Benzylmercaptomagnesium Iodide ($C_6H_5CH_2SMgI$) and Phenyl Isocyanate.—Twenty-one and two-tenths g. or 0.18 molecular equivalent of phenyl isocyanate in ether was added to about 0.2 equivalent of benzylmercaptomagnesium iodide; 19.5 g., or a 40.6% yield, of benzyl phenyl-thiolcarbamate, m. p. 94.5°, was obtained.

Anal. Calcd. for $C_{14}H_{13}ONS$: S, 13.16. Found: 13.01.

β-Naphthylmercaptomagnesium Iodide and Carbon Dioxide.—Dry carbon dioxide was passed for four hours over the surface of 0.125 molecular equivalent of the iodide, cooled by ice and salt. Since there was no evidence of a reaction, the ether was replaced by xylene and the mixture refluxed for four hours during which the passage of carbon dioxide was continued. A white precipitate formed. The alkali extract of the ether solution yielded 17 g. of β-thionaphthol. In addition, 1.5 g. of di-β-naphthyl disulfide was obtained. This may have been formed by air oxidation of the mercaptan subsequent to hydrolysis.

Summary

A study has been made of some reactions of mercaptomagnesium halides (RSMgX).

The —SMgX group can be identified satisfactorily by acylating agents, alkyl sulfates, RX compounds such as benzyl bromide and bromo-acetophenone which have very active halogens,[25] and phenyl isocyanate.[26]

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

DERIVATIVES OF PARA-HYDROXYMETHYL-BENZOIC ACID

I. ESTERS[1,2]

BY FRANCIS H. CASE[3]

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Within recent years the search for a non-toxic cocaine substitute adapted to anesthesia of the mucous membrane has resulted in the discovery of "butyn,"[4] "tutocaine,"[5] and "psicain,"[6] all of which are now being marketed. Among the alcohol derivatives, Sollman[7] introduced benzyl al-

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[25] Conant and Kirner, THIS JOURNAL, **46**, 232 (1924).

[26] It is probable that phenyl-carbamic bromide ($C_6H_5NHCOBr$) is even better, for it reacts more readily than phenyl isocyanate with —OMgX compounds.

[1] Presented before the Division of Organic Chemistry, 68th Meeting of the American Chemical Society at Ithaca, N. Y., 1924.

[2] This investigation has been carried out in collaboration with the National Research Council Sub-committee on Local Anesthetics (A. J. Hill, Chairman). The physiological properties of the new compounds will be subsequently reported by Dr. A. D. Hirschfelder of the University of Minnesota.

[3] National Research Fellow.

[4] Adams, Kamm and Volwiler, U. S. Pat. 1,358,751.

[5] Schulemann, *Klin. Wochschr.*, **3**, 676 (1924).

[6] Willstätter, *Münch. med. Wochschr.*, **71**, 849 (1924).

[7] Sollman, *J. Pharmacol.*, **13**, 355 (1919).

cohol, Hjort and Kaufmann,[8] benzoyl carbinol, and Hirschfelder,[9] saligenin. These latter compounds are all far less toxic than cocaine, and although somewhat weaker in anesthetic power have been reported to be adequate for certain types of operations. They have not, however, come into common use.

The mild anesthetic properties of simple aromatic esters, such as ethyl benzoate, ethyl *p*-aminobenzoate and benzyl benzoate are well recognized. It seemed to us that in the esters of *p*-hydroxymethyl-benzoic acid, *p*-$HOCH_2C_6H_4COOH$, it should be possible to combine the anesthetic properties of benzyl alcohol with those of aromatic esters.

As an intermediate for the preparation of *p*-hydroxymethyl-benzoic acid, *p*-cyanobenzyl bromide was used. This was prepared from *p*-tolyl cyanide by a slight modification of the method developed by H. S. Johnson[10] and Nicholas,[11] as described in the experimental part. It was found that *p*-hydroxymethyl-benzoic acid may be readily prepared by merely hydrolyzing the *p*-cyanobenzyl bromide with concd. hydrochloric acid.

The simple esters prepared were the ethyl, propyl, butyl, *iso*butyl and benzyl esters. Due to the fact that we could not prepare an acid chloride of *p*-hydroxymethyl-benzoic acid, the preparation of some of these esters was attended with difficulty. The esterification was further complicated by the fact that *p*-hydroxymethyl-benzoic acid forms an internal ether[10] with itself in the presence of concd. sulfuric acid, and undergoes a similar reaction when heated to a temperature above 150°. Furthermore, it has a tendency toward the formation of a mixed ether under the conditions employed for esterification (namely, alcohol in the presence of a trace of sulfuric acid; also, the silver salt method). This accounts for the low yield in the case of the benzyl ester. Attempts to prepare the diethylamino-ethyl ester are now in progress.

The importance of the benzoyl group in local anesthetics (for example, cocaine and benzoyl carbinol) led us to prepare the benzoyl derivative of the ethyl ester of *p*-hydroxymethyl-benzoic acid. By reducing the nitrobenzoyl derivative, we obtained the aminobenzoate in which we might expect to be combined the anesthetic properties of benzyl alcohol, ethyl benzoate and ethyl *p*-aminobenzoate.

The urethan and phenylurethan were prepared with the idea that they might also be pharmacologically active, especially as hypnotics.

Experimental Part

Preparation of *p*-Cyanobenzyl Bromide.—One hundred g. of *p*-tolyl cyanide was placed in a Soxhlet flask heated by an oil-bath. By means of a three-way tube, a drop-

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[8] Hjort and Kaufmann, *Proc. Soc. Exptl. Biol. Med.*, **17**, 79 (1919).

[9] Hirschfelder, Lundholm and Norrgard, *J. Pharmacol.*, **15**, 261 (1920).

[10] Hill and H. S. Johnson, unpublished thesis.

[11] Hill and Nicholas, unpublished thesis.

ping funnel, reflux condenser, and mechanical stirrer were attached. The contents of the flask, heated to 180°, were exposed to bright sunlight, and 150 g. of bromine was allowed to run in as fast as it became decolorized. The addition was complete in one hour, but the stirring was continued for one-half hour longer. The liquid was then allowed to cool, the solid washed with water, and crystallized twice from alcohol; yield of pure product, 78 g., or 46.5%; m. p., 115–116°.

Preparation of *p*-Hydroxymethyl-benzoic Acid.—Twenty g. of *p*-cyanobenzyl bromide was digested on the water-bath with 400 cc. of concd. hydrochloric acid for ten hours. The mixture was cooled and the crude acid filtered off. It was dissolved in dil. ammonium hydroxide, the solution filtered from impurities, and reprecipitated with concd. hydrochloric acid. The acid thus obtained was recrystallized from water; yield, 14 g., or 90%; m. p., 179–180°.

Esters of *p*-Hydroxymethylbenzoic Acid.—A series of homologous esters was prepared by dissolving the acid in an excess of the alcohol, adding a small amount of sulfuric acid, and refluxing on the steam-bath for four hours. The reaction mixture was then extracted with ether, washed with saturated sodium bicarbonate solution, dried and distilled. The results of the various esterification reactions are given in Table I.

TABLE I

ESTERS OF PARA-HYDROXYMETHYL-BENZOIC ACID

				H		C	
Ester	B. p. °C.	Press. Mm.	Yield %	Calcd. %	Found %	Calcd. %	Found %
Ethyl	161–163	5	81	6.67	6.84	66.67	66.47
Propyl	164–165	4	82	7.22	7.07	68.04	68.25
n-Butyl	169–174	3	71	7.69	7.97	69.23	68.99
*iso*Butyl	169–172	5	77	7.69	7.72	69.23	69.51
Benzyl	(m. p.) 63		6	5.79	5.85	74.38	74.38

In an effort to increase the yield of the benzyl ester, several other esterification methods were tried, as described.

1. Aqueous Sodium Carbonate Method.[12]—Ten g. of *p*-hydroxymethyl-benzoic acid was dissolved in a solution of 3.5 g. of sodium carbonate in 100 cc. of water, and treated with 8 g. (1 molecular equivalent) of benzyl chloride. The mixture was heated for five hours in an oil-bath at 110–115° and constantly stirred. On cooling, 5 g. of unchanged *p*-hydroxymethyl-benzoic acid precipitated. The oily filtrate was dissolved in ether, the solution washed with sodium carbonate solution, and dried. After removal of the ether, the residue was fractionally distilled. The fraction boiling at 200–210° (2 mm.) formed a white solid in the receiver. It was crystallized from a mixture of ether and petroleum ether; m. p., 63°; yield, 1 g.

2. By Direct Union of Acid and Alcohol.[13]—Eight g. of *p*-hydroxymethyl-benzoic acid was heated at 245° for two hours with 5.7 g. of benzyl alcohol (1 molecular equivalent) in a small flask provided with an air condenser. The mixture was then extracted with ether, washed with sodium carbonate solution and dried. During the extraction some alkali-insoluble material appeared, due no doubt to the reaction of the acid with itself. The residue from the ether solution was distilled in a vacuum, the fraction boiling at 210–220° (4 mm.) being recrystallized from a mixture of ether and petroleum ether; yield, 1.2 g.

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[12] Gomberg, THIS JOURNAL, **42,** 2062 (1920).

[13] Thompson and Leuck, *ibid.*, **44,** 2894 (1922).

3. Silver Salt Method.—Sixteen g. of the silver salt of *p*-hydroxymethyl-benzoic acid was digested on the steam-bath for four hours with 50 cc. of an absolute ether solution of benzyl bromide. The ether solution was filtered, washed with sodium bicarbonate solution, dried and distilled. From the fraction boiling at 210–230° (3–5 mm.), 1 g. of benzyl ester was obtained. A large amount of high-boiling material was discarded. This was no doubt an ether-ester similar to those obtained by Purdie and Lander[14] from the silver salts of malic and lactic acids.

THE BENZOATE OF THE ETHYL ESTER, *p*-$C_6H_5COOCH_2C_6H_4COOC_2H_5$.—Ten g. of ethyl *p*-hydroxymethyl-benzoate was dissolved in 100 cc. of absolute ether and refluxed with 8 g. of benzoyl chloride (1 molecular equivalent) and 8 g. of dry sodium carbonate for four hours. After removal of the sodium carbonate by filtration, the ether solution was washed with a 5% aqueous solution of sodium carbonate, dried, and the residue from evaporation distilled in a vacuum. The benzoyl derivative distilled at 203–207° (3 mm.) as a heavy, colorless oil insoluble in water; yield, 5.5 g., or 35%.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.83; H, 5.63. Found: C, 72.10; H, 5.37.

THE *p*-NITROBENZOATE OF THE ETHYL ESTER, *p*-$NO_2C_6H_4COOCH_2C_6H_4COOC_2H_5$.—A solution of 13 g. of ethyl *p*-hydroxymethyl-benzoate and 15 g. of nitrobenzoyl chloride in 30 g. of pyridine was allowed to stand for ten minutes. The resulting mass was washed with 1–1 hydrochloric acid, and extracted with ether. The ethereal solution was washed twice with 5% sodium carbonate solution, then with water and dried. The residue from the evaporation of the ether was crystallized from alcohol, from which it separated in light yellow crystals; m. p., 86°; yield, 18.5 g., or 77%. It is insoluble in water.

Anal. Calcd. for $C_{17}H_{15}O_6N$: C, 61.99; H, 4.59. Found: C, 61.92; H, 4.92.

THE *p*-AMINOBENZOATE OF THE ETHYL ESTER, *p*-$NH_2C_6H_4COOCH_2C_6H_4COOC_2H_5$. HYDROCHLORIDE.—Eight g. of the nitrobenzoate described above was dissolved in a mixture of 160 cc. of alcohol and 20 cc. of water, and the solution refluxed on the steam-bath for one hour with 4 g. of aluminum amalgam. The aluminum hydroxide was filtered off, the alcoholic solution poured into water, the precipitate filtered off, dried, and dissolved in dry ether. On passing dry hydrogen chloride into the ether solution, a white solid precipitated which, on recrystallization from absolute alcohol, melted gradually at 198–203°. It is soluble in alcohol, and very slightly soluble in water. On boiling with water it is converted into the free base.

Anal. Calcd. for $C_{17}H_{18}O_4NCl$: Cl, 10.58. Found: 10.43.

FREE BASE.—The hydrochloride was boiled with a 5% solution of sodium carbonate. The solution was cooled, and the resulting brown solid filtered off. After recrystallization from a mixture of petroleum ether and benzene, this substance melted at 95°. It is insoluble in water, but soluble in alcohol.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.69. Found: C, 68.32; H, 5.98.

The Urethan of Ethyl *p*-Hydroxymethyl-benzoate, *p*-$NH_2COOCH_2C_6H_4COOC_2H_5$.—Seven g. of ethyl *p*-hydroxymethyl-benzoate was poured into the liquid phosgene obtained from 50 g. of a 20% toluene solution. The mixture was allowed to warm slowly to room temperature, and was then heated on the steam-bath for five hours, while a current of air was passed through it. The liquid, which could be crystallized on cooling, was poured into a cooled, saturated solution of ammonia in benzene. Ether was then added, and the precipitated ammonium chloride filtered off. The residue from the evaporation of the ether was recrystallized from a mixture of benzene and petroleum ether; m. p., 119°. It is soluble in alcohol and insoluble in water.

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[14] Purdie and Lander, *J. Chem. Soc.*, **73**, 287 (1898).

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.19; H, 5.83. Found: C, 59.17; H, 6.18.

The Phenyl-urethan of Ethyl *p*-Hydroxymethyl-benzoate, *p*-$C_6H_5NHCOOCH_2$-$C_6H_4COOC_2H_5$.—A mixture of 7 g. of ethyl *p*-hydroxymethyl-benzoate and 5 g. (one molecular equivalent) of phenyl isocyanate was heated on the steam-bath for one hour. On cooling, the contents of the flask solidified. The colorless solid was soluble in alcohol and benzene, and insoluble in water. Recrystallized from a mixture of benzene and petroleum ether, it melted at 107°; yield, 10.5 g., or 80%.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.23; H, 5.69. Found: C, 68.22; H, 6.03.

Pharmacological tests of these substances are now in progress.

Summary

1. A new and convenient synthesis of *p*-hydroxymethyl-benzoic acid is described.

2. A series of esters of this acid of possible value as local anesthetics has been prepared. These consist of (a) simple esters obtained by esterifying the carboxyl group; (b) esters (such as the benzoate derivatives and urethans) derived from the hydroxyl group of the ethyl ester of the acid.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

PLATINUM AND PALLADIUM OXIDES AS CATALYSTS IN THE REDUCTION OF ORGANIC COMPOUNDS. IX. THE REDUCTION OF OLEFINS[1]

BY J. W. KERN[2] AND R. L. SHRINER WITH ROGER ADAMS

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The conversion of ethylene compounds into their corresponding ethane derivatives is not always readily accomplished by chemical reagents. The advantage of hydrogenation by catalysis, since it is general in application and quantitative, has been recognized by numerous investigators[3] and many types of compounds have been successfully hydrogenated by means of nickel, platinum or palladium. Most of these reductions have been made at high temperatures (usually 180° for hydrogenation in the gaseous phase or at the boiling point of some solvent when hydrogenating in solution) and in no case has a careful, complete study of the reduction of different types of ethylenic compounds been made. Frequently the reductions reported in the literature were carried out on small amounts of material with large amounts of catalyst and were, for the most part, time

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[1] Part of the platinum and palladium used in this investigation was purchased with the aid of a grant from the Bache Fund of the National Academy of Sciences. For this aid the authors are greatly indebted.

[2] This communication is an abstract of theses submitted by J. W. Kern and R. L. Shriner in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[3] See "Catalysis in Organic Chemistry" by Sabatier, translated by Reid, D. Van Nostrand Co., 1922.