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The Reaction between Carbon Dioxide and Dimethoxyphenylmagnesium Bromides

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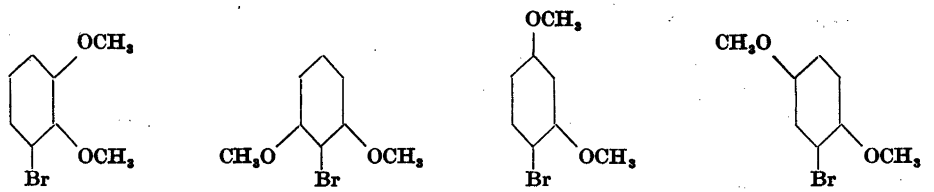
Some time ago the author published a report on the reaction between carbon dioxide and methoxy substituted phenylmagnesium and tolylmagnesium bromides [1]. It was then stated that a methoxy group in ortho position relative to the magnesium atom leads to the formation of the corresponding ketone in addition to the normal reaction product, the carboxylic acid. However, a methyl group in ortho position relative to the magnesium atom or relative to the methoxy group prevented the ketone formation.

The investigations have now been extended to the dimethoxyphenylmagnesium bromides. Some of the reactions have previously been carried out. Grignard [2] isolated veratric acid from the reaction products of carbon dioxide and 3,4-dimethoxyphenylmagnesium bromide. 2,4-Dimethoxybenzoic acid has been prepared from 2,4-dimethoxyphenylmagnesium bromide and carbon dioxide by Rice [3] and from the corresponding iodide and carbon dioxide by Kauffmann and Kieser [4]. However, since in none of these investigations attention has been paid to the formation of ketones, it was considered necessary to repeat the reactions with 3,4- and 2,4-dimethoxyphenylmagnesium bromides.

Indeed, Kauffmann and Fritz [5] isolated 2,5,2′,5′-tetramethoxybenzophenone and 2,5-dimethoxybenzoic acid from the reaction products of 2,5-dimethoxyphenylmagnesium bromide and carbon dioxide, but to be sure that the same conditions prevailed in all experiments also this reaction was repeated.

During the course of the work, results very similar to those obtained in the investigations with the methoxyphenylmagnesium and methoxytolylmagnesium bromides were obtained. It was found that if neither of the methoxy groups was in ortho position relative to the magnesium atom, only the corresponding carboxylic acids were formed. Two of the four compounds in which a methoxy group and the magnesium atom were in ortho position relative each other, *viz.* those prepared, from 2,3-dimethoxybromobenzene (3-bromoveratrole; I) and 2,6-dimethoxybromobenzene (II), reacted to give only the acids, whereas the Grignard reagents prepared from 2,4-dimethoxybromobenzene (III) and 2,5-dimethoxybromobenzene (IV) gave both ketones and acids.



I II III IV

If, thus, as in the preceding report, the ketone formation is considered a type of ortho effect, this effect is cancelled by a second methoxy group in ortho position relative to either the magnesium atom or the first methoxy group, *i. e.* the first ortho effect is again cancelled by a second ortho effect.

These results are in good accordance with those of Wittig and Pockels [6]. In addition to other reactions between carbon dioxide and organic lithium compounds, they investigated the reactions between carbon dioxide on one hand and 2,4-dimethoxyphenyllithium and 2,6-dimethoxyphenyllithium on the other, and established that the corresponding acids, ketones and triphenylcarbinols are formed in both cases. It is not surprising that 2,6-dimethoxyphenyllithium gives the above-mentioned products while the corresponding Grignard reagent gives only the carboxylic acid, since the organolithium compounds are more reactive than the organomagnesium compounds.

For the sake of completeness, it should be mentioned that Gilman, Swiss and Cheney [7] have isolated *o*-veratric acid from the reaction mixture of 2,3-dimethoxyphenyllithium and carbon dioxide. However, attention has not been paid to the formation of the corresponding ketone.

EXPERIMENTAL

2,3-Dimethoxybromobenzene (3-Bromoveratrole). Guajacol (124 g), dissolved in an aqueous solution (560 ml) of potassium hydroxide (56 g), was methylated with dimethyl sulphate (126 g) by shaking for 15 minutes. Any unchanged sulphate was then destroyed by heating the mixture for 30 minutes on a boiling water bath. The oil that had formed was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with water and dried with calcium chloride. After the solvent had been evaporated, veratrole was distilled under reduced pressure. The yield of material boiling at 88—90°/10 mm was 72.5 % (100 g).

The veratrole was nitrated to yield 4-nitroveratrole according to Cardwell and Robinson [8]. This substance could have been converted into 3-bromo-5-nitroveratrole by bromination according to Jones and Robinson [9], but as the method is time-consuming and a considerable portion of the desired compound is hydrolyzed to 6-bromo-4-nitroguaiacol during the performance, another method was chosen. 4-Nitroveratrole was hydrolyzed with aqueous potassium hydroxide to give 4-nitroguaiacol according to Pollecoff and Robinson [10]. It was, however, found that the period of heating in this synthesis could be shortened from 36 to 12 hours. The 4-nitroguaiacol obtained was brominated according to Robinson [11] to yield 6-bromo-4-nitroguaiacol. As no experimental details are to be found in the literature, the procedure followed in the bromination is given here.

4-Nitroguaiacol (66 g) was dissolved in acetic acid (330 ml) and a solution of bromine (21 ml) in acetic acid (130 ml) was added. After a few minutes, crystals of the 6-bromo compound began to separate. Forty-five minutes after the bromine addition, water (1.5 l) was added. The precipitated 6-bromo-4-nitroguaiacol was filtered and dried. The yield of material melting at 150—151° was 93.5 % (90.5 g).

Methylation of 6-bromo-4-nitroguaiacol with dimethyl sulphate in aqueous potassium hydroxide is not satisfactory, because the yield is only 35 % owing to the low solubility of the potassium salt of the bromo compound. The methylation is more conveniently performed by allowing an excess of undistilled diazomethane in ether solution to react with 6-bromo-4-nitroguaiacol (35 g) dissolved in ether (1 l). After the addition of the diazomethane solution, the mixture was allowed to stand for 15 minutes. The excess of diazomethane was then destroyed by adding acetic acid in ether. In order to remove the acid and any unreacted 6-bromo-4-nitroguaiacol, the mixture was shaken with an aqueous solution (200 ml) of potassium hydroxide (30 g). After the ether solution had been washed with water, it was dried with anhydrous calcium chloride. Evaporation of the solvent yielded a solid residue from which 3-bromo-5-nitroveratrole (34.2 g; m.p. 112—113°) was isolated after boiling with methanol (50 ml) and allowing the mixture to cool. A small amount (1.1 g) of the same compound was isolated after addition of water to the filtrate. The total yield was thus 95.5 %.

This 3-bromo-5-nitroveratrole was reduced to the corresponding amino compound in the following way. A solution of stannous chloride was prepared by dissolving tin (178 g) in concentrated hydrochloric acid (720 ml) in a three-necked flask, fitted with a reflux condenser and a stirrer. Ethyl alcohol (250 ml) was added, the stirrer started, and the temperature raised to 45°. A boiling solution of 3-bromo-5-nitroveratrole (10 g) in ethyl alcohol (70 ml) was added through the free neck of the flask. The bromonitro compound precipitated at first, but the precipitate disappeared in a few minutes. The addition of the bromonitro compound was then continued in portions (15 g, 25 g, 25 g, 25 g, and 26.5 g) dissolved in ethyl alcohol (105 ml, 175 ml, 175 ml, 175 ml, and 185 ml, respectively). Before each addition the temperature was adjusted to 45°, and the precipitated bromonitro compound was allowed to disappear before the next portion was added. Half an hour after the last precipitate of 3-bromo-5-nitroveratrole had disappeared, the stirrer was stopped. On the next day, the alcohol was removed by distillation under reduced pressure. After cooling, the precipitate that had formed during the distillation was filtered and treated with a mixture of ether (1 l) and technical sodium hydroxide (500 g) dissolved in water (3 l). The mixture was thoroughly shaken and the layers were separated. The water phase was extracted once more with ether and the combined ether solutions were dried with potassium hydroxide. After the ether had been evaporated, a yellowish white solid substance remained, which yielded 5-amino-3-bromoveratrole upon crystallization from benzene (250 ml). This substance (85.9 g) was isolated by filtration. The filtrate was concentrated to half its volume, and after addition of ligroin to the hot solution until a turbidity appeared, a small amount of impure amino compound was isolated. After recrystallization from benzene the purified substance (11.8 g) was combined with the main portion. The total yield of 5-amino-3-bromoveratrole, m.p. 100—100.5°, was 87 %.

Kimoto, Kimura, and Sakai [12] who performed the reduction with iron and hydrochloric acid, have reported the melting point 95—97° for this compound.

A small amount of the amine was converted into its acetyl derivative. After recrystallization from aqueous ethyl alcohol, 5-acetamino-3-bromoveratrole melting at 159—160° was obtained. (Found: N 5.38; Calc. for $C_{10}H_{12}O_3NBr$: N 5.43).

5-Amino-3-bromoveratrole has previously been deaminated in good yields by Kimoto, Kimura, and Sakai [12] by treating the corresponding diazonium salt with 40 % hypophosphorous acid. As the last-mentioned reagent could not be obtained, the deamination had to be performed in another way. Reduction of the diazonium salt with ethyl alcohol did not seem suitable, because only a small amount of acetaldehyde was detected when the reaction was performed on a test-tube scale. As a consequence of this fact, the diazonium salt was reduced with alkaline sodium stannite in the following way.

The amine (79 g) was dissolved in a hot mixture of concentrated sulphuric acid (31.6 ml) and water (475 ml). Crushed ice was added until the temperature had dropped to 0°, after which a solution of sodium nitrite (24 g) in water (200 ml) was gradually added. As the amine reacts slowly, the rate of addition was held very low. When the addition was completed, the mixture was allowed to stand for some time, and then added in small portions to an ice-cold mixture of stannous chloride (127 g) in water (650 ml), and sodium hydroxide (160 g) in water (190 ml). During this addition, nitrogen was evolved, and a tarry semi-liquid lump was formed. After the mixture had stood for an hour, crude 3-bromoveratrole was distilled over with steam. The oil in the distillate was dissolved in

ether, and the ether solution was shaken with a dilute solution of sodium hydroxide. After washing with water, the ether solution was dried with anhydrous sodium sulphate. Evaporation of the solvent followed by distillation under reduced pressure yielded pure 3-bromoveratrole, b.p. 128—129°/17 mm. The yield was 20 % (14.9 g).

2,4-Dimethoxybromobenzene. Resorcinol (30 g) dissolved in an aqueous solution (200 ml) of sodium hydroxide (22 g) was methylated with dimethyl sulphate (69 g) by shaking for an hour. Any unchanged sulphate was then destroyed by heating the mixture for 30 minutes on a boiling water bath. The methoxy compound was distilled with steam from the reaction mixture. The distillate was extracted with ether and the ether phase dried with anhydrous sodium sulphate. Evaporation of the solvent and distillation of the residue under reduced pressure yielded 1,3-dimethoxybenzene, b.p. 92—95°/16 mm. The yield was 85 % (32 g).

2,4-Dimethoxybromobenzene was prepared from this dimethoxybenzene according to the procedure described by Noelting and Werner [13] for the corresponding 2,5-dimethoxy compound.

2,5-Dimethoxybromobenzene. Hydroquinone was converted into 1,4-dimethoxybenzene by the method given for 1,3-dimetoxybenzene under the sub-heading "2,4-Dimethoxybromobenzene". The yield of material boiling at 109—110°/20 mm was 70 %.

The preparation of 2,5-dimethoxybromobenzene from 1,4-dimethoxybenzene was performed according to Noelting and Werner [13].

2,6-Dimethoxybromobenzene. Resorcinol was nitrated according to Kauffmann and de Pay [14] to give 2-nitroresorcinol. This compound was methylated according to Baeyer [15] and the 2,6-dimethoxynitrobenzene obtained was reduced according to Kauffmann and Franck [16] to 2,6-dimethoxyaniline.

This amine (20 g) was dissolved in 48 % hydrobromic acid (39.5 ml). The solution was cooled to 0° and a solution of sodium nitrite (9 g) in water (64 ml) was added gradually. In the meantime, a mixture of cuprous bromide (10.5 g) and 48 % hydrobromic acid (10.5 ml) was prepared in a flask provided with a dropping funnel, a steam inlet tube, and a condenser set for distillation. While steam was led through the mixture of cuprous bromide and hydrobromic acid the solution of the diazotized amine was allowed to run through the dropping funnel into the flask rather rapidly. During this operation, some crude 2,6-dimethoxybromobenzene distilled with steam. When the addition had been completed, the steam distillation was continued until no more organic material passed over. The solid in the distillate was filtered, broken up, and washed with dilute sodium hydroxide and water. After recrystallization from ethyl alcohol (50 ml), pure 2,6-dimethoxybromobenzene, m. p. 93—94°, was obtained. The yield was 53 % (15 g). (Found: Br 36.90; Calc. for $C_8H_9O_2Br$: Br 36.82).

3,4-Dimethoxybromobenzene. (4-Bromoveratrole) was prepared according to Freudenberg, Fikentscher, and Marden [17] by bromination of guaiacol followed by methylation with dimethyl sulphate in alkaline solution. The boiling point of the 4-bromoveratrole was 127—128°/13 mm.

3,5-Dimethoxybromobenzene. 3,5-Dinitroanisole (54.5 g), prepared according to Organic Syntheses [18], was dissolved in ethyl alcohol (100 ml). To this solution 15 % ammonium hydrogen sulphide solution (210 ml) was added in portions. After each addition, the mixture was thoroughly shaken. When all the sulphide solution had been added, the mixture was heated for 15 minutes on a boiling water bath. After cooling, the solid substance was filtered, washed with water, and extracted with hot dilute hydrochloric acid. The extraction was repeated several times or until no precipitate was formed when the extracts were made alkaline. Ammonia was then added to the combined extracts until they were alkaline. The precipitated 3-amino-5-nitroanisole was filtered off and recrystallized from ethyl alcohol. The yield of the compound, melting at 119—120° was 85 % (39 g).

This amino compound was converted into 3-bromo-5-nitro-anisole according to Blanksma [19]. When the synthesis was continued to 5-bromo-3-aminoanisole, the description for the corresponding iodo compound given by Hodgson and Wignall [20] was followed. From the bromoamine, 5-bromo-3-methoxyphenol was prepared according to Hodgson and Wignall [21] and this compound was methylated to yield 3,5-dimethoxybromobenzene by the following method.

The phenol (20.3 g) was dissolved in an aqueous solution (63 ml) of potassium hydroxide (7 g) and to this solution dimethyl sulphate (15.8 g) was added. The mixture was

Table 1. Yields, melting points, and analyses.

Dimethoxybromo benzene	Carboxylic acids				Ketones			
	g	m. p.	*p*-Nitrobenzyl esters Calc. N 4.41		g	m. p.	2,4-Dinitrophenylhydrazones Calc. N 11.61	
			m. p. [a]	Found N			m. p. [a]	Found N
2,3—	1.13	121.5—122.5 [b]	97—98	4.53	—			
2,4—	0.50	106—108 [b]	128—130	4.63	1.05	132—133 [c]	146—147	11.43
2,5—	1.00	74—76 [d]	128—130	4.39	1.30	108—109 [a]	175—176	11.53
2,6—	0.78	172—174 [b]	154—155	4.52	—			
3,4—	0.71	177—179 [b]	143—144	e	—			
3,5—	0.57	180—181 [c]	121—122	4.50	—			

[a] Recrystallized from ethyl alcohol.
[b] Recrystallized from water.
[c] Recrystallized from a mixture of water and alcohol.
[d] Recrystallized from ligroin.
[e] Previously prepared.

shaken for one hour and after addition of dilute sodium hydroxide solution, 3,5-dimethoxybromobenzene was distilled with steam. It was collected from the distillate by filtration. After recrystallization from ethyl alcohol, it melted at 64—65°. (Found: Br 37.01; Calc. for $C_8H_9O_2Br$: Br 36.82).

The yield was 83 % (18 g).

The reactions between Grignard reagents and carbon dioxide were examined as has been described previously [1]. The results are collected in Table 1.

SUMMARY

1. Dimethoxyphenylmagnesium bromides in which neither methoxy group is in ortho position relative to the magnesium atom react with carbon dioxide to give the corresponding carboxylic acids only.

2. If one of the methoxy groups is in ortho position relative to the magnesium atom and the other in ortho position relative to the first-mentioned methoxy group or relative to the magnesium atom, the dimethoxyphenylmagnesium bromide gives only the corresponding carboxylic acid in the reaction with carbon dioxide.

3. The other dimethoxyphenylmagnesium bromides react with carbon dioxide to give both the corresponding carboxylic acids and the corresponding tetramethoxybenzophenones.

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