Recrystallization from DMF–EtOH afforded XIII [$R_2 = (CH_3)_2$] as colorless needles: mp 255–256° dec; yield 7.4 g (85%); ir, ν_{max}^{Nujol} (cm^{-1}) 3130, 1720, 1625, 1555. Analytical data are listed in Table I.

1-[2-(Disubstituted amino)ethyl]-2-methyl-3-aryl-4-oxodihydroquinazolinium diperchlorates were prepared in a similar way, without isolation of XII. The products are shown in Table I (**2–9**).

B.—AcCl (0.15 g) was added to a mixture of XIII (0.28 g), powdered K_2CO_3 (0.2 g), and dry C_6H_6 (3 ml). The mixture was stirred overnight at room temperature, treated with H_2O (5 ml), and made alkaline with 10% K_2CO_3. The benzene layer was separated, washed with H_2O, and dried (K_2CO_3). Distillation of the solvent gave an oily residue (0.3 g), which was dissolved in Et_2O and treated with excess 60% $HClO_4$. The crude crystalline product and EtOH (3 ml) were refluxed for 10 min and cooled. The separated crystals were collected, mp 255–256° dec, yield 0.35 g. Ir spectra of the product and a sample obtained by method A were superimposable.

1-(2-Dimethylaminoethyl)-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline [XIV, $R_2 = (CH_3)_2$]. **A.**—To a stirred suspension of XII [$R_2 = (CH_3)_2$] (5.0 g) in EtOH (50 ml) was added a solution of $NaBH_4$ (0.8 g) in EtOH (90 ml) at −5 to −2° over a period of 3 hr. The mixture became clear after the addition and the solvent was distilled under reduced pressure. To the residue was added H_2O and separated oil was extracted with Et_2O. The dried extract was evaporated and the residue was distilled at 250–255° (0.2 mm) to give a viscous oil, yield 2.0 g (66%). *Anal.* ($C_{19}H_{23}N_3O$) H, N; C: calcd, 73.75; found, 73.29.

The **oxalate** yielded colorless plates (from Me_2CO), mp 86–89° dec. Analytical data are listed in Table II (**14**).

1-[2-(Disubstituted amino)ethyl]-2-methyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazolines were prepared by the same way as above. The products are shown in Table II (**15–22**).

B.—A solution of XIII (1.4 g) and paraldehyde (0.66 g) in absolute EtOH (20 ml) was saturated with dry HCl at 0–5° and the mixture was allowed to stand at room temperature overnight. The solvent was distilled under reduced pressure. The residue was made alkaline with concentrated NH_4OH and the separated oil was extracted with Et_2O. Distillation of the extract gave an oily residue (1.5 g), which was dissolved in dry C_6H_6 and chromatographed over Al_2O_3. The C_6H_6–MeOH (98:2) eluate afforded a colorless viscous oil, which was distilled, bp 280° (bath temperature) (0.2 mm), yield 0.5 g (32%). Ir spectra of the product and a sample obtained by method A were superimposable.

Acknowledgments.—The authors wish to express their thanks to Mr. T. Takayanagi, Manager of Development Division, Dr. N. Sugimoto, Technological Director, and Dr. K. Fujii, Director of Institute of Chemical Research in Tanabe Seiyaku Co., Ltd., for their encouragement. Thanks are extended to the staff of the analytical section for determination of physical properties.

Derivatives of 3-Piperidinol as Central Stimulants

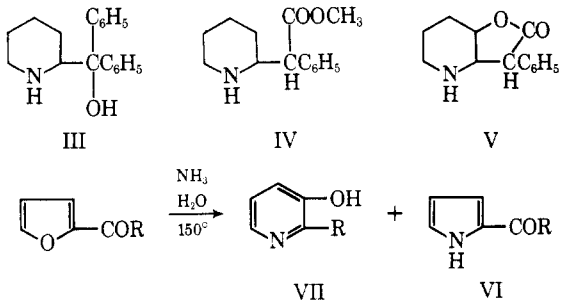
LEWIS A. WALTER, CECILE K. SPRINGER, JOANNE KENNEY, SUSAN K. GALEN, AND NATHAN SPERBER

Medicinal Chemistry Department of the Schering Corporation, Bloomfield, New Jersey

Received January 11, 1968

A number of 2-aralkyl-3-pyridinols, prepared by the ammonolysis of aralkyl 2-furyl ketones, were hydrogenated to 3-piperidinols. Several of these latter compounds and their N-substituted derivatives were potent central stimulants. Two of the most active compounds were resolved and the activity was found predominantly in one optical isomer in each case.

The clinical usefulness of pipradrol (III) and methylphenidate (IV) as central stimulants prompted the preparation of the 2-aralkyl-3-piperidinols I (Table I). These compounds were obtained by hydrogenating the corresponding 3-pyridinols II (Table II), followed by alkylation or acylation where necessary. The 3-pyridinols II (Table II), where X = H, were prepared by the ammonolysis and concomitant ring closure of 2-furyl ketones to a mixture of the desired II and an aralkyl 2-pyrryl ketone VI.



Ammonia or ammonium salts in various solvent combinations have been used for this reaction,[1] but in the present study ammonia in aqueous methanol gave the best yields. In some instances the reaction failed. For example, 2-furoylphenylacetonitrile cleaved to furamide; 2-furyl 9-fluorenyl ketone gave fluorene quantitatively, and 2-furyl 9-xanthenyl ketone gave xanthene and a small amount of the desired 3-pyridinol. A 5-methyl group in the furan ring reduced the yield of pyridinol to less than 5%. No effort was made to isolate the by-product 2-pyrryl ketones.

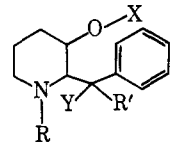
The diarylmethyl 2-furyl ketones (Table III) were obtained in good yield from ethyl furoate and a diphenylmethane with $NaNH_2$ or KNH_2 in liquid ammonia. Several attempts to acylate furan with diphenylacetyl chloride and stannic chloride gave only traces of ketone, although this method[2] has been used successfully for similar compounds.

The hydrogenation of the 3-pyridinols to the 3-piperidinols was difficult. With Pt hydrogenation of the bases in acetic acid or the hydrochloride salts in ethanol gave complex mixtures containing most of the possible combinations of phenyl, cyclohexyl, pyridine,

(1) (a) H. Leditschke, *Angew. Chem.*, **61**, 446 (1949); (b) *Chem. Ber.*, **85**, 202 (1952); (c) *ibid.*, **86**, 123 (1953); (d) A. P. Dunlop and S. Swadesh, U.S. Patent 2,636,882 (March 16, 1954); (e) W. Gruber, *Can. J. Chem.*, **31**, 564 (1953); (f) *Chem. Ber.*, **88**, 178 (1955); (g) B. R. Baker and E. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955); (h) H. Rapaport and E. Volcheck, *J. Am. Chem. Soc.*, **78**, 2451 (1956).

(2) Ya. Goldfarb and L. Smorgonskii, *J. Gen. Chem. USSR*, **8**, 1523 (1938).

TABLE I: 3-PIPERIDINOLS AND DERIVATIVES

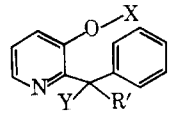


No.	X	Y	R	R′	Salt[a]	Mp, °C[b]	Crystn solvent[c]	Formula	Analyses[z]
1	CH_3	H	H	$COOC_2H_5$[d,e]	HCl	218–219	I	$C_{16}H_{24}ClNO_3$	C, H
6	H	H	NO	C_6H_5[f]		160–162	EA	$C_{18}H_{20}N_2O_2$	N
3	H	H	H	C_6H_5		96–98	H	$C_{18}H_{21}NO$	C, H
					HCl	298–300	A	$C_{18}H_{22}ClNO$	H; C[g]
					AS	199–201	A	$C_{22}H_{27}NO_5$	C, H
					l-PS	171–174	A	$C_{46}H_{52}N_2O_6$	C, H
4	H	H	H	C_6H_5[h]		94–96	E	$C_{18}H_{21}NO$	C, H
					d-AT·H_2O	214–215	A-W	$C_{22}H_{29}NO_8$	C, H
					AS[i]	211–212	A	$C_{22}H_{27}NO_5$	C, H
5	H	H	H	C_6H_5[j]	d-AT·H_2O	170–190	A-W	$C_{22}H_{29}NO_8$	C, H
					AS	210–212	A	$C_{22}H_{27}NO_5$	C, H
6	H	OH	H	C_6H_5[d]		190–192	A	$C_{18}H_{21}NO_2$	C, H
					HCl	281–286	A	$C_{18}H_{22}ClNO_2$	C, H
7	H	H	NH_2	C_6H_5[k]		171–174	IA	$C_{18}H_{22}N_2O$	C, H
					HCl	224–226	A-E	$C_{18}H_{23}ClN_2O$	C, H
8	H	H	H	*p*-ClC_6H_4[d,l]	HCl	270–274	I-E	$C_{18}H_{27}Cl_2NO$	C, H
9	H	H	H	C_6H_{11}[m]		104–106	H	$C_{18}H_{27}NO$	C, H
					HCl	305–307	W	$C_{18}H_{28}ClNO$	C, H
10	CH_3	H	H	C_5H_9[d,n]	HCl	263–265	AC	$C_{18}H_{28}ClNO$	C, H
11	H	H	H	C_6H_{11}[l,m]	HCl	312–314	W	$C_{18}H_{34}ClNO$	C, H
12	CH_3	H	H	C_6H_5		131–133	H	$C_{19}H_{23}NO$	C, H
					AM	194–195	I	$C_{23}H_{27}NO_5$	C, H
13	H	H	CH_3	C_6H_5[o]		148–150	M	$C_{19}H_{23}NO$	C, H
					HCl	253–254	A	$C_{19}H_{24}ClNO$	C, H
14	H	H	CH_3	C_6H_5[j]		127–129	I	$C_{19}H_{23}NO$	C, H
					HCl	269–270	A	$C_{19}H_{24}ClNO$	C, H
					l-APS	218–220	A-W	$C_{29}H_{33}NO_5$	C, H
15	H	H	CH_3	C_6H_5[h]	HCl	270–273	A	$C_{19}H_{24}ClNO$	C, H
16	H	H	H	$C_6H_5CH_2$[d]	AM	237–238	I	$C_{23}H_{27}NO_5$	H; C[v]
17	CH_3	OH	H	C_6H_5[d]		139–142	E	$C_{19}H_{23}NO_2$	C, H
					HCl	286–288	A-E	$C_{19}H_{24}ClNO_2$	C, H
18	H	H	H	*p*-$CH_3OC_6H_4$		142–143	H	$C_{19}H_{23}NO_2$	C, H
					HCl	287–289	A	$C_{19}H_{24}ClNO_2$	C, H
19	CH_3	H	H	C_6H_{11}[m]	HCl	307–310	W	$C_{19}H_{30}ClNO$	C, H
20	H	H	CH_3	C_6H_{11}[m,o]		159–161	I	$C_{19}H_{29}NO$	C, H
					HCl	268–269	A-E	$C_{19}H_{30}ClNO$	H; C[w]
21	H	H	CH_3CO	C_6H_5		184–186	B	$C_{20}H_{23}NO_2$	C; H[x]
22	H	H	CH_3CO	C_6H_5[p]		231–233	A	$C_{20}H_{23}NO_2$	C, H
23	CH_3CO	H	H	C_6H_5	HCl	315–318	A	$C_{20}H_{24}ClNO_2$	C, H
24	CH_3CO	H	H	C_6H_5[q]	HCl	318–322	A	$C_{20}H_{24}ClNO_2$	C, H
25	H	H	C_2H_5	C_6H_5[r]		90–92	H	$C_{20}H_{25}NO$	C, H
					AM	159–160	A-E	$C_{24}H_{29}NO_5$	C, H
26	CH_3	H	CH_3	C_6H_5		114–116	H	$C_{20}H_{25}NO$	C, H
					HCl	248–252	I-E	$C_{20}H_{26}ClNO$	C, H
27	H	H	C_3H_5	C_6H_5[s]		98–99	H	$C_{21}H_{25}NO$	C, H
					HCl	227–228	A-E	$C_{21}H_{26}ClNO$	C, H
28	CH_3CO	H	CH_3	C_6H_5[t]		93–94	H	$C_{21}H_{25}NO_2$	C, H
					HCl[u]	253–255	A-E	$C_{21}H_{26}ClNO_2$	C, H
29	C_2H_5CO	H	CH_3	C_6H_5	HCl	242–243	A-E	$C_{22}H_{28}ClNO_2$	C, H
30	$(CH_3)_2NCO$	H	H	C_6H_5[d]	AM	212–214	A-EA	$C_{25}H_{30}N_2O_6$	C, H
31	CH_3CO	H	CH_3CO	C_6H_5		168–170	IA	$C_{22}H_{25}NO_3$	C, H
32	H	H	C_6H_5CO	C_6H_5	HCl	192–195	B	$C_{25}H_{25}NO_2$	C, H
33	H	H	$C_6H_5CH_2$	C_6H_5	HCl	249–250	A	$C_{25}H_{28}ClNO$	H; C[y]
34	H	H	$C_6H_5CH_2CO$	C_6H_5		197–199	M	$C_{26}H_{27}NO_2$	C, H

[a] AM, acid maleate; AS, acid succinate; APS, acid phenylsuccinate; AT, acid tartrate; PS, phenylsuccinate. [b] Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected. [c] A, EtOH; AC, Me_2CO; B, benzene; EA, EtOAc; E, Et_2O; H, hexane; I, *i*-PrOH; IA, *i*-PrOAc; M, MeOH; W, H_2O. [d] From the pyridine analog with H_2 and Pt in AcOH. [e] Base bp 218–220° (1 mm). [f] By the procedure of H. H. Hatt in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 211. [g] C: calcd, 71.75; found, 70.80. [h] *l* isomer. [i] $[\alpha]^{25}D$ +26.6°. [j] D isomer. [k] From **2** with LAH in ether (Soxhlet addition procedure). [l] For this compound replace phenyl in the formula by cyclohexyl. [m] Cyclohexyl. [n] Cyclopentyl. [o] By N-methylation with $HCHO–HCO_2H$. [p] *l* isomer, $[\alpha]^{25}D$ −4.6°, obtained by acetylating the *d*-piperidine derivative. [q] By rearrangement of **22**, $[\alpha]^{25}D$ −48°. [r] From **3** with EtI and K_2CO_3 in Me_2CO. [s] From **3** with allyl bromide and K_2CO_3 in acetone. [t] *d* isomer, $[\alpha]^{25}D$ +133.4, from acetylation of **14**. [u] Sesquihydrate, $[\alpha]^{25}D$ +60.2. [v] C: calcd, 69.50; found, 69.07. [w] C; calcd, 70.45; found, 71.00. [x] H: calcd, 7.49; found, 8.08. [y] C: calcd, 76.24; found, 75.82. [z] Analyses for the elements indicated were within 0.4% of the theoretical values.

TABLE II

3-PYRIDINOLS AND DERIVATIVES



No.	X	Y	R′	Bp (mm) or mp, °C[a]	Crystn solvent[b]	% yield	Formula	Analyses[z]
37	H		=O[c,d]	102–103	EA	86	$C_{12}H_8ClNO_2$	C, H
38	H		=O[d]	63–65	H	90	$C_{12}H_9NO_2$	C, H
39	H	H	H[e]	219–220	I	48	$C_{12}H_{10}ClNO$	C, H
40	H	OH	H[e]	117–119	B	92	$C_{12}H_{11}NO_2$	C, H
41	CH_3		=O[e,f]	90–93	EA	74	$C_{13}H_{10}ClNO_2$	C, H
42	CH_3		=O[g]	140–145 (1)		81	$C_{13}H_{11}NO_2$	C, H
	Hydrochloride			148–151	I–IA		$C_{12}H_{12}ClNO_2$	C, H
43	CH_3	H	H[e,h]	74–76[i]	H	81	$C_{13}H_{12}ClNO$	C, H
44	CH_3	H	H[h,j]	46–47[k]	H	76	$C_{13}H_{13}NO$	C, H
	Hydrochloride			189–190	I		$C_{13}H_{14}ClNO$	C, H
45	CH_3	H	$COOC_2H_5$	105–107[l]	IA	63	$C_{16}H_{17}NO_3$	C, H
46	H	H	C_5H_9[m,d]	263–264	A		$C_{17}H_{19}NO$	C, H
47	CH_3	OH	2-Thenyl[n]	127–129	A	58	$C_{17}H_{15}NO_2S$	C, H
48	CH_3	H	$(CH_2)_2N(CH_3)_2$[e,o]	164–167 (1)		78	$C_{17}H_{21}ClN_2O$	C; H[aa]
	Acid maleate			124–127	EA		$C_{21}H_{25}ClN_2O_5$	C, H
49	CH_3	H	$(CH_2)_2N(CH_3)_2$	170–171 (2)		87	$C_{17}H_{22}N_2O$	C, H
	Acid maleate			124–126	EA		$C_{21}H_{26}N_2O_5$	C, H
50	H[p]			267–270	M	5	$C_{18}H_{13}NO_2$	C, H
51	H	H	o-ClC_6H_5	226–229	M	23	$C_{18}H_{14}ClNO$	C, H
52	H	H	p-ClC_6H_5	193–195	M	15	$C_{18}H_{14}ClNO_2$	C, H
53	H	H	C_6H_5	219–220	M	34	$C_{18}H_{15}NO$	C, H
54	Methosulfate			152–154	A–IA		$C_{20}H_{21}NO_5S$	C, H
55	H	OH	C_6H_5[q]	168–170	B	71	$C_{18}H_{15}NO_2$	C, H
56	H	H	C_6H_{11}[r]	272–275	EA	55	$C_{18}H_{21}NO$	C, H
57	CH_3	H	C_5H_9[m,s]	103–106	H	67	$C_{18}H_{21}NO$	C, H
58	CH_3	H	p-ClC_6H_5[h]	106–109	H	80	$C_{19}H_{16}ClNO$	C, H
59	CH_3	OH	p-ClC_6H_5[t]	133–134	H	68	$C_{19}H_{16}ClNO_2$	C, H
60	H[u]	H	C_6H_5	196–198	M	3.5	$C_{19}H_{17}NO$	C, H
61	CH_3	H	C_6H_5[h]	120–122	H	78	$C_{19}H_{17}NO$	C, H
62	H	H	$C_6H_5CH_2$[d]	216–217	M	60	$C_{19}H_{17}NO$	C, H
63	CH_3	OH	C_6H_5[v]	129–131	M	84	$C_{19}H_{17}NO_2$	C, H
64	H	H	p-$CH_3OC_6H_5$	206–208	M	8	$C_{19}H_{17}NO_2$	C, H
65	CH_3	H	C_6H_{11}[r,s]	142–144	H	74	$C_{19}H_{23}NO$	C, H
66	CH_3CO	H	C_6H_5	133–135	I	94	$C_{20}H_{17}NO_2$	C, H
67	Methosulfate			203–205	I		$C_{22}H_{23}NO_6S$	C, H
68	CH_3	H	$C_6H_5CH_2$[s]	71–73	H	72	$C_{20}H_{19}NO$	C, H
69	C_2H_5	H	C_6H_5[w]	96–98	H	85	$C_{20}H_{19}NO$	C, H
70	$(CH_3)_2NCO$	H	C_6H_5[x]	120–121[y]	A	86	$C_{21}H_{20}N_2O_2$	C, H
	Methosulfate			159–160	I		$C_{23}H_{26}N_2O_6S$	C, H

[a] See footnote *b*, Table I. [b] See footnote *c*, Table I. [c] For this compound replace phenyl in the formula by *p*-chlorophenyl. [d] From hydrolysis of the methyl ether with 48% HBr. [e] From **38** with H_2–Pt in AcOH. [f] From **43** with aqueous $KMnO_4$; see K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4006 (1930). [g] From **44**; see footnote *f*. [h] From the pyridol and phenyltrimethylammonium bromide; see ref 1g for procedure. [i] Bp 135° (1 mm). [j] From the pyridol; see ref 1b and 1e and footnote *h*. [k] Bp 120° (3 mm). [l] Bp 175° (2 mm). [m] Cyclopentyl. [n] 2-Thenyl-MgBr on **42**. [o] Alkylation of **43** with $NaNH_2$ in liquid NH_3. [p] This compound is 2-(9-xanthyl)-3-pyridinol. [q] Excess PhMgBr on **38**. [r] Cyclohexyl. [s] From **44** with *R*Br and $NaNH_2$ in liquid NH_3. [t] PhMgBr on **41**. [u] Replace pyridyl by 6-methylpyridyl in the formula. [v] PhMgBr on **42**. [w] From **39**, ethyl tosylate and NaOH in 70% EtOH. [x] From **53** with NaH and dimethylcarbamoyl chloride in DMF. [y] Bp 216–219° (1 mm). [z] See footnote *z*, Table I. [aa] H: calcd, 6.94; found, 6.50.

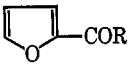
and piperidine groups. The hydrogenation of the pyridinols as their ether or acyl derivatives gave cleaner products, although some hydrogenolysis of the ether and ester functions did occur. The catalytic reduction of the N-methylpyridinium derivatives, either as the phenols or as their ethers or esters likewise did not give single products. In large-scale runs hydrogenation of 2-diphenylmethyl-3-pyridinol with Raney nickel was more successful. Only one conformational isomer of 2-diphenylmethyl-3-piperidinol was isolated from all the procedures, probably the *cis* form with an axial hydroxyl since its N-acetyl derivative rearranged to the ester in acid solution.

The lactone (V) of α-(3-hydroxy-2-piperidyl)phenylacetic acid also was prepared since it possesses the main structural features of methylphenidate (IV). Thus 2-benzyl-3-methoxypyridine was carbethoxylated with ethyl carbonate and the product was hydrogenated and cyclized to the lactone.

In addition to the compounds prepared as stimulants, 2-benzyl-3-methoxypyridine and its *p*-chloro analog were alkylated with dimethylaminoethyl chloride to give the 3-methoxypyridyl analogs of the antihistamines pheniramine and chlorpheniramine.

Pharmacology.—The stimulant effects of the piperidinols on mice were determined in the Pharmacology

TABLE III
2-FURYL KETONES



R	Bp (mm)[a] or mp, °C	Crystn[b] solvent	Yield, %	Formula	Analyses[d]
p-Chlorobenzyl	87–88	M	55	$C_{12}H_9ClO_2$	C, H
9-Fluorenyl	138–139	A	78	$C_{18}H_{12}O_2$	H; C[e]
9-Xanthyl	112–114	M	80	$C_{18}H_{12}O_3$	C, H
α-(*p*-Chlorophenyl)benzyl	206–212 (1)		35	$C_{18}H_{13}ClO_2$	C, H
α-(*o*-Chlorophenyl)benzyl	210–216 (4), 82–84	H	66	$C_{18}H_{13}ClO_2$	C, H
Diphenylmethyl	101–103	H	70	$C_{18}H_{14}O_2$	C, H
Diphenylmethyl[c]	163–164	B	63	$C_{19}H_{16}O_2$	C, H
α-(*p*-Methoxyphenyl)benzyl	115–118	M		$C_{19}H_{16}O_3$	C, H

[a] See footnote *b*, Table I. [b] See footnote *c*, Table I. [c] For this compound replace furyl by 5-methylfuryl in the formula. [d] See footnote *z*, Table I. [e] C: calcd, 83.06; found, 83.75.

TABLE IV
EFFECTS OF 3-PIPERIDINOLS AND DERIVATIVES IN MICE

No.	Stimulant dose,[a,b] mg/kg ip	Lethal dose,[b,c] mg/kg ip
1	100[d]	300
3	3	100
4	100	100
5	0.3	100
6	10	30
7	3	100
8	3	100
9	3	100
10	30	100
11	3	100
12	10	100
13	1	30
14	1	100
15	300	300
16	10	100
17	30	100
18	100	100
19	30	100
20	10	100
23	10	100
24	0.3	30
25	3	30
26	10	100
27	3	30
28	30[e]	100[e]
29	10	100
30	30	300
33	1	100
Amphetamine	1	60

[a] Lowest dose producing moderate increases in motor activity or reactivity (visual observation). [b] Compounds were administered in water as soluble salts; the dose is calculated as the free base. [c] Lowest dose administered at which deaths occurred; initial screen at doses of 3, 30, and 100 mg/kg. The deaths were invariably convulsive. [d] No stimulation; depression and muscle relaxation only. [e] Per oral administration.

Department of these laboratories. Dr. Samuel Irwin supervised this study and the procedure has been published.[3] The results are given in Table IV. Briefly summarized, the 3-piperidinols I, where R is hydrogen or alkyl, Y is hydrogen, and R^1 is phenyl, were potent stimulants. The ether and ester derivatives, excepting **24**, were less active as were the diphenylcarbinols and most compounds with substituents in the phenyl ring.

Compounds **5** and **14**, the *d* isomers of **3** and **13**, respectively, accounted for the activity of the latter since the *l* isomers were almost inactive. Compound **14** had minimal cardiac and respiratory effects at stimulant doses and was tried clinically.[4] It was a potent stimulant, but the dose–response effect was too marked. At a given dose, due to the variation in the individual patient response, the level of stimulation attained frequently was above or below that desired.

The lactone V had 0.01 times the activity of amphetamine. Subsequent studies[5] correlating the activity and configuration of the methylphenidate isomers have shown that the *threo* form (amino and ester groups adjacent) is responsible for the activity and that the *erythro* form is almost inactive. Molecular models indicate that in both the *cis* and *trans* forms of the lactone V, the amino and ester groups are more widely separated than they are in the *threo* form of methylphenidate, and this may account for its lack of activity.

Compounds **49** and **48**, the 3-methoxy analogs of pheniramine and chlorpheniramine, respectively, had 0.1 times the antihistaminic activity of the parent compound when tested *in vitro* on guinea pig ileum.

Experimental Section

α-2-Furoyl-*p*-chlorophenylacetonitrile.—A solution of 75.8 g of *p*-chlorophenylacetonitrile in 100 ml of C_6H_6 was added dropwise to a stirred refluxing mixture of 70 g of ethyl furoate and 30 g of $NaOCH_3$ in 300 ml of C_6H_6. During the reaction the benzene–alcohol azeotrope was removed through a helice-filled column topped by a total-reflux partial-takeoff condenser. After 4 hr the mixture was cooled and filtered, and the orange salt was washed (C_6H_6). It was stirred with 20% AcOH and Et_2O until it dissolved and the ether extract was washed neutral with $NaHCO_3$, dried (Na_2SO_4), filtered, and distilled. The yield of yellow viscous oil, bp 183–185° (1 mm), was 106 g (84%). *Anal.* ($C_{13}H_8ClNO$) N.

***p*-Chlorobenzyl 2-Furyl Ketone.**—The above nitrile (94 g), in 500 ml of MeOH, was saturated with dry HCl below 5° and kept at room temperature for 3 days. A crystalline imino ester salt separated. H_2O (1 l.) was added, the mixture refluxed vigorously for 3 hr, and the MeOH distilled. The product solidified when cooled.

Diphenylmethyl 2-Furyl Ketones.—The diphenylmethane (1 mole) was added with stirring to KNH_2 (1 mole) in 1200 ml of liquid NH_3 contained in an insulated (vermiculite) flask. Ten minutes after this addition, 0.5 mole of finely powdered ethyl furoate was added during 15 min and several hours later 500

(3) S. Irwin, N. Slabok, P. DeBiasse, and W. Govier, *Arch. Int. Pharmacodyn. Ther.*, **118**, 358 (1959).

(4) J. Nodine, T. Bode, J. Slap, H. Levy, and P. Siegler, *Antibiot. Med. Clin. Therapy*, **7**, 771 (1960).

(5) I. Weisz and A. Dudas, *Monatsh. Chem.*, **91**, 840 (1960).

ml of dry ether. Stirring was continued overnight and liquid NH_3 often was present the next day. Ether was added then, cautiously, 300 ml of H_2O. The ether was separated, dried (K_2CO_3), filtered, and evaporated on a steam bath. In most instances the dark oil crystallized when kept at room temperature for several days. This crude product containing tetraphenylethane was filtered, washed with hexane, and used without further purification. The mother liquor was distilled *in vacuo* to recover the diphenylmethane but yielded a negligible amount of product. This procedure was used with *o*-chloro-, *p*-chloro-, and *p*-methoxydiphenylmethane, xanthene, and fluorene. The fluorenyl ketone was alkali soluble and was precipitated from the aqueous phase with AcOH.

3-Pyridinols from 2-Furyl Ketones.—The ketone (0.6 mole) and 900 ml each of MeOH and 28% NH_4OH were heated to 150–160° in a rocking autoclave during 1 hr and kept at this temperature 12–15 hr. The dark mixture was evaporated to one-fourth volume on the steam bath, 500 ml of C_6H_6 was added to the hot residue with vigorous stirring, and after cooling, the product was filtered, washed (C_6H_6), and recrystallized. The aqueous benzene filtrate and washings were extracted with 200 ml of 3% NaOH, and this extract, saturated with CO_2, gave additional though more impure product. The initial treatment of the concentrated reaction mixture with alkali was avoided where possible as it produced colored impurities which were not easily removed. Very crude 2-diphenylmethyl-3-pyridinol was purified most easily by heating it with twice its weight of Ac_2O on a steam bath for 2 hr. An excellent yield of pure acetate ester separated on cooling.

2-Diphenylmethyl-3-piperidinol.—The pyridinol (50 g), 5 g of Raney nickel, 200 ml of purified dioxane, and two drops of 50% NaOH under H_2 at 125 kg/cm² in a rocking autoclave were heated rapidly to 130–135° and kept in this range until the theoretical pressure drop had taken place (about 2 hr). After removing the catalyst and solvent, the residue in 500 ml of ether was extracted with two 50-ml portions of 3% NaOH and once with H_2O. These extracts gave 3–5 g of starting material when saturated with CO_2. The ether solution was dried (K_2CO_3), filtered, concentrated on a steam bath, and dissolved in 50–60 ml of hexane. This solution, seeded and kept at room temperature for several days, gave 30–35 g of product, mp 94–97°.

2-(α-Cyclohexylbenzyl)-3-piperidinol and 2-Dicyclohexylmethyl-3-piperidinol Hydrochlorides.—Distillation of the above hexane liquors gave a complex mixture of compounds, bp 170–175° (1 mm). Fifty grams of this material in 750 ml of ether was extracted with successive portions of 5% HCl, each portion containing only enough acid to form the salt of one-tenth of the base. Each extraction was shaken vigorously for 10 min before separating the phases. The extracts were concentrated separately and the salt was recrystallized from water. The middle fractions gave the monocyclohexyl compound and the last fraction the dicyclohexyl compound in yields of 7 and 2.2 g, respectively.

Resolution of 2-Diphenylmethyl-3-piperidinol.[6]—A solution of 37.8 g of *d*-tartaric acid in 60 ml of hot H_2O was added to a solution of 67.2 g of base in 280 ml of warm EtOH. The solution was seeded with *l*-2-diphenylmethyl-3-piperidinol *d*-tartrate if available but, with or without seeds, was kept undisturbed for 48 hr. The mother liquor was decanted as completely as possible without disturbing the crystals which were then stirred briefly with 50 ml of 80% EtOH and filtered immediately. The mother liquor and washings were combined and scratched with a glass rod and a large crop of needle-shaped crystals separated. After 5 hr these were filtered and washed with a little EtOH. The 25 g of *d*-base *d*-acid tartrate so obtained was crystallized from 55 ml of 90% EtOH giving 19 g, mp 170–190°, $[\alpha]^{25}D$ −14.1°. The base from this salt had an $[\alpha]^{24}D$ +91.5°. The original crop of *l*-base *d*-tartrate was crystallized from 150 ml of 80% EtOH as initially done and gave 46.1 g of monohydrated salt, $[\alpha]^{24}D$ +12.9°. The base from this salt had $[\alpha]^{25}D$ −91.7°.

In an attempted resolution with *l*-phenylsuccinic acid in alcohol a very insoluble neutral salt separated despite the mole for mole combination of the reactants. This salt, $[\alpha]^{25}D$ −27.2°, gave pure racemic base and was used to remove the racemate from partially resolved mixtures.

(6) All rotations were done in DMF (*c* 1%).

Resolution of 1-Methyl-2-diphenylmethyl-3-piperidinol.—The base (115 g) in 1 l. of warm EtOH was mixed with 91.5 g of *d*-phenylsuccinic acid in 365 ml of EtOH and kept 20 hr at room temperature. The crystals were filtered, washed with EtOH, and recrystallized from 1750 ml of 85% EtOH yielding 53 g, mp 213–218°, $[\alpha]^{25}D$ −33.5°. This material, crystallized from 800 ml of 85% EtOH, gave 40 g of pure *l*-base *d*-acid phenylsuccinate, $[\alpha]^{25}D$ −37.7°. The base from this salt had an $[\alpha]^{25}D$ −201°; hydrochloride, $[\alpha]^{25}D$ −84.1°. Methylation of *l*-2-diphenylmethyl-3-piperidinol with HCHO–HCO_2H also gave the base, $[\alpha]^{25}D$ −201°.

2-(α-Cyclohexylbenzyl)-3-pyridinol.—2-Diphenylmethyl-3-pyridinol (12 g) in 200 ml of AcOH was hydrogenated at 50° with 1 g of PtO_2 and 4.2 kg/cm² of H_2 until 3 equiv were absorbed. After removing the catalyst and the solvent *in vacuo*, the gum was shaken with ether and 3% NaOH until it crystallized. The 4–5 g of product was filtered and washed (H_2O). The ether phase contained 2-diphenylmethyl- and 2-α-cyclohexylbenzyl-3-piperidinol, and the aqueous phase contained 4–5 g of starting material. The insolubility of the subject pyridinol in dilute NaOH was unexpected.

Ethyl α-(3-Methoxy-2-pyridyl)phenylacetate.—A solution of 84 g (0.46 mole) of 2-benzyl-3-methoxypyridine in 85 ml of ether was added with stirring to 17.9 g (0.46 mole) of $NaNH_2$ in 600 ml of liquid NH_3. Ten minutes later 28 g (0.23 mole) of ethyl carbonate in 50 ml of ether was added and after 1 hr the NH_3 was distilled by cautious warming. The ether solution was poured onto ice, separated, dried (K_2CO_3), filtered, and fractionated *in vacuo* to yield 45 g of starting material, 10 g of an intermediate fraction, and 46 g of product.

Ethyl α-(3-Methoxy-2-piperidyl)phenylacetate Hydrochloride.—The above compound (15 g) was hydrogenated with 1 g of PtO_2 in 200 ml of AcOH until 3 equiv were absorbed. The residue after removing the catalyst and the solvent *in vacuo* was stirred with ether below 5° while 5% NaOH was added until the pH was 10–12. The ether was separated, dried (K_2CO_3), filtered, and treated with dry HCl to give 15 g, mp 193–198°. This material crystallized from *i*-PrOH gave 8 g, mp 218–219°.

α-(3-Oxy-2-piperidyl)phenylacetic Acid Lactone Hydrochloride.—The *i*-PrOH liquor from above was evaporated to dryness, refluxed with 30 ml of 48% HBr for 2 hr, again concentrated to dryness on the steam bath, and heated for 1 hr. The residue was stirred with ether below 5° and basified with ice-cold 5% NaOH. The ether was separated and dried (K_2CO_3) and the product was precipitated with dry HCl. Three crystallizations from EtOH–Et_2O gave 0.5 g, mp 208–209.5°. *Anal.* ($C_{13}H_{16}ClNO_2$) C, H.

2-Diphenylmethyl-3-hydroxy-1-methylpyridinium Hydroxide.—2-Diphenylmethyl-3-pyridinol (17 g), 3 g of NaOH, 150 ml of H_2O, and 100 ml of dioxane were stirred vigorously below 5° and 9 g (10% excess) of Me_2SO_4 in 50 ml of dioxane was added dropwise. The mixture was kept at pH 9–11 by the dropwise addition of 5% NaOH and the reaction was continued for 3 hr. The dioxane was distilled and the mixture was made strongly alkaline and extracted with three 200-ml portions of ether. These extracts gave 8 g of 2-diphenylmethyl-3-methoxypyridine. The alkaline solution was concentrated on the steam bath, and, on cooling, the product crystallized as a monohydrate. It was filtered and recrystallized from acetone: mp 110–120°. *Anal.* ($C_{19}H_{19}NO_2 \cdot H_2O$) C, H.

1-Acetyl-2-diphenylmethyl-3-piperidinol.—A solution of 12.7 g (0.125 mole) of Ac_2O in 50 ml of dioxane was added with stirring to 66.7 g (0.25 mole) of the piperidinol in 600 ml of dioxane then warmed on a steam bath 2 hr. After 2 days the mixture was filtered to remove the acetate salt, concentrated *in vacuo* to a syrup, and poured in a thin stream into 400 ml of vigorously stirred 2% HCl. The product, 35 g, separated as a fine white powder. When refluxed for 24 hr with excess 2% HCl in 50% EtOH, this material rearranged to the ester hydrochloride quantitatively.

Acknowledgment.—The authors are grateful to Mr. Edwin Conner for the analyses, to Mrs. Ethel Sempf for the optical rotations, and to Mrs. Lorraine Meister for clerical contributions.