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

PIPERIDINE DERIVATIVES. VII. 1-ALKYL-4-PIPERIDYL BENZOATES AND PARA-AMINOBENZOATES[1]

BY N. W. BOLYARD AND S. M. McELVAIN

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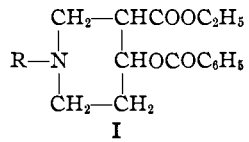
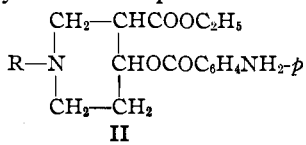
In previous communications[2] two series of piperidine derivatives, the 1-alkyl-3-carbethoxy-4-piperidyl benzoates (I) and the corresponding *p*-aminobenzoates (II) were described These substances are local anesthetics and it was shown that in both series an increase in size of the alkyl group attached to the nitrogen atom caused an increase in the anesthetic activity and a decrease in the toxicity of the compound.



I



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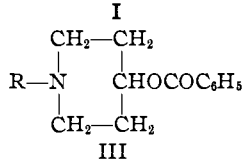
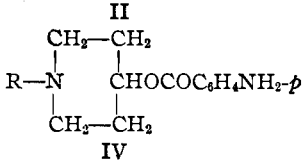
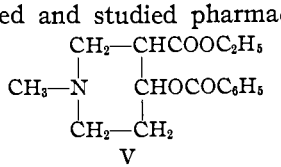


III

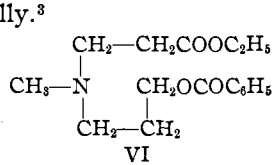


IV

It was desirable, it seemed, to continue the study of this type and to prepare two new series, the 1-alkyl-4-piperidyl benzoates (III) and *p*-aminobenzoates (IV). These compounds compared as to physiological activity with the former series would show the effect of the presence of the carbethoxy group in the molecule. They would also show whether or not the unusual relationship between the size of the alkyl group attached to the nitrogen and the pharmacological action of the compound that existed in Series I and II could be extended to another series of compounds. Still further relationship between structure and physiological action might be obtained by comparing the first member (where R is methyl) of Series III with 1-methyl-3-carbethoxy-4-piperidyl benzoate (V) and γ-(methyl-β-carbethoxy-ethyl)-aminopropyl benzoate (VI), which have already been described and studied pharmacologically.[3]



V



VI

[1] This paper is taken from the thesis submitted by N. W. Bolyard to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

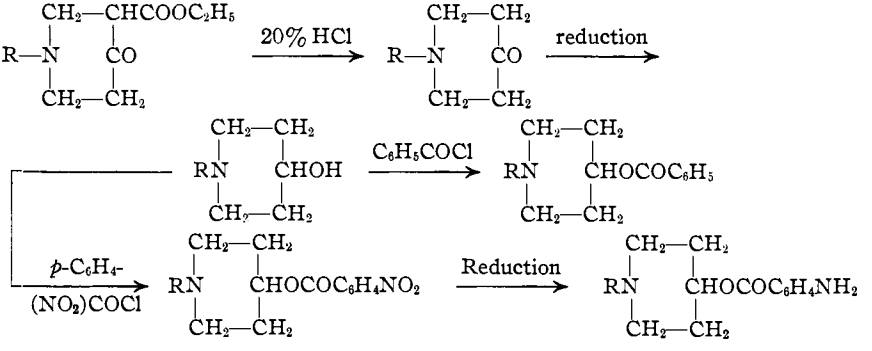
[2] McElvain, THIS JOURNAL, **48**, 2179, 2239 (1926).

[3] McElvain, *ibid.*, 46, 1721 (1924).

The pharmacological data indicated that VI was very much less active physiologically than V, from the standpoint of both toxic and anesthetic effects. It was suggested at the time that this difference might be due to the presence of the cyclic structure in V, or to the fact that V contained two points of asymmetry while VI contained none. Consequently it seemed that a pharmacological comparison of these compounds with 1-methyl-4-piperidyl benzoate, in which there is the same cyclic structure that is present in V but no points of asymmetry, would indicate which of these two points of difference was the more fundamental.

In the Series III and IV those compounds in which R is methyl, ethyl, *n*-propyl, *n*-butyl, *iso*-amyl and phenylethyl have been prepared and submitted for pharmacological study. The phenylethyl derivative was included because it has been found[4] that when this group was attached to the nitrogen in Series II an extremely powerful anesthetic of relatively low toxicity resulted.

These members of Series III and IV were prepared from the corresponding 1-alkyl-3-carbethoxy-4-piperidones.[1] The carbethoxypiperidones were hydrolyzed and decarboxylated by treatment with 20% hydrochloric acid. The 1-alkyl-4-piperidones so obtained were catalytically reduced to the corresponding 4-hydroxypiperidines, which were acylated with benzoyl chloride and *p*-nitrobenzoyl chloride. The *p*-nitrobenzoates were catalytically reduced to the *p*-aminobenzoates. These reactions may be indicated thus



The hydrolysis and decarboxylation of the carbethoxypiperidones took place quite smoothly and yields of 70–92% of the theoretical for the 1-alkyl-4-piperidones were obtained. These piperidones were easily isolated and crystallized as the hydrochlorides. The reduction of these piperidones was carried out using Adams' platinum-oxide platinum black catalyst and proceeded much more rapidly than the reduction of the corresponding carbethoxypiperidones. The latter compounds required about fifty hours for complete reduction, while the 1-alkyl-4-piperidones were

[4] Thayer and McElvain, THIS JOURNAL, 49, 2862 (1927).

completely reduced in six to eight hours. The resulting 1-alkyl-4-hydroxypiperidones were not isolated as such, but were directly acylated and obtained as the hydrochlorides of the benzoates and *p*-nitrobenzoates and as the monohydrochlorides of the *p*-aminobenzoates.

Experimental

1-Alkyl-3-carbethoxy-4-piperidone Hydrochlorides.—These compounds were prepared by the internal condensation of β,β'-dicarbethoxydiethylalkylamines by sodium in xylene.[1] Due to more careful manipulation of the reaction and isolation of the products, yields of 63–78% of the alkyl derivatives, as compared to 50–60% yields originally reported, and 50% yields of the phenylethyl derivative, as compared to a 40% yield reported by Thayer and McElvain, have consistently been obtained.

1-Alkyl-4-piperidone Hydrochlorides.—To 0.1 mole of the 1-alkyl-3-carbethoxy-4-piperidone hydrochloride was added 120 cc. of 20% hydrochloric acid and the resulting solution refluxed for one hour. At the end of this time no coloration was produced in a ferric chloride solution by a drop of the reaction solution. The latter was then evaporated to dryness under diminished pressure and the residue treated with a few small pieces of sodium hydroxide and just enough water to permit the decomposition of the piperidone hydrochloride. The free piperidone was extracted with three 75-cc. portions of ether and the combined extract dried over anhydrous sodium sulfate. The hydrochloride was then precipitated from the ether solution with dry hydrogen chloride and recrystallized from an alcohol–ether mixture. A summary of these piperidones is given in Table I.

TABLE I

1-ALKYL-4-PIPERIDONE HYDROCHLORIDES

1-Substituent	Formula	M. p. (corr.), °C.	Yield, %	Analyses, Cl, % Calcd.	Found
Methyl	$C_6H_{12}ONCl$	94– 95	84	23.71	23.25
Ethyl	$C_7H_{14}ONCl$	105–106	70	21.67	21.80
n-Propyl	$C_8H_{16}ONCl$	117–118	70	19.96	19.67
n-Butyl	$C_9H_{18}ONCl$	178–180	70	18.50	14.62[a]
Iso-amyl	$C_{10}H_{20}ONCl$	183–185	70	17.24	17.24
Phenylethyl	$C_{13}H_{18}ONCl$	182–184	92	14.79	11.49[a]

[a] The analyses for the *n*-butyl and phenylethyl derivatives gave values for the percentage of chlorine that were considerably lower than the theoretical. Unusual care was exercised in their preparation and purification but no change in the analytical data could be obtained. The sharpness of their melting points suggested that the low analyses might be due to alcohol of crystallization, but drying *in vacuo* at 100° did not cause any change in weight of the material. The benzoyl derivatives obtained from the reduction products of these piperidones showed the calculated halogen content, so it was assumed that the cause of the abnormal halogen content in the case of the piperidones was not fundamental.

1-Alkyl-4-piperidyl Benzoate Hydrochlorides.—A solution of 10 g. of the 1-alkyl-4-piperidone hydrochloride in 75 cc. of 95% alcohol was shaken with 0.3 g. of Adams' platinum-oxide platinum black catalyst and hydrogen under a pressure of 2–3 atmospheres. The reduction proceeded quite rapidly and at the end of six to eight hours the theoretical amount of hydrogen had been absorbed. The solution was then separated from the catalyst and the alcohol removed under diminished pressure. To the gummy residue which remained 20 cc. of benzoyl chloride was added and the mixture heated in an oil-bath at 150–165° for one hour. When the benzoylation had finished 25 cc.

of absolute alcohol was added to decompose the excess of benzoyl chloride. The resulting alcoholic solution was diluted with 300 cc. of ether and the precipitated hydrochloride of the 1-alkyl-4-piperidyl benzoate allowed to crystallize. These hydrochlorides were recrystallized from an alcohol–ether mixture. They are summarized in Table II.

TABLE II

1-ALKYL-4-PIPERIDYL BENZOATE HYDROCHLORIDES

1-Substituent	Formula	M. p. (corr.), °C.	Yield,[a] %	Analyses, Cl, % Calcd.	Found
Methyl	$C_{13}H_{18}O_2NCl$	219–220	64	13.87	13.75
Ethyl	$C_{14}H_{20}O_2NCl$	204–205	74	13.15	12.73
n-Propyl	$C_{15}H_{22}O_2NCl$	210–211	83	12.50	12.56
n-Butyl	$C_{16}H_{24}O_2NCl$	223–224	73	11.91	12.06
Iso-amyl	$C_{17}H_{26}O_2NCl$	199–200	50	11.38	11.60
Phenylethyl	$C_{20}H_{24}O_2NCl$	236–238	82	10.25	10.17

[a] Recrystallized product based on the piperidone hydrochloride used.

1-Alkyl-4-piperidyl-*p*-nitrobenzoate Hydrochlorides.—These substances were prepared in a manner similar to the benzoates described above except that an equivalent amount of *p*-nitrobenzoyl chloride was used instead of benzoyl chloride. Acylation took place at a lower temperature (130–145°) in this case. A summary of these *p*-nitrobenzoate hydrochlorides is given in Table III.

TABLE III

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

1-Substituent	Formula	M. p. (corr.), °C.	Yield, %	Analyses, Cl, % Calcd.	Found
Methyl	$C_{13}H_{17}O_4N_2Cl$	197–199	40	11.79	11.71
Ethyl	$C_{14}H_{19}O_4N_2Cl$	204–206	53	11.27	11.20
n-Propyl	$C_{15}H_{21}O_4N_2Cl$	219–220	48	10.79	11.01
n-Butyl	$C_{16}H_{23}O_4N_2Cl$	242–243	48	10.35	10.30
Iso-Amyl	$C_{17}H_{25}O_4N_2Cl$	243–245	52	9.94	10.15
Phenylethyl	$C_{20}H_{23}O_4N_2Cl$	242–244	55	9.08	9.08

1-Alkyl-4-piperidyl-*p*-aminobenzoate Hydrochlorides.—A solution of 5 g. of the nitrobenzoate hydrochloride in 75 cc. of 95% alcohol was shaken with 0.25 g. of Adams' platinum-oxide platinum black catalyst and hydrogen at 2–3 atmospheres' pressure. The absorption was so rapid that the theoretical amount of hydrogen was taken up in a few minutes. The shaking was continued for one hour to insure complete reduction. The catalyst was then filtered off and the solution evaporated nearly to dryness under diminished pressure. The aminobenzoate was precipitated as the monohydrochloride by the addition of 200 cc. of ether to the concentrated alcoholic solution and it was allowed to crystallize. These hydrochlorides were readily recrystallized from an alcohol–ether mixture. They are summarized in Table IV.

TABLE IV

1-ALKYL-4-PIPERIDYL-*p*-AMINOBENZOATE HYDROCHLORIDES

1-Substituent	Formula	M. p. (corr.), °C.	Yield, %	Analyses, Cl, % Calcd.	Found
Methyl	$C_{13}H_{19}O_2N_2Cl$	231–233	73	13.11	13.47
Ethyl	$C_{14}H_{21}O_2N_2Cl$	183–184	83	12.46	12.50
n-Propyl	$C_{15}H_{23}O_2N_2Cl$	201–203	94	11.87	12.06
n-Butyl	$C_{16}H_{25}O_2N_2Cl$	234–236	82	11.34	11.47
Iso-amyl	$C_{17}H_{27}O_2N_2Cl$	233–235	94	10.86	10.98
Phenylethyl	$C_{20}H_{25}O_2N_2Cl$	238–240	88	9.83	9.82

Pharmacological Report

The 1-alkyl-4-piperidyl benzoates and *p*-aminobenzoates are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Indianapolis, Indiana. A preliminary report of this work is summarized in Table V. The anesthetic efficiencies were determined in the usual way by application of a 2% solution of the hydrochloride to the rabbit's cornea and noting the duration of anesthesia. Both intravenous and subcutaneous toxicity measurements were made. For comparison the corresponding values that have been obtained for the 1-alkyl-3-carbethoxy-4-piperidyl benzoates and *p*-aminobenzoates with the same 1-substituent are given in parentheses in the table. The data for procaine and cocaine are also included.

TABLE V

PHARMACOLOGICAL DATA

1-Substituent	Av. 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
1-Alkyl-4-piperidyl Benzoate Hydrochlorides							
Methyl	27.8 (8)	100 (50)	125 (100)	15 (12)	15	17.5	9
Ethyl	26.6 (0)	250 (100)	300 (150)	26 (15)	20	25	9
n-Propyl	38 (16)	200 (200)	250 (250)	17 (13)	10	12.5	9
n-Butyl	35.5 (29)	100 (1500)	150 (1600)	21 (23)	10	12.5	7
Iso-amyl	34 (40)	600 (4000)	650 (4500)	43 (6)	15	17.5	9
Phenylethyl	202	800	1000	6	20	25	8
1-Alkyl-4-piperidyl *p*-Aminobenzoate Hydrochlorides							
Methyl	4.5 (26)	10 (50)	15 (100)	20 (9)	7.5	10	8
Ethyl	0 (34)	20 (150)	25 (200)	13 (10)	30	35	14
n-Propyl	9 (35)	20 (200)	25 (250)	13 (17)	17.5	20	7
n-Butyl	48 (43)	50 (450)	75 (550)	9 (34)	12.5	15	6
Iso-amyl	58 (72)	75 (500)	100 (550)	32 (25)	10	12.5	11
Phenylethyl	116 (46)	50 (1150)	100 (1200)	12 (40)	10	12.5	10
Cocaine	29	100	150	18	15	17.5	9
Procaine	0	950	1000	20	35	40	15

Discussion of the Pharmacological Data

It will be seen from the data in Table V that the 1-alkyl-4-piperidyl benzoates as a group show a greater anesthetic effect and have very much lower toxicities than the corresponding *p*-aminobenzoates, while in the series in which there is a 3-carbethoxy substituent in the piperidine nucleus the *p*-aminobenzoyl derivatives show a greater anesthetic effect than the benzoyl derivatives. The carbethoxy group apparently is responsible for this variation in physiological effect.

The 1-alkyl-4-piperidyl benzoates and *p*-aminobenzoates also show the unusual relationship between the size of the alkyl group attached to the nitrogen and toxicity of the compound that was observed in the series

containing a 3-carbethoxy substituent. Although the differences are not so great in the new series, it is evident from the data in Table V that in both series an increase in the size of the alkyl group attached to the nitrogen causes an increase in anesthetic effect and a decrease in subcutaneous toxicity.

Particular attention is called to the phenylethyl derivatives, especially 1-phenylethyl-4-piperidyl benzoate. This compound possesses about seven times the anesthetic power of cocaine, a subcutaneous toxicity approximately equal to procaine and an intravenous toxicity intermediate between that of cocaine and procaine. So far as the authors know there is no local anesthetic that approaches this substance in its ability to produce and sustain anesthesia of the rabbit's cornea.

A comparison of the pharmacological data for 1-methyl-3-carbethoxy-4-piperidyl benzoate with those for 1-methyl-4-piperidyl benzoate indicates that there is no apparent connection between the physiological action and the points of asymmetry which are present in the molecule. The latter compound has no asymmetric carbon atoms and is more active than the former which has two such carbon atoms. It would seem, therefore, that one possible explanation that was advanced[3] for the difference in the physiological activity of 1-methyl-3-carbethoxy-4-piperidyl benzoate and γ-(methyl-β-carbethoxy-ethyl)-aminopropyl benzoate (V and VI) was of little or no significance. Such a conclusion, however, is not entirely justified when 1-methyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoate and 1-methyl-4-piperidyl-*p*-aminobenzoate are considered, for in this case the former with two points of asymmetry is much more active than the latter with no such points of asymmetry. This variation may be due to the presence or absence of the carbethoxy group or to the points of asymmetry in the molecule which the presence of the carbethoxy group causes. The greater the number of different series of compounds that are considered, the more difficult it appears to attribute physiological action to any particular point of structure. Generalizations which fit one series may be quite inapplicable to another. It is probable that the entire molecule functions in producing a certain physiological effect, and what appear to be important structural groupings so modify the effect of each other when they are present in the same molecule that generalizations are extremely difficult, if not impossible.

Summary

1. Two new series of piperidine derivatives, 1-alkyl-4-piperidyl benzoates and *p*-aminobenzoates, have been prepared and described.

2. The members of these series are local anesthetics and show the same relationship between the size of the alkyl group and pharmacological action of the compound as was found to exist in the 1-alkyl-3-carbethoxy-4-piperidyl benzoates and *p*-aminobenzoates.

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.

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[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

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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.