Antispasmodics. II.[1] α-Phenyl-α-substituted 2-Pyridinebutanols and Related Compounds

JOHN KRAPCHO

The Squibb Institute for Medical Research, New Brunswick, New Jersey

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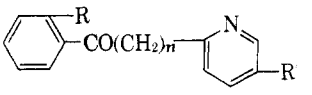
During the course of study of a variety of chemical structures as possible antispasmodic agents, we found the methobromide salt of α-cyclohexyl-α-phenyl-2-pyridinebutanol was about 20% as active as atropine in controlling acetylcholine-induced spasms of the isolated rabbit ileum. In order to determine the structural requirements for optimum activity of this class of compounds, 4-(2-pyridyl)butyrophenone[2] and the related ketones listed in Table I were prepared and allowed to react with the appropriate Grignard reagent to give the corresponding tertiary alcohols, usually in 85% yields, listed in Table II. The reaction of these pyridyl compounds with methyl bromide in acetone solution yielded the quaternary salts. Two of the methobromides **4** and **8** and one hydrochloride **7** (Table II) were reduced to the corresponding piperidyl compounds listed in Table III. Compounds **15** and **18** were neutralized to give the free bases and the latter materials converted to the methobromides **16** and **19**.

The activities of these compounds, with respect to their ability to control acetylcholine-induced spasms on the isolated rabbit ileum, are included in Tables II and III. Of the variety of tertiary alcohols containing an unsubstituted phenyl group, the highest activity was shown by the methobromide of the isopropyl derivative **4**. The potency of this compound was enhanced by the introduction of a chlorine atom into the *ortho* position of the phenyl group **11**. The latter material had the same antispasmodic activity as atropine in this test. A decrease in activity was noted when (a) an ethyl group was introduced into the 5-position of the pyridyl ring **13**, or (b) the distance between the tertiary hydroxyl group and the quaternary nitrogen was decreased by a methylene group **14**. The methobromides of the piperidyl compounds listed in Table III were less active than the corresponding pyridyl analogs. Although the quaternary salts of the pyridyl compounds of Table II were considerably more potent than their corresponding acid-addition salts, there was no significant difference in activity of the quaternary and acid-addition salts in the piperidyl compounds. The methobromide of 4-(2-pyridyl)butyrophenone (*see* Experimental part) exhibited no significant antispasmodic activity.

TABLE I

PHENYLPYRIDYLALKYL KETONES



R	R′	n	Form	M.p. or b.p., °C. (mm.)	Formula	Analysis, % Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
Cl	H	3	Base	165–170 (0.5)[a]	$C_{15}H_{14}ClNO$			5.39	5.33
Cl	H	3	HCl[b]	89–91	$C_{15}H_{15}Cl_2NO$	11.97	11.88[c]	4.73	4.79
H	CH_2CH_3	3	Base	171–173 (0.7)[d]	$C_{17}H_{19}NO$			5.53	5.32
H	CH_2CH_3	3	HCl[b]	117–119	$C_{17}H_{20}ClNO$	12.23	12.03	4.83	4.93
H	H	2	Base	146–147 (0.8)[e]	$C_{14}H_{13}NO$			6.63	6.92
H	H	2	HCl[f]	121–123	$C_{14}H_{14}ClNO$	14.31	14.09	5.66	5.88

[a] Obtained in 71% yield by reaction of ethyl *o*-chlorobenzoylacetate with 2-vinylpyridine according to the reference procedure.[2] [b] Crystallized from butanone. [c] Chloride ion. [d] Prepared in 86% yield by reaction of ethyl benzoylacetate with 5-ethyl-2-vinylpyridine according to the reference procedure.[2] [e] Obtained in 46% yield by reaction of 3-(2-pyridyl)propionitrile [L. A. Walter, W. H. Hunt, and R. J. Fosbinder, *J. Am. Chem. Soc.*, **63**, 2771 (1941)] with phenylmagnesium bromide, followed by hydrolysis with 15% hydrochloric acid. [f] Crystallized from isopropyl alcohol.

Experimental[3]

α-Isopropyl-α-phenyl-2-pyridinebutanol.—To a solution of isopropyl magnesium bromide, prepared from 24.3 g. (1.0 g.-atom) of magnesium turnings, 100 g. (0.81 mole) of isopropyl bromide and 300 ml. of ether, was added 98.0 g. (0.43 mole) of 4-(2-pyridyl)butyrophenone[2] in 100 ml. of ether. A gray precipitate separated from the mixture. The reaction mixture was refluxed for 8 hr., cooled, and poured onto a cold solution of 80 g. of ammonium chloride in 250 ml. of water. The organic layer was separated and the aqueous phase extracted with ether. The organic phases were combined, washed with 200 ml. of 5% ammonium chloride and then with 200 ml. of water, and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to give 100.5 g. (86%) of pale yellow liquid, b.p. 150–152° (0.3 mm.). This material slowly crystallized, m.p. 46–48°.

Anal. Calcd. for $C_{18}H_{23}NO$: N, 5.20. Found: N, 5.16.

The maleate **3** of this product was obtained by treatment of a solution of 38.4 g. (0.14 mole) of the base in 50 ml. of ethyl acetate with a suspension of 19.2 g. (0.16 mole) of maleic acid in 100 ml. of warm ethyl acetate. The resulting solution was cooled and the crystalline product was filtered; yield, 44.0 g., m.p. 95–96°. It was recrystallized from ethyl acetate, m.p. 96–97°.

2-(4-Hydroxy-5-methyl-4-phenylhexyl)-1-methylpyridinium Bromide (4).—A suspension of 26.0 g. (0.067 mole) of the maleate **3** in 100 ml. of water was treated with a solution of 20 g. of potassium carbonate in 40 ml. of water. The liberated base was extracted with ether. The ether extracts were combined, dried over magnesium sulfate, and the solvent was evaporated. The residue was dissolved in 100 ml. of acetone and treated with 14.2 g. (0.15 mole) of methyl bromide in 30 ml. of acetone. After standing at room temperature for two days, the mixture was

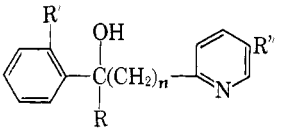
(1) Previous paper: J. Krapcho, C. F. Turk, and E. J. Pribyl, *J. Am. Chem. Soc.*, **77**, 3632 (1955).

(2) V. Boekelheide and E. J. Agnello, *ibid.*, **72**, 5005 (1950).

(3) Microanalyses by Mr. J. Alcino and his associates. Infrared spectra by Miss B. Keeler. Melting points are uncorrected.

TABLE II

PHENYLPYRIDYLALKYL ALCOHOLS

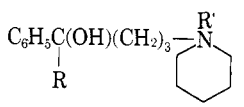


Compound no.	R	R′	R″	n	Salt	Solvent[a]	M.p., °C.	Formula	Analyses, % Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found	Activity atropine = 100[b]
1	CH_3	H	H	3	CH_3Br[c]	A	119–121	$C_{17}H_{22}BrNO$	23.77	23.77	4.17	4.38	0.4[d]
2	CH_2CH_3	H	H	3	CH_3Br[e]	A	140–142	$C_{18}H_{24}BrNO$	22.81	22.77	4.00	4.22	3
3	$CH(CH_3)_2$	H	H	3	Maleate	B	96–97	$C_{22}H_{27}NO_5$		[f]	3.63	3.65	0.1[d]
4	$CH(CH_3)_2$	H	H	3	CH_3Br	CD	134–135	$C_{19}H_{26}BrNO$	21.94	21.93	3.85	4.13	59
5	$CH_2CH(CH_3)_2$	H	H	3	CH_3Br[g]	C	158–160	$C_{20}H_{28}BrNO$	21.12	21.21	3.70	3.87	22
6	$(CH_2)_5CH_3$	H	H	3	CH_3Br[h]	E	118–120	$C_{22}H_{32}BrNO$	19.67	20.00	3.45	3.58	6
7	C_6H_{11}[i]	H	H	3	HCl[j]	A	172–173	$C_{21}H_{23}ClNO$	10.25	10.17	4.05	4.25	0.3[d]
8	C_6H_{11}	H	H	3	CH_3Br	F	190–191	$C_{22}H_{30}BrNO$	19.76	19.68	3.46	3.41	20
9	C_6H_5	H	H	3	CH_3Br[k]	GH	185–186	$C_{22}H_{24}BrNO$	20.06	19.71	3.52	3.78	34
10	$CH(CH_3)_2$	Cl	H	3	HCl[l]	A	185–187	$C_{18}H_{23}Cl_2NO$	10.42	10.44[m]	4.12	4.14	0.1[a]
11	$CH(CH_3)_2$	Cl	H	3	CH_3Br	C	178–181	$C_{15}H_{25}BrClNO$	20.04	19.81[n]	3.51	3.66	100[o]
12	$CH(CH_3)_2$	H	CH_2CH_3	3	HCl[p]	C	151–153	$C_{20}H_{28}ClNO$	10.62	10.60	4.20	4.40	0.1[d]
13	$CH(CH_3)_2$	H	CH_2CH_3	3	CH_3Br	A	92–94	$C_{21}H_{30}BrNO \cdot {}^1/_2(CH_3)_2CHOH$[q]	18.92	18.82	3.32	3.55	6[d]
14	C_6H_5	H	H	2	CH_3Br[r]	D	228 dec.[s]	$C_{21}H_{22}BrNO$	20.80	20.81	3.65	3.67	5[d]

[a] Recrystallization solvents: A, isopropyl alcohol; B, ethyl acetate; C, acetonitrile; D, acetone; E, butanone; F, ethanol; G, methanol; and H, ether. [b] Activity against acetylcholine-induced spasms on the rabbit ileum. These results were determined by Dr. Byron B. Clark and his associates at Tufts College Medical School. [c] The base was reported by V. Boekelheide and J. H. Mason, *J. Am. Chem. Soc.*, **73**, 2356 (1951). [d] Approximate value obtained from screening data. [e] The base distilled at 159–161° (0.7 mm.). *Anal.* Calcd. for $C_{17}H_{21}NO$: N, 5.49. Found: N, 5.19. [f] Calcd. for C, 68.55; H, 7.06. Found: C, 68.95; H, 7.10. [g] The base distilled at 158–160°. (0.1 mm.). *Anal.* Calcd. for $C_{19}H_{25}NO$: N, 4.94. Found: N, 5.19. [h] Base m.p. 71–72° (from hexane). *Anal.* Calcd. for $C_{21}H_{29}NO$: N, 4.50. Found: N, 4.72. [i] Cyclohexyl. [j] Base m.p. 99–100° (from hexane). *Anal.* Calcd. for $C_{21}H_{27}NO$: N, 4.53. Found: N, 4.45. [k] Base m.p. 150–152° (from butanone). *Anal.* Calcd. for $C_{21}H_{21}NO$: N, 4.62. Found: N, 4.84. Due to the low solubility of this base in acetone, the conversion to the methobromide salt was carried out in chloroform. [l] The base distilled at 175–180° (1 mm.). *Anal.* Calcd. for $C_{18}H_{22}ClNO$: Cl, 11.67. Found: Cl, 11.69. [m] Chloride ion. [n] Bromide ion. [o] The LD_{50} in mice was estimated at 520 mg./kg. (oral). [p] The base distilled at 174–175° (0.1 mm.). It crystallized from hexane, m.p. 85–87°. *Anal.* Calcd. for $C_{20}H_{27}NO$: C, 80.76; H, 9.15. Found: C, 80.45; H, 9.12. [q] Calcd. for C, 63.97; H, 8.11. Found: C, 63.66; H, 7.70. Treatment of a chloroform solution of this material with anhydrous ether gave a solvent-free, amorphous, hygroscopic solid. *Anal.* Calcd.: Br, 20.37; N, 3.57. Found: Br, 20.35; N, 3.53. [r] Base m.p. 109–110° (from isopropyl alcohol). *Anal.* Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62. Found: C, 83.57; H, 6.57. [s] This material crystallized directly from the reaction mixture. Recrystallization from hot methanol or ethanol lowered the melting point, probably due to partial dehydration of the product during the heating period.

TABLE III

PHENYLPIPERIDYL ALCOHOLS



Compound no.	R	R′	Salt	Solvent[a]	M.p., °C.	Formula	Analyses, % Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found	Activity atropine = 100[b]
15	$CH(CH_3)_2$	CH_3	HBr	F	176–178	$C_{19}H_{32}BrNO$	21.58	21.49	3.78	4.12	6
16	$CH(CH_3)_2$	CH_3	CH_3Br	C	232–235	$C_{20}H_{34}BrNO$	20.79	21.15	3.64	3.94	8[d]
17	C_6H_{11}[i]	H	HCl	A	199–200	$C_{21}H_{34}ClNO$	10.07	10.14	3.98	4.18	2[d]
18	C_6H_{11}	CH_3	HBr	E	184–185	$C_{22}H_{36}BrNO$	19.47	19.36	3.41	3.65	4
19	C_6H_{11}	CH_3	CH_3Br	C	258–259	$C_{23}H_{38}BrNO$	18.83	18.59	3.30	3.18	4

[a,b,d,i] Footnotes correspond with those of Table II.

filtered to give 17.7 g. (72%) of colorless product, m.p. 132–133°. This material was recrystallized from acetonitrile–acetone (40:40), m.p. 134–135°; λ_{max}^{Nujol} 2.90 (OH), 6.14 (pyridinium), 8.37 μ (C–OH).

α-Isopropyl-N-methyl-α-phenyl-1-piperidinebutanol Hydrobromide (15).—A solution of 20.8 g. (0.057 mole) of the methobromide **4** in 160 ml. of absolute alcohol was treated with 0.5 g. of platinum oxide and the mixture placed on a Parr apparatus under 3 atm. of hydrogen at room temperature. The theoretical quantity of hydrogen was consumed in 25 min. The mixture was filtered and the filtrate concentrated under reduced pressure until the product began to crystallize. The residue was cooled, diluted with 200 ml. of ether, and filtered to give 18.4 g. (87%) of colorless product, m.p. 174–176°. This material was recrystallized from absolute alcohol, m.p. 176–178°; λ_{max}^{Nujol} 2.92 (OH), 3.80 (NH^+), 8.30 μ (C–OH).

2-(3-Benzoylpropyl)-1-methylpyridinium Bromide.—A solution of 15.8 g. (0.07 mole) of 4-(2-pyridyl)butyrophenone[2] in 50 ml. of acetone was treated with 13.3 g. (0.14 mole) of methyl bromide in 30 ml. of acetone. After standing for five days at room temperature, the colorless product was filtered to give 19.1 g. (85%) of material, m.p. 164–166°. Recrystallization from absolute alcohol did not change the melting point; λ_{max}^{Nujol} 5.94 (C=O), 6.13 μ (pyridinium).

Anal. Calcd. for $C_{16}H_{18}BrNO$: Br, 24.96; N, 4.37. Found: Br, 24.95; N, 4.67.