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Central Depressants. Phosphoramidates Derived from α,α-Disubstituted 4-Piperidinemethanols[1]

FREDERICK J. McCARTY, CHARLES H. TILFORD, AND M. G. VAN CAMPEN, JR.[2]

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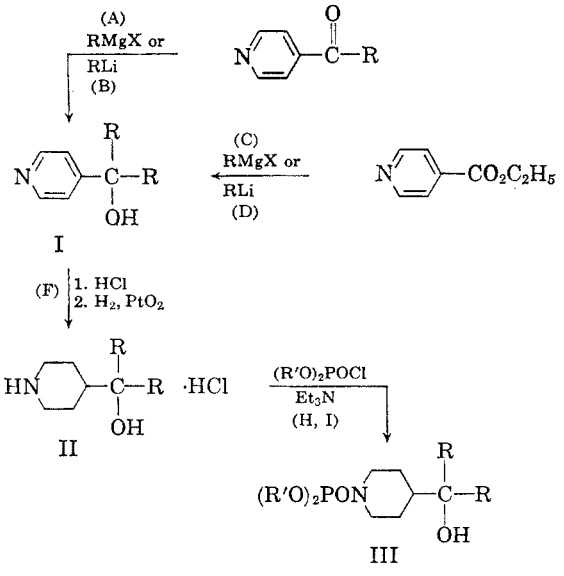
A series of α,α-disubstituted 4-pyridinemethanols was prepared and hydrogenated to obtain the corresponding 4-piperidinemethanols. 1-Dialkylphosphono derivatives (phosphoramidates) were prepared from the piperidinemethanols. A number of these compounds possess central depressant activity.

As part of a synthetic program for the preparation of central depressants, several α,α-disubstituted 4-piperidinemethanols were converted to 1-dialkylphosphono derivatives (phosphoramidates).[3]

Earlier publications from these laboratories have disclosed the central depressant properties of α,α-diphenyl-4-piperidinemethanol hydrochloride[4] (Azacyclonol) and the central stimulant properties of α,α-diphenyl-2-piperidinemethanol hydrochloride[5,6] (Pipradol). The central stimulant properties and synthesis of a series of α,α-disubstituted 2-piperidinemethanols and related hexahydrooxazolo[3,4-a]pyridines have also been described.[7]

Several of the phosphoramidates and α,α-disubstituted 4-piperidinemethanols of this investigation possess central depressant properties. All of these compounds and the intermediate α,α-disubstituted 4-pyridinemethanols have been listed in Table I.

The synthetic methods (A, B, C, D, F, H, and I) are outlined by the scheme below.



R = phenyl, *p*-chlorophenyl, *p*-anisyl, *p*-phenetyl, cyclohexyl, benzyl, *o*-methylbenzyl, *o*-tolyl, *p*-tolyl, or mesityl

R′ = ethyl, *n*-butyl, or *n*-octyl

The intermediate α,α-disubstituted 4-pyridinemethanols (I) were prepared by Methods A, B, C, and D. 4-Benzoylpyridine or 4-(*o*-methylbenzoyl)-pyridine were employed as the ketones in Methods A and B. The latter ketone was obtained by the reaction of *o*-tolyllithium with 4-cyanopyridine. Methods C and D gave pyridinemethanols in which the R groups were identical.

The pyridinemethanols were isolated in the form of the bases, then converted to the hydrochloride salts and hydrogenated in alcoholic solutions in the presence of platinum oxide (Method F) to produce the α,α-disubstituted 4-piperidinemethanol hydrochlorides (II).

Synthesis of the *N*-dialkylphosphono derivatives (III) was carried out by refluxing a mixture of the 4-piperidinemethanol hydrochloride, triethylamine, the required dialkylchlorophosphate, and benzene (Methods H and I). 1-Diethylphosphono-α,α-diphenyl-2-piperidinemethanol was obtained from the reaction of α,α-diphenyl-2-piperidinemethanol hydrochloride with diethylchlorophosphate in this procedure.

α,α-Diphenyl-3-pyridinemethanol[8] and α,α-di(*p*-anisyl)-3-pyridinemethanol were prepared by the addition of 3-pyridyllithium to benzophenone and di(*p*-anisyl) ketone, respectively. These compounds were hydrogenated in the presence of platinum oxide to produce the corresponding 3-piperidinemethanols. α,α-Diphenyl-3-piperidinemethanol was converted to 4,4-diphenyl-3-oxa-1-

(1) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

(2) Present address: Cutter Laboratories, Berkeley, California.

(3) C. H. Tilford, F. J. McCarty, and M. G. Van Campen, Jr., U. S. Patent 2,832,786.

(4) E. L. Schumann, M. G. Van Campen, Jr., and R. C. Pogge, U. S. Patent 2,804,422.

(5) H. W. Werner and C. H. Tilford, U. S. Patent 2,624,739.

(6) B. B. Brown and H. W. Werner, *J. Pharmacol. Exptl. Therap.*, 110, 180 (1954).

(7) F. J. McCarty, C. H. Tilford, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, 79, 472 (1957).

(8) L. C. Anderson and N. V. Seeger, *J. Am. Chem. Soc.*, 71, 343 (1949).

azabicyclo[3.1.3]nonane by reaction with formalin in methanol solution.

Pharmacological activity. Compounds 37C, 40C, 41C, and 43C were administered to mice by intraperitoneal injection and screened by the photoelectric cell method.[9] Compound 41C was the most potent, causing an 80% reduction in motor activity at a dose of 81 mg./kg. It was found to antagonize Pipradol and cocaine induced hyperactivity in mice and to markedly prolong the hexobarbital induced sleeping time in mice. A study of the mechanism of action of the latter potentiation indicated an inhibition of the metabolism of hexobarbital in the liver. The LD_{50}'s of Compounds 38C, 42C, 45C, and 47C were greater than 4000 mg./kg. and at this dose only slight depression was observed.

EXPERIMENTAL

Intermediate halo compounds. The halo compounds used in the preparation of Grignard and lithio reagents were all commercially available.

4-(2-Methylbenzoyl)pyridine. *o*-Bromotoluene (125 g., 0.73 mole) was added, dropwise, during a 1-hr. period to a stirred mixture of 10 g. (1.45 g.-atoms) of lithium and 400 ml. of dry ether. The mixture was stirred and refluxed 1 hr. A solution of 73 g. (0.70 mole) of 4-cyanopyridine in 200 ml. of toluene was added to the stirred mixture at −20° over a 20 min. period. The reaction mixture was decomposed by the addition of 500 ml. of 20 % hydrochloric acid and made alkaline with potassium hydroxide. The organic layer was separated, dried, and the solvent was removed. The residue was distilled; b.p. 170–172 (14 mm.); yield 87 g. (65%). The distillate solidified and the solid was recrystallized from ether-petroleum ether (b.p. 75–90); m.p. 41–42°.

Anal. Calcd. for $C_{13}H_{11}ON$: C, 79.18; H, 5.61; N, 7.10. Found: C, 79.20; H, 5.62; N, 7.25.

General procedures. The structures of the products obtained by Methods A-I are shown in Table I. The letter after each compound number indicates the general formula (A, B, or C of Table I) to which the compound conforms. Variations from the procedures are described separately after each method.

Substituted 4-pyridinemethanols. The four synthetic methods are illustrated by representative examples.

(1) *Method A. α-Benzyl-α-phenyl-4-pyridinemethanol* (1A). To the Grignard reagent, prepared from 29 g. (1.2 g.-atoms) of magnesium turnings, 126 g. (1.0 mole) of benzyl chloride, and 500 ml. of dry ether, was added at −20° 136 g. (0.75 mole) of 4-benzoylpyridine in 250 ml. of dry toluene over a period of 1 hr. The reaction mixture was refluxed 1 hr. and decomposed with ammonium chloride solution. The mixture was filtered and the precipitate washed with water. Yield 236 g. (86%); m.p. 188–189° after recrystallization from ethyl acetate.

The Grignard reagents used for the preparation of compounds 3A, 5A and 9A were obtained from α-bromo-*o*-xylene, cyclohexyl chloride, and *p*-bromoanisole, respectively.

Compound 7A. The halide employed was *p*-bromochlorobenzene. The reaction mixture was decomposed with 50% acetic acid instead of ammonium chloride solution.

Compound 10A. 4-(*o*-Methylbenzoyl)pyridine was substituted for 4-benzoylpyridine in Method A.

(2) *Method B. α-Phenetyl-α-phenyl-4-pyridinemethanol* (16A). A solution of 100.5 g. (0.50 mole) of *p*-bromophenetole in 100 ml. of dry ether was added over a 1.5-hr. period to a stirred refluxing mixture of lithium (6.94 g.; 1.0 g.-atom) and 350 ml. of dry ether. To the *p*-phenetyllithium thus formed was added, at −25°, over a 30-min. period, 86 g. (0.47 mole) of 4-benzoylpyridine. The reaction mixture was stirred 1 hr. allowing the temperature to increase to 25° and decomposed with ammonium chloride solution. The mixture was filtered and the precipitate washed with water. Yield 100 g. (70%) m.p. 187–189° after two recrystallizations from methanol.

Compound 12A. *o*-Bromotoluene was employed for the preparation of the lithio reagent.

Compound 14A. 2-Bromomesitylene was used for the preparation of the lithio reagent. The product did not precipitate from the decomposed reaction mixture. The ether-toluene layer was concentrated to one-half volume, diluted with 3 volumes of petroleum ether (b.p. 80–90°), cooled, and filtered.

(3) *Method C. α,α-Di(p-anisyl)-4-pyridinemethanol* (19A). The Grignard reagent was prepared by the addition of 187 g. (1.0 mole) of *p*-bromoanisole in 200 ml. of dry ether to 27 g. (1.1 g.-atoms) of magnesium turnings in 300 ml. of dry ether over a period of 1.5 hr. Ethyl isonicotinate (35 g., 0.23 mole) was dissolved in 100 ml. of dry ether and added to the Grignard reagent with stirring at −20° over a period of 45 min. The reaction mixture was refluxed 1 hr. and decomposed with ammonium chloride solution. The ether layer was concentrated to 200 ml. and diluted to 450 ml. with petroleum ether (b.p. 75–90°). The solution was cooled whereupon the product precipitated. Yield 22 g. (31%); m.p. 168–170° after recrystallization from methanol.

Compound 17A. Benzyl chloride was used for the preparation of the Grignard reagent. The crude product precipitated from the decomposed reaction mixture. The precipitate was extracted with 1.5 l. of ethanol and the extract was diluted with 400 ml. of water. The solution was concentrated to 1.5 l., cooled, and filtered.

(4) *Method D. α,α-Di(o-tolyl)-4-pyridinemethanol* (20A). To a stirred refluxing mixture of 12 g. (1.7 g.-atoms) of lithium and 600 ml. of dry ether was added a solution of 148 g. (0.86 mole) of *o*-bromotoluene in 150 ml. of dry ether over a period of 1 hr. The mixture was cooled to −20° and 50 g. (0.33 mole) of ethyl isonicotinate, dissolved in 150 ml. of dry ether, was added during a 30-min. period. The reaction mixture was refluxed 1 hr. and decomposed with ammonium chloride solution. The precipitated product was removed by filtration and washed with water. The product was recrystallized from 1.8 l. of 75% ethanol. Yield 78 g. (82%); m.p. 185–186° after recrystallization from petroleum ether (b.p. 75–90°).

Compound 22A.—*p*-Bromotoluene was used for the preparation of the lithio reagent. After decomposition of the reaction mixture with ammonium chloride, the ether layer was separated, concentrated to a volume of 350 ml., diluted with 500 ml. of petroleum ether (b.p. 40–60°), cooled, and filtered.

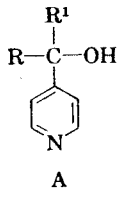
(5) *Method E. Substituted 4-pyridinemethanol hydrochlorides.* The bases were dissolved in methanol, the solution cooled and acidified with alcoholic hydrogen chloride solution. Ether or ethyl acetate was added until a faint cloudiness persisted or crystallization was induced. The mixture was cooled to −12° and the hydrochloride salt removed by filtration.

Pure crystalline hydrochlorides were not obtained from Compounds 9A, 16A, 19A, or 22A.

Method F. Hydrogenation of 4-pyridinemethanols. A mixture of 0.1 mole of the substituted pyridinemethanol hydrochloride, 250 ml. of methanol (or 95% ethanol), and 0.6–0.8 g. of platinum oxide catalyst was shaken with hydrogen at 3–4 atm. in a Parr hydrogenation apparatus. After the theoretical amount (0.3 mole) of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was concentrated to about one-half volume. Approximately 150 ml. of ethyl acetate or ether was added, the solution was cooled to −12° and filtered to obtain the crystalline piperidinemethanol hydrochloride.

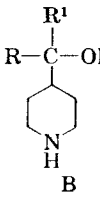
(9) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).

TABLE I. SUBSTITUTED PYRIDINEMETHANOLS, PIPERIDINEMETHANOLS, AND PHOSPHORAMIDATES



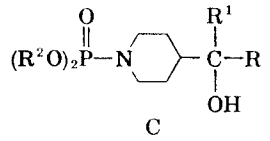
A

(Compounds 1–22, incl.)



B

(Compounds 23–36, incl.)



C

(Compounds 37–47, incl.)

No.	R	R¹	Method	M.P., Corr.[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	RS[b]
1A	Phenyl	Benzyl	A	188–189	86	$C_{19}H_{17}NO$	82.88	82.86	6.22	6.29	J
2A	Phenyl	Benzyl	E	267–269		$C_{19}H_{18}ClNO$[c]	73.21	73.40	5.82	5.82	C
3A	Phenyl	*o*-Methylbenzyl	A	173–175	30	$C_{20}H_{19}NO$	83.00	83.41	6.62	6.58	K
4A	Phenyl	*o*-Methylbenzyl	E	234–236		$C_{20}H_{20}ClNO$[c]	73.72	73.42	6.19	6.25	C
5A	Phenyl	Cyclohexyl	A	193–194	80	$C_{18}H_{21}NO$	80.83	80.60	7.92	7.80	A
6A	Phenyl	Cyclohexyl	E	205–207		$C_{18}H_{22}ClNO$[c]	71.17	70.97	7.30	7.28	C
7A	Phenyl	*p*-Chlorophenyl	A	202–204	54	$C_{18}H_{14}ClNO$	73.09	73.10	4.77	4.83	F
8A	Phenyl	*p*-Chlorophenyl	E	207–209		$C_{18}H_{15}Cl_2NO$[c]	65.08	65.13	4.55	4.66	H
9A	Phenyl	*p*-Anisyl	A	200–204	68	$C_{19}H_{17}NO_2$	78.33	78.48	5.88	5.89	F
10A	Benzyl	*o*-Tolyl	A	237–238	60	$C_{20}H_{19}NO$	83.00	83.07	6.62	6.69	I
11A	Benzyl	*o*-Tolyl	E	244–246		$C_{20}H_{20}ClNO$[c]	73.72	74.10	6.19	6.23	C
12A	Phenyl	*o*-Tolyl	B	229–231	75	$C_{19}H_{17}NO$	82.88	82.02	6.22	6.36	B
13A	Phenyl	*o*-Tolyl	E	214–215		$C_{19}H_{18}ClNO$[c]	73.21	72.96	5.82	5.86	D
14A	Phenyl	Mesityl	B	185–187	24	$C_{21}H_{21}NO$	83.14	83.12	6.98	7.12	L
15A	Phenyl	Mesityl	E	180–182		$C_{21}H_{22}ClNO$[c]	74.20	74.07	6.53	6.61	C
16A	Phenyl	*p*-Phenetyl	B	187–189	70	$C_{20}H_{19}NO_2$	78.65	78.71	6.27	6.38	A
17A	Benzyl	Benzyl	C	145–146	12	$C_{20}H_{19}NO$	83.00	82.72	6.62	6.46	K
18A	Benzyl	Benzyl	E	237–238		$C_{20}H_{20}ClNO$[c]	73.72	73.72	6.19	6.24	C
19A	*p*-Anisyl	*p*-Anisyl	C	168–170	31	$C_{20}H_{19}NO_3$	74.76	74.76	5.93	5.84	M
20A	*o*-Tolyl	*o*-Tolyl	D	185–186	82	$C_{20}H_{19}NO$	83.00	82.72	6.62	6.46	K
21A	*o*-Tolyl	*o*-Tolyl	E	208–210		$C_{20}H_{20}ClNO$[c]	72.72	73.72	6.19	6.26	C
22A	*p*-Tolyl	*p*-Tolyl	D	154–156	34	$C_{20}H_{19}NO$	83.00	83.18	6.62	6.94	D
23B	Phenyl	Benzyl	F	239–241	68	$C_{19}H_{24}ClNO$	71.81	71.63	7.61	7.74	D
24B	Phenyl	Benzyl	G	121–123		$C_{19}H_{23}NO$[d]	81.10	80.88	8.23	7.80	K
25B	Phenyl	*o*-Methylbenzyl	F	245–246	96	$C_{20}H_{26}ClNO$	72.40	72.39	7.90	7.80	G
26B	Phenyl	Cyclohexyl	F	280–281	98	$C_{18}H_{28}ClNO$	69.75	69.42	9.11	9.10	H
27B	Phenyl	*p*-Chlorophenyl	F	263–264	71	$C_{18}H_{21}Cl_2NO$	63.90	63.82	6.26	6.36	G
28B	Phenyl	*p*-Anisyl	F	226–227	70	$C_{19}H_{24}ClNO_2$	68.35	67.99	7.25	7.39	C
29B	Benzyl	*o*-Tolyl	F	255–257	88	$C_{20}H_{26}ClNO$	72.40	72.51	7.90	8.03	H
30B	Benzyl	*o*-Tolyl	G	106–108		$C_{20}H_{25}NO$[d,e]	81.31	80.77	8.53	8.47	M
31B	Phenyl	*o*-Tolyl	F	256–257	61	$C_{19}H_{24}ClNO$	71.79	71.43	7.61	7.47	A
32B	Phenyl	Mesityl	F	258–259	10	$C_{21}H_{28}ClNO$	72.94	73.01	8.16	8.03	F
33B	Phenyl	*p*-Phenetyl	F	198–199	34	$C_{20}H_{26}ClNO_2$	69.06	69.17	7.54	7.67	A
34B	Benzyl	Benzyl	F	258–259	97	$C_{20}H_{26}ClNO$	72.40	72.57	7.90	8.35	H
35B	*o*-Tolyl	*o*-Tolyl	F	286–287	64	$C_{20}H_{26}ClNO$	72.40	72.27	7.90	8.02	G
36B	*p*-Tolyl	*p*-Tolyl	F	188–190	40	$C_{20}H_{26}ClNO$	72.40	72.49	7.92	8.13	F

TABLE I (*continued*)

	R	R[1]	R[2]	Method	M.P. Cor.	Yield, %	Formula[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Phosphorous, % Calcd.	Phosphorous, % Found	RS[b]
37C	Phenyl	Phenyl	Ethyl	I[f]	223–224	67	$C_{22}H_{30}NO_4P$	3.47	3.68	7.68	7.35	A
38C	Phenyl	Phenyl	*n*-Butyl	H[f]	162–163	71	$C_{26}H_{38}NO_4P$	3.05	3.23	6.74	6.61	A
39C	Phenyl	Phenyl	*n*-Octyl	H[f]	89–91	17	$C_{34}H_{54}NO_4P$	2.45	2.51	5.42	5.20	J
40C	Phenyl	Benzyl	Ethyl	I	109–112	87	$C_{23}H_{32}NO_4P$	3.36	3.29	7.42	7.21	B
41C	Phenyl	Cyclohexyl	Ethyl	I	113–114	62	$C_{22}H_{36}NO_4P$	3.42	3.32	7.56	7.60	B
42C	Phenyl	*p*-Chlorophenyl	Ethyl	H	150–151	61	$C_{22}H_{29}ClNO_4P$	3.20	3.28	7.08	6.95	J
43C	Phenyl	*p*-Anisyl	Ethyl	I	143–145	48	$C_{23}H_{32}NO_5P$	3.23	3.24	7.15	7.08	B
44C	Phenyl	*p*-Phenetyl	Ethyl	H	149–151	11	$C_{24}H_{34}NO_5P$	3.13	3.12	6.92	6.90	K
45C	Phenyl	*o*-Tolyl	Ethyl	H	179–180	82	$C_{23}H_{32}NO_4P$	3.36	3.38	7.42	7.58	D
46C	Benzyl	*o*-Tolyl	Ethyl	H	146–147	95	$C_{24}H_{34}NO_4P$	3.25	3.32	7.18	6.85	L
47C	*o*-Tolyl	*o*-Tolyl	Ethyl	H	130–131	91	$C_{24}H_{34}NO_4P$	3.25	3.30	7.18	7.09	D

[a] The hydrochlorides melted with some decomposition. [b] Recrystallization solvent: A, methanol; B, methanol-water; C, methanol-ether; D, methanol-ethyl acetate; E, methanol-benzene; F, ethanol; G, ethanol-water; H, ethanol-ether; I, ethanol-benzene; J, ethyl acetate; K, petroleum ether (b.p. 75–90°); L, benzene-petroleum ether (b.p. 75–90°); M, ether-petroleum ether (b.p. 40–60°). [c] Hydrochloride salt. [d] Free base. [e] Calcd.: N, 4.74. Found: N, 4.70. [f] For the intermediate α,α-diphenyl-4-piperidinemethanol hydrochloride see ref. 4.

The pyridinemethanol base with an equivalent of alcoholic or aqueous hydrogen chloride can be substituted for the pyridinemethanol hydrochlorides in this procedure.

During the preparation of compounds 25B, 27B, 33B, and 35B the temperature of the reaction mixture was maintained at 60°.

In several cases (Compounds 27B, 29B, 32B, 33B, 35B, and 36B) the piperidinemethanol hydrochlorides precipitated during the hydrogenation. In these instances, the product was dissolved by heating with larger quantities of solvent before removing the catalyst by filtration.

Compound 28B was prepared by hydrogenation of the pyridinemethanol base (9A) in 200 ml. of acetic acid solution. The catalyst was removed by filtration and the filtrate was made alkaline with potassium carbonate. The product was removed by filtration, dissolved in benzene, and the benzene solution was acidified with alcoholic hydrogen chloride to precipitate the product.

Method G. α,α-Disubstituted 4-piperidinemethanol free bases. A mixture of the appropriate piperidinemethanol hydrochloride, a slight excess of 5% sodium hydroxide, and hot benzene was stirred 1 hr. The benzene layer was concentrated to remove solvent and the residue crystallized from petroleum ether (b.p. 75–90°).

N-Dialkylphosphonopiperidinemethanols. (1) *Method H.* A mixture of 0.04 mole of the piperidinemethanol hydrochloride 0.08 mole of triethylamine and 250 ml. of dry benzene was stirred and refluxed 1 hr. The dialkylchlorophosphate[10] (0.045 mole) was added to the stirred reaction mixture at 45–50° over a 20-min. period. The mixture was stirred and refluxed 6 hr. and filtered to remove triethylamine hydrochloride. The benzene filtrate was concentrated to about one-third volume, cooled, and filtered to obtain the product.

Compounds 39C *and* 44C.—After removal of the triethylamine hydrochloride the filtrate was concentrated to an oil; the oil crystallized from ethyl acetate (39C) or petroleum ether (b.p. 40–60°) (44C).

Compound 46C. Equimolar amounts of α-benzyl-α-(*o*-tolyl)-4-piperidinemethanol, triethylamine, and diethylchlorophosphate were used in Procedure H. The mixture was refluxed 4 hr., and the concentrated benzene filtrate was diluted with petroleum ether (b.p. 75–90°) to precipitate the product.

(2) *Method I.* The procedure was the same as Method H, except that the reaction mixture was refluxed 16 hr. and approximately 6 volumes of petroleum ether (b.p. 40–60°) was added to the concentrated filtrate. The mixture was cooled and filtered.

Compound 37C. At the end of the reflux period the reaction mixture was cooled and filtered. The solid was extracted with hot water and filtered to obtain the product.

1-Diethylphosphono-α,α-diphenyl-2-piperidinemethanol. A mixture of 22.4 g. (0.074 mole) of α,α-diphenyl-2-piperidinemethanol hydrochloride,[11] 15 g. (0.148 mole) of triethylamine, and 300 ml. of dry benzene was stirred and refluxed 1 hr. Diethyl chlorophosphate (13.7 g., 0.08 mole) was added to the stirred reaction mixture at 40° during a 15 minute period. The reaction mixture was refluxed 15 hours and filtered. The benzene filtrate was concentrated to one-third volume and acidified with alcoholic hydrogen chloride. The precipitated α,α-diphenyl-2-piperidinemethanol hydrochloride (14.5 g.) was removed by filtration. The filtrate was concentrated under reduced pressure to remove solvent and the oily residue crystallized when stirred with methanol-ether. Yield 3.5 g. (11 %); m.p. 171–172° after recrystallization from methanol.

Anal. Calcd. for $C_{22}H_{30}NO_4P$: C, 65.50; H, 7.50. Found: C, 65.54; H, 7.43.

(10) Diethyl, dibutyl, and dioctylchlorophosphates were obtained from the Victor Chemical Co.

(11) C. H. Tilford, R. S. Shelton, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **70**, 4001 (1948).

α,α-Diphenyl-3-pyridinemethanol. An ether solution of *n*-butyllithium was prepared from 11.2 g. (1.62 g.-atoms) of lithium and 111 g. (0.81 mole) of *n*-butyl bromide in 900 ml. of dry ether at −10° under nitrogen. The reaction mixture was stirred 1.5 hr., cooled to −60°, and 128 g. (0.81 mole) of 3-bromopyridine dissolved in 150 ml. of dry ether was added over a 20-min. period at −60 to −40°. The stirred solution was again cooled to −60° and 109 g. (0.60 mole) of benzophenone dissolved in 250 ml. of dry ether was added during a 30-min. period. The mixture was stirred at −40° for 2 hr., the temperature was allowed to increase to 20° and the reaction mixture was decomposed with ammonium chloride solution. The ether layer was evaporated to give the crystalline product; m.p. 115–117° (lit.[8] m.p. 115–116°) after two recrystallizations from methanol; yield 99 g. (64%).

The hydrochloride obtained by Method E melted at 221–231° dec. The salt was recrystallized twice from methanol; m.p. 227–232° dec. (lit.[12] m.p. 150–155° chars).

Anal. Calcd. for $C_{18}H_{16}ClNO$: C, 72.58; H, 5.42; Cl, 11.92. Found: C, 72.70; H, 5.54; Cl, 11.79.

α,α-Diphenyl-3-piperidinemethanol hydrochloride. The hydrogenation of 25 g. (0.08 mole) of α,α-diphenyl-3-pyridinemethanol hydrochloride was carried out in 200 ml. of methanol in the presence of 0.6 g. of platinum oxide, as described in Method F. Yield 20 g. (78%); m.p. 184–186°. Recrystallization of the product from methanol-ether resulted in two crops which apparently are polymorphic crystalline forms: (a) 11 g., m.p. 206–208° after recrystallization from methanol-ether; (b) 8 g., m.p. 184–186° after recrystallization from methanol-ether.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30. (a) Found: C, 71.35; H, 7.57. (b) Found: C, 71.11; H, 7.52.

A solution of 2.5 g. of (a) in methanol was made alkaline with 10% sodium hydroxide. The precipitated product was recrystallized from methanol-water; m.p. 158–160°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.84; H, 7.92. Found: C, 80.78; H, 7.97.

4,4-Diphenyl-3-oxa-1-azabicyclo[3.1.1]nonane. A mixture of 2 g. of α,α-diphenyl-3-piperidinemethanol, 2.3 ml. of formalin and 40 ml. of methanol was refluxed 20 hr. Water was added until the reaction mixture became cloudy. The mixture was cooled and filtered. Yield 1.2 g. (54%); m.p., 118–121° after recrystallization from 50% methanol.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.69; H, 7.58. Found: C, 81.48; H, 7.72.

The acid maleate salt was prepared by dissolving 1 g. of the base in ethanol which contained 0.5 g. of maleic acid. The solution was diluted with ether, cooled, and filtered. The salt was recrystallized from ethanol-ether; m.p. 202–203°.

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.38. Found: C, 69.79; H, 6.43.

α,α-Di(p-anisyl)-3-pyridinemethanol. To a solution of 3-pyridyllithium, prepared from 6.5 g. (0.94 g.-atom) of lithium, 64.5 g. (0.47 mole) of *n*-butyl bromide, 71 g. (0.45 mole) of 3-bromopyridine, and 700 ml. of dry ether was added a suspension of 83 g. (0.34 mole) of di(*p*-anisyl) ketone in 200 ml. of dry toluene as described above for the preparation of α,α-diphenyl-3-pyridinemethanol. The mixture was stirred 2 hr. at −40° and the temperature was allowed to increase to 25°. After the reaction mixture had been decomposed with ammonium chloride solution, it was filtered to recover 30 g. of di(*p*-anisyl) ketone. The ether-toluene filtrate was concentrated to remove solvent and the residue crystallized from methanol. Yield 30 g. (27%); m.p. 74–80° after two recrystallizations from methanol.

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96. Found: C, 74.77; H, 6.10.

The hydrochloride salt was prepared by Method E. It was recrystallized from isopropyl alcohol–petroleum ether (b.p. 75–90°); m.p. 176–178°.

Anal. Calcd. for $C_{20}H_{20}ClNO_3$: C, 67.13; H, 5.63. Found: C, 67.29; H, 5.79.

α,α-Di(p-anisyl)-3-piperidinemethanol. A mixture of 15 g. (0.047 mole) of α,α-di(*p*-anisyl)-3-pyridinemethanol, 0.4 g. of platinum oxide, and 250 ml. of 80% acetic acid was hydrogenated as described by Method F. The platinum oxide was removed by filtration and the filtrate was made basic with ammonium hydroxide. The precipitated product was recrystallized from methanol. Yield 6 g. (39%); m.p. 169–171°.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.38; H, 7.70. Found: C, 73.46; H, 7.51.

The hydrochloride salt was obtained by Method E and recrystallized from methanol-ether; m.p. 166–168°.

Anal. Calcd. for $C_{20}H_{26}ClNO_3$: C, 66.03; H, 7.21. Found: C, 66.10; H, 7.09.

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CINCINNATI, OHIO

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[CONTRIBUTION FROM THE SOAP RESEARCH AND DEVELOPMENT DEPARTMENT, GROCERY PRODUCTS DIVISION, ARMOUR AND CO.]

Synthesis and Antibacterial Activity of Some New Aminophosphinic Acids[1]

W. M. LINFIELD, ERIC JUNGERMANN, AND A. T. GUTTMANN

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A series of aminophosphinic acids were prepared by the reaction of aryl or long-chain amines with aldehydes and hypophosphorous acid. The antibacterial properties and surface activity of these compounds were studied.

During the past quarter of a century numerous types of antibacterial agents have been synthesized. Among these the surface active quaternary ammonium compounds, various phenolic compounds, and especially bisphenols as well as substituted carbanilides and salicylanilides have received widespread application in the soap and detergent field. The structures of the "soap-germicides"

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