## Summary

1. The sodium salts of *m*-arsanilic, *p*-arsanilic and 3-methyl-4-amino-phenylarsonic acids were condensed with the three isomeric nitrobenzoyl chlorides.

2. By reduction with ferrous hydroxide the nitrobenzoyl-amino-phenylarsonic acids were converted into aminobenzoyl-amino-phenyl-arsonic acids.

3. *Sym.-bis*-arsono-aryl-benzamido-ureas were obtained by condensing various aminobenzoyl-amino-phenylarsonic acids with phosgene.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF MIAMI UNIVERSITY]

# THE PROPERTIES OF ARYL ESTERS AND ETHERS OF N- PIPERIDINO ALKYL COMPOUNDS

BY HARVEY C. BRILL

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In the preparation of synthetic bodies with anesthetic properties similar to those of cocaine, the attention of the investigators has usually been focused on the relative positions of the basic and the carboxyl groups.[1]

The application of this principle has resulted in the preparation of a considerable number of excellent compounds which function as substitutes for cocaine and tropacocaine for anesthetic purposes.

The presence of the piperidine residuum in cocaine and tropacocaine and its possible part in the production of the desirable properties of these two alkaloids have more generally been ignored in the synthesis of new cocaine substitutes. J. v. Braun[2] has prepared a substance, in his eccaine, of a constitution that departs from that of cocaine and tropacocaine in that the alkylbenzoate is attached to the nitrogen of the ecgonine portion instead of to a carbon as in cocaine. This compound has anesthetic properties similar to those of cocaine.[3] Pyman[4] has used piperidine itself without the substituting groups in the preparation of the hydrochloride of β-N-piperidino-ethyl benzoate. This compound he found to possess anesthetic properties but to be irritating. The properties of these two substances indicate that the piperidine residuum can take the place of the alkylamine group in the preparation of Procaine-like compounds. In order to test this relationship somewhat more thoroughly, the salts of γ-N-piperidino-propyl benzoate, γ-N-piperidino-propyl phenyl ether, and β-N-piperidino-ethyl phenyl ether were prepared, and their properties studied.

[1] Kamm, THIS JOURNAL, **42**, 1030 (1920).

[2] J. v. Braun and Müller, *Ber.*, **51**, 235 (1918).

[3] Fraenkel, "Die Arzneimittel Synthese," Julius Springer, Berlin, 5th ed., **1921**, p. 355.

[4] Pyman, *J. Chem. Soc.*, **93**, 1793 (1908).

## Experimental Part

**The Hydrochloride of γ-N-Piperidino-propyl Benzoate,** $C_5H_{10}NCH_2CH_2CH_2OCOC_6H_5.HCl$.—A mixture of 8.5 parts of piperidine with 9.4 parts by weight of γ-chloropropyl alcohol is heated until the reaction is complete. The base is obtained from the hydrochloride by the addition of sodium hydroxide, extracted with ether, dried and distilled. The distillate, γ-N-piperidino-propyl alcohol was collected between 228° and 232°.[5] The boiling point given by Gabriel and Colman for this compound is 228° while Laun gives 194°. The latter has prepared γ-N-piperidino-propyl benzoate but does not record its properties. One part by weight of the γ-N-piperidino-propyl alcohol was dissolved in dry, cold benzene and one part by weight of cold benzoyl chloride added. The reaction began at once and after several hours was completed by warming the mixture on the water-bath. The hydrochloride precipitates from the benzene solvent as a white, needle-like, crystalline mass, that melts at 192° when recrystallized from alcohol. It is readily soluble in water, fairly soluble in alcohol and only slightly in ether and benzene.

*Anal.* Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.94. Found: 4.85.

The base, γ-N-piperidino-propyl benzoate, prepared from the hydrochloride by means of alkali, is a liquid at room temperature, very slightly soluble in water, but quite soluble in ether, benzene and alcohol. Both it and the salt have anesthetic properties.

**The Hydrochloride of β-N-Piperidino-ethyl Phenyl Ether,** $C_5H_{10}NCH_2CH_2OC_6H_5.HCl$.—A mixture of 5 parts by weight of β-bromo-ethyl phenyl ether and 2 parts of piperidine, using alcohol as the solvent, was warmed on the steam-bath for four hours. As the mixture cooled, the hydrobromide of β-N-piperidino-ethylphenyl ether separated in the form of white, needle-like crystals. An additional amount can be caused to separate by the addition of ether to the mother liquor. This salt is practically as soluble in alcohol as it is in water; m. p., 168°.

The base, β-N-piperidino-ethylphenyl ether is prepared in the usual manner, and is a liquid at room temperature. It is converted into the hydrochloride salt by passing dry hydrogen chloride into the alcoholic solution; m. p., 180°. Both the hydrobromide and the hydrochloride have pronounced anesthetic effects. The effect of the hydrobromide is somewhat more irritating than that of the hydrochloride.

*Anal.* Calcd. for $C_{13}H_{20}ONCl$: N, 5.80. Found: 5.91.

**The Hydrochloride of γ-N-Piperidino-propyl Phenyl Ether,** $C_5H_{10}NCH_2CH_2CH_2OC_6H_5.HCl$.—The hydrochloride, hydrobromide and free base were prepared in the same manner as those of the homolog just described. It has been prepared by Gabriel and Stelzner[6] by the reaction of piperidine with γ-chloropropyl phenyl ether with rather poor yield; by J. v. Braun[7] from piperidine and γ-iodopropyl phenyl ether. The free base is somewhat gelatinous at room temperature. The melting point of the hydrobromide is 160°, and of the hydrochloride of γ-N-piperidino-propylphenyl ether is 179°. The solubilities are the same as those of the corresponding, preceding compounds. The hydrochloride seems somewhat stronger in its anesthetic effects than the hydrobromide.

*Anal.* Calcd. for $C_{14}H_{22}ONCl$: N, 5.09. Found: 5.14.

## Summary

Methods of preparation for, and the properties of (1) γ-N-piperidino-propyl alcohol, (2) γ-N-piperidinopropyl benzoate (3) its hydrochloride

[5] Gabriel and Colman, *Ber.*, **40**, 425 (1907). Laun, *Ber.*, **17**, 680 (1884).

[6] Gabriel and Stelzner, *Ber.*, **29**, 2381 (1896).

[7] v. Braun, *Ber.*, **42**, 2040 (1909). See also Ger. pat. 184,196.

(4) β-N-piperidino-ethyl phenyl ether (5) its hydrochloride, and (6) its hydrobromide (7) γ-N-piperidinopropyl phenyl ether (8) its hydrobromide, and (9) its hydrochloride are discussed. Of these compounds, 2, 3, 4, 5, 6, 7, 8 and 9 have anesthetic properties.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

# SOME REACTIONS OF SUBSTITUTED MERCAPTOMAGNESIUM HALIDES

BY HENRY GILMAN AND W. BERNARD KING[1]

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## Introduction

The reaction between organomagnesium halides and organic sulfur compounds is generally associated with the intermediate formation of the mercaptomagnesium halide group (—SMgX). In connection with studies concerned with the mechanism of reaction and the proof of structure, it was necessary to find some reliable reagent that will replace the —MgX group attached to sulfur by another in order to get a compound that lends itself to ready identification. Accordingly, a study has been made of the reactions of several substituted mercaptomagnesium halides with some compounds that undergo ready reaction with the more commonly known Grignard reagents. Some of the results, as might have been predicted, have been extended successfully to the chemistry of the —OMgX group.

Although many reactions have been carried out between organic sulfur compounds and the Grignard reagent, comparatively little work has been done on the chemistry of mercaptomagnesium halides. Taboury,[2] in connection with the reaction between RMgX compounds and sulfur, treated the intermediate mercaptomagnesium halides with various reagents. With acid halides and acid anhydrides the —MgX group was replaced by acyl, giving the corresponding thiol esters (RCOSR); with alkyl halides, particularly the iodides, and with dimethyl sulfate the —MgX group was replaced by an alkyl group, giving the corresponding sulfides. Houben and Schultze[3] treated the bromomagnesium salts of dithio acids (RCSSMgBr) with acid halides and obtained mixed anhydrides of the dithio and carboxylic acids ($RCS_2COR$). In earlier work, Houben and Pohl[4] suggested the probable formation of thioketones and mercaptans from the reaction between RCSSMgX and an excess of Grignard reagent.

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[1] This paper is an abstract of a thesis presented by W. Bernard King in partial fulfilment of the requirements for the degree of Master of Science in Chemistry at Iowa State College.

[2] Taboury, *Ann. chim. phys.*, [8] **15,** 5 (1908). This paper comprises essentially all of the earlier work reported by him in the *Bull. soc. chim.*, **29,** 761 (1903); **31,** 646, 1183 (1904); **33,** 836 (1905); **35,** 668 (1906); and in the *Compt. rend.*, **138,** 982 (1904).

[3] Houben and Schultze, *Ber.*, **43,** 2481 (1910); also *Ber.*, **44,** 3226 (1911). N. J. Beaber in this Laboratory has prepared ethyl dithiobenzoate from bromomagnesium dithiobenzoate ($C_6H_5CS_2MgBr$) and diethyl sulfate.

[4] Houben and Pohl, *Ber.*, **39,** 3219 (1906).