3. The phenylethyl-4-piperidyl benzoate is a very potent local anesthetic, possessing about seven times the anesthetic power of cocaine and considerably less toxicity.
4. The relationship between physiological action and certain types of structure is discussed.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

IMPROVEMENTS IN THE METHOD FOR THE PREPARATION OF MERCURY DIALKYLS FROM ORGANOMAGNESIUM HALIDES

BY HENRY GILMAN AND ROBERT E. BROWN

RECEIVED NOVEMBER 9, 1928 PUBLISHED MARCH 6, 1929

One of the best methods for the preparation of mercury dialkyls is the reaction between mercuric chloride and the Grignard reagent. Marvel and Gould[1] have described the preparation of several mercury dialkyls by this general reaction. They added the powdered mercuric chloride (about 100 g.) through a condenser in 5- to 10-g. lots over a period of about forty-five minutes and found that a large excess of Grignard reagent and long heating were apparently necessary in order to obtain good yields.

Having a need for large quantities of some mercury dialkyls in connection with studies of magnesium dialkyls, we found that a few variations markedly improved the yields and made the method somewhat more convenient. First, the extra manipulation involved in finely powdering the mercuric chloride and adding it in small portions can be obviated by the use of a Soxhlet extractor. Second, the time of heating was extended from ten to twelve hours to twenty to twenty-four hours. Third, a larger volume of ether was used. These alterations in procedure reduced the tendency of caking and they can be applied to similar reactions involving reactants that are sparingly soluble in ether.

Experimental Part

The reactants were used in the proportions described by Marvel and Gould.[1,2] The Grignard reagent, prepared in 500 cc. of ether, was carefully decanted from the excess magnesium into a two-liter, three-necked flask fitted with an efficient stirrer and a Soxhlet extractor, on top of which was connected a long condenser provided with a drying tube filled with a mixture of calcium chloride and soda lime. The stirrer used was of the

---

[1] Marvel and Gould, THIS JOURNAL, **44**, 153 (1922). This article contains a review of earlier work. The authors are indebted to Dr. C. S. Marvel for the suggestion that extended heating would improve the yields. Marvel and Hager, *ibid.*, **48**, 2689 (1926) obtained a 90% yield of mercury di-*n*-heptyl from mercuric chloride and *n*-heptylmagnesium bromide after a four-day period of refluxing. Marvel and Calvery, *ibid.*, **45**, 820 (1923), extended the method to the preparation of branched-chain mercury dialkyls.

[2] Although an excess of Grignard reagent is desirable for higher yields, it is possible that the liberal excess used in these experiments can be reduced.

centrifugal type.[3] It consists of a section of glass tube 0.75 inch in diameter and 1.25 inches long with a hole about 0.5 inch in diameter in the center. This is fused opposite the hole onto a glass rod.

The unpowdered mercuric chloride was placed in an extraction thimble and the Grignard reagent was diluted to one liter with anhydrous ether. The flask was warmed by a water-bath until gentle boiling started. The ether solution of mercuric chloride siphoned over into the reaction flask. Care was taken that the ether solution of mercuric chloride did not strike the side of the flask.[4] When all the mercuric chloride had dissolved, usually after about four hours with 100 g. of material, the extractor was removed and the condenser was attached directly to the flask.[5] The temperature of the water-bath was increased to 55–60° and refluxing was continued for an additional eighteen to twenty hours. The reaction mixture was then cooled by an ice-bath and 400 cc. of water was slowly added from a dropping funnel. The ether layer was separated and the water layer was extracted with 50 cc. of ether. After drying the combined ether extracts with calcium chloride, the ether was removed by distillation and the mercury dialkyls fractionally distilled *in vacuo.*

In the following table the time of refluxing includes the four-hour period generally required to extract the mercuric chloride.

TABLE I

MERCURY DIALKYLS

Alkyl bromide			Magnesium		Mercuric chloride		Reflux, hours	Mercury dialkyls,	yield[b]
	G.	Moles	G.	Atoms	G.	Moles		G.	%
Ethyl[a]	125	1.15	30	1.23	97	0.32	22	80	86.5
Ethyl	125	1.15	30	1.23	97	.32	24	82	88.7
Ethyl	250	2.30	60	2.46	194	.64	24	164	88.7
Ethyl	250	2.30	60	2.46	194	.64	24	162	87
n-Butyl[c]	134	0.98	25	1.03	97	.32	16	58.5	52
n-Butyl	134	.98	25	1.03	97	.32	28	75	66.7
n-Butyl	134	.98	25	1.03	97	.32	28	74	66

[a] The mercury diethyl distilled at 65–66° (18 mm.) uncorrected.

[b] Marvel and Gould (ref. 1) obtained yields of mercury diethyl ranging from 61 to 75% and their yield of mercury di-*n*-butyl was 47%. Dr. Marvel has recently carried out some promising experiments on mercury di-*n*-butyl by first preparing the butyl-mercury halide and then treating this with an excess of Grignard reagent. Also, Mr. Hager obtained excellent yields of mercury di-*n*-butyl by using a special apparatus for the addition of mercuric chloride. The advantage of the Soxhlet extractor is its general availability.

[c] The mercury di-*n*-butyl was distilled twice from a Claisen flask provided with a specially indented fractionating side-arm of about 6 inches height to separate the mercury *n*-butyl halides, of which a considerable quantity was recovered in the distilling flask. The mercury di-*n*-butyl distilled at 116–118° (18 mm.). It is probable that the yield of mercury dialkyls can be increased significantly by a more protracted period of refluxing.

---

[3] "The Preparation of Synthetic Organic Chemicals at Rochester," Eastman Kodak Co., see Fig. 21, p. 26.

[4] If this solution strikes on or close to the side of the flask, caking may result.

[5] It is probably not necessary to remove the Soxhlet extractor but this was always done. A second condenser may be attached to the other neck of the flask if this is necessary to condense all of the ether vapor.

Summary

Improved directions are given for the preparation of mercury dialkyls from organomagnesium halides.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF GRINNELL COLLEGE]

THE SUPPOSED ALPHA,BETA,BETA-TRIMETHYLGLUTARIC ACID OF NOYES AND SKINNER

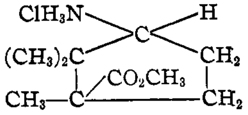
BY FRANCIS EARL RAY

RECEIVED NOVEMBER 15, 1928 PUBLISHED MARCH 6, 1929

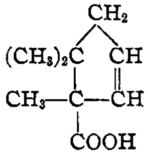
Introduction

In a previous paper[1] an attempt was made to elucidate the course of the reaction which occurs when the methyl ester of iso-aminocamphonanic acid, I, is decomposed by nitrous acid.

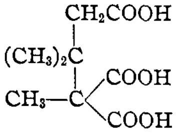
It was thought by Noyes and Skinner[2] that the reaction gave, in part, the unsaturated compound, II, because on oxidation of this product with alkaline permanganate and decomposition with heat, an acid was obtained which was considered to be α,β,β-trimethylglutaric acid, IV.



I

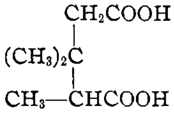


II



$$\begin{array}{l} CH_2COOH \\ | \\ (CH_3)_2C \\ | \\ CH_3{-}C(COOH)_2 \end{array}$$

III



$$\begin{array}{l} CH_2COOH \\ | \\ (CH_3)_2C \\ | \\ CH_3{-}CHCOOH \end{array}$$

IV

It was shown[1] that the acid obtained was not α,β,β-trimethylglutaric acid. The suggestion that α,β,γ-trimethylglutaric acid might be formed by the migration of one of the β-methyl groups was also disproved.

As it then seemed probable that IV was α,α,β-trimethylglutaric acid, Dr. Skinner suggested[3] that a methyl group might migrate from the β- to the α-position when carbon dioxide is liberated by heat from III. It is this possibility with which the present investigation deals.

Discussion

Perkin and Thorpe[4] had obtained α,β,β-trimethylglutaric acid by decomposing the ethyl ester of α,β,β-trimethyl-α-cyanoglutaric acid with hydrochloric acid in a sealed tube at 200° without isolating the intermediate α,β,β-trimethyl-α-carboxyglutaric acid. It seemed possible that this vigorous treatment might prevent a migration that would take place under the influence of heat alone.

---

[1] Ray, THIS JOURNAL, **50**, 558 (1928).

[2] Noyes and Skinner, *ibid.*, **39**, 2692 (1917).

[3] Private communication.

[4] Perkin and Thorpe, *J. Chem. Soc.*, **75**, 65 (1899).