[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF THE SCHERING CORPORATION]

PARASYMPATHETIC BLOCKING AGENTS. II[1, 2]

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Received February 18, 1955

In recent years the synthetic and pharmacological approach to anticholinergic drugs has changed from a study of the conventional tertiary basic esters to a study of quaternary amines. With the advent of "Banthine,"[3] "Prantal"[4] and other anticholinergic drugs, greater specificity of action upon smooth muscle has been obtained with reduction in effect upon the pupils and salivary glands.

The present investigation was undertaken with the view of exploring the pharmacology of selected quaternary salts of a limited group of basic esters. It was hoped that the combination of the acid and alcohol moieties of reported highly active antispasmodic agents, would, upon quaternization, yield a more potent agent with minimal toxicity side effects. Thus in this paper are reported our findings with disubstituted acetic acid esters of 3- and 4-piperidinols together with their quaternary salts.

The use of the cyclic amino alcohols was prompted by the findings of Burtner and Cusic (1) and Cusic and Robinson (2) that certain esters of 1-methyl-4-piperidinol possessed interesting pharmacological properties.[5] Similarly, certain acid moieties such as cyclopentenylacetic acids and cyclohexenylacetic acids were utilized on the basis of the findings of Moffett, *et al.* (3, 4).

With the exception of compounds 30 and 38 in Table I, the esters were prepared by allowing an acid chloride to react with the appropriate amino alcohol in benzene solvent in the presence of triethylamine. However, in the case of compound 30, the presence of the tertiary β-hydroxyl group necessitated modification whereby the free acid was reacted with the appropriate dialkylaminoethyl halide (5).

Difficulty in obtaining an accurate analysis of 1,2,6-trimethyl-3-piperidinol necessitated a different approach to the preparation of compound 38. Condensation of 1,2,6-trimethyl-3-hydroxypyridine with the appropriate acid chloride, and quaternization of the pyridyl ester followed by reduction of the quaternary salt resulted in the formation of compound 38 in about 55% yield.[6]

The esters and their quaternary salts were screened for their antispasmodic

[1] Part I, Sperber, Villani, Sherlock, and Papa, *J. Am. Chem. Soc.*, **73**, 5010 (1951).

[2] Presented in abstract at the Meeting-in-Miniature of the American Chemical Society's New York Section at Hunter College, New York, N. Y., February 12, 1954.

[3] Registered trade mark of G. D. Searle and Co. for diethylaminoethyl 9-xanthenecarboxylate methobromide.

[4] Registered trade mark of Schering Corporation for N,N-dimethyl 4-piperidylidene-1,1-diphenylmethane methosulfate.

[5] Concurrently with our investigation, the syntheses and activities of esters of 1-alkyl-3-piperidinol were reported by Biel, Friedman, Leiser, and Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952).

[6] It is of interest to note that reduction of 3-pyridyl diphenylacetate is reported by Biel, *et al.*, *loc. cit.*, to result mainly in cleavage products.

action against acetylcholine on the excised guinea pig ileum using atropine sulfate as reference standard and for their oral parasympathetic blocking activity in mice (6) and dogs (7) using Prantal and Pro-Banthine as reference standards.

In general, with the exception of compounds 30, 31, and 32, the 3-piperidyl and the dialkylaminoethyl esters were relatively inactive, exhibiting less than 30% of the activity of atropine sulfate and of Prantal in the tests described. The activities of the hydroxylated ester, compound 30, and its quaternary salts, 31 and 32, fall within the range of 1–3 times the potency of the standards in the *in vitro* antispasmodic and *in vivo* anticholinergic test. Except for compound 5, all the 4-piperidyl esters exhibited moderate activity in the range of 0.5–5 times atropine sulfate and 0.5–2.5 times Prantal. Of the compounds shown in Table I, the more active substances were the quaternary salts of compounds 8, 30, and 33, whose potencies were well above the mid-point of the ranges cited. As a general rule, the anticholinergic activity of the basic ester was enhanced by quaternization and decreased by alkylation of the piperidine ring.

Acknowledgment. The authors wish to express their appreciation to Dr. Solomon Margolin[7] and staff for the pharmacological evaluation and to Mr. Edwin Conner and staff for the microanalyses reported herein.

EXPERIMENTAL

PREPARATION OF THE ACIDS

The following acids were prepared according to methods reported in the literature: phenyl-Δ^2-cyclohexenylacetic (8), phenyl-Δ^2-cyclopentenylacetic (8, 9), *n*-propyl-Δ^2-cyclopentenylacetic (9), *n*-propylcyclopentylacetic (3). Isobutyl-Δ^2-cyclopentenylacetic acid was prepared according to the general procedures of Horclois (9) and Moffett, *et al.* (3), b.p. 135–139°/5 mm., n_D^{31} 1.4609.

α-(1-Hydroxycyclopentyl)isocaproic acid. The intermediate, ethyl α-bromoisocaproate, was prepared from isocaproic acid according to the procedure described by Schwenk and Papa (10), b.p. 95–97°/22–23 mm. n_D^{27} 1.4432. By condensing the α-bromoester with cyclopentanone in the presence of zinc according to described procedures for the Reformatsky reaction (11), ethyl α-(1-hydroxycyclopentyl)isocaproate was obtained in 50% yield, b.p. 95–99°/2 mm., n_D^{23} 1.4625.

A solution of 60 g. (0.26 mole) of ethyl α-(1-hydroxycyclopentyl)isocaproate, 32 g. of potassium hydroxide, 145 ml. of water, and 145 ml. of ethanol was stirred and refluxed for four hours. The solvent was removed *in vacuo* and the residue was treated with 100 ml. of ice-water. The aqueous mixture was extracted with ether (from which 33 g. of unsaponified ester was obtained) and then acidified with dilute hydrochloric acid. The aqueous mixture was again extracted thoroughly with ether and the combined extracts were washed with water and dried over sodium sulfate. Evaporation of the ether followed by recrystallization of the residue from petroleum ether (35–50°) yielded 22 g. (42%) of white crystals, m.p. 95.2–96.2°.

Anal. Calc'd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07.
Found: C, 65.46; H, 9.93.

PREPARATION OF THE AMINO ALCOHOLS

1,6-Dimethyl-3-hydroxypiperidine. In our hands, the procedure of Graf (12) yielded only small quantities of the requisite intermediate, 6-methyl-3-pyridol. Therefore we employed the following procedure:

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TABLE I

Basic Esters and Quaternary Salts $\begin{matrix} R_1 \\ \diagdown \\ \quad CHCOOR_3 \cdot X \\ \diagup \\ R_2 \end{matrix}$

No.	R_1	R_2	R_3	X[a]	M.p. or B.p., °C.	mm.	n_D	°C.	Yield,[b] %	Empirical Formula	Nitrogen Analyses	
											Calc'd	Found
1	C_6H_5	C_6H_5	1-Methyl-3-piperidyl[c]	—	188–193	1	1.5520	23	70.0	$C_{20}H_{23}NO_2$	4.53	4.44
2	C_6H_5	C_6H_5	1-Methyl-3-piperidyl	CH_3I	130.0–132.0		—	—	65.2	$C_{21}H_{26}INO_2$	3.10	3.18
3	C_6H_5	C_6H_5	1-Methyl-4-piperidyl[d]	—	184–188	1	1.5548	23	58.0	$C_{20}H_{23}NO_2$	4.53	5.28
4	C_6H_5	C_6H_5	1-Methyl-4-piperidyl	CH_3I	212.5–212.9		—	—	64.5	$C_{21}H_{26}INO_2$	3.10	2.86
5	C_6H_5	C_6H_5	1-Methyl-4-piperidyl	n-C_4H_9Br	158.0–159.5		—	—	75.5	$C_{24}H_{32}BrNO_2$	3.15	3.30
6	C_6H_5	C_6H_9[e]	1-Methyl-4-piperidyl	—	186–190	3	—	—	48.0	$C_{20}H_{27}NO_2$	4.47	4.74
7	C_6H_5	C_6H_9	1-Methyl-4-piperidyl	CH_3I	98.0–100.0		—	—	89.0	$C_{21}H_{30}INO_2$	3.07	3.01
8	C_6H_5	C_5H_7[f]	1-Methyl-4-piperidyl	—	186–191	4	1.5298	24	67.0	$C_{19}H_{25}NO_2$	4.68	4.52
9	C_6H_5	C_5H_7	1-Methyl-4-piperidyl	CH_3I	139–0.140.2		—	—	63.2	$C_{20}H_{26}INO_2$	3.15	3.44
10	C_6H_5	C_5H_7	1-Methyl-4-piperidyl	CH_3Br[g]	211.5–212.0		—	—	79.3	$C_{20}H_{26}BrNO_2$	3.55	3.18
11	C_6H_5	C_5H_7	1-Methyl-3-piperidyl	—	159–161	2	1.5234	24	80.0	$C_{19}H_{25}NO_2$	4.68	4.59
12	C_6H_5	C_5H_7	1-Methyl-3-piperidyl	CH_3I	164.0–164.2		—	—	71.0	$C_{20}H_{26}INO_2$	3.15	3.35
13	C_6H_5	C_5H_7	1,2,2,6-Tetramethyl-4-piperidyl	—	162–167	1	1.5267	28	51.3	$C_{22}H_{33}NO_2$	4.10	3.97
14	C_6H_5	C_5H_7	1,2,2,6-Tetramethyl-4-piperidyl	CH_3I	190.8–192.0		—	—	50.0	$C_{23}H_{34}INO_2$	2.90	2.80
15	C_6H_5	C_5H_7	2-(N-methyl-N-isopropylamino)ethyl	—	156–159	1	1.5098	26	80.0	$C_{19}H_{27}NO_2$	4.65	4.81
16	C_6H_5	C_5H_7	2-(N-methyl-N-isopropylamino)ethyl	CH_3I	129.2–130.0		—	—	85.0	$C_{20}H_{30}INO_2$	3.14	2.82
17	C_6H_5	C_5H_7	2-(N-methyl-N-isopropylamino)ethyl	CH_3Br[g]	172.5–173.5		—	—	78.7	$C_{20}H_{30}BrNO_2$	3.53	3.32
18	C_6H_5	C_5H_7	2-Diisopropylaminoethyl	—	168–172	2	1.5102	26	63.0	$C_{21}H_{31}NO_2$	[h]	
19	C_6H_5	C_5H_7	2-Diisopropylaminoethyl	CH_3Br	164.0–165.0		—	—	25.0	$C_{22}H_{34}BrNO_2$	3.30	3.43
20	n-C_3H_7	C_5H_7	1-Methyl-4-piperidyl	—	127–129	1	1.4770	23	80.3	$C_{16}H_{27}NO_2$	5.28	5.03
21	n-C_3H_7	C_5H_7	1-Methyl-4-piperidyl	CH_3I	158.4–159.6		—	—	90.0	$C_{17}H_{30}INO_2$	3.44	3.15
22	n-C_3H_7	C_5H_7	1,2,2,6-Tetramethyl-4-piperidyl	—	134–139	1	1.4762	32	60.0	$C_{19}H_{33}NO_2$	4.55	4.56
23	n-C_3H_7	C_5H_7	1,2,2,6-Tetramethyl-4-piperidyl	CH_3I	193.0–194.8		—	—	53.0	$C_{20}H_{36}INO_2$	3.12	3.06
24	n-C_3H_7	C_5H_7	Tropyl	—	152–156	1	1.4933	26	67.4	$C_{18}H_{29}NO_2$	[i]	
25	n-C_3H_7	C_5H_7	Tropyl	CH_3I	255.0–256.0		—	—	50.2	$C_{19}H_{32}INO_2$	3.23	2.70

26	n-C_3H_7	C_5H_7	2-(N-methyl-N-isopropyl-amino)ethyl	—	138–140	3	1.4592	29	67.1	$C_{16}H_{29}NO_2$	5.24	5.20
27	n-C_3H_7	C_5H_7	2-(N-methyl-N-isopropyl-amino)ethyl	CH_3I	184.5–185		—	—	59.0	$C_{17}H_{32}INO_2$	3.42	3.28
28	i-C_4H_9	C_5H_7	2-(N-methyl-N-isopropyl-amino)ethyl	—	133–138	3	1.4622	24	68.5	$C_{17}H_{31}NO_2$	4.98	4.83
29	i-C_4H_9	C_5H_7	2-(N-methyl-N-isopropyl-amino)ethyl	CH_3I	192.6–193.2		—	—	35.0	$C_{18}H_{34}INO_2$	3.31	3.03
30	i-C_4H_9	$C_5H_{10}O$[i]	2-(N-methyl-N-isopropyl-amino)ethyl	—	150	1	1.4639	27	58.0	$C_{17}H_{33}NO_3$	4.68	4.53[k]
31	i-C_4H_9	$C_5H_{10}O$	2-(N-methyl-N-isopropyl-amino)ethyl	CH_3I	182.6–184.5		—	—	75.0	$C_{18}H_{36}INO_3$	3.17	2.86
32	i-C_4H_9	$C_5H_{10}O$	2-(N-methyl-N-isopropyl-amino)ethyl	CH_3Br[g]	206.0–207.0		—	—	82.1	$C_{18}H_{36}BrNO_3$	3.55	3.00
33	n-C_3H_7	C_5H_9[l]	1-Methyl-4-piperidyl	—	129–132	1	1.4670	23	55.0	$C_{16}H_{29}NO_2$	5.24	5.11
34	n-C_3H_7	C_5H_9	1-Methyl-4-piperidyl	CH_3I	176.8–177.5		—		95.0	$C_{17}H_{32}INO_2$	3.43	3.27
35	n-C_3H_7	C_5H_9	1-Methyl-4-piperidyl	CH_3Br[g]	221.8–222.5		—		80.0	$C_{17}H_{32}BrNO_2$	3.86	3.66
36	n-C_3H_7	C_5H_9	1,6-Dimethyl-3-piperidyl	—	159–164	4	1.4690	25	40.0	$C_{17}H_{21}NO_2$	[m]	
37	n-C_3H_7	C_5H_9	1,6-Dimethyl-3-piperidyl	CH_3I	222.0–223.0		—		80.2	$C_{18}H_{34}INO_2$	[n]	
38	n-C_3H_7	C_5H_9	1,2,6-Trimethyl-3-piperidyl	—	141–148	1	1.4750	28	55.0	$C_{18}H_{33}NO$	[o]	
39	n-C_3H_7	C_5H_9	1,2,6-Trimethyl-3-piperidyl	CH_3I	141–142		—	—	75.3	$C_{18}H_{36}INO_2$	[p]	

[a] The quaternary salts were recrystallized from ethanol-ether. [b] Yields of quaternary salts are for once recrystallized products. [c] Originally reported by Biel, Friedman, Sprengeler, Leiser, and Horner, Abst. of papers presented at Division of Medicinal Chemistry of Amer. Chem. Soc., Chicago, 1953 p. 25N. [d] Hydrochloride preparted by Burtner and Cusic, *J. Amer. Chem. Soc.*, **65**, 262 (1943). [e] Δ^2-Cyclohexenyl. [f] Δ^2-Cyclopentenyl. [g] Prepared from corresponding iodide. [h] *Anal.* Calc'd: C, 76.79; H, 9.51. Found: C, 76.80; H, 9.48. [i] *Anal.* Calc'd: C, 74.18; H, 10.00. Found: C, 74.20; H, 10.18. [j] 1-Hydroxycyclopentyl. [k] *Anal.* Calc'd: C, 68.1; H, 11.2. Found: C, 67.52; H, 10.97. [l] Cyclopentyl. [m] *Anal.* Calc'd: C, 72.59; H, 11.03. Found: C, 73.17; H, 10.66. [n] *Anal.* Calc'd: C, 51.06; H, 8.04. Found: C, 51.06; H, 8.41. [o] *Anal.* Calc'd: C, 73.17; H, 11.25. Found: C, 72.92; H, 10.78. [p] *Anal.* Calc'd: C, 51.48; H, 8.30. Found: C, 51.45; H, 8.49.

To a solution of 129.6 g. (1.2 moles) of 3-amino-6-methylpyridine in 200 ml. of concentrated sulfuric acid and 1.0 liter of water at −10° was added, dropwise, a chilled solution of 110 g. of sodium nitrite in 400 ml. of water. After stirring for two hours, the solution of the diazonium salt was added to a stirred refluxing solution of 400 ml. of concentrated sulfuric acid in 1200 ml. of water. The resultant mixture was refluxed for three hours and allowed to stand overnight at room temperature. After cooling, the mixture was neutralized with aqueous ammonia and extracted with ether in a continuous extraction apparatus for 72 hours. Evaporation of the solvent yielded 116 g. (88.5%) of crude 6-methyl-3-pyridol, m.p. 159–162° (reported 165–167°) (12).

The pyridol was converted to the corresponding piperidinol in the following manner: A mixture of 21.8 g. (0.2 mole) of 6-methyl-3-pyridol and 40 g. (0.22 mole) of methyl *p*-toluenesulfonate was heated on a steam-bath for 20 minutes and cooled. Benzene was added and the crystalline product was removed by filtration and recrystallized from alcohol-ether, yielding 38 g. (65%) of *1,6-dimethyl-3-hydroxypyridinium p-toluene sulfonate* as a light green substance, m.p. 165–167°.

A solution of 38 g. (0.129 mole) of the quaternary salt, in 250 ml. of absolute ethanol was hydrogenated in a Parr apparatus in the presence of platinum oxide. After filtering off the catalyst, the alcohol was removed *in vacuo* and the residue treated with dilute aqueous ammonium hydroxide. The mixture was extracted with ether and the extracts were dried with potassium carbonate, concentrated and distilled, yielding 5.0 g. (30.5%) of 1,6-dimethyl-3-hydroxypiperidine, b.p. 65–67°/8 mm., n_D^{27} 1.4700.

Anal. Calc'd for $C_7H_{15}NO$: C, 65.11; H, 11.62.

Found: C, 64.99; H, 12.00.

1,2,6-Trimethyl-3-hydroxypiperidine methiodide. In a manner similar to that described above, there was obtained 1,2,6-trimethyl-3-hydroxypiperidine as white needles, m.p. 57.0–57.5° from petroleum-ether. The aminoalcohol easily sublimed and difficulty was experienced in obtaining an analysis. In order to obtain proper identification, the aminoalcohol was converted to its quaternary methiodide and was recrystallized from methanol-ether, m.p. 304.5–305°.

Anal. Calc'd for $C_9H_{20}INO$: N, 4.91. Found: N, 4.87.

The following aminoalcohols were prepared by methods described in the literature: β-N-methyl-N-isopropylaminoethanol, b.p. 162–163° (13); β-diisopropylaminoethanol, b.p. 186–190° (14); 1-methyl-4-piperidinol, b.p. 101–103°/16 mm. (15); 1-methyl-3-piperidinol, b.p. 80–86°/17 mm. (16); 1,2,2,6-tetramethyl-4-piperidinol, m.p. 76–77° (17).

PREPARATION OF THE ESTERS

The following example is typical of the esterification procedure employed: *2,6-Dimethyl-3-pyridyl n-propylcyclopentylacetate.* A solution of 0.10 mole of *n*-propylcyclopentylacetic acid in 100 ml. of thionyl chloride was refluxed for two hours whereupon the excess thionyl chloride was removed by distillation *in vacuo*, with the last traces being removed by co-distillation with anhydrous benzene. The residual acid chloride was dissolved in 25 ml. of benzene and dropwise added to a solution of 0.10 mole of 2,6-dimethyl-3-hydroxypyridine and 0.10 mole of pyridine (or triethylamine) in 100 ml. of benzene. The mixture was stirred and refluxed for two hours, cooled, and poured into water. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with water, dried over potassium carbonate, and evaporated *in vacuo*. Upon distillation *in vacuo*, there was obtained 21 g. (76.5%), b.p. 140–150°/1 mm., n_D^{26} 1.4948.

Anal. Calc'd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.16.

Found: C, 73.70; H, 9.63.

1,2,6-Trimethyl-3-piperidyl n-propylcyclopentylacetate: Compound 38. A mixture of 15 g. (0.055 mole) of the 2,6-dimethyl-3-pyridyl *n*-propylcyclopentylacetate and 12.5 g. (0.067 mole) of methyl *p*-toluenesulfonate was heated on a steam-bath for 6 hours. After cooling, the mass was treated with ether which, upon decantation, left a red gummy solid. The gum was dissolved in ethanol and treated with hydrogen in a Parr apparatus using platinum

oxide catalyst. After filtering off the catalyst, the alcohol was removed *in vacuo* and the residue treated with water. The aqueous mixture was made alkaline and extracted with ether. The ether extracts were dried over potassium carbonate, filtered, and distilled *in vacuo* yielding Compound 38.

Compound 31 in Table I was prepared from N-methyl-N-isopropylaminoethyl chloride and α-(1-hydroxycyclopentyl)isocaproic acid in the usual manner (1, 6).

PREPARATION OF THE QUATERNARY SALTS

Except as noted in Table I, the quaternary salts were prepared by reacting the basic ester with an excess of the alkyl halide, generally in refluxing ether solution. The reaction mixture was allowed to stand overnight and filtered. The purified salt was obtained by recrystallization from absolute ethanol-absolute ether.

The quaternary methobromides were, as noted in Table I, prepared in the usual manner by *trans*-halogenation of the iodide in methanol solution with freshly prepared silver bromide. The bromides were purified by recrystallization from absolute alcohol-absolute ether.

SUMMARY

A series of alkamine esters and quaternary salts of disubstituted acetic acids have been prepared and examined for their anticholinergic activity. Despite the increased anticholinergic and antispasmodic properties of a few of the compounds cited, these compounds, as well as the less potent ones, generally exhibited mydriasis and xerostomia in animals.

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