hydantoin nucleus and reduced the isatin portion to the corresponding oxindole.

2. Toward barium hydroxide solution hydantoin-5,3′-oxindole and its 5′-methyl homolog differ in their behavior in that the former is converted into 2-quinolone-4-carboxylic acid and the latter into 5-methyloxindole.

3. The synthesis of 2-quinolone-4-carboxylic acid by Hill, Schultz and Lindwall has been confirmed, whereas the conflicting research of Kotake has, in part, been shown to be in error.

AUSTIN, TEXAS

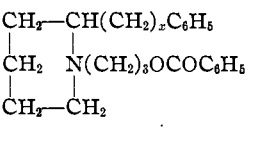
RECEIVED JULY 13, 1933
PUBLISHED NOVEMBER 7, 1933

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

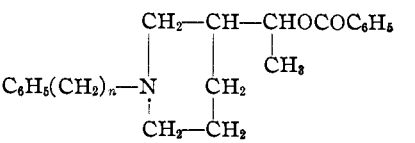
Piperidine Derivatives. XIII.[1] Phenyl and Phenylalkyl Substituted Piperidinopropyl Benzoates

BY L. A. WALTERS AND S. M. MCELVAIN

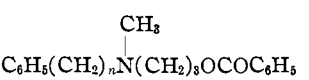
In a previous paper[1] the unusual local anesthetic action of compounds of type I on mucous surfaces was reported. Since the substances in which x is 1 and 2 were many times more effective as anesthetics than the compound in which a phenylethyl group substitutes the 4 position of the piperidine nucleus, it appeared that there might be an optimum position of the phenyl group relative to the nitrogen atom for maximum anesthetic action. In subsequent work an effort was made to test this possibility by the preparation of series of anesthetics of types II[2] and III[3] in which the number of carbon atoms separating the nitrogen atom from the phenyl group was varied from 1 to 5. However, compounds of type II and III proved to be so irritating to the mucous surfaces (rabbit's cornea) that no definite conclusion could be drawn in this connection.



I



III



II

It therefore seemed desirable to extend the study to structures of type I. The present paper reports the preparation and properties of the 2-phenyl-

(1) Bailey and McElvain, THIS JOURNAL, **52**, 1633 (1930).
(2) Cope and McElvain, *ibid.*, **53**, 1587 (1931).
(3) Strong and McElvain, *ibid.*, **55**, 816 (1933).

(x = 0) 2-phenylpropyl-(x = 3), 2-phenylbutyl-(x = 4), 3-phenyl-, 3 benzyl- and 4-phenyl-piperidinopropyl benzoates. The compounds were prepared by the condensation of γ-chloropropyl benzoate with the appropriately substituted piperidines, the preparations of which are described in the experimental part.

Experimental

Phenyl and Phenylalkyl Pyridines.—2-Phenylpyridine was prepared in 40% yield by the method of Ziegler and Zeiser,[4] in which the following modification was used. In order that the heating of the ethereal solution of lithium phenyl and pyridine in a sealed tube might be avoided, the ether was removed by distillation and simultaneously replaced by toluene. The decomposition into lithium hydride and 2-phenylpyridine took place readily when the toluene solution was heated to 100° for four hours; b. p. 270–272° (740 mm.); m. p. of picrate 173–174°; reported by Ziegler and Zeiser,[4] 175°.

2-(γ-Phenylpropyl)- and 2-(δ-phenylbutyl)-pyridine were prepared by the action of γ-phenylpropyl bromide and δ-phenylbutyl bromide on lithium picolyl.[5] In these preparations it was found necessary to add the phenylalkyl bromide to the reaction mixture immediately after the addition of the α-picoline to the lithium butyl had been completed. If the addition of the bromide is delayed, even for a short time, the yield of the phenylalkyl pyridines is very materially lowered. The properties and yields of these new substituted pyridines that were prepared are summarized in Table I.

4-Phenylpyridine was prepared in 28% yields by the procedure of Forsyth and Pyman;[6] b. p. 266–269° (730 mm.); m. p. 74°.

Attempts to prepare 3-phenylpyridine by the method of Ciamician[7] as well as by the procedure of Pictet[8] were unsuccessful. A small amount of impure 3-phenylpyridine was obtained by the decarboxylation of o-β-pyridylbenzoic acid,[9] but this procedure was finally abandoned as impractical.

Phenyl- and Phenylalkylpiperidines.—The above-mentioned pyridines were reduced catalytically in methylcyclohexane solution over a nickel catalyst at 150° and under a pressure of 2000 pounds of hydrogen to the corresponding piperidines. 3-Benzylpiperidine was likewise prepared by the catalytic reduction of 3-benzoylpyridine.[10] The authors are indebted to Mr. B. H. Wojcik of this Laboratory for carrying out these reductions.

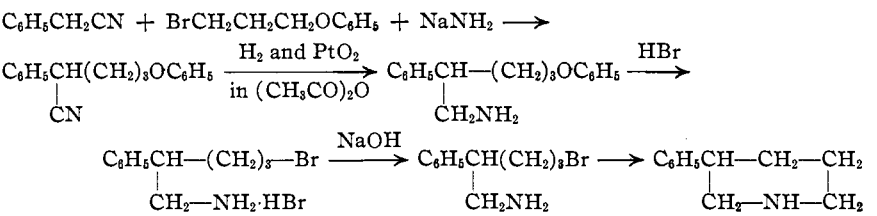
TABLE I

CERTAIN PHENYL AND PHENYLALKYL SUBSTITUTED PYRIDINES

Substituent	B. p., °C. mm.	Yield, %	d_{25}^{25}	n_D^{25}	Analyses, N, % Calcd.	Found
2-(γ-Phenylpropyl)	132–135 (2)	20	1.0171	1.5571	6.91	7.10
2-(δ-Phenylbutyl)	142–145 (2)	25	1.0040	1.5472	6.63	6.99

Since it was not possible to obtain 3-phenylpyridine in sufficient quantities to allow for its reduction to 3-phenylpiperidine, this latter compound was prepared by the following series of reactions

(4) Ziegler and Zeiser, *Ber.*, **63**, 1849 (1930).
(5) Ziegler and Zeiser, *Ann.*, **485**, 192 (1931).
(6) Forsyth and Pyman, *J. Chem. Soc.*, 2922 (1926).
(7) Ciamician, *Ber.*, **20**, 192 (1887).
(8) Pictet, *ibid.*, **38**, 1946 (1905).
(9) Skraup and Cobenzl, *Monatsh.*, **4**, 456 (1883).
(10) LaForge, THIS JOURNAL, **50**, 2484 (1928).



α-Phenyl-δ-phenoxybutyl Cyanide.—In a 1-liter 3-necked flask, equipped with a stirrer, reflux condenser and dropping funnel were placed 39 g. (1 mole) of powdered sodamide and 400 cc. of ether. Then 118 g. (1 mole) of benzyl cyanide was added at such a rate that the ether refluxed gently.[11] When all of the nitrile had been added the solution was refluxed for four hours, after which time the flask was cooled to 0° in an ice salt mixture and 215 g. (1 mole) of phenoxypropyl bromide slowly added. After stirring for four hours at room temperature water was added and the ether layer separated. After removal of the ether the residue was fractionated. Lower boiling fractions consisting of benzyl cyanide and phenoxypropyl bromide came over first, after which 154 g. (63%) of α-phenyl-δ-phenoxybutyl cyanide, b. p. 190–195 (2 mm.), was collected as a pale yellow viscous liquid; d_{25}^{25} 1.0876; n_D^{25} 1.5704.

Anal. Calcd. for $C_{17}H_{17}ON$: N, 5.58. Found: N, 5.56.

β-Phenyl-ε-phenoxyamylamine Hydrochloride.—A solution of 40 g. of α-phenyl-δ-phenoxybutyl cyanide in 100 cc. of acetic anhydride was reduced catalytically over 0.5 g. of Adams platinum oxide catalyst.[12] After the reduction was complete the excess acetic anhydride was removed under diminished pressure. A thick sirup, which could not be caused to crystallize, remained. A 2-g. sample of this sirup when refluxed for thirty-six hours with 50 cc. of 20% hydrochloric acid gave, on cooling, the hydrochloride of β-phenyl-ε-phenoxyamylamine, m. p. 127–128°.

Anal. Calcd. for $C_{17}H_{22}ONCl$: C, 69.93; H, 7.62. Found: C, 69.63; H, 7.68.

3-Phenylpiperidine.—The remainder of the sirup which was obtained from the reduction of the nitrile in acetic anhydride solution was refluxed for thirty-six hours with 200 cc. of 48% hydrobromic acid and the resulting solution evaporated to dryness. The dry residue was decomposed with 5% sodium hydroxide solution and the amine layer extracted with 400 cc. of toluene. This toluene solution was separated and treated with 100 cc. of 10% sodium hydroxide solution and the mixture refluxed for four hours. The toluene layer was then distilled. A 10-g. fraction boiling at 250–260° (740 mm.) was collected as 3-phenylpiperidine. This impure product was purified by conversion into the hydrochloride and recrystallization of the latter from an alcohol–ether mixture. From the purified hydrochloride the free base was obtained by treatment with alkali.

The properties of the various phenyl and phenylalkylpiperidines which were prepared in this work together with the analyses of the new compounds are summarized in Table II.

The melting points and analyses of the hydrochlorides of the new piperidines listed in Table II are given in Table III.

Phenyl and Phenylalkyl Piperidinopropyl Benzoate Hydrochlorides.—A mixture of two moles of the substituted piperidine and one mole of γ-chloropropyl benzoate was heated at 100° until the reaction was at least 80% complete as shown by the amount of the hydrochloride of the secondary amine which precipitated when the reaction mix-

(11) *Cf.* Bodroux and Taboury, *Bull. soc. chim.*, [4] **7**, 666 (1910); Knowles and Cloke, THIS JOURNAL, **54**, 2032 (1932).

(12) *Cf.* Carothers and Jones, *ibid.*, **47**, 3051 (1925).

TABLE II

CERTAIN PHENYL AND PHENYLALKYL SUBSTITUTED PIPERIDINES

Substituent	B. p., °C. (mm.)	d_{25}^{25}	n_D^{25}	Formula	Analyses, N, % Calcd.	Found
2-Phenyl[a]	108–110 (9)	....	....	.....	..	..
2-(γ-Phenylpropyl)	161–163 (10)	0.9721	1.5189	$C_{14}H_{21}N$	6.89	6.99
2-(δ-Phenylbutyl)	164–166 (9)	0.9575	1.5152	$C_{15}H_{23}N$	6.46	6.50
3-Phenyl	255–256 (740)	1.0040	1.5473	$C_{11}H_{15}N$	8.69	8.98
3-Benzyl[b]	279–281 (740)	....	....	.....	..	..
4-Phenyl[c]	255–258 (730)	....	....	.....	..	..

[a] *Cf.* Gabriel, *Ber.*, **41**, 2012 (1908). [b] Chloroplatinate decomposes at 191°. *Cf.* Tschitschibabin, *ibid.*, **36**, 2711 (1903). [c] M. p. 58°. Chloroplatinate melts at 205°. *Cf.* Bally, *ibid.*, **20**, 2590 (1887).

TABLE III

HYDROCHLORIDES OF SUBSTITUTED PIPERIDINES

Substituent	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-(γ-Phenylpropyl)	139–141	$C_{14}H_{22}NCl$	70.11	9.25	69.80	9.30
2-(δ-Phenylbutyl)	129–131	$C_{15}H_{24}NCl$	70.96	9.53	70.87	9.69
3-Phenyl	146–147	$C_{11}H_{16}NCl$	66.80	8.16	66.87	8.23

ture was diluted with ether. After removal of this hydrochloride the ether solution of the tertiary amine was treated with dry hydrogen chloride and the precipitate purified by recrystallization from an alcohol–ether mixture. The melting points and analyses of the various substituted piperidinopropyl benzoate hydrochlorides are summarized in Table IV.

TABLE IV

PHENYL AND PHENYLALKYLPIPERIDINOPROPYL BENZOATE HYDROCHLORIDES

Substituent	M. p., °C.	Formula	Analyses, % Cl Calcd.	Found
2-Phenyl	186–187	$C_{21}H_{26}O_2NCl$	9.86	9.93
2-(γ-Phenylpropyl)	103–105	$C_{24}H_{32}O_2NCl$	8.82	8.68
2-(δ-Phenylbutyl)	179–181	$C_{25}H_{34}O_2NCl$	8.51	8.56
3-Phenyl	180–181	$C_{21}H_{26}O_2NCl$	9.86	10.07
3-Benzyl	163–164	$C_{22}H_{28}O_2NCl$	9.49	9.48
4-Phenyl	174–175	$C_{21}H_{26}O_2NCl$	9.86	9.96

Pharmacological Report.—The piperidinopropyl benzoate hydrochlorides which have been described in this paper are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A preliminary report on some of their pharmacological properties is summarized in Table V. Anesthetic efficiencies were determined by application of 1% solutions of the hydrochlorides to the rabbit's cornea and noting the duration of anesthesia. Toxicities were determined by intravenous injection into white rats. The values given are, in each case, the average of a representative number of pharmacological tests.

The various anesthetics are listed by the substituent in the piperidine nucleus. For comparison the corresponding pharmacological values for the

previously reported compounds containing a 2-benzyl (No. 7), a 2-phenylethyl (No. 8) and a 4-phenylethyl (No. 9) substituent are included in the table.

TABLE V

PHARMACOLOGICAL PROPERTIES OF PHENYL AND PHENYLALKYL SUBSTITUTED PIPERIDINOPROPYL BENZOATES

No.	Substituent	Duration of corneal anesthesia, minutes	Intravenous toxicity to white rats, M. L. D., mg./kg.
1	2-Phenyl	15	26
2	2-(γ-Phenylpropyl)	45	30
3	2-(δ-Phenylbutyl)	37	28
4	3-Phenyl	26	42
5	3-Benzyl	31	35
6	4-Phenyl	26	26
7	2-Benzyl	5–6 days (2% soln.)	15
8	2-(β-Phenylethyl)	5–6 days (2% soln.) 1–2 days (1% soln.)	22
9	4-(β-Phenylethyl)	51 (2% soln.)	30

Discussion of the Pharmacological Data.—It is apparent from the data in Table V that the extremely long durations of anesthesia are associated only with those substances which contain a benzyl or phenylethyl substituent in the 2 position of the piperidine nucleus (Nos. 7 and 8). Increasing the length of the carbon chain which separates the phenyl group from the nitrogen atom to more than three carbon atoms (Nos. 2 and 3) or decreasing it to one carbon atom (No. 1) diminishes very considerably the anesthetic activity of the resulting compounds. So far as the substituents in the 2 position are concerned, maximum anesthetic activity appears to reside in those structures in which the nitrogen atom is separated from the phenyl group by two or three carbon atoms. However, a comparison of compounds 4 and 7 (2 carbons between the nitrogen atom and phenyl group) and of compounds 5, 6 and 8 (3 carbons between the nitrogen atom and phenyl group) indicates that this relationship of structure to pharmacological action does not exist when the substituent groups are transferred to the 3 and 4 positions of the piperidine nucleus.

Summary

The preparation and properties of certain new phenyl and phenylalkyl piperidines have been described. These and other similarly substituted piperidines have been condensed with γ-chloropropyl benzoate to give a series of phenyl- and phenylalkyl-piperidinopropyl benzoates. Some of the pharmacological properties of these latter compounds have been described and discussed.

MADISON, WISCONSIN

RECEIVED JULY 14, 1933
PUBLISHED NOVEMBER 7, 1933