[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis and Anticholinergic Activity of Ester and Amide Derivatives of 2-Substituted Piperidines

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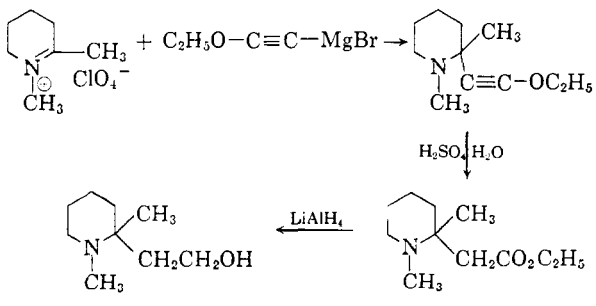
The preparation of some thirty ester and amide derivatives of 2-piperidines, together with their pharmacological activity is described.

The diphenylacetate and benzilate esters of 3- and 4-piperidine alcohols have been thoroughly investigated, and several members possess marked antispasmodic activity.[1] Surprisingly, there has been no report of a systematic investigation of the corresponding 2-piperidine compounds despite the fact that the 2-pyrrolidine derivatives have been studied.[2]

We have been interested in this laboratory for some time in 2-piperidine compounds and have noted especially the pharmacological effect of the 6-methyl-2-piperidine moiety.[3] This paper reports the preparation of two series of piperidine derivatives. The first concerns a group of esters of 1-alkyl-2-hydroxymethyl and 2-hydroxyethylpiperidines and the corresponding 6-methyl compounds. Representative esters of benzilic, phenylcyclohexylglycolic, dicyclohexylglycolic, diphenylacetic, and phenylcyclohexylacetic acids were prepared and are described in Table I.

The piperidine alcohols were prepared by the catalytic reduction of pyridine alcohols followed by the standard formaldehyde–formic acid reaction to give *N*-methyl-2-piperidine alcohols. 2-(1,2-Dimethyl-2-piperidyl)-1-ethanol was prepared according to the following reaction sequence and represents an extension of the Leonard and Hauck alkylation reaction[4] of Δ^1-tetrahydropyridinium salts.



The second group of compounds that was prepared was composed of propionamides and butyramides of the 2-piperidine series. The starting piperidine chlorides used to alkylate the substituted acetonitriles were prepared from the corresponding piperidine alcohols. The nitriles were hydrolyzed by standard procedures[5] to form the substituted amides that are listed in Table II.

The compounds reported in this paper were all examined by infrared and ultraviolet analyses and showed the expected absorption characteristics.

Preliminary pharmacological evaluation of the compounds contained in Tables I and II indicated that several of the compounds were of activity comparable with the corresponding 3- and 4-piperidine derivatives. However, quaternization of the tertiary compounds did not markedly increase the pharmacological activity of the compounds of the 2-piperidine series here reported.

EXPERIMENTAL[6]

Preparation of piperidine alcohols. The piperidine alcohols were obtained by hydrogenation of the corresponding pyridine alcohols as illustrated by the preparation of 6-methyl-2-piperidylmethanol that is described later. The piperidine alcohols were converted to the 1-methyl compounds according to the method used for the preparation of 1,6-dimethyl-2-piperidylmethanol hydrochloride. The physical constants of 1-methyl-2-piperidylmethanol,[2a] 1-(1-methyl-2-piperidyl)-1-ethanol,[7] 2-(1-methyl-2-piperidyl)-1-ethanol,[8] 1-(1-methyl-2-piperidyl)-2-propanol,[9] and 2-(1,6-dimethyl-2-piperidyl)-1-ethanol[10] agreed well with literature values.

6-Methyl-2-piperidylmethanol. A mixture of 201 g. (1.63 moles) of 6-methyl-2-pyridylmethanol, 300 ml. of absolute ethanol, and 12 g. of 5% rhodium-on-alumina catalyst was reduced, at room temperature, with hydrogen at an initial

(1) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952); R. F. Feldkamp, *J. Am. Chem. Soc.*, **74**, 3834 (1952); J. H. Biel, *et al.*, *J. Am. Chem. Soc.*, **77**, 2250 (1955); S. B. Coan, B. Jaffe, and D. Papa, *J. Am. Chem. Soc.*, **78**, 3701 (1956).

(2) (a) F. F. Blicke and Chi-Jung Lu, *J. Am. Chem. Soc.*, **77**, 29 (1955). (b) F. P. Doyle, M. D. Mehta, G. S. Sach, and J. L. Pearson, *J. Chem. Soc.*, 4458 (1958).

(3) J. Mills, U. S. Patent 2,903,459 (1959).

(4) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(5) L. C. Cheney, *et al.*, *J. Org. Chem.*, **17**, 770 (1952); R. B. Moffett and B. D. Aspergren, *J. Am. Chem. Soc.*, **79**, 4451 (1957).

(6) The melting points were determined with a Fisher-Johns assembly and are reported as read.

(7) G. R. Clemo, R. Raper, and H. J. Vipond, *J. Chem. Soc.*, 2095 (1949).

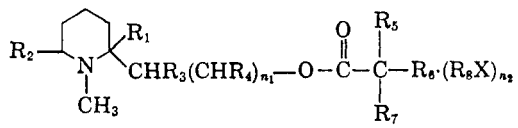
(8) A. Ladenburg, *Ber.*, **24**, 1619 (1891).

(9) J. Meisenheimer and E. Mahler, *Ann.*, **462**, 308 (1928).

(10) K. Hess, C. Vibrig, and A. Eichel, *Ber.*, **50**, 344 (1917).

TABLE I

1-METHYL-2-PIPERIDINE ESTERS



Compound	R_1	R_2	R_3	R_4	n_1	R_5	R_6	R_7	R_8	X	n_2	M.P.	Yield, %	Method
Ia	H	H	H		0	OH	C_6H_5	C_6H_5	H	Cl	1	235–236[a]	25[b]	A
Ib	H	H	H		0	OH	C_6H_5	C_6H_5	CH_3	I	1	122–123	50[b]	
IIb	H	H	H		0	OH	C_6H_{11}	C_6H_{11}[k]	H	Cl	1	246–247	38[b]	A
IIb	H	H	H		0	OH	C_6H_{11}	C_6H_{11}	CH_3	I	1	131–133	37[c]	
IIIa	H	H	CH_3		0	OH	C_6H_5	C_6H_5	H	Cl	1	244–245[a]	72[d]	B
IIIb	H	H	CH_3		0	OH	C_6H_5	C_6H_5	CH_3	I	1	227–228	63[e]	
IV	H	CH_3	H		0	H	C_6H_5	C_6H_5	H	Cl	1	149–150	82[f]	A
Va	H	CH_3	H		0	OH	C_6H_5	C_6H_5	H	Cl	1	180–181	50[b]	A
Vb	H	CH_3	H		0	OH	C_6H_5	C_6H_5	CH_3	I	1	129–130	49[b]	
VIa	H	CH_3	H		0	OH	C_6H_{11}	C_6H_{11}	H	Cl	1	229–230	77[b]	A
VIb	H	CH_3	H		0	OH	C_6H_{11}	C_6H_{11}	CH_3	I	1	90–91	51[c]	
VIIa	H	H	H	H	1	H	C_6H_5	C_6H_5	H	Cl	1	153–154[l]	49[f]	A
VIIb	H	H	H	H	1	H	C_6H_5	C_6H_5	CH_3	I	1	88–89	85[g]	
VIIIa	H	H	H	H	1	H	C_6H_5	C_6H_{11}	H	Cl	1	144–146	51[f]	A
VIIIb	H	H	H	H	1	H	C_6H_5	C_6H_{11}	CH_3	I	1	184–185	45[g]	
IXa	H	H	H	H	1	OH	C_6H_5	C_6H_5			0	107–108	57[b]	A
IXb	H	H	H	H	1	OH	C_6H_5	C_6H_5	CH_3	I	1	169–170	71[b]	
X	H	H	H	H	1	OH	C_6H_5	C_6H_{11}	CH_3	I	1	170–172	62[f]	A
XIa	H	H	H	H	1	OH	C_6H_{11}	C_6H_{11}	H	Cl	1	185–186	59[f]	A
XIb	H	H	H	H	1	OH	C_6H_{11}	C_6H_{11}	CH_3	I	1	154–155	48[b]	
XIIa	CH_3	H	H	H	1	OH	C_6H_5	C_6H_5			0	57–59	64[h]	B
XIIb	CH_3	H	H	H	1	OH	C_6H_5	C_6H_5	CH_3	I	1	163–165	68[e]	
XIIIa	H	H	H	CH_3	1	OH	C_6H_5	C_6H_5			0	128–131	40[c]	B
XIIIb	H	H	H	CH_3	1	OH	C_6H_5	C_6H_5	CH_3	Br	1	214–216	53[e]	
XIVa	H	CH_3	H	H	1	OH	C_6H_5	C_6H_5			0	84–85	59[b]	A
XIVb	H	CH_3	H	H	1	OH	C_6H_5	C_6H_5	CH_3	I	1	173–174	71[b]	
XV	H	CH_3	H	H	1	OH	C_6H_{11}	C_6H_{11}	H	Cl	1	152–153	49[f]	A

[a] Melted with decomposition. Recrystallization solvent: [b] ethyl alcohol, [c] ethyl acetate, [d] ethyl alcohol–ether, [e] methanol–ethyl acetate, [f] ethanol-ethyl acetate, [g] methyl ethyl ketone, [h] petroleum ether (b.p. 60–70°). [i] Minimum effective dose in mg./kg. that reduced acid secretion of the Shay rat by at least 20% when the compound was administered orally.

pressure of 270 atm. The theoretical amount of hydrogen was taken up after 20 hr. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure. The solid residue that formed was recrystallized from 1 l. of ether and gave 171 g. (82% yield) of product, m.p. 75°.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.84. Found: N, 10.28.

1,6-Dimethyl-2-piperidylmethanol hydrochloride. A solution of 170 g. (1.32 moles) of 6-methyl-2-piperidylmethanol, 135 g. (2.64 moles) of 90% formic acid, and 122 g. (1.50 moles) of 37% formaldehyde was heated under reflux for 5 hr. Concentrated hydrochloric acid (150 ml.) was then added, and the solution was concentrated under reduced pressure by heating on a steam bath. The crystalline residue was recrystallized from isopropyl alcohol and gave 203 g. (86% yield) of product, m.p. 213–215°.

Anal. Calcd. for $C_8H_{17}NO.HCl$: C, 53.47; H, 10.10; N, 7.80. Found: C, 52.93; H, 9.97; N, 7.86.

1-(1,2-Dimethyl-2-piperidyl)-2-ethoxyacetylene. An ethylmagnesium bromide solution prepared from 4.3 g. (0.18 g.-atom) of magnesium, 19.5 g. (0.17 mole) of ethyl bromide, and 100 ml. of dry ether was cooled by means of an ice bath and 12.5 g. (0.18 mole) of ethoxyacetylene[11] dissolved in 100 ml. of dry ether was added. After stirring in the cold for 1 hr., 20 g. (0.095 mole) of 1,2-dimethyl-Δ^1-tetrahydropyridinium perchlorate[4] was added, and stirring was continued for 10 min. The mixture was heated under reflux for 2 hr., and then was poured with stirring into an ice-acid (40 ml. of concd. hydrochloric acid) mixture. The aqueous layer was separated and was made basic with potassium carbonate. The oil that separated was dissolved in ether and dried with anhydrous potassium carbonate. After removal of the ether by heating on a steam bath, the residue was distilled under reduced pressure and 9.1 g. (53% yield) of product, b.p. 95–99° (7 mm.), n_D^{25} 1.4672, was obtained.

Anal. Calcd. for $C_{11}H_{19}NO$: N, 7.74. Found: N, 7.39.

Ethyl (1,2-dimethyl-2-piperidyl)acetate. A solution of 50 g. (0.29 mole) of 1-(1,2-dimethyl-2-piperidyl)-2-ethoxyacet-

(11) T. L. Jacobs, R. Cramer, and J. E. Hanson, *J. Am. Chem. Soc.*, **64**, 223 (1942).

TABLE I (*Continued*)

Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Pharmacological Data	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Shay rat, M.E.D.[i]	Antispasmodic effect,[j] atropine = 1.0
$C_{21}H_{25}NO_3 \cdot HCl$	67.09	67.10	6.97	7.20	3.73	3.51	>40	0.5
$C_{22}H_{28}INO_3 \cdot H_2O$	52.91	52.91	6.05	6.04	2.81	2.60	>40	0.5
$C_{21}H_{37}NO_3 \cdot HCl$	65.01	65.01	9.87	10.01	3.61	3.46	>40	0.01
$C_{22}H_{40}INO_3 \cdot H_2O$	53.54	53.36	8.17	8.23	2.84	2.60		
$C_{22}H_{27}NO_3 \cdot HCl$	67.76	67.72	7.24	7.56	3.59	3.64	40	0.50
$C_{23}H_{30}INO_3$	55.76	56.11	6.10	5.95	2.83	3.04	>40	0.25
$C_{22}H_{27}NO_2 \cdot HCl$	70.66	70.58	7.55	7.47	3.75	3.66	>40	0.05
$C_{22}H_{27}NO_3 \cdot HCl$	67.76	67.95	7.24	7.36	3.59	3.41	>40	1.0
$C_{23}H_{30}INO_3 \cdot H_2O$	53.80	54.04	6.28	6.55	2.73	2.73	>40	
$C_{22}H_{39}NO_3 \cdot HCl$	65.72	65.35	10.02	9.92	3.48	3.35	20	0.02
$C_{23}H_{42}INO_3 \cdot H_2O$	52.57	52.37	8.44	8.29	2.67	2.37	>40	0.05
$C_{22}H_{27}NO_2 \cdot HCl$	70.66	70.87	7.55	7.78	3.75	3.77	>40	0.02
$C_{23}H_{30}INO_2$	57.64	57.74	6.31	6.94	2.92	2.70	>40	0.10
$C_{22}H_{33}NO_2 \cdot HCl$	69.54	69.26	9.02	8.72	3.69	3.76	>40	0.40
$C_{23}H_{36}NO_2 \cdot HCl$	56.90	57.22	7.48	7.66	2.89	2.85	>40	0.50
$C_{22}H_{27}NO_3$	74.75	75.07	7.70	7.81	3.96	3.71	>40	1.0
$C_{23}H_{30}INO_3$	55.76	55.31	6.10	6.42	2.83	2.68	>40	
$C_{23}H_{36}INO_3$	55.09	55.01	7.24	7.26	2.79	2.75	20	0.20
$C_{22}H_{39}NO_3 \cdot HCl$	65.72	65.58	10.02	10.22	3.48	3.28	>40	0.1
$C_{23}H_{42}INO_3$	54.23	54.01	8.34	8.59	2.76	2.50	>40	0.25
$C_{23}H_{29}NO_3$	75.17	75.02	7.95	7.98	3.81	3.82	40	0.50
$C_{24}H_{32}INO_3$	56.58	55.99	6.33	6.24	2.75	2.80	>40	0.50
$C_{23}H_{29}NO_3$	75.17	75.29	7.95	7.74	3.81	3.63	>40	0.02
$C_{24}H_{32}BrNO_3 \cdot H_2O$	59.99	60.37	7.13	6.94	2.92	2.88	>40	0.01
$C_{23}H_{29}NO_3$	75.17	75.25	7.95	8.04	3.81	3.59	>40	0.01
$C_{24}H_{32}INO_3$	56.58	56.03	6.33	6.37	2.75	2.60	>40	
$C_{23}H_{41}NO_3 \cdot HCl$	66.40	66.09	10.18	10.12	3.37	3.21	>40	0.05

[i] Spasm induced in isolated guinea pig ileum with methacholine. [k] C_6H_{11} is cyclohexyl. [l] R. R. Burtner and J. M. Brown [*J. Am. Chem. Soc.*, 69, 630 (1947)] reported m.p. 152–153°.

ylene and 300 ml. of 10% sulfuric acid was stirred for 15 min. at room temperature.[11] It was then made basic with potassium carbonate and was extracted with ether. The ether solution was dried with anhydrous potassium carbonate, concentrated, and distilled under reduced pressure to give 45.5 g. (79% yield) of product, b.p. 110–115° (7 mm.), n_D^{25} 1.4620.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 65.91; H, 10.57; N, 7.16.

2-(1,2-Dimethyl-2-piperidyl)-1-ethanol. A solution of 18.9 g. (0.095 mole) of ethyl (1,2-dimethyl-2-piperidyl)acetate and 50 ml. of dry ether was added dropwise to a suspension of 2 g. of lithium aluminum hydride in 500 ml. of dry ether. After heating under reflux for 30 min., the reaction mixture was treated by the successive addition of 2 ml. of water, 1.5 ml. of 20% sodium hydroxide solution, and 7 ml. of water. The solid was removed by filtration and the ether solution was concentrated by heating on a steam bath. The residue was distilled under reduced pressure and 12.0 g. (81% yield) of product, b.p. 110–115° (9 mm.), n_D^{25} 1.4875, was obtained.

Anal. Calcd. for $C_9H_{19}NO$: N, 8.91. Found: N, 8.70.

2-(1,6-Dimethyl-2-piperidyl)ethyl chloride hydrochloride. A solution of 20 g. (0.13 mole) of 2-(1,6-dimethyl-2-piperidyl)-1-ethanol and 140 ml. of chloroform was acidified with anhydrous hydrogen chloride. Thionyl chloride (50 ml.) was added, and the reaction mixture was heated on a steam bath for 1 hr. It was then concentrated by heating on a steam bath under reduced pressure. About 50 ml. of ethanol was added, and the mixture was again concentrated. The residue was dissolved in acetone and then was placed in a refrigerator overnight. The solid that separated was collected by filtration, and 19.0 g. (69% yield) of product, m.p. 116°, was obtained.

Anal. Calcd. for $C_9H_{18}ClN.HCl$: C, 50.94; H, 9.03; N, 6.60. Found: C, 50.80; H, 8.86; N, 6.47.

Synthesis of esters (Table I). *Method A. 2-(1,6-Dimethyl-2-piperidyl)ethyl benzilate.* A solution of 15 g. (0.071 mole) of 2-(1,6-dimethyl-2-piperidyl)ethyl chloride hydrochloride, 17 g. (0.075 mole) of benzilic acid, and 7.6 g. (0.14 mole) of sodium methoxide dissolved in 200 ml. of isopropyl alcohol was heated under reflux overnight. The solids that separated

TABLE II

1-METHYL-2-PIPERIDINEAMIDES

Compound	R_1	n_1	R_2	X	n_2	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Pharmacological Data: Shay rat, M.E.D.[d]	Pharmacological Data: Anti-spasmodic effect,[d] atropine = 1.0
XVI	H	1			0	172–174	32[a]	$C_{21}H_{26}N_2O$	78.22	78.25	8.13	8.39	8.69	8.55	10	0.01
XVIIa	CH_3	1			0	157–158	30[a]	$C_{22}H_{28}N_2O$	78.53	78.60	8.39	8.42	8.33	8.24	40	0.50
XVIIb	CH_3	1	CH_3	CH_3SO_4	1	189–190	51[b]	$C_{24}H_{34}N_2O_5S$	62.31	61.95	7.41	7.48	6.06	6.08	>40	0.02
XVIII	H	2			0	125–126[e]	63[a]	$C_{22}H_{28}N_2O$	78.53	78.72	8.39	8.47	8.33	8.21	40	1.0
XIXa	CH_3	2			0	149–151	39[a]	$C_{23}H_{30}N_2O$	78.81	78.94	8.63	8.68	7.99	7.93	40	0.50
XIXb	CH_3	2	CH_3	I	1	226–228	57[c]	$C_{24}H_{33}IN_2O$	58.53	58.94	6.75	6.90	5.69	5.63	40	0.20

[a] Recrystallization solvent: [a] ethyl acetate, [b] isopropyl alcohol-ethyl acetate, [c] ethanol. [d] See Table I. [e] L. A. Walter, R. H. Barry, and J. R. Clark, U. S. Patent 2,649,456, reported m.p. 124–126°.

were removed by filtration, and the filtrate was concentrated by heating under reduced pressure on the steam bath. The residue was recrystallized from 95% ethanol, and 15.5 g. (59% yield) of ester (XIVa), m.p. 84–85°, was obtained.

Method B. 2-(1,2-Dimethyl-2-piperidyl)ethyl benzilate. A mixture of 5 g. (0.03 mole) of 2-(1,2-dimethyl-2-piperidyl)-1-ethanol, 7.3 g. (0.03 mole) of methyl benzilate, 100 ml. of *n*-heptane, and a trace of sodium methoxide was heated under reflux overnight. A Dean-Stark water separator was used to remove methanol.

The reaction mixture was then cooled, washed with 50 ml. of water, and extracted with two 25-ml. portions of 6*N* hydrochloric acid. The acid solutions were combined, made basic with potassium carbonate, and extracted with two 50-ml. portions of benzene. The benzene extract was dried with anhydrous potassium carbonate, and the benzene was removed by heating on a steam bath. The residue solidified and was recrystallized from petroleum ether to give 7.5 g. (64% yield) of product (XIIa), m.p. 57–59°.

Quaternary salt formation. 2-(1,2-Dimethyl-2-piperidyl)-ethyl benzilate methiodide. A solution of 1.5 g. (0.004 mole) of 2-(1,2-dimethyl-2-piperidyl)ethyl benzilate (XIIa), 10 ml. of methyl iodide, and 10 ml. of ether was heated on a steam bath overnight. The solid was collected and was twice recrystallized from a methanol–ethyl acetate mixture. The yield of XIIb, m.p. 163–165°, was 1.4 g. (68%).

The quaternary salts contained in Table I were prepared according to the above procedure.

Preparation of amides (Table II). *2,2-Diphenyl-4-(1,6-dimethyl-2-piperidyl)butyramide.* To a stirred suspension of 11 g. (0.44 mole) of sodium amide and 200 ml. of dry toluene was added a solution of 85 g. (0.44 mole) of diphenylacetonitrile and 400 ml. of dry toluene. After heating under reflux for 4 hr., a solution of 2-(1,6-dimethyl-2-piperidyl)-ethyl chloride (from 90 g., 0.43 mole, of the hydrochloride salt) dissolved in 200 ml. of benzene was added dropwise. The reaction mixture was then heated under reflux for 16 hr., cooled, and cautiously diluted with 25 ml. of methanol and 400 ml. of water. The water layer was discarded, and the organic layer was extracted twice with 200 ml. of 2*N* hydrochloric acid. The acid fraction was made basic with potassium carbonate and then was extracted three times with 200-ml. portions of benzene. The benzene extract was concentrated by heating on a steam bath under reduced pressure. The crude 2,2-diphenyl-4-(1,6-dimethyl-2-piperidyl)butyronitrile that remained weighed 124 g. Without further purification, the nitrile was dissolved in 250 ml. of 90% sulfuric acid and was heated for 4 hr. on a steam bath. The solution was cooled and then was added to about 2 kg. of ice. Concentrated ammonium hydroxide was added until the solution was basic. The mixture was extracted with chloroform, and the extract was shaken with dilute potassium carbonate solution and then was dried with anhydrous potassium carbonate. The chloroform was removed by heating on a steam bath, and the residue that resulted was recrystallized from methyl ethyl ketone. The first crop of material melted at 138–142° and was recrystallized from ethyl acetate to give 58 g. (39% yield) of XIXa, m.p. 149–151°.

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