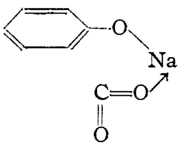

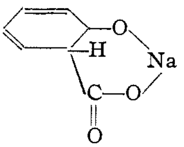

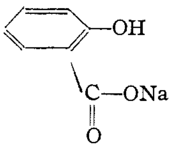

The specific applications of this hypothesis to such reactions will be discussed in a subsequent communication.

Summary

An hypothesis is presented to account for the abnormal reactions of benzylmagnesium chloride, without the assumption of rearrangement of free benzyl ions or radicals. This explanation is derived from the postulation of primary addition complexes in which certain definite factors are operative and lead, through chelation and ring opening, to abnormal products.

It is suggested that similar explanations may be used for a number of reactions which are not adequately elucidated by the conventional mechanisms.

ITHACA, NEW YORK RECEIVED MARCH 20, 1933
PUBLISHED JULY 6, 1933

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

Rotenone. XXV. The Synthesis of Tetrahydrotubanol and Tetrahydrotubaic Acid

BY H. L. HALLER

In a brief note recently published[1] in THIS JOURNAL it was reported that the synthesis of tetrahydrotubanol[2] (2,6-dihydroxyisoamylbenzene) had been accomplished. The present paper presents the experimental evidence for this statement and also records the conversion of the synthetic tetrahydrotubanol into tetrahydrotubaic acid[2] (2,4-dihydroxy-3-isoamylbenzoic acid).

The synthesis of tetrahydrotubanol was effected through the following sequence of reactions: 2,6-dimethoxybenzonitrile ⟶ 2,6-dimethoxyphenyl isobutyl ketone ⟶ 2,6-dimethoxyisoamylbenzene ⟶ 2,6-dihydroxyisoamylbenzene.

The 2,6-dimethoxybenzonitrile was prepared from 2-nitro-6-methoxybenzonitrile, which was obtained from *m*-dinitrobenzene by a modification of the procedure described by Lobry de Bruyn.[3] In the preparation of the nitromethoxybenzonitrile it was found preferable to extract the crude

---

(1) Haller, THIS JOURNAL, **54**, 4755 (1932).

(2) Haller and LaForge, *ibid.*, **53**, 4460 (1931); **54**, 1988 (1932).

(3) Lobry de Bruyn, *Rec. trav. chim.*, **2**, 210 (1883).

nitrile directly from the reaction mass with benzene rather than with chloroform.[4]

The 2,6-dimethoxyphenyl isobutyl ketone was obtained on hydrolysis of the corresponding imide, which was prepared by the action of isobutylmagnesium bromide on 2,6-dimethoxybenzonitrile. Mauthner has reported that only unchanged nitrile was obtained when this reaction was carried out with equimolecular proportions of nitrile and methylmagnesium iodide.[5] He failed to obtain any ketone probably because the imide, which is the acid-soluble intermediary product, was not hydrolyzed. It is essential to employ an excess of the Grignard reagent to obtain a maximum yield. The use of four moles of the Grignard reagent to one mole of the nitrile gave the same quantity of ketone as when a ratio of 2.5 moles of the Grignard reagent to one of the nitrile was employed. The yield of ketone is increased appreciably by gradually replacing the ether with dry toluene and finally refluxing the reaction mixture in boiling toluene.

The 2,6-dimethoxyphenyl isobutyl ketone was reduced to the corresponding alkyl derivative with the Clemmensen reagent. For this reaction it was necessary to use a large excess of the reagent. In addition to the desired product some higher boiling fractions were obtained. When the reaction mixture was vigorously stirred, as well as refluxed, the proportion of these higher boiling fractions was increased. From these fractions a crystalline compound ($C_{26}H_{38}O_4$) was isolated which is in all probability formed by the reduction of the pinacol corresponding to the ketone.

Demethylation of the dimethoxyalkylbenzene can be effected either with hydriodic acid or better with aluminum chloride in toluene. It was found that the kind of hydriodic acid used was important. Hydriodic acid obtained from Eastman Kodak Co. invariably yielded an iodine-containing body, whereas an acid obtained from Merck and Co. gave the desired tetrahydrotubanol, although in poor yields. Demethylation with aluminum chloride in toluene proceeded smoothly, and the demethylated product was obtained in good yield.

A comparison of the physical and optical properties of the synthetic 2,6-dihydroxyisoamylbenzene with those of tetrahydrotubanol showed them to be identical.

On refluxing the synthetic tetrahydrotubanol with a saturated solution of sodium bicarbonate, a product identical with tetrahydrotubaic acid was obtained.

Experimental

2,6-Dimethoxyphenyl Isobutyl Ketone.—The Grignard reagent was prepared from 32.5 g. (2.375 moles) of isobutyl bromide in 65 cc. of ether and 6.07 g. (2.5 moles) of magnesium suspended in 200 cc. of ether in the usual manner. To this ether solution was added in the course of ten minutes and with constant stirring 16.3 g. (1 mole) of

---

(4) Mauthner, *J. prakt. Chem.*, **121**, 259 (1929).

(5) Mauthner, *ibid.*, **124**, 319 (1930).

2,6-dimethoxybenzonitrile,[3,4] dissolved in 150 cc. of warm dry toluene (the dropping funnel was warmed as the nitrile had a tendency to crystallize from the solution). The reaction mixture was then heated in a water-bath and the ether was removed by distillation. When the temperature of the reaction mixture reached about 60°, the water-bath was replaced with an oil-bath, 100 cc. of dry toluene was added, and distillation was continued until pure toluene distilled over. The reaction mixture was then refluxed for three hours, cooled and poured onto ice and hydrochloric acid. The acid solution was extracted first with benzene, and then with ether. It was then placed in a beaker and heated on a steam-bath to remove most of the dissolved ether and was finally refluxed vigorously for two hours. The solution was cooled, the oil was separated, and the aqueous acid solution was extracted several times with ether. The ether extracts and the oil were combined, washed with 5% sodium carbonate, then with water and dried over sodium sulfate. After removal of the ether, the oil was distilled. It boiled at 136° and 1 mm. pressure. The yield was 16.5 g.

Anal. (micro)[6] Calcd. for $C_{13}H_{18}O_3$: C, 70.14; H, 8.17. Found: C, 70.06; H, 8.13.

On concentration of the toluene–ether solution, about 1.5 g. of the dimethoxybenzonitrile was recovered.

The ketone did not yield a semicarbazone or an oxime.

2,6-Dimethoxyisoamylbenzene.—Five grams of the ketone was added to 60 g. of amalgamated zinc and 200 cc. of 1:1 hydrochloric acid. The reaction mixture was refluxed for six hours, and at intervals of one hour 10 cc. of dilute (1:1) acid was added. The oil was then separated and the aqueous acid solution was extracted with ether. The ether extracts and the oil were combined and extracted with water, 10% sodium carbonate solution, and finally with water. The ether extract was dried over sodium sulfate, the ether was removed, and the remaining oil was fractionated under reduced pressure. A fraction boiling at 102° and 1 mm. pressure was collected. The yield was two grams.

Anal. (micro) Calcd. for $C_{13}H_{18}O_3$: OCH_3(2), 27.90. Found: OCH_3, 27.70.

From the higher boiling fractions a crystalline solid was isolated and purified by recrystallization from methyl alcohol. It melted at 188°.

Anal. (micro) Found: C, 75.56, 75.56; H, 9.17, 9.05. $C_{26}H_{38}O_4$ requires C, 75.31; H, 9.24. The compound is probably 2,7-dimethyl-4,5-di-(2,6-dimethoxyphenyl)-octane.

2,6-Dihydroxyisoamylbenzene (Demethylation with Hydriodic Acid).—One gram of 2,6-dimethoxyisoamylbenzene was refluxed with 10 cc. of hydriodic acid (Merck) for three hours. The solution was cooled, diluted with water, and extracted several times with ether. The combined ether extracts were washed successively with water, 5% sodium carbonate solution, 5% sodium thiosulfate solution and water. The solution was then dried over sodium sulfate. The ether was removed and the remaining sirup was distilled. The distillate crystallized readily. The substance was recrystallized from 15% benzene–85% petroleum ether. It melted at 83°. A comparison of its optical properties with those of tetrahydrotubanol showed them to be identical.[7]

Anal. (micro) Calcd. for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 72.81; H, 9.08.

Demethylation with Aluminum Chloride in Toluene.—Two grams of 2,6-dimethoxyisoamylbenzene was dissolved in 25 cc. of dry toluene. The solution was

---

[6] I am indebted to Mr. J. R. Spies of this Laboratory for the microcombustions reported in this paper.

[7] I am indebted to G. L. Keenan of the Microchemical Laboratory of the Food and Drug Administration, U. S. Department of Agriculture, for the optical identifications.

cooled in an ice-water bath, and three grams of anhydrous aluminum chloride was added slowly. The solution was then warmed in an oil-bath and finally refluxed. After fifteen minutes of refluxing a solid cake formed. Heating was continued for an hour. The reaction mixture was then cooled and poured into ice-cold dilute hydrochloric acid, and the acid solution was extracted several times with ether. The ether extracts were combined and washed with water and 10% sodium carbonate. The phenol was then extracted from the ether solution with 5% sodium hydroxide, and after acidification of the alkaline extract the phenol was extracted with ether. The ether extract was washed with water and dried over sodium sulfate. The ether was removed and the remaining sirup was distilled. The distillate readily crystallized. The substance was recrystallized from benzene–petroleum ether. It melted at 83°. The yield was 1.2 g. It was identified by its optical properties as tetrahydrotubanol.

Tetrahydrotubaic Acid from Synthetic Tetrahydrotubanol.—Five-tenths gram of the product obtained on demethylation of 2,6-dimethoxyisoamylbenzene with aluminum chloride in toluene was refluxed in 100 cc. of saturated sodium bicarbonate solution for one hour. The solution was cooled, filtered and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water and dried. The substance was then twice recrystallized from benzene. It melted at 206°. It was found to be identical with tetrahydrotubaic acid.

Summary

2,6-Dihydroxyisoamylbenzene was synthesized and found to be identical with tetrahydrotubanol.

On refluxing 2,6-dihydroxyisoamylbenzene with a saturated solution of sodium bicarbonate, tetrahydrotubaic acid (2,4-dihydroxy-3-isoamylbenzoic acid) was obtained.

WASHINGTON, D. C.

RECEIVED MARCH 22, 1933
PUBLISHED JULY 6, 1933

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY]

The Thermal Decomposition of Organic Compounds from the Standpoint of Free Radicals. III. The Calculation of the Products Formed from Paraffin Hydrocarbons

BY F. O. RICE

A difficulty in connection with the theoretical treatment of the thermal decomposition of paraffin hydrocarbons from the standpoint of free radicals[1] lies in the behavior of the higher free radicals formed in the primary dissociation as well as those formed by loss of a hydrogen atom from the hydrocarbon in the chain mechanism. Such a radical may either decompose into an olefin and a smaller free radical, or it may react with the surrounding molecules to form a hydrocarbon and generate a new free radical.

It now appears from experimental work carried out in this Laboratory during the past two years that a sharp distinction must be drawn between

---

(1) Rice, THIS JOURNAL, **53**, 1958 (1931).