[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Antispasmodics. Esters of 3-(1-Methylpiperidyl)-carbinol

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In a previous communication[2] a synthesis of 3-(1-methylpiperidyl)-carbinol was described which gave better yields and a product differing somewhat in physical properties from the original product of Sandborn and Marvel.[3] This paper reports a series of esters of this alcohol which have been prepared as their hydrohalide or quarternary salts and screened for their cholinolytic activities. Complete pharmacology on some of the compounds will be reported elsewhere.

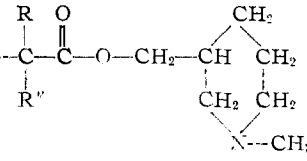
In a search for useful antispasmodic agents it was found that 1-methyl-3-piperidylmethyl diphenylacetate hydrochloride compared most favorably with tropyl diphenylacetate,[4] when tested by the Magnus technique against acetylcholine induced spasms. This led to the preparation of quite a diversified series of esters, some of which have shown exceptional activity in both *in vitro* and *in situ* animal tests and preliminary clinical trials. A discussion of this activity in comparison to 2-diethylaminoethyl and tropyl esters has been published by Lands.[5]

thienylglycolic acid[6] and 2-hydroxy-2-(4-xenyl)-propionic acid[7] were prepared from phenyl- and 4-xenylglyoxylic acids by a Grignard reaction and the corresponding acetic acids obtained by succeeding reductions of the hydroxy groups. The 2-cyclopentyl-4-methylpentanoic acid[8] was prepared by a malonic ester synthesis and 3-hydroxy-2-phenylbutanoic acid through the Ivanoff[9] reaction as modified by Blicke and Raffelson.[10]

Esterifications offered somewhat of a problem in the cases of the hydroxy acids. Although 1-methyl-3-piperidylmethyl chloride[2] could be easily

TABLE I

ESTERS OF 3-(1-METHYLPIPERIDYL)-CARBINOL



Cpd.	R	R'	R''	R'—C(R)(R'')—	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Method	Atropine, %
1				C_6H_5	177–178.1	$C_{14}H_{19}NO_2 \cdot HCl$	62.33	62.43	7.47	7.23	13.18	13.21	I	< 1
2				C_6H_5	196.6–197.2	$C_{14}H_{19}NO_2 \cdot CH_3I$	48.00	47.96	5.91	5.70	33.80	33.60	I	< 1
3				C_4H_3S[b]	150–153.1	$C_{12}H_{17}NO_2S \cdot HCl$	11.62[c]	11.63			12.88	12.83	I	< 1
4				C_4H_3S[b]	194.7–195.8	$C_{13}H_{21}NO_2S \cdot CH_3I$	8.40[c]	8.61			33.30	33.25	I	< 1
5				C_6H_4N[d]	147–148.8	$C_{18}H_{18}N_2O_2 \cdot 2HCl \cdot H_2O$[e]	48.04	48.13	6.99	6.51	21.83	21.80	I	...
6	C_6H_5	C_6H_5	H		198.2–199.3	$C_{21}H_{25}NO_2 \cdot HCl$	70.08	70.16	7.28	7.11	9.85	9.93	I	6
7	C_6H_5	C_4H_3S[b]	H		176–177.2	$C_{18}H_{23}NO_2S \cdot HCl$[f]	8.74[c]	8.98			9.70	9.43	III	10
8	C_6H_5	C_4H_3S[b]	H		153.7–154.8	$C_{19}H_{25}NO_2S \cdot CH_3I$[f]	51.40	51.26	5.34	5.45	26.90	26.63	III	16
9	C_5H_9[g]	C_4H_9[h]	H		159.6–162.6	$C_{18}H_{28}NO_2 \cdot CH_3Br$	58.45	58.49	9.29	9.08	20.47	20.55	III	200
10	$C_{12}H_9$[i]	CH_3	H		192.0–194.2	$C_{22}H_{27}NO_2 \cdot CH_3Br$	63.88	63.84	6.99	7.03	18.48	18.43	III	<1
11	C_6H_5	C_6H_5	OH		217.6–219.8	$C_{21}H_{25}NO_3 \cdot HCl$	67.10	67.15	6.97	7.04	9.43	9.48	II	9
12	C_6H_5	C_6H_5	OH		227.7–229.8	$C_{21}H_{25}NO_3 \cdot CH_3Br$[j]	60.83	60.69	6.49	6.35	18.39	18.45	II	33
13	C_6H_5	C_4H_3S[b]	OH		150–151	$C_{19}H_{23}NO_3S \cdot CH_3Br$	54.60	54.44	5.94	5.88	18.14	17.90	II	5
14	$C_{12}H_9$[i]	CH_3	OH		148–172 d	$C_{22}H_{27}NO_3 \cdot HBr$	60.83	61.04	6.49	6.40	18.40	18.39	III	< 1
15	$C_{12}H_9$[i]	CH_3	OH		117–118.6	$C_{23}H_{30}NO_3 \cdot CH_3Br$	61.60	61.20	6.74	6.51	17.82	17.90	III	< 1
16	C_6H_5	CH_3—C(H)(OH)—	H		158–162.2	$C_{15}H_{25}NO_2 \cdot CH_3I$[k]	49.80	49.50	6.52	6.55	29.23	29.25	III	4
17	C_6H_5	CH_3—C(H)(OH)—	H		186.8–189.8	$C_{17}H_{25}NO_2 \cdot CH_3Br$[k]	55.90	55.84	7.31	7.05	20.64	20.62	III	2

[a] All melting points are corrected. [b] 2-Thienyl. [c] Sulfur analysis. [d] 3-Pyridyl. [e] Calcd. for 1 H_2O: 5.53. Found: H_2O, 5.18. [f] U. S. Patent 2,533,002. [g] Cyclopentyl. [h] Isobutyl. [i] 4-Xenyl. [j] Ford-Moore and Ing made the methochloride, *J. Chem. Soc.*, 55 (1947). [k] U. S. Patent 2,533,003. Compounds 2, 4, 11, 12 and 15 were recrystallized from anhydrous ethanol; compounds 6, 7 and 10 from isopropyl alcohol; compound 8 from acetone; compound 9 from ethyl acetate; compounds 1, 3, 5, 14, 16 and 17 from a mixture of ethanol and ethyl ether and compound 13 from a mixture of isopropyl alcohol and ethyl acetate.

The acids esterified by 3-(1-methylpiperidyl)-carbinol were either purchased or prepared by published methods. The hydroxy acids, phenyl-2-

prepared, it was found to be unreactive in the ideal Horenstein and Pählicke[11] method even when cata-

(1) Smith-Dorsey, Lincoln, Nebraska.

(2) R. F. Feldkamp, J. A. Faust and A. J. Cushman, THIS JOURNAL, **74**, 3831 (1952).

(3) L. T. Sandborn and C. S. Marvel, *ibid.*, **50**, 563 (1928).

(4) K. Miescher and K. Hoffmann, U. S. Patent 2,143,491 (1939).

(5) A. M. Lands, *J. Pharm. Exp. Ther.*, **102**, 219 (1951).

(6) F. F. Blicke and M. U. Tsao, THIS JOURNAL, **66**, 1645 (1944).

(7) F. F. Blicke and N. Grier, *ibid.*, **65**, 1725 (1943).

(8) R. B. Moffett, U. S. Patent 2,535,085 (1950).

(9) D. Ivanoff and N. I. Nicoloff, *Bull. soc. chim. France*, **51**, 1325 (1932).

(10) F. F. Blicke and H. Raffelson, THIS JOURNAL, **74**, 1730 (1952).

(11) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1654 (1938).

lyzed with potassium iodide. This chloride likewise failed to react with either the silver or sodium salt of phenyl-2-thienylacetic acid. Esters were therefore prepared, (I) by action of an acid chloride on the basic alcohol in benzene solution, (II) by ester exchange[12] with methyl esters using sodium methoxide as catalyst in refluxing *n*-heptane and (III) by direct esterification of an acid with the alcohol in refluxing benzene with gaseous hydrogen chloride. This latter method was used when acid chlorides could not be made or were not available and in those cases where methyl esters were unstable toward sodium methoxide.

Hydrohalides were prepared by conventional methods or obtained as products of the esterifications. Quaternary salts were best prepared in acetonitrile solutions from free bases and the desired alkyl halide.

The preliminary antispasmodic screening data reported herein were graciously supplied by Dr. A. M. Lands and co-workers in the Pharmacological Research Laboratories. All activities were obtained by means of the Magnus technique against acetylcholine induced spasms in isolated strips of rabbit jejunum and are recorded as relative activities in comparison to atropine at 100%.

Experimental

Methyl Phenyl-2-thienylglycolate.—A solution of 37.4 g. (0.1595 mole) of phenyl-2-thienylglycolic acid, 300 cc. of anhydrous methanol and 5 cc. of 98% sulfuric acid was refluxed for 17 hours. The excess methanol was removed by distillation and the red residue treated with water. The insoluble ester was extracted with ether, the extract back washed once with dilute sodium bicarbonate solution and then dried with anhydrous magnesium sulfate. After filtration and removal of solvent by distillation the deep red colored residual oil was distilled; yield of light straw colored oil 29.3 g. (74%), b.p. 109–113° (0.02–0.03 mm.), $n^{25}D$ 1.5694.

Anal. Calcd. for $C_{13}H_{12}O_2S$: sapn. equiv., 248.3. Found: sapn. equiv., 250.3.

Methods of Esterification. I. With Acid Chlorides.—Equimolar quantities of an acid chloride and 3-(1-methylpiperidyl)-carbinol were refluxed in a benzene solution. Invariably the crystalline ester hydrochloride separated out during this process.

II. With Methyl Esters.—A solution of a methyl ester and an equivalent quantity of 3-(1-methylpiperidyl)-carbinol in *n*-heptane (b.p. 98°) was placed in a flask connected to a water separator with 0.5 g. of sodium methoxide. Ester exchange was readily observed as liberated methanol separated from the refluxing mixture. The free crude basic ester was obtained by first removing the solvent by distillation *in vacuo* and then treating the residue with dilute sodium carbonate solution. The insoluble oil was extracted with ether and the extract dried with anhydrous magnesium sulfate. After filtration the ether was removed by distillation leaving the oily base in crude form for conversion to either a hydrohalide or quaternary salt.

III. With Acids.—A mixture of equimolar quantities of acid and 3-(1-methylpiperidyl)-carbinol with benzene was placed in a flask fitted with a submerged gas inlet tube, water separator, condenser, etc. Hydrogen chloride was bubbled into the reaction at a moderate rate while refluxing. The rate of esterification was readily followed by the separation of water. Usually the theoretical amount collected within 15 hours depending somewhat upon the rate of gas introduction. Hydrochlorides of the basic ester were isolated in yields ranging from 50 to 60% by usual methods.

Acknowledgment.—The author wishes to thank Mr. M. E. Auerbach and Mr. K. D. Fleischer and their staffs for the analytical data reported herein.

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(12) A. R. Surrey, THIS JOURNAL, **70**, 2190 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Synthesis of a 4-Pyridyl Analog of Papaverine

BY C. R. NOLLER AND E. A. WUNDERLICH

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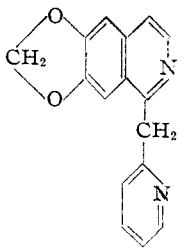
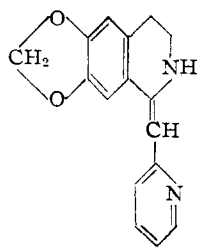
Comparison of the ultraviolet absorption spectrum of 1-(4-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline with those of the 2- and 3-pyridyl isomers indicates that the stability of the exocyclic form of the 2-isomer, and possibly its resistance to dehydrogenation, is the result of proton bonding between the two nitrogen atoms. The 4-pyridylmethyl isomer undergoes very rapid autoxidation to 1-isonicotinyl-3,4-dihydro-6,7-methylenedioxyisoquinoline. The latter compound has been converted to the papaverine analog, 1-(4-pyridylmethyl)-6,7-methylenedioxyisoquinoline, which has practically no spasmolytic activity.

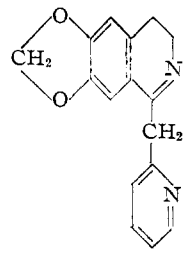
During attempts to synthesize 1-(2-pyridylmethyl)-6,7-methylenedioxyisoquinoline (I), the ultraviolet absorption spectrum of the intermediate 3,4-dihydro derivative indicated that it was 1-(2-pyridylmethylene)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (II) rather than the expected 1-(2-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (III).[1] Later the 3-pyridylmethyl analog was synthesized,[2] and its absorption spectrum indicated that it has the expected structure, namely, that of 1-(3-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (IV).



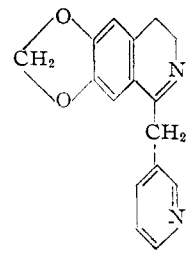
I



II



III



IV

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