[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

PIPERIDINE DERIVATIVES IV. SUBSTITUTED PIPERIDINE-ALKYL BENZOATES AND PARA-AMINOBENZOATES

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The numerous investigations of the amino-alkyl benzoate type of local anesthetics have produced a few compounds in which the piperidine nucleus comprises the amino group. Pyman[1] prepared piperidyl[2] ethylbenzoate. It was found to have local anesthetic properties but a rather high toxicity. Brill[3] prepared N-piperidinopropylbenzoate and mentioned that it had local anesthetic properties. Recently the piperidino-ethyl esters of propylaminobenzoic acid and methoxy-ethylaminobenzoic acid have been described[4] as local anesthetics. Since the completion of the work described below, Barnes and Adams[5] have described the *p*-aminobenzoates of N-(β-hydroxy-ethyl)-piperidine, N-(γ-hydroxypropyl)-piperidine, β-(β-carbomethoxypiperidyl)-ethyl alcohol and γ-(β-carbomethoxypiperidyl)-propyl alcohol. They were local anesthetics, the substituted piperidine derivatives being less effective than the unsubstituted.

It seemed probable that the presence of certain substituent groups in the piperidine nucleus of such compounds would produce a definite effect on their physiological properties. Accordingly, a number of substituted piperidino-alkylbenzoates were prepared and submitted for pharmacological study. These compounds do not form a well-defined series, but are merely some of the possible types that offered a particular preparational advantage on account of the availability of the necessary substituted piperidines. Work is at present under way which will, it is hoped, sufficiently complete the various indicated series to point to some fairly definite conclusions relative to the effect of structure on physiological action.

This paper deals with the preparation and the preliminary pharmacological study of the following compounds: γ-piperidinopropylbenzoate (I), γ-2-methylpiperidinopropylbenzoate (II), γ-2-propylpiperidinopropylbenzoate (III), γ-3-methylpiperidinopropylbenzoate (IV), β-3-methylpiperidino-ethylbenzoate (V), γ-3-carbethoxypiperidinopropylbenzoate (VI),

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

[2] The nomenclature used in this paper is that suggested by Meyer and Jacobson and designates as "piperidino" the radical formed by dropping the hydrogen from the nitrogen atom of piperidine and as "piperidyl" the radical formed by droppping a hydrogen from one of the carbon atoms of piperidine. By this nomenclature Pyman's compound would be "piperidino-ethyl benzoate."

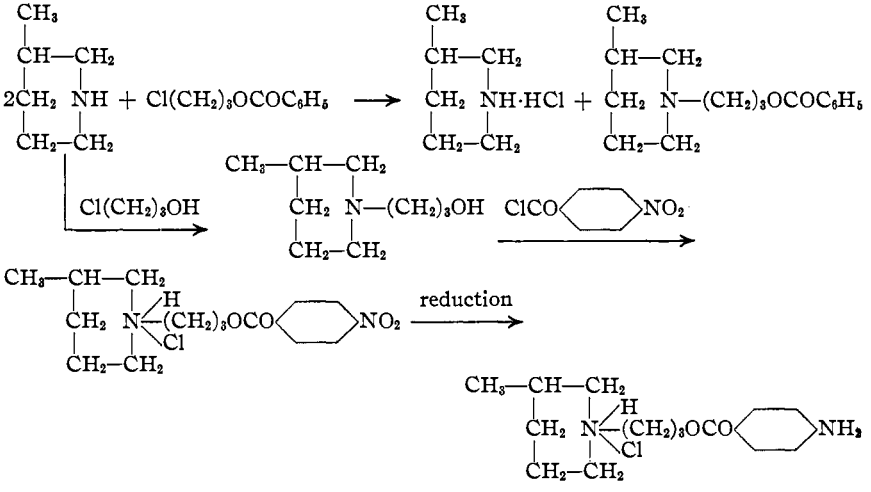
[3] Brill, THIS JOURNAL, **47**, 1134 (1925).

[4] Brit. pat. 241,767; *C. A.*, **20**, 3539 (1926).

[5] Barnes with Adams, THIS JOURNAL, **49**, 1307 (1927).

γ-piperidinopropyl-*p*-aminobenzoate (VII), γ-3-methylpiperidinopropyl-*p*-aminobenzoate (VIII), γ-3-carbethoxypiperidinopropyl-*p*-aminobenzoate (IX). The unsubstituted piperidino derivatives (I and VII) were included in the above list for comparison. All of these substances were isolated and used as the hydrochlorides.

The benzoates were most conveniently prepared by the condensation of the substituted piperidine with a chloro-alkylbenzoate. The *p*-aminobenzoates were prepared by first condensing the piperidine with trimethylene chlorohydrin, acylating the resulting piperidinopropyl alcohol with *p*-nitrobenzoyl chloride, and finally reducing the resulting *p*-nitrobenzoate catalytically to the *p*-aminobenzoate. These reactions are represented with 3-methylpiperidine, thus



A marked difference in the reactivity of the 2 substituted piperidines and the 3 substituted piperidines was noted in the above condensation. The 3-methyl- and 3-carbethoxypiperidines reacted practically completely with γ-chloropropylbenzoate when heated for twenty to thirty minutes at 100°. The amount of reaction was determined by the quantity of the hydrochloride of the secondary amine that was obtained when the reaction mixture was diluted with ether. Under the same conditions there was hardly any reaction between the 2-methyl- or 2-propylpiperidine and the chloro ester. It was found necessary to heat these reactants for one to three hours at temperatures of 125–150° in order to produce a satisfactory reaction.

Experimental

3-Carbethoxypiperidine (ethyl nipecotate).—This compound was prepared by the procedure described by McElvain and Adams.[6]

[6] McElvain and Adams, THIS JOURNAL, **45**, 2745 (1923).

3-Methylpiperidine.—3-Methylpyridine (β-picoline) was prepared from glycerol ammonium phosphate and phosphorus pentoxide according to the method of Schwarz.[7] The hydrochloride was prepared and reduced catalytically, using the same procedure as that employed for the preparation of 3-carbethoxypiperidine. The 3-methylpiperidine so obtained boiled at 123–126°.

2-Methylpiperidine.—2-Methylpyridine (α-picoline) was isolated from the picoline fraction of coal tar bases which boiled at 127–132° by the method of Heap, Jones and Speakman.[8] It was reduced in a manner similar to that used for 3-methylpyridine. The 2-methylpiperidine boiled at 114–116°.

2-Propylpiperidine.—This base was obtained by the action of aqueous sodium hydroxide on a sample of Merck's coniine hydrobromide. After drying it boiled at 164–166°.

Substituted Piperidino-alkylbenzoate Hydrochlorides.—The general procedure for the preparation of these compounds consisted of heating together 2 molecular equivalents of the secondary amine (a substituted piperidine) and 1 molecular equivalent of the chloro-alkyl benzoate. The reaction mixture was cooled, diluted with several volumes of ether and the precipitated secondary amine hydrochloride filtered off. From the ether solution the tertiary amine was precipitated with dry hydrogen chloride as the hydrochloride, which was further purified by recrystallization from an alcohol-ether mixture.

There was a marked difference between the condensations of the 2 substituted piperidines and those of the other piperidines which were used with the chloro ester. It was found that the unsubstituted piperidine and 3 substituted piperidines condensed quite completely with the chloro ester in twenty to thirty minutes at 100°, while the 2 substituted piperidines required temperatures of 125–150° for two to three hours. Even under these conditions the condensations of the 2 substituted piperidines were sufficiently incomplete to cause considerable secondary amine hydrochloride to be mixed with the tertiary amine hydrochloride. In such cases it was necessary to treat the mixed hydrochlorides with dilute aqueous sodium hydroxide and shake the resulting aqueous suspension of the free bases with benzoyl chloride. The tertiary amine was then extracted from this

TABLE I

SUBSTITUTED PIPERIDINO-ALKYLBENZOATE HYDROCHLORIDES

Piperidino-alkyl group	M. p., °C.	Analyses, Cl, % Calcd.	Found
γ-Piperidinopropyl	186–188[a]	12.52	12.58
γ-2-Methylpiperidinopropyl	167–169	11.93	11.96
γ-2-Propylpiperidinopropyl	184–186	10.90	10.84
γ-3-Methylpiperidinopropyl	178–180	11.93	11.90
β-3-Methylpiperidino-ethyl	134–136	12.52	12.72
γ-3-Carbethoxypiperidinopropyl	161–163	10.01	10.10

[a] Brill (ref. 3) describes this compound as melting at 192°.

[7] Schwarz, *Ber.*, **24**, 1676 (1891).

[8] Heap, Jones and Speakman, THIS JOURNAL, **43**, 1936 (1921).

reaction mixture with ether and reprecipitated as the hydrochloride. This treatment, followed by recrystallizations from an alcohol-ether mixture, gave quite pure products. The yields of the recrystallized products in the case of the 2 substituted piperidino compounds were 35–40%, while in the case of the piperidino and 3 substituted piperidino compounds they amounted to 60–65%.

γ-Substituted Piperidinopropyl-*p*-nitrobenzoate Hydrochlorides.—Two molecular equivalents of the piperidine and 1 molecular equivalent of trimethylene chlorohydrin were heated together at 100° for thirty minutes. The reaction mixture was cooled, treated with several volumes of ether and the precipitated secondary amine hydrochloride filtered off. The piperidinopropyl alcohol was precipitated from the ether solution as the hydrochloride, the ether decanted off and the precipitate, a sirupy, amorphous mass, dried under diminished pressure at 150° for twenty minutes. To this dried hydrochloride 1.5 molecular equivalent of *p*-nitrobenzoyl chloride was added and the mixture heated until the evolution of hydrogen chloride had ceased. The reaction mixture was cooled, diluted with ether and the precipitate allowed to crystallize. Recrystallizations from an alcohol-ether mixture gave pure products. The yields were 50–63%.

TABLE II

γ-SUBSTITUTED PIPERIDINOPROPYL-*p*-NITROBENZOATE HYDROCHLORIDES

Piperidinopropyl group	M. p., °C.	Analyses, Cl, % Calcd.	Found
γ-Piperidinopropyl	201–203	10.80	10.68
γ-3-Methylpiperidinopropyl	190–192	10.36	10.46
γ-3-Carbethoxypiperidinopropyl	177–179	8.86	9.03

γ-Substituted Piperidinopropyl-*p*-aminobenzoate Hydrochlorides.—A solution of 15 g. of the piperidinopropyl-*p*-nitrobenzoate hydrochloride in 150 cc. of absolute alcohol was reduced catalytically with 0.2 g. of catalyst by the method which has been described for the 1-alkyl-3-carbethoxy-4-piperidyl-*p*-nitrobenzoates.[9] After reduction the solvent was evaporated off and the remaining monohydrochloride of the *p*-aminobenzoate recrystallized from an alcohol-ether mixture. The yields were 65–75%.

TABLE III

γ-SUBSTITUTED PIPERIDINOPROPYL-*p*-AMINOBENZOATE HYDROCHLORIDES

Piperidinopropyl group	M. p., °C.	Analyses, Cl, % Calcd.	Found
γ-Piperidinopropyl	214–216	11.90	12.05
γ-3-Methylpiperidinopropyl	158–160	11.03	10.90
γ-3-Carbethoxypiperidinopropyl	113–115	9.64	9.90

Pharmacological Report

These anesthetics are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A brief report of a portion of this work is included in this paper.

The anesthetic efficiencies were determined in the usual way by the application of a 2% solution of the anesthetic to the rabbit's cornea and

[9] McElvain, THIS JOURNAL, **48**, 2240 (1926).

noting the duration of anesthesia. The toxicities were determined by subcutaneous injection into white mice and also by intravenous injection into white rats. The toxicity values for the maximum tolerated dose and the minimum lethal dose are expressed in milligrams per kilogram body weight of the animals. The results of these pharmacological studies are summarized in Table IV and the various anesthetics are designated by the Roman numerals which accompany them in the introductory portion of the paper. The corresponding values for cocaine and procaine are included for comparison.

TABLE IV

PHARMACOLOGICAL DATA

Compound	Average duration of anesthesia, min.	Subcutaneous toxicity to white mice (mg./kg.) M. T. D.	M. L. D.	No. of mice used	Intravenous toxicity to white rats (mg./kg.) M. T. D.	M. L. D.	No. of rats used
I	0	400	450	8	15	17.5	10
II	15	800	900	21	15	17.5	9
III	8	600	700	20	7.5	10	10
IV	11	450	500	7	20	25	9
V	0	3000	3500	29	25	30	11
VI	0	750	800	18	30	35	8
VII	0	50	100	10	7.5	10	11
VIII	10	200	250	13	25	30	17
IX	0	1200	1300	19	30	35	10
Cocaine	29	200	250	18	15	17.5	12
Procaine	0	900	1000	17	45	50	10

Discussion of the Pharmacological Data

It is interesting to note that the only compounds in the above group that show any mucous membrane anesthesia are those in which an alkyl group is substituted in the piperidine nucleus. Those compounds (VI and IX), containing a carbethoxy substituent in the piperidine nucleus show no anesthetic action towards mucous membranes. These findings correspond to those of Barnes and Adams[5] for the analogous 3-carbomethoxypiperidino derivative. The difference between the anesthetic action of Compounds IV and V is striking. Compound IV, which is γ-3-methylpiperidino-propylbenzoate, possesses distinct local anesthetic action, while the β-3-methylpiperidino-ethylbenzoate (V) shows no such action. Apparently this loss of anesthetic effect is caused in V by decreasing the number of methylene groups between the nitrogen and the benzoyl group from three to two.

Very few generalizations can be made from the toxicity data for this group of compounds. It is apparent that the substituted piperidino derivatives are less toxic than the corresponding unsubstituted piperidino derivatives. With the exception of IX, the p-aminobenzoates are more toxic subcutaneously than the corresponding benzoates. The same difference

was observed between the 1-alkyl-3-carbethoxy-4-piperidylbenzoates and *p*-aminobenzoates.[10] In the above data there does not seem to be much correlation between the subcutaneous and absolute (intravenous) toxicities.

Summary

1. Several substituted piperidino-alkylbenzoates and *p*-aminobenzoates have been prepared and described.

2. The alkyl substituted piperidino compounds which contain three methylene groups between the piperidine nitrogen and the benzoyl group possess local anesthetic action, while the corresponding unsubstituted and carbethoxy substituted piperidino derivatives show no local anesthetic activity.

3. In general, the substituted piperidino derivatives are less toxic than the corresponding unsubstituted piperidino derivatives.

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THE MERCURATION OF *o*-NITROPHENOL

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Iodination of *o*-nitrophenol by the aid of yellow mercuric oxide was found by the author[1] to take place preferentially in the 4 as compared with the 6 position whether the medium employed was alcohol or glacial acetic acid, and in addition considerable di-iodination took place even when a deficiency of iodine was used. In consequence it became of interest to ascertain whether mercuration would exhibit a like preference.

Previous work on this subject by Hantzsch and Auld[2] established that when an alcoholic solution of *o*-nitrophenolate (1 mole) and aqueous mercuric acetate (1 mole) were boiled together, the mono-mercuri product formed yielded *p*-bromo-*o*-nitrophenol when brominated, thereby establishing mercuration in the 4 position. Later Raiziss and Proskouriakoff[3] proved that considerable dimercuration occurred under the above conditions and, although the various products were not orientated by them, tacit assumption of mercuration in the 4 position was made for the mono-mercuri products.

In the present investigation mercuration has been effected both by fusion of *o*-nitrophenol with mercuric acetate and also according to the directions of Raiziss and Proskouriakoff. In the former case marked

[10] McElvain, THIS JOURNAL, **48**, 2184, 2241 (1926).

[1] Hodgson, *J. Chem. Soc.*, **1927**, 1141.

[2] Hantzsch and Auld, *Ber.*, **39**, 1105 (1906).

[3] Raiziss and Proskouriakoff, THIS JOURNAL, **44**, 787 (1922).