The volume of permanganate reduced by the substance was then calculated and is shown in Table II.

The first two determinations on glucose were made without the buffer and clearly show the variable results obtained without buffer.

Summary and Conclusions

The character of the products obtained by methylating mannose with dimethyl sulfate and sodium hydroxide at temperatures between 30 and 50° has been studied.

A sirup having the analysis and properties of trimethyl-γ-methyl-mannoside was formed in a solution between P_H 7.0 and 8.5 at a temperature of 30°. The product formed on similar treatment at 35° had no gamma properties and was a mixture of sugar methylated to varying degrees.

The method of Kuhn and Jauregg for studying the rate of oxidation of sugars by permanganate was applied to the oxidation of polymethyl methyl mannosides. The results showed clearly the very great difference in the behavior of stable and unstable forms toward potassium permanganate.

MANHATTAN, KANSAS

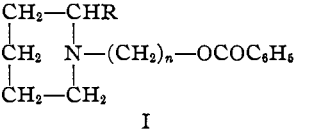
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

PIPERIDINE DERIVATIVES. VIII. SUBSTITUTED PIPERIDINO-ALKYL BENZOATES

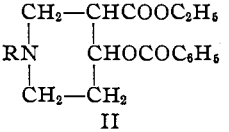
BY C. F. BAILEY AND S. M. MCELVAIN

RECEIVED DECEMBER 20, 1929 PUBLISHED APRIL 7, 1930

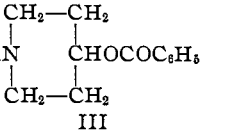
In a previous communication[1] from this Laboratory a number of substituted piperidino-alkyl benzoates (Type I) were reported. It was found that when a methyl group substituted the 2- or 3-position of the piperidine nucleus, a much more effective local anesthetic was produced than when the piperidine nucleus remained unsubstituted or was substituted by a *n*-propyl group or a carbethoxy group. Other types of structure which have been found to produce quite pronounced local anesthetic effect are the 1-alkyl-3-carbethoxy-4-piperidyl benzoates (Type II)[2] and the 1-alkyl-4-piperidyl benzoates (Type III).[3] In those cases in which the R of Types II and III is a phenylethyl group extraordinary local anesthetic action is shown.



I



II



III

[1] McElvain, THIS JOURNAL, **49**, 2835 (1927).

[2] McElvain, *ibid.*, **48**, 2179 (1926); Thayer and McElvain, *ibid.*, **49**, 2862 (1927).

[3] Bolyard and McElvain, *ibid.*, **51**, 922 (1929).

On account of the efficiency of the methyl group as a substituent in compounds of Type I, it seemed desirable to prepare the 4-methyl isomers of the 2- and 3-methylpiperidino-alkyl benzoates. Also it was reasonable to expect that certain phenyl-alkyl groups, such as had proved valuable in compounds of Types II and III, would enhance the pharmacological properties of Type I when they were substituted in the piperidine nucleus.

Accordingly the following substances have been prepared and submitted for pharmacological study: (1) 4-methylpiperidino-ethyl benzoate, (2) 4-methylpiperidino-propyl benzoate, (3) 2-benzylpiperidino-propyl benzoate, (4) 2-phenylethylpiperidino-ethyl benzoate, (5) 2-phenylethylpiperidino-propyl benzoate, (6) 4-phenylethylpiperidino-ethyl benzoate.

These esters were prepared by the condensation of the correspondingly substituted piperidine with β-chloro-ethyl benzoate and γ-chloropropyl benzoate. It should be pointed out that the 2-phenylethyl- and 2-benzyl-substituted piperidines condense with the chloro esters with much more difficulty than the 4-phenylethylpiperidine. A similar difference in reactivity was noted[1] in the case of 2-methyl- and 3-methylpiperidine. All of the piperidino-alkyl benzoates were isolated and purified as the hydrochlorides with the exception of the 2-phenylethylpiperidino-ethyl benzoate (4). No salt of this amino ester could be induced to crystallize. The free base was finally purified by distillation under diminished pressure.

In the preparation and crystallization of 2-phenylethylpiperidino-propyl benzoate hydrochloride, two distinctly different compounds were obtained. They are probably geometric isomers.[4] One of these compounds melts at 123–125° and the other at 149–151°. The ratio in which they are formed seems to be dependent upon the temperature at which the tertiary amino ester is formed. At lower reaction temperatures both isomers appeared, but at higher reaction temperatures only the higher-melting isomer was isolated. It will be seen from the pharmacological data that these two compounds show a distinctly different physiological activity.

The 4-methylpiperidine that was used was obtained by the reduction of γ-picoline. This latter compound was obtained rather unexpectedly in an attempt to isolate β-picoline from coal tar bases. It was thought that the fraction boiling at 142–146° obtained by the fractionation of the "Denaturing Pyridine" of Barrett and Company would contain a mixture of β- and γ-picoline along with some 2,6-dimethylpyridine and possibly other higher-boiling dimethylpyridines. A statement by Meyer and Jacobson[5] that β-picoline could be separated from the α- and γ-isomers by treatment of the mixture with benzaldehyde and zinc chloride followed by the removal of the unchanged β-picoline from the condensation products of the α- and γ-isomers (α- and γ-stilbazole) suggested the possibility of the fraction of the

[4] *Cf.*, Mills, Parkin and Ward, *J. Chem. Soc.*, 2613 (1927).

[5] Meyer and Jacobson, "Lehrbuch der Organischen Chemie," **1920,** Vol. 2 [3], 807.

coal tar bases boiling at 142–146° being a source of β-picoline. After treatment of this fraction with benzaldehyde in the presence of zinc chloride, a base boiling at 140–145° and thought to be β-picoline was recovered from the reaction mixture. The recovered product amounted in weight to about 35% of the crude basic fraction that was taken. This recovered base, however, was shown to be fairly pure γ-picoline rather than β-picoline by the fact that on oxidation it yielded isonicotinic acid, m. p. 304–306° (nicotinic acid melts at 228–229°), and also formed a picrate which melted at 158–161°.[6] The picrate of synthetic β-picoline melted at 144–147° and a mixed melting pount of the two picrates was 127–135°.

It appears from these results that the 142–146° fraction from this particular mixture of coal tar bases contains very little β-picoline, and that under the conditions used the γ-picoline which is present does not condense to any great extent with benzaldehyde. Because of these facts this particular mixture of coal tar bases can be recommended as a very satisfactory source of γ-picoline. In this connection it is interesting to note that Freudenberg[7] has pointed out that the nicotinic acid prepared by Hess and Leibbrandt[8] by the oxidation of supposed β-picoline from coal tar bases was mainly isonicotinic acid resulting from the oxidation of γ-picoline.

2-Benzylpiperidine was obtained by the catalytic reduction of α-benzylpyridine. The 2- and 4-phenylethylpiperidines were prepared by the catalytic reduction of α- and γ-stilbazoles.

Experimental

γ-Picoline from Coal Tar Bases.—The "Denaturing Pyridine" of Barrett and Company was fractionated twice through a 45-cm. column packed with glass rings. The following fractions were taken: up to 120°, 120–126°, 126–130°, 130–135°, 135–142°, 142–146°, above 146°. A mixture of 186 g. of the 142–146° fraction, 212 g. of benzaldehyde and 272 g. of pulverized, freshly fused zinc chloride was heated under a reflux condenser in an oil-bath at 200–210° for twenty to twenty-four hours. Sufficient concentrated solution of sodium hydroxide was then added to insure complete decomposition of the zinc chloride and the mixture steam distilled until the distillate failed to show a basic reaction to litmus paper. By this time the distillate amounted to 4–6 liters. Hydrochloric acid was added to the distillate until it showed an acid reaction to congo red paper. The acid solution was then evaporated to dryness on a steam-bath. The free base was liberated from its salt with concentrated sodium hydroxide. It separated as an oil which, after drying over solid potassium hydroxide, boiled at 140–145°. The yield was 55–65 g. (30–35% of the original amount of mixed bases).

The picrate of this material was prepared by adding 0.5 cc. of the base to a solution of 0.5 g. of picric acid in 15 cc. of alcohol. After two recrystallizations from alcohol the picrate melted at 158–161°. The picrate made from a sample of synthetic β-picoline,

[6] Mulliken, "Identification of Pure Organic Compounds," **1916**, Vol. II, p. 139, gives 167° as the melting point of the picrate of γ-picoline.

[7] Freudenberg, *Ber.*, **51**, 1668 (1918).

[8] Hess and Leibbrandt, *ibid.*, **50**, 385 (1917).

prepared by the method of Schwarz,[9] melted at 144–147°. The melting point of a mixture of these two picrates was 127–135°.

A 15-g. sample of the γ-picoline was oxidized at 70° with 51 g. of potassium permanganate in about 500 cc. of water. After the reaction was complete, the precipitated manganese dioxide was filtered off and the clear filtrate evaporated to about one-half its volume and then made just neutral with sulfuric acid. The correct amount of a copper sulfate solution was then added to precipitate the copper salt of the acid. Seven g. of this salt was obtained. The copper salt was suspended in 200 cc. of hot water and the copper removed by precipitation with hydrogen sulfide. After filtering off the copper sulfide the filtrate was concentrated and the isonicotinic acid allowed to crystallize. After recrystallization 2.9 g. of the acid that melted at 304–306° was obtained.[10]

No attempt was made to isolate any of the benzaldehyde condensation products from the reaction mixture after the removal of the unchanged base.

α-Benzylpyridine.—This compound was prepared by the method of LaForge.[11] The product that was used boiled at 277.8–280°.

α-Stilbazole (Symmetrical α-Pyridylphenylethylene).—A mixture of 186 g. of the picoline fraction that boiled at 126–130°, 212 g. of benzaldehyde and 272 g. of pulverized freshly fused zinc chloride was heated for twelve to fourteen hours at 200–210° under a reflux condenser. Sufficient concentrated sodium hydroxide solution was then added to react with the zinc chloride and the mixture steam distilled to remove any unchanged picoline and benzaldehyde. The brown, tarry α-stilbazole was then extracted from the reaction mixture with benzene. After removal of the solvent by distillation, the α-stilbazole was distilled under diminished pressure. It boiled at 175–177° (3 mm.) and solidified in the receiver. After two recrystallizations from 70% alcohol it melted at 87–88.5°. The yield was 27–33 g.

The hydrochloride of this α-stilbazole melted at 176–177°.[12]

γ-Stilbazole (Symmetrical γ-Pyridylphenylethylene).—This compound has been prepared by Friedländer,[13] by heating γ-picoline, benzaldehyde and zinc chloride in sealed tubes at 220–230° for eight hours. When these conditions were tried an excessive amount of tar was formed from which it was practically impossible to isolate any of the desired γ-stilbazole. It was found that heating for a shorter period of time at a somewhat lower temperature appreciably reduced this tar formation and increased the yield of the stilbazole. Accordingly the following procedure was used: six sealed bomb tubes, each containing 35 g. of γ-picoline, 40 g. of benzaldehyde and 51 g. of zinc chloride were heated for three hours at 200°. The tubes were then opened, their contents combined and the γ-stilbazole isolated in the manner described above for α-stilbazole. The material boiling at 180–200° (3 mm.) was collected and recrystallized several times from 95% alcohol. A yield of 19.4 g. of product melting at 125–127° was obtained.

4-Methylpiperidine.—To a solution of 76 g. of γ-picoline in 1.5 liters of absolute alcohol contained in a 3-liter flask fitted with an efficient reflux condenser was added 227 g. of sodium over a period of one hour. After the addition of all of the sodium, a further 750 cc. of absolute alcohol was added and the mixture heated until all of the sodium had disappeared. The condenser was then set for downward distillation and the alcohol and base were distilled off. During this process 900 cc. of water was slowly

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

[10] The above oxidation of γ-picoline was carried out by Mr. Mortimer C. Denison in the course of a study of the preparation of pyridine carboxylic acids by the oxidation of picolines. The details of this work will be the subject of a future communication.

[11] LaForge, THIS JOURNAL, **50**, 2484 (1928).

[12] *Cf.* Baurath, *Ber.*, **21**, 818 (1888).

[13] Friedländer, *ibid.*, **38**, 159 (1905).

added to the reaction mixture through a separatory funnel. The distillation was continued as long as the distillate showed a basic reaction. One hundred cc. of concentrated hydrochloric acid was then added to the distillate and the alcohol distilled off from a steam-bath. The hydrochloride of 4-methylpiperidine was obtained by evaporating the remainder of the solution to dryness. The free base was liberated with saturated sodium hydroxide solution, separated and dried over solid potassium hydroxide. Distillation of this material gave 56 g. (68%) of 4-methylpiperidine which boiled at 122–129°.

Several attempts were made to reduce the γ-picoline with Adams' platinum-oxide platinum black catalyst according to the procedure used[1] for the reduction of α- and β-picolines. There was some absorption of hydrogen but it soon stopped and could not be caused to continue either by activation of the catalyst or the addition of fresh catalyst.

2-Benzylpiperidine, 2-Phenylethylpiperidine and 4-Phenylethylpiperidine.—These compounds were obtained by the catalytic reduction of α-benzylpyridine, α-stilbazole and γ-stilbazole in alcoholic solution using a nickel catalyst at temperatures of 150–165° and at pressures of 150–200 atmospheres of hydrogen.[14] The physical properties of these substituted piperidines are given in Table I.

TABLE I

PHYSICAL PROPERTIES OF SUBSTITUTED PIPERIDINES

Piperidine substituent	B. p., °C.	d_{20}^{20}	n_D^{25}	Hydrochloride m. p., °C.	Hydrochloride analyses, % Cl Calcd.	Found
2-Benzyl	266.6–269	0.9749	1.5237	.....[a]	...	...
2-Phenylethyl	137.5–138.5 (3 mm.)	.9483	1.5207	156–158[b]	15.74	15.64
4-Phenylethyl	126–130 (3 mm.)	.9713	1.5293	171–173[c]	15.74	15.50

[a] The picrate was prepared. It melted at 154–156°. Tschitschibabin reported [Tschitschibabin, *Chem. Centr.*, II, 597 (1902)] 156–157° as the melting point of this picrate. [b] Baurath (Ref. 12) reported 155°. [c] Friedländer [Friedländer, *Ber.*, **38**, 2837 (1905)] stated that this hydrochloride was an oil.

The phenylsulfonamides of 2-phenylethyl- and 4-phenylethylpiperidine were prepared. They melted at 129–130° and 130–131°, respectively (mixed m. p. 110–114°).

Anal. Calcd. for $C_{19}H_{23}O_2NS$: N, 4.26. Found: N, 4.26 and 4.04, respectively.

Substituted Piperidino-alkyl Benzoates.—These compounds were prepared by the general procedure of heating 2 moles of the substituted piperidine with 1 mole of β-chloro-ethyl benzoate or γ-chloropropyl benzoate. The 4-substituted piperidines could be caused to react by heating for one to three hours at 100–120°. These conditions, however, caused very little if any reaction in the case of the 2-substituted piperidines. It was necessary to use temperatures of 130–150° for at least six hours to cause them to condense. The tertiary amino esters with the exception of β-2-phenylethylpiperidino-ethyl benzoate, were isolated as the hydrochlorides, by the procedure previously employed[1] for compounds of this type. These hydrochlorides are summarized in Table II.

Numerous efforts were made to obtain a crystalline hydrochloride, hydrobromide and sulfate of the β-2-phenylethylpiperidino-ethyl benzoate. In all cases, however, these salts were obtained as thick oils which could not be induced to crystallize. Since this anesthetic was particularly desired for pharmacological comparison, it was purified as the free base by distillation under diminished pressure. It boiled at 202–207° (1 mm.).

[14] This work was done by Mr. Howard Cramer under the direction of Professor Homer Adkins and will be described in detail by them in a forthcoming paper.

TABLE II

SUBSTITUTED PIPERIDINO-ALKYL BENZOATE HYDROCHLORIDES

	Piperidino-alkyl group	M. p., °C.	Analyses, Cl % Calcd.	 Found
1	β-4-Methylpiperidino-ethyl	181–184	12.52	12.43
2	γ-4-Methylpiperidinopropyl	165–168	11.93	11.91
3	γ-2-Benzylpiperidinopropyl	169–171	9.50	9.55
4	β-2-Phenylethylpiperidino-ethyl	Oil	...	...
5	γ-2-Phenylethylpiperidinopropyl	123–125	9.16	9.11
6	γ-2-Phenylethylpiperidinopropyl	149–151	9.16	9.10
7	β-4-Phenylethylpiperidino-ethyl	163–165	9.50	9.32

Anal. Calcd. for $C_{22}H_{27}O_2N$: C, 78.29; H, 8.07. Found: C, 78.58, 78.21; H, 8.69, 8.58.

When γ-2-phenylethylpiperidinopropyl benzoate was prepared by heating together the secondary amine and the chloro ester at 140–150° for six hours, two different hydrochlorides were isolated. As the hydrochlorides were recrystallized from an alcohol–ether mixture it was noticed that one type of crystals formed as a somewhat discolored cake on the bottom of the flask, while in the supernatant liquid a flocculent precipitate of pure white, needle-like crystals appeared. These were separated by decanting the supernatant liquid which carried along the white crystals. These apparently different substances were recrystallized separately several times. The one which had appeared as a white flocculent precipitate was found to melt finally at 123–125° and the other at 149–151°. The melting point of a mixture of the two was indefinite, over a considerable range, but between the melting points of the individual compounds. From 12 g. of 2-phenylethyl-piperidine (2 mol.) and 6.3 g. of γ-chloropropyl benzoate (1 mol.) were obtained in purified form 1.6 g. of the lower-melting compound and 2.1 g. of the higher-melting compound. If the reaction in which the tertiary amine was prepared were carried on for one hour at 200–210° the only product obtained was the higher-melting compound.

These two compounds are probably geometric iosmers but the evidence at hand does not warrant a definite conclusion on this point. Further work is contemplated in this direction.

Pharmacological Report

These benzoates are being studied pharmacologically by Mr. Charles L. Rose of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A brief report of this work is summarized in Table III. Each of the compounds is designated in this table by the number which is associated with it in Table II. In the case of No. 4 which was obtained as the free base a solution of the hydrochloride was prepared by titration of the base with standard acid. Anesthetic efficiencies were determined by application of a 2% solution of the hydrochloride to the rabbit's cornea and noting the duration of anesthesia. In some cases the infiltration anesthesia values as determined from intracutaneous injection into the guinea pig are reported. Subcutaneous toxicity to white mice and intravenous toxicity to white rats were determined. The corresponding values for cocaine (8) and procaine (9) are included in Table III for comparison.

Discussion of the Pharmacological Data.—A comparison of the

TABLE III

PHARMACOLOGICAL DATA

Compound	Av. duration of anesthesia: Rabbits cornea, minutes	Infiltration, minutes	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	11 (2% sol.)	..	1300	1400	..	40	42.5	12
2	14 (2% sol.)	..	..	..[a]	..	20	22.5	17
3	5–6 days (2% sol.) 13 min. (0.1% sol.)	71[b]	450	500	21	12.5	15	18
4	136 (0.5% sol.)	34[c]	1200	1250	18	26	28	13
5	5–6 days (2% sol.) 22 min. (0.1% sol.)	77[b]	500	550	15	12.5	15	6
6	5–6 days (2% sol.) 1–2 days (1% sol.) 19 min. (0.1% sol.)	21[b]	600	700	16	20	22.5	13
7	51 (2% sol.)	..	1600	1700	23	25	30	10
8	29 (2% sol.)	..	200	250	18	15	17.5	12
9	0	..	900	1000	17	45	50	10

[a] Not determined because of scarcity of material. [b] The dose in each of these cases was 0.1 cc. of a 1% solution. [c] The dose in this case was 0.1 cc. of a 0.5% solution.

pharmacological behavior of β-4-methylpiperidino-ethyl benzoate (1) with the isomeric 2- and 3-methyl derivatives shows a striking and unexpected difference. These latter compounds are without any apparent action on the rabbit's cornea,[1] but it is seen that (1) possesses considerable of such anesthetic action, nearly as much, in fact, as its propyl homolog.

Those compounds, (3), (4), (5), (6) and (7), that contain a phenyl-alkyl group are unusually effective in producing mucous membrane anesthesia, the anesthesia resulting from an application of a 2% solution lasting in some cases for five to six days. The ordinary durations of anesthesia are produced by these compounds in quite dilute solutions (0.1%). It should be noted that when a phenylethyl group is in the 4-position of the piperidine nucleus (Compound 7) the anesthetic action is considerably less than when a benzyl or phenylethyl group substitutes the 2-position of the piperidine nucleus. This suggests the possibility of an optimum position of the phenyl group relative to the nitrogen atom, for in the 2-benzyl-piperidinopropyl benzoate (3) and the 2-phenylethylpiperidino-alkyl benzoates (4, 5 and 6) the phenyl group is separated from the nitrogen atom by 2 and 3 carbon atoms, respectively, *i. e.*, the nuclei of phenylethyl and phenylpropyl groups are present in the anesthetic molecules, while in the case of the 4-phenylethylpiperidino-ethyl benzoate (7) the phenyl group is separated from the nitrogen atom by five carbon atoms, *i. e.*, the nucleus of a phenylpentyl group exists. It is expected that some work now under way in this Laboratory will evaluate this possible relationship of structure to pharmacological action.

It is interesting to note that Compounds 5 and 6, which appear to be

geometric isomers, show a difference in their pharmacological properties as well as in their physical properties. As nearly as can be judged they show about the same effect on the rabbit's cornea, but the durations of anesthesia produced by intracutaneous injection into the guinea pig and the subcutaneous and intravenous toxicities are markedly different. It should be noted that the less stable isomer (*i. e.*, the lower-melting one) is the more active physiologically.

Summary

1. A method for the isolation of γ-picoline from coal tar bases has been described.

2. A number of new substituted piperidino-alkyl benzoates have been prepared.

3. All of these substances are local anesthetics. Certain of the phenyl-alkyl substituted derivatives are unusually potent anesthetics, producing anesthesia of the rabbit's cornea for a period of five to six days.

4. Some relationships between structure and pharmacological action are discussed.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

COMPARATIVE REACTIVITIES OF SOME SUBSTITUTED BENZYL HALIDES[1]

BY MURRAY M. SPRUNG[2]

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The present investigation is a study of the influence of substitution in the aromatic nucleus upon the reactivity of the benzyl halides. The metathetical reaction which has been chosen for investigation is that which occurs between the benzyl halides and an alkali sulfite, a reaction which has been used considerably in organic chemistry since its early discovery by Strecker,[3] and which occurs with an easily measurable speed at ordinary temperatures. The products of the reaction are a benzyl sulfonate and an inorganic halide.

The results of previous investigations of the velocity of replacement of halogen in the benzyl halides are not entirely concordant. Concordancy, in fact, may hardly be expected at present, in view of the complexity of this sort of problem, an insufficient understanding, as yet, of the more fundamental physico-chemical relationships involved, and the present sparsity of accurate experimental data. For the sake of brevity,

[1] Presented, in part, at the Minneapolis meeting of the American Chemical Society, September, 1929.

[2] National Research Fellow in Chemistry.

[3] Strecker, *Ann.*, **148**, 90 (1868).