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

PIPERIDINE DERIVATIVES. V. THE PREPARATION AND REDUCTION OF CERTAIN PHENYL SUBSTITUTED 3-CARBETHOXY-4-PIPERIDONES. 1-CYCLOHEXYL- AND 1-PHENYLETHYL-3-CARBETHOXY-4-PIPERIDYL-PARA-AMINOBENZOATES[1]

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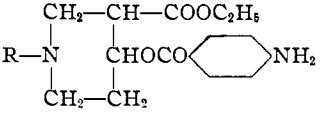
In an earlier communication by one of us[2] the preparation of a series of 1-alkyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoates of the formula

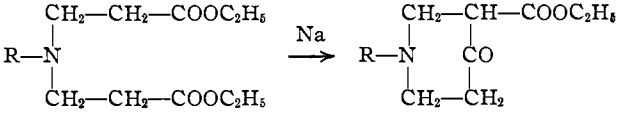


was described.

These substances showed very marked and unexpected physiological action. It was found that the size of the alkyl group in the 1 position had a pronounced effect on the physiological activity of the compounds, for, as the size of the alkyl group was increased, the subcutaneous toxicity was lowered and the efficiency for corneal anesthesia raised.

Because of this unexpected behavior, it seemed advisable to study the effect of substituting certain aryl and aryl-alkyl groups in the 1 position of the piperidine nucleus of the type compound shown above.

The preparation of such derivatives necessarily involved the synthesis of the corresponding piperidones by the same internal aceto-acetic ester condensation of the proper dicarbethoxy tertiary amines that was used for the 1-alkyl-3-carbethoxy-4-piperidones.[3] The piperidones in which



R was the phenyl, benzyl and phenylethyl group were prepared. Very satisfactory yields (40–70%) of these piperidones were obtained, showing that the above condensation is of quite general application and is not materially affected by the nature of the R group.

The reduction of these phenyl substituted piperidones was interesting, particularly as compared to the reduction of the 1-alkyl-3-carbethoxy-4-piperidones. When these latter compounds were reduced catalytically

[1] This paper is an abstract of a portion of the thesis submitted by J. R. Thayer 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**, 2239 (1926).

[3] (a) McElvain, *ibid.*, **46**, 1721 (1924); (b) **48**, 2179 (1926).

with Adams' platinum-oxide platinum black catalyst it was found that 15–20 hours were required to reduce the ketone group to a point where it showed no coloration with ferric chloride. This reduction to a negative ferric chloride test generally required 10–20% excess of the theoretical amount of hydrogen necessary to convert the ketone into the secondary alcohol.

The 1-phenyl derivative, in the first three hours of the reduction, absorbed about 50% of the theoretical amount of hydrogen necessary to reduce both the ketone group and the benzene ring, and the reduction of the ketone group was not complete at this stage. The rate of reduction decreased somewhat after this rapid, initial absorption but at the end of twelve to fifteen hours the reduction was complete, as shown by the fact that approximately 15% excess of the hydrogen necessary to reduce both the ring and the ketone group had been absorbed and the reduction product gave no coloration with ferric chloride. Inasmuch as there was unreduced ketone present after hydrogen in excess of that required completely to reduce the ring had been absorbed, it is difficult to arrive at any conclusions as to the order in which the reduction took place. From the observations which were made, it may be that the ring and ketone group are reduced simultaneously, or that the ring was reduced before the reduction of the ketone began. In either case the final reduction product, as determined by derivatives, was 1-cyclohexyl-3-carbethoxy-4-hydroxypiperidine.

In the reduction of the 1-benzylpiperidone, there was no rapid initial absorption of hydrogen and both the ring and the ketone group seemed to reduce simultaneously. The reduction to a negative ferric chloride test took place in about 24 hours and required 65–75% of the theoretical amount of hydrogen necessary for the complete reduction of both the ring and ketone group. From this point the reduction was very slow but could be continued to a stage where an excess of 12–15% of the theoretical amount of hydrogen necessary to reduce both groups had been absorbed. It was not possible to isolate a crystalline derivative of the reduction product, either at the point where the ketone was completely reduced or at the point where more than sufficient hydrogen had been absorbed to reduce both the ketone and the ring. From the standpoint of producing a definite final product, the catalytic reduction of the 1-benzyl-3-carbethoxy-4-piperidone was unsuccessful, but it did show the effect of the separation of the aromatic nucleus from the amino nitrogen on the rate of nuclear hydrogenation.

In the case of the 1-phenylethyl-3-carbethoxy-4-piperidone, in which the aromatic nucleus is two carbon atoms removed from the amino nitrogen, the reduction proceeded in much the same manner as that of the 1-alkyl-3-carbethoxy-4-piperidones. A negative test for the ketone was obtained with ferric chloride after 10–12 hours of reduction and at this

point approximately 20% excess of the hydrogen necessary for the reduction of the ketone group had been absorbed. Thereafter there was practically no absorption of hydrogen even on prolonged exposure to reduction. As mentioned above, the 1-alkyl-3-carbethoxy-4-piperidones generally absorbed an excess of 10–20% of the hydrogen necessary for the reduction of the ketone to the secondary alcohol. From such data it is apparent that the reduction of the aromatic nucleus in the 1-phenylethylpiperidone does not take place to any marked extent, if at all.

The reduction products of these piperidones were acylated with *p*-nitrobenzoyl chloride. The derivative obtained from the 1-phenyl-3-carbethoxy-4-piperidone was assumed to be 1-cyclohexyl-3-carbethoxy-4-piperidyl-*p*-nitrobenzoate on account of (1) the amount of hydrogen absorbed during the reduction of the piperidone and (2) the absence of unsaturation in the *p*-nitrobenzoate as shown by dilute potassium permanganate solution.

It was not possible to isolate a crystalline *p*-nitrobenzoate from the acylation of the reduction product of the 1-benzylpiperidone. This reduction product showed a distinctly different behavior from the others with *p*-nitrobenzoyl chloride. There was very little evolution of hydrogen chloride when the reactants were heated together. Under the same conditions, the reduction products of the other piperidones gave a vigorous evolution of hydrogen chloride with *p*-nitrobenzoyl chloride. Such behavior would indicate that considerable reduction of the secondary alcohol group to a methylene group had taken place.

1-Phenylethyl-3-carbethoxy-4-piperidyl-*p*-nitrobenzoate was shown to be the derivative obtained from the acylation of the reduction product of the 1-phenylethyl-3-carbethoxy-4-piperidone by (1) the amount of hydrogen absorbed in the reduction of the piperidone and (2) the fact that benzoic acid was obtained by the oxidation of the reduction product.

The 1-cyclohexyl- and 1-phenylethyl-3-carbethoxy-4-piperidyl-*p*-nitrobenzoates were converted by catalytic reduction into the corresponding *p*-aminobenzoates, which were isolated as the crystalline dihydrochlorides.

Experimental

β-Carbethoxyethylphenylamine.—This substance has been prepared by Harries and Loth[4] from aniline and β-iodopropionate. The following procedure was used in this work. A mixture of 180 g. (1 mole) of ethyl-β-bromopropionate and 190 g. (2 moles) of freshly distilled aniline was heated to 70–80° in an oil-bath with stirring. At this temperature a rather vigorous reaction took place, whereupon the heating was discontinued until this initial reaction had subsided. The mixture was then heated at 110–120° for two to three hours, after which it was cooled and the precipitated aniline hydrobromide filtered off by suction. The precipitate was washed with 200 cc. of ether. The ether was evaporated from the filtrate and the secondary amine distilled under

[4] Harries and Loth, *Ber.*, **29**, 514 (1896).

diminished pressure. The yield was 140–145 g. (72–75% of the theoretical); b. p. 133–135° (2 mm.); n_D^{20} 1.5315; d_{20}^{20} 1.0709. The hydrochloride melted at 98–99°.

Anal. (of the hydrochloride). Subs., 0.2020: AgCl, 0.1261. Calcd. for $C_{11}H_{16}O_2NCl$: Cl, 15.46. Found: 15.44 (of the free base).

Subs., 0.7972, 0.7169: 43.2, 40.4 cc. of 0.0911 *N* HCl. Calcd. for $C_{11}H_{15}O_2N$: N, 7.25. Found: 6.91, 7.12.

β-Carbethoxyethylbenzylamine.—To a solution of 54 g. of benzylamine in 400 cc. of alcohol was added 90 g. (0.5 mole) of ethyl β-bromopropionate at such a rate that the temperature of the mixture did not exceed 50°. The mixture was then allowed to stand for about three hours. During this time it was shaken occasionally. Sixty g. of silver oxide was then added and the mixture shaken intermittently for two hours. The alcoholic solution of the amine was filtered with suction and the precipitate washed with 125–150 cc. of alcohol. The alcohol was removed from the filtrate by distillation and the amine dissolved in 400 cc. of ether. The ethereal solution was washed twice with 10% potassium cyanide solution, after which the solvent was removed and the amine distilled under diminished pressure. The yield was 63–68 g. (60–65% of the theoretical); b. p. 132–134° (2 mm.); n_D^{20} 1.5059; d_{20}^{20} 1.9126. The hydrochloride melted at 147–149°.

Anal. (free base). Subs., 1.1128, 1.2086: 56.77, 62.90 cc. of 0.0911 *N* HCl. Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: 6.51, 6.64.

(Hydrochloride). Subs., 0.2700: AgCl, 0.1551. Calcd. for $C_{12}H_{18}O_2NCl$: 14.58. Found: 14.20.

β-Carbethoxyethylphenylethylamine.—This amine was prepared in exactly the same manner as that described above for β-carbethoxyethylbenzylamine. The yields were 68–72 g. (62–65% of the theoretical); b. p. 145–147° (2 mm.); n_D^{20} 1.5040; d_{20}^{20} 1.0098. The hydrochloride melted at 161–163°.

Anal. (free base). Subs., 0.9994, 0.7326: 46.8, 36.3 cc. of 0.0911 *N* HCl. Calcd. for $C_{13}H_{19}O_2N$: N, 6.33. Found: 5.97, 6.32.

(Hydrochloride). Subs., 0.2310: AgCl, 0.1277. Calcd. for $C_{13}H_{20}O_2NCl$; Cl, 13.78. Found: 13.66.

β,β′-Dicarbethoxydiethylphenylamine.—A mixture of 195 g. (1 mole) of β-carbethoxyethylphenylamine and 90 g. (0.5 mole) of ethyl-β-bromopropionate was heated at 110–120° for 36–40 hours. The reaction mixture was then treated with alkali solution and the free amines were extracted with three 200cc. portions of ether. The ether was removed by distillation and the amines were fractionally distilled under diminished pressure, the fraction boiling at 180–200° (2 mm.) being collected as the tertiary amine. The yield was 126–135 g. For analyses and physical constants this amine was further purified by shaking with an alkaline aqueous suspension of benzoyl chloride. On redistillation, the tertiary amine boiled at 182–184° (2 mm.); n_D^{20} 1.5176; d_{20}^{20} 1.0948.

Anal. Subs., 1.0248, 1.0295: 36.76, 37.47 cc. of 0.091 *N* HCl. Calcd. for $C_{16}H_{23}O_4N$: N, 4.78. Found: 4.58, 4.64.

β,β′-Dicarbethoxydiethylbenzylamine.—To 104 g. (0.5 mole) of β-carbethoxyethylbenzylamine in 100 cc. of alcohol was added 90 g. (0.5 mole) of ethyl-β-bromopropionate. The mixture was allowed to stand for two and a half to three hours with occasional shaking and then heated to 100° for a half hour. The mixture was cooled to 20–30° and diluted with 300 cc. of alcohol. Sixty g. of silver oxide was then added and the mixture shaken intermittently for about two hours. The silver bromide was filtered off and the precipitate washed with 150 cc. of alcohol. The alcohol was removed from the filtrate, the amine dissolved in 400 cc. of ether and the ethereal solution washed twice with a dilute solution of potassium cyanide. After the removal of the ether the

amine was distilled under diminished pressure. The yield amounted to 92–95 g. (62–65% of the theoretical). The tertiary amine was freed from any secondary amine by treatment with benzoyl chloride. It then boiled at 181–183° (2 mm.); n_D^{20} 1.4942; d_{20}^{20} 1.0598.

Anal. Subs., 1.3649, 1.3025: 49.1, 46.5 cc. of 0.0911 *N* HCl. Calcd. for $C_{17}H_{25}O_4N$: N, 4.57. Found: 4.58, 4.56.

β,β′-Dicarbethoxydiethylphenylethylamine.—This amine was prepared according to the procedure given above for β,β′-dicarbethoxydiethylbenzylamine. The yield was 80–84 g. (50–52% of the theoretical); b. p. 190–193° (2 mm.); n_D^{20} 1.4990; d_{20}^{20} 1.0454.

Anal. Subs., 1.2533, 1.2248: 43.37, 40.80 cc. of 0.0911 *N* HCl. Calcd. for $C_{18}H_{17}O_4N$: N, 4.36. Found: 4.42, 4.25.

1-Phenyl-, 1-Benzyl- and 1-Phenylethyl-3-carbethoxy-4-piperidone Hydrochlorides.—These substances were prepared by the internal condensation of the corresponding dicarbethoxy tertiary amines with sodium in xylene and isolated by the procedure described by McElvain.[3b]

TABLE I

1-Substituent	Formula	M. p., °C.	Yield, %	Analyses (%Cl) calcd.	found
Phenyl	$C_{14}H_{18}O_3NCl$	144–145	70	12.54	12.50
Benzyl	$C_{15}H_{20}O_3NCl$	170–172	50	11.93	11.84
Phenylethyl	$C_{16}H_{22}O_3NCl$	165–167	40	11.42	11.45

Reduction of 1-Phenyl-3-carbethoxy-4-piperidone Hydrochloride.—A solution of 20 g. of the piperidone in 125 cc. of alcohol was reduced catalytically using 0.5 g. of Adams' platinum-oxide platinum black catalyst, at room temperature and under a pressure of 2.5–3.5 atmospheres. The reduction of the ketone group was followed by testing portions of the solution for coloration with ferric chloride, and the reduction of the aromatic nucleus was estimated from the amount of hydrogen absorbed. Four molecular equivalents of hydrogen were necessary for the reduction of both the ketone group and the ring. In the first three hours of reduction approximately 2 molecular equivalents of hydrogen were absorbed. The absorption of hydrogen at the end of twelve hours amounted to 4.31 molecular equivalents, which was in excess of that theoretically necessary to reduce both groups. At this point a positive test for the ketone was obtained with ferric chloride. For complete reduction of the ketone it was necessary to continue the reduction for an additional six to eight hours, at the end of which time the ferric chloride test was negative and the total absorbed hydrogen amounted to 4.46 molecular equivalents. No attempt was made to isolate or purify the reduction product.

Reduction of 1-Benzyl-3-carbethoxy-4-piperidone Hydrochloride.—Twenty g. of this piperidone was reduced catalytically in the manner described above. In the first nine hours of reduction there was an absorption of 1.80 molecular equivalents of hydrogen and the ketone group was not completely reduced. In a series of six runs the minimum absorption of hydrogen necessary for the complete reduction of the ketone group was 2.51 molecular equivalents, while in the other cases it varied between 2.59 and 2.81 molecular equivalents. At the end of thirty-six to forty hours of exposure to reduction the amount of hydrogen absorbed amounted to 4.29–4.44 molecular equivalents.

Reduction of 1-Phenylethyl-3-carbethoxy-4-piperidone Hydrochloride.—The reduction procedure was the same as that outlined above for the 1-phenyl derivative. In the first twelve hours of reduction the amount of hydrogen absorbed was 1.49 molecular equivalents. This amount was approximately a 50% excess over that necessary for the ketone reduction. Upon exposure to reduction for an additional twenty-four

hours, there was practically no further absorption of hydrogen. This reduction product, after the removal of the solvent, yielded benzoic acid when oxidized with an aqueous potassium permanganate solution.

1-Cyclohexyl-3-carbethoxy-4-piperidyl-*p*-nitrobenzoate Hydrochloride.—The catalyst was filtered from the solution of the reduction product of the 1-phenyl-3-carbethoxy-4-piperidone and the alcohol removed by distillation under diminished pressure. After the complete removal of the solvent, 25 g. of *p*-nitrobenzoyl chloride was added and the mixture heated at 140–145° in an oil-bath until the evolution of hydrogen chloride ceased. The nitro ester was isolated by the same procedure as that used for the corresponding 1-alkyl compounds. The yield was 8–9 g. An aqueous solution of the hydrochloride of this *p*-nitrobenzoate gave no indication of unsaturation when treated with dilute aqueous potassium permanganate. The recrystallized *p*-nitrobenzoate hydrochloride melted at 188–190°.

Anal. Subs., 0.2530: AgCl, 0.0819. Calcd. for $C_{21}H_{23}O_6N_2Cl$: Cl, 8.05. Found: 8.00.

Attempted Acylation of the Reduction Product of 1-Benzyl-3-carbethoxy-4-piperidone Hydrochloride.—Several attempts were made to acylate the reduction product obtained when the reduction was stopped at the point where a negative test for the ketone was indicated. This product gave very little reaction with *p*-nitrobenzoyl chloride. The reduction product obtained when the reduction was continued to the point where an excess of hydrogen over that required to reduce both the ketone group and the ring had been absorbed, was treated with *p*-nitrobenzoyl chloride. In this case also there was very little evolution of hydrogen chloride. From neither of these attempted acylations was it possible to obtain a crystalline derivative of the reduction products. The lack of reaction with *p*-nitrobenzoyl chloride would indicate, it seems, that the ketone group had been converted, to a very large extent, to a methylene group.

1-Phenylethyl-3-carbethoxy-4-piperidyl-*p*-nitrobenzoate Hydrochloride.—The reduction product from the 1-phenylethyl-3-carbethoxy-4-piperidone, after the removal of the solvent, was treated with *p*-nitrobenzoyl chloride under the conditions described above. The reaction appeared to proceed normally and produced a copious evolution of hydrogen chloride. The hydrochloride of the *p*-nitrobenzoate crystallized well and behaved in all respects like the corresponding 1-alkyl derivatives. The yield was 15 g. of a product melting at 195–197°.

Anal. Subs., 0.2570: AgCl, 0.0805. Calcd. for $C_{23}H_{27}O_6N_2Cl$: Cl, 7.67. Found: 7.75.

1-Cyclohexyl- and 1-Phenylethyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoate Dihydrochlorides.—Ten g. of the *p*-nitrobenzoate hydrochloride was dissolved in 250 cc. of absolute alcohol and reduced catalytically using 0.25 g. of Adams' platinum-oxide platinum black catalyst. The reduction was complete in twenty to thirty minutes and the *p*-aminobenzoates were isolated as the dihydrochlorides by the procedure that was used for the 1-alkyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoate dihydrochlorides.[2]

TABLE II

1-Substituent	Formula	M. p., °C.	Analyses (% Cl) Calcd.	Found
Cyclohexyl	$C_{21}H_{32}O_4N_2Cl_2$	220–222	15.85	15.47
Phenylethyl	$C_{23}H_{30}O_4N_2Cl_2$	215–218	15.12	14.85

Pharmacological Report

The authors are indebted to Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, for this

pharmacological report on the 1-cyclohexyl- and 1-phenylethyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoates.

The anesthetic efficiencies were tested by application of 1% solutions of the anesthetics ($P_H = 5$) to the rabbit's cornea and noting the duration of anesthesia. The toxicities were measured by subcutaneous injection into white mice. These data, together with comparative values for cocaine, are summarized in Table III.

TABLE III

PHARMACOLOGICAL DATA

1-Substituent	Duration of anesthesia in minutes with 1% solution (aver. for 5 rabbits)	Toxicity to white mice mg. per kg. M. T. D.	M. L. D.
Cyclohexyl	26.1	100	150 (28 mice used)
Phenylethyl	46.4	1150	1200 (40 mice used)
Cocaine	20.4	200	250

The above data indicate that the 1-cyclohexyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoate is somewhat more efficient than cocaine in producing corneal anesthesia, while the corresponding 1-phenylethyl derivative is over twice as efficient as cocaine. The toxicity of the cyclohexyl derivative is slightly greater than that of cocaine, while the toxicity of the 1-phenylethyl derivative is approximately one-fifth that of cocaine.

The toxicity of the cyclohexyl derivative is interesting when compared with the corresponding 1-alkyl derivatives. In the case of these latter compounds it was found that the subcutaneous toxicity to white mice decreased as the size of the alkyl group in the 1 position was increased. The 1-methyl and 1-*iso*-amyl derivatives had values of 100 mg. per kg. and 550 mg. per kg., respectively, as the minimum lethal doses for white mice. It is seen from Table III that the 1-cyclohexyl derivative is approximately equivalent to the 1-methyl derivative in toxicity. It might have been expected that the presence of a group of such a carbon content as the cyclohexyl group in the 1 position would have produced a physiological effect of the order of that shown by the higher alkyl radicals, such as the *iso*-amyl radical. Since this expected similarity in behavior between the cyclohexyl group and the higher alkyl groups was not found to exist, it appears that the abnormal action of the former is due to its cyclic structure. The toxicity of the phenylethyl derivative is exceptionally low and, since at the same time its anesthetic efficiency is quite high, it indicates that phenyl-alkyl radicals may be very desirable N-substituent groups in local anesthetics.

Summary

1. The preparation of some 1,3,4-tri-substituted piperidines and the reduction of the corresponding 4-piperidones have been described.

2. A preliminary pharmacological report on the 1-cyclohexyl- and

1-phenylethyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoates has been included.

3. This pharmacological report indicates that the cyclohexyl group does not correspond to the higher alkyl groups in its physiological effect and is a much less desirable N-substituent group than the phenylethyl group for this particular type of local anesthetic.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

AZO DYES CONTAINING ANTIMONY. II

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In a previous paper,[1] the preparation of a series of azo dyes containing antimony has been described. These compounds were prepared for a study of their possible therapeutic action. Since that time another series of dyes and several miscellaneous antimonials have been prepared. These compounds have been tested as to their activity against trypanosomes and as to their toxicities. The pharmacological findings, which are summarized here, will be published more fully elsewhere.

As these compounds are, for the most part, dyes, it was thought of interest to ascertain the effect of the antimony group on the color. Dyes containing the group $-SbO_3H_2$ have been contrasted with those having the $-SO_3H$ group and with some containing neither.

Results

The compounds which have been prepared are for the most part derivatives of stibanilic acid, *p*-aminophenylstibinic acid—$H_2NC_6H_4SbO_3H_2$. The method of preparation of this compound has been further improved. This consists in breaking down the molecular compound formed by diazotized *p*-amino-acetanilide and antimony trichloride with hot sodium hydroxide. Thus stibanilic acid is obtained from the molecular compound in one step.

The first series of compounds, Nos. I to VI, described in the previous paper, were obtained by coupling diazotized stibanilic acids with substituted phenols. In the second series, diazotized stibanilic acid has been coupled with dimethyl- and diethylaniline to form *p*-dimethylamino-azobenzene-4′-stibinic acid and the corresponding diethyl compound (Nos. VII and VIII). The disodium salts, $Na_2O_3SbC_6H_4N{:}NC_6H_4N(R)_2$, are normally formed and are readily soluble in water. The solutions are comparatively stable.

The third series has been prepared by coupling diazotized stibanilic acid with various substituted naphthalene sulfonic acids.

[1] Dunning and Reid, THIS JOURNAL, **48**, 2959 (1926).