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

PIPERIDINE DERIVATIVES. III. 1-ALKYL-3-CARBETHOXY-4-PIPERIDYL PARA-AMINOBENZOATES

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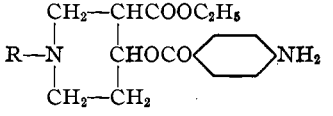
In a previous paper[1] the preparation and pharmacological properties of a series of 1-alkyl-3-carbethoxy-4-piperidyl benzoates were described. Some of these substances were quite active local anesthetics with very low toxicities. There was, however, an objectionable property encountered in their use in the fact that the aqueous solutions of their halogen acid salts showed an acid reaction to litmus. This property caused considerable irritation and hyperemia in the rabbit's cornea and, as was pointed out at that time, possibly tended to shorten the duration of anesthesia.

It seemed probable that this undesirable property would not be present in the 1-alkyl-3-carbethoxy-4-piperidyl *p*-aminobenzoates if they were used as the monohydrochlorides. Accordingly, a series of these substances with the general formula



was synthesized. This paper deals with the preparation and a preliminary pharmacological study of the compounds in which **R** is methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*butyl and *iso*-amyl.

The method of synthesis of these compounds was analogous to that which was used for the piperidyl benzoates,[1] except that *p*-nitrobenzoyl chloride instead of benzoyl chloride was used in the acylation of the 1-alkyl-3-carbethoxy-4-hydroxypiperidines. The piperidyl *p*-nitrobenzoates formed readily and offered no difficulties in crystallization.

The reduction of the nitro compounds to the corresponding amino derivatives was first accomplished by iron and hydrochloric acid. This procedure, however, was abandoned partly on account of low yields and mainly because catalytic reduction was found to be much more efficient for the conversion. The hydrochlorides of the *p*-nitrobenzoates in alcohol solution were completely reduced in a few minutes with Adams' platinum oxide-platinum black catalyst. Although this reduction yielded the monohydrochlorides directly, they were not isolated as such, but were converted into the dihydrochlorides because these salts were found to crystallize much more readily.

Experimental Part

1-Alkyl-3-carbethoxy-4-piperidyl *p*-Nitrobenzoate Hydrochlorides.—The amorph-

[1] McElvain, THIS JOURNAL, **48**, 2179 (1926).

ous residue obtained from the catalytic reduction of 10 g. of the 1-alkyl-3-carbethoxy-4-piperidone hydrochloride after the evaporation of the solvent was treated with 15 g. of *p*-nitrobenzoyl chloride. This mixture was heated in an oil-bath at 140–160° until the evolution of hydrochloric acid ceased. The resulting solution was then cooled, diluted with 200 cc. of ether and the oily precipitate allowed to crystallize in an ice box. This solidified precipitate was recrystallized from an alcohol-ether mixture. The yields were 50–70% of those theoretically possible from the piperidones.

TABLE I

1-ALKYL-3-CARBETHOXY-4-PIPERIDYL *p*-NITROBENZOATE HYDROCHLORIDES

Alkyl group	Formula	M. p., °C.	Cl, % Calcd.	Found
Methyl	$C_{16}H_{21}O_6N_2Cl$	193–195	9.54	9.38
Ethyl	$C_{17}H_{23}O_6N_2Cl$	214–216	9.20	9.18
n-Propyl	$C_{18}H_{25}O_6N_2Cl$	206–208	8.87	8.81
*iso*Propyl	$C_{18}H_{25}O_6N_2Cl$	203–205	8.87	8.73
n-Butyl	$C_{19}H_{27}O_6N_2Cl$	192–194	8.55	8.68
*iso*Butyl	$C_{19}H_{27}O_6N_2Cl$	204–206	8.55	8.44
iso-Amyl	$C_{20}H_{29}O_6N_2Cl$	167–169	8.28	8.20

1-Alkyl-3-carbethoxy-4-piperidyl *p*-Aminobenzoate Dihydrochlorides.—A solution of 5 g. of the 1-alkyl-3-carbethoxy-4-piperidyl *p*-nitrobenzoate hydrochloride in 100 cc. of 95% alcohol and 0.25 g. of Adams' platinum oxide catalyst were shaken with hydrogen at 2–2⅔ atmospheres' pressure. The reduction began at once and proceeded with such vigor that the mixture became warm. The calculated amount of hydrogen was absorbed in five to ten minutes. The first reductions were carried out with 5 cc. of acetic acid in the alcoholic solution of the nitro compound for the purpose of combining with the amino group as soon as it was formed, but it was found that this procedure was unnecessary, for the reduction took place just as satisfactorily without the acetic acid as with it. The catalyst was filtered off and the filtrate evaporated nearly to dryness under diminished pressure. The residue was dissolved in water and the free base precipitated with sodium carbonate. This free base was extracted with ether and reprecipitated from the ethereal solution as the dihydrochloride with dry hydrogen chloride. This precipitate was first allowed to solidify in an ice box and then recrystallized from an alcohol-ether mixture. The yields were 60–80% of those calculated.

TABLE II

1-ALKYL-3-CARBETHOXY-4-PIPERIDYL *p*-AMINOBENZOATE DIHYDROCHLORIDES

Alkyl group	Formula	M. p., °C.	Cl, % Calcd.	Found
Methyl	$C_{16}H_{24}O_4N_2Cl_2$	190–192	18.73	18.52
Ethyl	$C_{17}H_{26}O_4N_2Cl_2$	204–206	18.06	17.89
n-Propyl	$C_{18}H_{28}O_4N_2Cl_2$	221–223	17.45	17.31
*iso*Propyl	$C_{18}H_{28}O_4N_2Cl_2$	196–198	17.45	17.30
n-Butyl	$C_{19}H_{30}O_4N_2Cl_2$	228–230	16.86	16.84
*iso*Butyl	$C_{19}H_{50}O_4N_2Cl_2$	230–232	16.86	16.67
iso-Amyl	$C_{20}H_{32}O_4N_2Cl_2$	213–215	16.32	16.10

Pharmacological Studies[2]

The dihydrochlorides were dissolved in water and titrated with sodium hydroxide to the point of precipitation of the free base in order to form the

[2] The author is indebted to Mr. Ralph E. Jones of the Department of Pharmacology of the University of Wisconsin for these studies.

neutral monohydrochlorides. The durations of anesthesia and the toxicities were determined with the monohydrochloride solutions in the same manner as described for the 1-alkyl-3-carbethoxy-4-piperidyl benzoates. These *p*-aminobenzoates produced toxic symptoms similar to those of cocaine.

TABLE III

PHARMACOLOGICAL DATA

	Duration of anesthesia with 2% soln., min.				Toxicity to white mice, mg. per kg. body weight		
Alkyl group	Individual expts.			Av.	No. of mice	Max. tol. dose	Minimum lethal dose
Methyl	23	27	27				
	25	21		26	9	50	100
Ethyl	37	33	33				
	36	29	35	34	10	150	200
n-Propyl	33	36	33				
	37	34		35	17	200	250
*iso*Propyl	33	33	30				
	44	47	23	36	13	100	150
n-Butyl	32	53	37				
	33	55	43				
	40	43		43	34	450	550
*iso*Butyl	40	45	36				
	41	50	23	39	16	450	550
iso-Amyl	65	39	100				
	30	76	73				
	62	77		72	25	500	550
Cocaine	36	31	28				
	24	33	29				
	24	32	29	29	18	100	150

Discussion of the Pharmacological Data

From the above pharmacological report it is seen that the members of this series of piperidine derivatives exhibit the variations in physiological action that were noticed in the case of the 1-alkyl-3-carbethoxy-4-piperidyl benzoates. In both cases an increase in the size of the alkyl group attached to the piperidine nitrogen caused an increase in the duration of anesthesia and a decrease in toxicity. The members of the *p*-aminobenzoate series, however, showed decidedly greater durations of anesthesia and higher toxicities than the corresponding benzoates. The increase in anesthesia is probably explained in part by the fact that the solutions of the monohydrochlorides of the *p*-aminobenzoates that were used in the tests were neutral to litmus and caused no irritation or hyperemia in the rabbit's cornea. It does not seem possible to explain the increase in the toxicities at present, but it is hoped that future work will point to an explanation of this observation.

It is interesting to note that the 1-*iso*-amyl-3-carbethoxy-4-piperidyl *p*-aminobenzoate shows two and one-half times the anesthetic power and about one-fourth the toxicity of cocaine.

Summary

1. A series of 1-alkyl-3-carbethoxy-4-piperidyl *p*-aminobenzoates have been prepared and some of their properties noted.

2. These substances are local anesthetics. They show an increase in anesthetic action and a decrease in toxicity as the size of the alkyl group in the 1 position is increased. The *iso*-amyl derivative possesses two and one-half times the anesthetic power and about one-fourth the toxicity of cocaine.

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NOTE

The Melting Point of 4-Chloro-2,6-dibromo-aniline.—It was found necessary to prepare this compound in the course of an investigation recently undertaken and the melting point is recorded in the literature differently by different investigators; 97°[1] and 95°.[2] The melting point obtained by us was still different, so extreme care was used in establishing the correct temperature.

The compound was prepared by the bromination of pure *p*-chloroaniline (m. p., 71–72°) obtained from three different sources. Bromination was carried out both in aqueous solution and in glacial acetic acid. The compound was then recrystallized variably from dil. alcohol, absolute alcohol or glacial acetic acid. Four recrystallizations failed to change the melting point. The temperature was measured with two recently calibrated thermometers, one having a short stem with practically no stem correction. The melting point was established both by the cooling curve of a quantity of the material and by the usual method using a small tube. In every instance it was 92.9°, corrected.

It is believed that this should be reported since the melting points of the isomeric chlorodibromo-anilines are very close together, and the melting point in question is at present in considerable error.

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[1] Chattaway and Orton, *J. Chem. Soc.*, **79**, 816 (1901).

[2] Zincke, *Ann.*, **333**, 338 (1904).