.\textsuperscript{1-5} An exception is the reaction of acridine with butyllithium.\textsuperscript{3} In the case of Grignard reagents the reactions may involve both 1,2-additions\textsuperscript{6} and 1,4-additions\textsuperscript{2,6-9} within the heterocyclic nucleus. These differences are explained by Gilman \textit{et al.}\textsuperscript{7} in terms of localization energies of the heterocycles and the reactivities of the organometallic compounds.

With unsubstituted pyridazine, as shown by Letsinger and Lasco,\textsuperscript{2} the reaction takes place as may be inferred from above, \textit{i.e.} the alkyl of the lithium compound enters the 3-position (1,2-addition) and the alkyl of the Grignard reagent enters the 4-position (1,4-addition). In contrast to the above findings it has now been found that in the case of 3,6-dimethoxypyridazine the butyllithium attacks the 4-position.

RESULTS AND DISCUSSION

The reactions investigated are illustrated by the chart. 3,6-Dimethoxypyridazine (I) is allowed to react with the organometallic compounds (R = butyl or \textit{t}-butyl) in ether and the resulting complex is decomposed with methanol.\textsuperscript{9} The reaction products, formulated as the dihydro compounds (II), may undergo hydrolysis either to the pyridazinone (III) (only if R = \textit{t}-butyl) or to the substituted dimethyl succinate (IV) (only if R = butyl).

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Since the overall yields of the addition reactions are far from quantitative (see Experimental) the possibility that some 1,2-addition does take place cannot be excluded. On the other hand, the latter reaction route should lead to 3-alkyl-6-methoxypyridazines (by elimination of methanol) and no products of that type were observed.

The reaction between butylmagnesium bromide and 3,6-dimethoxypyridazine is slow (Table 1) as compared to the corresponding reaction involving t-butyilmagnesium chloride (nearly complete conversion 8) or butyllithium (see Experimental).

The dihydropyridazines formulated as II are cyclic hydrazino esters and might be expected in analogy with imino esters 10 to afford the corresponding esters (IV, R = C₄H₉) on acid hydrolysis; the imino esters, as a rule, only yield amides on heating their hydrochlorides. 10, 11 However, only if R = butyl the ester (IV) is formed; surprisingly, in the case R = t-butyl, the pyridazinone (III) is the sole product. 8

EXPERIMENTAL

Butyllithium and 3,6-dimethoxypyridazine. Butyllithium dissolved in ether was prepared and the molarity determined according to the method of Gilman. 13 To a stirred suspension of 3,6-dimethoxypyridazine 12 (14.0 g, 0.1 mole) in dry ether (50 ml) was added butyllithium in ether (90 ml, 0.115 mole) at 5°. The reaction mixture was heated until beginning reflux and the complex immediately decomposed by cautious addition of methanol (20 ml) in ether (80 ml). The ether was removed by decantation and the residue washed with ether. The combined ether extracts were concentrated in vacuo and the resulting oil (18 g) distilled. A fraction (b.p. 94°/0.7 mm → 96°/0.4 mm, nD 15° = 1.4800, 13.1 g) consisted (according to gas-chromatographic analysis) of 4 % 3,6-dimethoxypyridazine, 3 % dimethyl butylsuccinate (see below) and 93 % (total yield 61 %) of the dihydropyridazine (II, R = butyl). The product was fractionated, b.p. 100°/1.5 mm, nD 15° = 1.4750. (Found: C 60.80; H 9.14; N 15.80. Calc. for C₁₉H₁₈N₄O₂ (198) (II, R = butyl): C 60.55; H 9.18; N 14.14). As in the case of the corresponding t-buty1 derivative, the N-value is too high.

Dimethyl butylsuccinate (IV, R = butyl). The dihydropyridazine (II, above) was further characterized by hydrolysis in cold 4 N hydrochloric acid for 24 h. The ester

| Butylmagnesium bromide, mmole | 130 | 130 | 280 |
| Butyllithium, mmole | 100 | 100 | 100 |
| Reaction time at reflux temperature, min. | 10 | 60 | 10 |
| Dihydropyridazine obtained, mmole | 31 | 39 | 49 |
| Recovered 3,6-dimethoxypyridazine, mmole | 39 | 29 | 10 |

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separated as an oil and was distilled (b.p. 94°/0.5 mm; nD²⁰ = 1.4320; yield 62 %). The product was pure according to gas-chromatographical analysis. (Found: C 59.75; H 8.81. Calc. for C₁₆H₁₄O₄ (202): C 59.35; H 9.00). Saponification (equivalent 103) yielded butylic acid, m.p. 82—83°, cf. 82—83°.¹⁴

4- (or 5-) Butyl-1,4,5,6-tetrahydro-3-methoxy-6-oxopyridazine (III, R = butyl) was only obtained in very small amounts: The high boiling fraction (> 84°/0.4 mm) from the distillation of the butylic acid ester was saponified, extracted with ether and the ether evaporated. The resulting crystalline product was washed with petroleum ether and recrystallized from water, m.p. 81—82°. (Found: C 58.55; H 8.81; N 15.55. Calc. for C₁₆H₁₄N₂O₄ (184): C 58.63; H 8.82; N 15.20). The infrared spectrum showed a strong and broad band between 1650 and 1670 cm⁻¹ (C=O and C=N) and two medium bands at 3050 and 3150 cm⁻¹ (NH) and was also in other respects similar to the infrared spectrum of III, R = t-butyl, thus indicating the structure III, R = butyl. No evidence as to the exact position of the butyl group has been found.

t-Butylthiuram and 3,6-dimethoxypyridazine afforded (cf. above) an oil, which on hydrolysis in 6 N hydrochloric acid gave the pyridazinone (III, R = t-butyl), yield 12 % based on 3,6-dimethoxypyridazine, m.p. 150—151°; no depression on admixture with the product previously prepared using t-butylmagnesium chloride.⁶

Butylmagnesium bromide and 3,6-dimethoxypyridazine. The solution of butylmagnesium bromide (see Table 1) in ether (200 ml) was added to a stirred suspension of 3,6-dimethoxypyridazine (14.0 g, 0.1 mol) in dry ether (100 ml), the rate of addition and the external cooling being adjusted so as to keep the temperature of the reaction mixture between 5 and 10°. The reaction mixture was refluxed (cf. Table 1), cooled and treated with methanol at 10° with vigorous stirring. The precipitate was filtered and washed thoroughly with ether, and the combined filtrate and washings concentrated in vacuo and distilled, the fraction up to ca. 108°/1 mm being collected. Gas-chromatographic analysis indicated only 3,6-dimethoxypyridazine (the starting material) and the dihydroxyridazine (II, R = butyl) to be present. The yields given in Table 1 are calculated from the gas-chromatographic data. The amount of Grignard reagent employed in the syntheses is calculated on the basis of consumed magnesium.

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* The infrared spectra were taken by cand. pharm. I. G. Krogh Andersen on an Infraacord model 137. Analyses were by Mr. Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen.