2-(2-Pyridyl)-1,2-diarylalkanols as Hypocholesteremic Agents[1]

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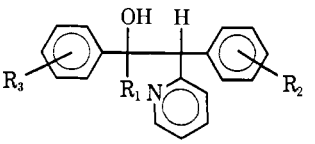
A series of 133 2-(2-pyridyl)-1,2-diarylalkanols, or compounds closely related to them, were synthesized and assayed for their hypocholesteremic and estrogenic activities in rats. Many of these compounds were active in both tests, but there is no necessary correlation between the two effects. Compound **16** was selected for preclinical toxicologic study, followed by a study of its hypocholesteremic effect in man. The compound selected was remarkably nontoxic in all species studied, but it had no hypocholesteremic effect in the dog, the monkey, or in man.

We have been attracted by the possibility that chemical modification of one of the many known synthetic estrogens[3] might lead to a hypocholesteremic agent free of the clinical stigmata associated with use of frank estrogens in the male.[4] This report describes a series of compounds that approaches this goal.

The series to be described conforms, for the most part, to generic structure I; the specific members of the series and their biologic properties are described in

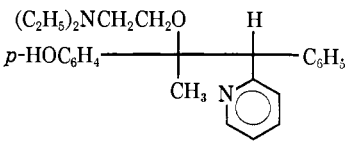


I

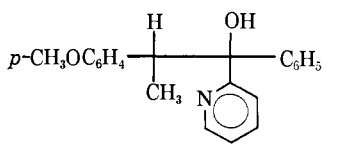
Tables I–VI. The hypocholesteremic activities reported in the tables were determined by already published methods,[5] and refer to oral dosages in the male Holtzman rat for 7 days at the dose level shown in parentheses. The estrogenicity figures (estrogenicity will be abbreviated as ES) refer to the number of micrograms of diethylstilbestrol that produces an estrogenic response equivalent to that produced by 1 mg of the test compound, both given orally. Each of these figures was obtained by a standard modification[6] of the Allen–Doisy vaginal smear bioassay method,[7] by using adult ovariectomized rats of the Carworth CFN strain. The larger the ES figure the more estrogenic the compound.

Compounds of type I were prepared by conversion of the appropriate benzylpyridine to its anion with phenyllithium, and addition of the anion to an appropriate carbonyl reagent (Tables I, II, and V). The presence of two asymmetric carbon atoms leads to the possible formation of two diastereoisomeric pairs. In many cases the two DL pairs, separated by fractional crystallization, exhibited different biological activities. Several attempts were made to resolve one of the more active DL pairs, but none was successful.

Oxidation of the two DL pairs of I (R_1 = Me, R_2 = H, R_3 = 4-SMe) (**52**, **53**) with peracetic acid provided the sulfones, **61** and **62**. To prepare the *p*-hydroxylated compounds (**27**, **28**) the phenols were protected as the tetrahydropyranyl ethers before addition of the lithium reagent to the carbonyl group. Mild acid hydrolysis effected cleavage of the ethers to the desired phenolic products. Alkylation of the intermediate tetrahydropyranyl ether with 2-chlorotriethylamine followed by *in situ* acid hydrolysis afforded the ether, II.



II



III

Oxidation of certain of the analogs of I with peracetic acid provided the corresponding pyridine N-oxides tabulated in Table III. Several of the parent compounds were reduced to the piperidine derivatives by hydrogenation in acid over PtO_2 (Table IV). The reduced materials were uniformly inactive as hypocholesteremic agents.

Some of the analogs of I were dehydrated to the corresponding propylenes (Table VI) by treatment with 85% phosphoric acid or other mineral acid. The olefins were generally as active or more active than the parent carbinols.

Treatment of the Grignard reagent from *p*-chlorobenzyl chloride with phenyl 2-thienyl ketone followed by the usual work-up gave the olefin, 2-[2-(*p*-chloro-

(1) (a) Presented in part before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964. (b) Taken in part from a Ph.D. Thesis of W. D. Dixon, The University of Kansas, 1960.

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(3) U. V. Solmssen, *Chem. Rev.*, **37**, 481 (1945); J. Grundy, *ibid.*, **57**, 281 (1957); J. A. Hogg and J. Korman in "Medicinal Chemistry," Vol. 2, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 34.

(4) (a) C. Moses, "Atherosclerosis," Lea and Febiger, Philadelphia, Pa., 1963, p 128; (b) R. Pick, J. Stamler, and L. N. Katz in "Hormones and Atherosclerosis," G. Pincus, Ed., Academic Press Inc., New York, N. Y., 1959, p 229.

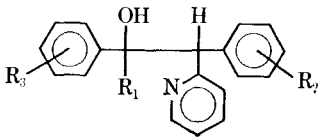
(5) G. Rodney, M. L. Black, and O. D. Bird, *Biochem. Pharmacol.*, **14**, 1336 (1965).

(6) C. W. Emmens, *Methods Hormone Res.*, **2**, 65 (1962).

(7) E. Allen and E. A. Doisy, *J. Am. Med. Assoc.*, **81**, 819 (1923).

TABLE I

2-(2-PYRIDYL)-1,2-DIARYLALKANOLS

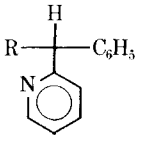


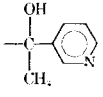
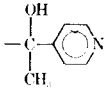
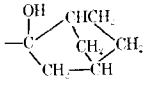
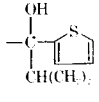
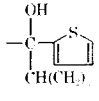
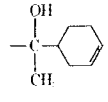
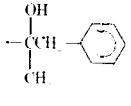
No.	R_1	R_2	R_3	Yield purified, %	Mp, °C	Purifien solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Decrease in serum cholesterol, % (mg/kg/day)	Estrogenicity
1	H	H	2-Cl	18	122–125	A	$C_{19}H_{16}ClNO$	73.66	73.59	5.20	5.48			7 (5)	0.2
2	H	H	4-Cl	37	168–172	C	$C_{19}H_{16}ClNO$	73.66	73.82	5.20	5.26	4.52	4.37	0 (5)	1.22
3	H	H	H	14	144–146	A	$C_{19}H_{17}NO$	82.89	82.97	6.22	6.27			0 (5)	1.28
4	H	H	1,2,5,6-H_4	21	123–129	C	$C_{19}H_{21}NO$	81.68	81.72	7.58	7.51	5.01	5.26	0 (5)	0.51
5	H	H	1,2,3,4,5,6-H_6	46	102–104	B	$C_{19}H_{23}NO$	81.10	80.87	8.24	8.41	4.98	5.03	0 (5)	0.55
6	CH_3	H	2,3-Cl_2	18	129–131	B	$C_{20}H_{17}Cl_2NO$	67.04	67.27	4.79	5.02			15 (5)	...
7	CH_3	H	2,3-Cl_2	9.4	160–164	B	$C_{20}H_{17}Cl_2NO$	67.04	66.82	4.79	4.80	3.91	3.77	19 (5)	...
8	CH_3	H	2,4-Cl_2	1.2	142–144	C	$C_{20}H_{17}Cl_2NO$	67.05	67.15	4.79	4.88			91 (5)	>4
9	CH_3	H	2,4-Cl_2	16	152–153	B	$C_{20}H_{17}Cl_2NO$	67.05	67.17	4.79	4.99			46 (5)	>4
10	CH_3	H	2,5-Cl_2	34	125–126	B	$C_{20}H_{17}Cl_2NO$	67.05	66.92	4.79	4.96			51 (5)	>4
11	CH_3	H	3-Br	3.5	116–119	*c*	$C_{20}H_{18}BrNO$	65.22	65.25	4.93	4.88			0 (5)	...
12	CH_3	H	3-Br	24	158–160	*d*	$C_{20}H_{18}BrNO$	65.22	65.59	4.93	5.09			0 (5)	...
13	CH_3	H	4-Br	17	122–124	V	$C_{20}H_{18}BrNO$	65.22	65.65	4.93	5.19	3.81	3.90	37 (5)	>4
14	CH_3	H	2-Cl	13	113–115	D	$C_{20}H_{18}ClNO$	74.18	74.30	5.60	5.66	4.33	4.21	67 (5)	9.4
15	CH_3	H	2-Cl	25	112–114	D	$C_{20}H_{18}ClNO$	74.18	74.27	5.60	5.70	4.33	4.16	23 (5)	3.2
16	CH_3	H	3-Cl	16.5	134–136	J	$C_{20}H_{18}ClNO$	74.18	73.92	5.60	5.67			32 (5)	2.9
17	CH_3	H	3-Cl	1	108–110	J	$C_{20}H_{18}ClNO$	74.18	74.44	5.60	5.51			5 (5)	0.67
18	CH_3	H	4-Cl	69	152–154	T	$C_{20}H_{18}ClNO$	74.18	74.53	5.60	5.86			0 (5)	2.7
19	CH_3	4-Cl	H	5[b]	135–140	E	$C_{20}H_{18}ClNO$	74.18	73.65	5.60	5.54	4.33	4.09	0 (25)	...
20	CH_3	4-Cl	H	3.4	140–145	E	$C_{20}H_{18}ClNO$	74.18	74.02	5.60	5.55	4.33	4.21	10 (25)	2.40
21	CH_3	H	2-F	6.8	103–105	E	$C_{20}H_{18}FNO$	78.15	78.11	5.90	6.34	4.56	4.67	44 (25)	...
22	CH_3	H	3-F	2	107–110	H	$C_{20}H_{18}FNO$	78.15	78.26	5.90	6.07			57 (5)	>4
23	CH_3	H	3-F	2	97.5–100	I	$C_{20}H_{18}FNO$	78.15	78.41	5.90	5.99			0 (5)	0.20
24	CH_3	H	4-F	63	116–118	C	$C_{20}H_{18}FNO$	78.15	78.44	5.90	6.02			0 (5)	0.65
25	CH_3	H	H	30	133–135	B	$C_{20}H_{19}NO$	83.01	82.91	6.62	6.70			34 (5)	20
26	CH_3	H	H	1.8	106–107	B	$C_{20}H_{19}NO$	83.01	83.05	6.62	6.77			0 (5)	0.79
27	CH_3	H	3-OH	23	125.5–126.5	L	$C_{20}H_{19}NO_2$	78.66	79.65	6.27	6.43	4.59	4.20	0 (25)	...
28	CH_3	H	4-OH	43	139–140	O	$C_{20}H_{19}NO_2$	78.66	78.49	6.27	6.24	4.59	4.69	20 (25)	1.40
29	H	H	2-OCH_3	24	126–129	B	$C_{20}H_{19}NO_2$	78.66	78.67	6.27	6.50			88 (25)	1.80
30	H	H	3-OCH_3	37	134–137	B	$C_{20}H_{19}NO_2$	78.66	78.90	6.27	6.41			0 (25)	1.22
31	H	H	4-OCH_3	55	160–162	A	$C_{20}H_{19}NO_2$	78.66	78.50	6.27	6.42			14 (5)	<4
32	CH_3	H	2-CF_3	10	144–146	A	$C_{21}H_{18}F_3NO$	70.58	70.44	5.08	5.08	3.92	4.09	21 (25)	...
33	CH_3	H	2-CF_3	10	156–159	A	$C_{21}H_{18}F_3NO$	70.58	70.66	5.08	5.09	3.92	4.03	42 (25)	...
34	CH_3	H	3-CF_3	10	156–157	C	$C_{21}H_{18}F_3NO$	70.58	70.55	5.08	5.21	3.92	3.70	14 (25)	1.93
35	CH_3	2-OCH_3	2,4-Cl_2	28	165–167	C	$C_{21}H_{19}Cl_2NO_2$	64.95	65.04	4.93	5.19	3.61	3.54	31 (5)	>4
36	CH_3	2-OCH_3	2,4-Cl_2	15	139–142	C	$C_{21}H_{19}Cl_2NO_2$	64.95	65.35	4.93	5.31	3.61	3.28	0 (25)	...
37	CH_3	4-CH_3	3-Cl	2	125–127	C	$C_{21}H_{20}ClNO$	74.65	74.52	5.97	5.85	4.14	4.30	0 (25)	...
38	CH_3	4-CH_3	3-Cl	17	142–143.5	C	$C_{21}H_{20}ClNO$	74.65	74.85	5.97	5.67	4.14	3.99	0 (25)	...

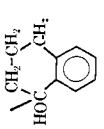
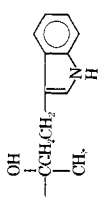
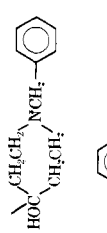
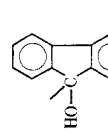
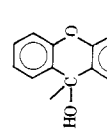
39	CH_3	4-Cl	4-CH_3	70	148–150	C	$C_{21}H_{20}ClNO$	74.65	74.69	5.97	6.04			0 (5)	>4
40	C_2H_5	H	4-Cl	9	126–128	C	$C_{21}H_{20}ClNO$	74.65	74.29	5.96	6.13			22 (5)	3.70
41	C_2H_5	H	4-Cl	3	158	C	$C_{21}H_{20}ClNO$	74.65	74.38	5.96	5.88			0 (5)	2.60
42	CH_3	4-Cl	4-OCH_3	75	135–137	C	$C_{21}H_{20}ClNO_2$	71.27	71.39	5.70	5.75			0 (5)	0.43
43	CH_3	2-OCH_3	3-Cl	20	155–156	G	$C_{21}H_{20}ClNO_2 \cdot HCl$	64.60	64.64	5.43	5.68	3.59	3.55	19 (25)	...
44	CH_3	2-OCH_3	3-Cl	12	141.5–143	G	$C_{21}H_{20}ClNO_2 \cdot HCl$	64.60	64.74	5.43	5.68	3.59	3.52	0 (25)	...
45	CH_3	H	2-CH_3	23	79–83	D	$C_{21}H_{21}NO$	83.14	83.29	6.98	7.27	4.62	4.50	61 (25)	...
46	CH_3	H	3-CH_3	17	108–110.5	K	$C_{21}H_{21}NO$	83.13	83.04	6.98	7.11			0 (5)	...
47	CH_3	H	4-CH_3	72	127–129	C	$C_{21}H_{21}NO$	83.13	82.98	6.98	7.01			0 (5)	0.38
48	CH_3	H	4-CH_3	23	130–131	B	$C_{21}H_{21}NO$	83.13	83.15	6.98	7.13			0 (5)	0.92
49	C_2H_5	H	H	78	153–156	..	$C_{21}H_{21}NO$	83.13	83.43	6.98	6.94			63 (5)	15.3
50	CH_3	H	2-SCH_3	42	141–143	..	$C_{21}H_{21}NOS$	75.19	75.29	6.31	6.50	4.18	4.18	0 (25)	...
51	CH_3	H	2-SCH_3	23	98–101	D	$C_{21}H_{21}NOS$	75.19	75.29	6.31	6.50	4.18	4.28	0 (25)	...
52	CH_3	H	4-SCH_3	40	145–149	P	$C_{21}H_{21}NOS$	75.19	75.15	6.31	6.24	4.18	3.84	19 (5)	0.74
53	CH_3	H	4-SCH_3	29	95–98	P	$C_{21}H_{21}NOS$	75.19	75.56	6.31	6.57	4.18	3.93	0 (5)	0.87
54	CH_3	H	2-OCH_3	5.4	140–142	A	$C_{21}H_{21}NO_2$	78.94	78.81	6.64	6.73			20 (5)	0.8
55	CH_3	H	2-OCH_3	31	109–110	B	$C_{21}H_{21}NO_2$	78.94	79.17	6.64	6.88			0 (25)	0.78
56	CH_3	H	3-OCH_3	11	97–98	E	$C_{21}H_{21}NO_2$	78.97	79.12	6.63	6.90			57 (5)	>4
57	CH_3	H	3-OCH_3	21	121–123	C	$C_{21}H_{21}NO_2$	78.97	79.25	6.63	6.90			0 (5)	0.18
58	CH_3	H	4-OCH_3	6	135–137	D	$C_{21}H_{21}NO_2$	78.97	78.71	6.63	6.56			58 (5)	>4
59	CH_3	H	4-OCH_3	9	146–151	A	$C_{21}H_{21}NO_2$	78.97	79.18	6.63	6.79	4.39	4.50	15 (5)	1.03
60	CH_2OCH_3	H	H	25	130–133	C	$C_{21}H_{21}NO_2$	78.97	79.27	6.63	6.88	4.39	4.71	0 (25)	...
61	CH_3	H	4-SO_2CH_3	85	151–152	Q	$C_{21}H_{21}NO_3S$	68.66	68.31	5.77	5.78	3.81	3.55	0 (10)	...
62	CH_3	H	4-SO_2CH_3	85	148–150	Q	$C_{21}H_{21}NO_3S$	68.66	68.50	5.77	5.86	3.81	3.49	0 (10)	...
63	H	H	4-$N(CH_3)_2$	16	156–159	C	$C_{21}H_{22}N_2O$	79.21	79.45	6.96	7.02	8.80	8.86	0 (5)	1.14
64	$CH(CH_2)_2$	H	4-Br	4	112–116	B	$C_{22}H_{20}BrNO$	67.01	67.31	5.11	5.17	3.55	3.58	0 (5)	...
65	$CH(CH_2)_2$	H	4-Cl	14	118–122	B	$C_{22}H_{20}ClNO$	75.53	75.59	5.76	5.68	4.00	4.10	0 (25)	...
66	$CH(CH_2)_2$	H	4-F	14	128–130	B	$C_{22}H_{20}FNO$	79.25	79.61	6.05	6.40	4.20	4.22	0 (25)	...
67	$CH(CH_2)_2$	H	H	12	141–142	C	$C_{22}H_{21}NO$	83.77	84.18	6.71	6.90	4.44	4.67	39 (5)	>4
68	CH_3	H	4-$NHCOCH_3$	3	164–167	B	$C_{22}H_{22}N_2O_2$	76.27	76.08	6.40	6.49	8.09	8.17	0 (10)	...
69	CH_3	H	2,4-$(CH_3)_2$	18	148–149	B	$C_{22}H_{23}NO$	83.25	83.48	7.31	7.34			28 (5)	0.65
70	CH_3	H	3,4-$(CH_3)_2$	8	108–109	V	$C_{22}H_{23}NO$	83.24	83.51	7.30	7.51			0 (25)	...
71	C_3H_7	H	H	96	150–153	D	$C_{22}H_{23}NO$	83.24	83.14	7.30	7.38			0 (25)	...
72	CH_3	H	2-OC_2H_5	58	112–115	D	$C_{22}H_{23}NO_2$	79.25	79.33	6.95	7.08	4.20	4.06	14 (25)	...
73	C_2H_5	H	4-OCH_3	55	145–148	D	$C_{22}H_{23}NO_2$	79.25	79.42	6.95	6.79			62 (25)	31.23
74	CH_3	H	2,5-$(OCH_3)_2$	14	128–134	A	$C_{22}H_{23}NO_3$	75.62	75.50	6.63	6.58			0 (5)	...
75	CH_3	H	4-$SO_2N(CH_3)_2$	46	166–168	R	$C_{22}H_{24}N_2O_3S$	66.65	66.62	6.10	5.85	7.07	6.98	0 (25)	>4
76	2-Thienyl	H	H	26	153–159	W	$C_{23}H_{19}NOS$	77.28	77.25	5.36	5.26	3.92	3.91	0 (25)	...
77	$CH(CH_2)_2$	H	4-CH_3	5	115–116	C	$C_{23}H_{23}NO$	83.85	84.01	7.04	7.35	4.25	4.09	24 (10)	0.88
78	$CH(CH_2)_2$	H	4-CH_3	4	137.5–139.5	C	$C_{23}H_{23}NO$	83.85	83.92	7.04	7.07	4.25	4.28	32 (10)	1.07
79	$CH(CH_2)_2$	H	4-OCH_3	17	105–106	B	$C_{23}H_{23}NO_2$	79.97	79.70	6.71	6.82	4.06	3.96	39 (25)	>4
80	CH_3	H	4-O-$(CH_2)_2N(CH_3)_2$	11	123–125	B	$C_{24}H_{28}N_2O_2$	76.56	76.47	7.50	7.56			16 (5)	2.50
81	C_6H_5	H	H	75	186–189	D	$C_{25}H_{21}NO$	85.44	85.50	6.02	5.70			0 (25)	27.04
82	CH_3	H	3-O-C_5H_9O[e]	26	135.5–136	G	$C_{25}H_{27}NO_3$	77.09	76.90	6.99	7.00	3.60	3.76	0 (25)	...
83	CH_3	H	4-O-C_5H_9O[e]	2.5	134.5–135.5	M	$C_{25}H_{27}NO_3$	77.09	77.10	6.99	6.96	3.60	3.47	37 (25)	3.10
84	CH_3	H	4-O-C_5H_9O[e]	21	165.5–166	N	$C_{25}H_{27}NO_3$	77.09	77.18	6.99	7.43	3.60	3.49	35 (25)	>4
85	CH_3	H	4-O-$(CH_2)_3N(CH_3)_2$	3.1	93–95	K	$C_{25}H_{30}N_2O_2$	76.89	76.50	7.74	7.69			0 (5)	...
86	CH_3	H	4-C_6H_5	74	157–159	S	$C_{26}H_{23}NO$	85.44	85.26	6.34	6.55			0 (5)	81.84

[a] AEtOAc; B, EtOH–H_2O; C, EtOH; D, MeOH; E, heptane; F, CCl_4; G, EtOH–Et_2O; H, cyclohexane; I, isooctane; J, benzene–petroleum ether (bp 32–59°); K, MeOH–H_2O; L, benzene; M, acetone–MeOH; N, acetone; O, acetone–isooctane; P, MeOH–Et_2O; Q, acetone–H_2O; R, Et_2O–THF; S, Skellysolve C (bp 44–96°); T, cyclohexane–EtOH; U, $CHCl_3$–heptane; V, petroleum ether–hexane; W, acetonitrile. [b] Combined yield before separation 57%. [c] Extracted with ether. [d] Extracted with $CHCl_3$. [e] Tetrahydropyranyl.

Table II: Miscellaneous 2-(2-Pyridyl)alkanols



No.	R	Yield purified, %	Mp, °C	Purifica solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Decrease in serum cholesterol, % (mg/kg/day)	Estrogenicity
87		12	93–99	C	$C_{18}H_{17}NOS$	72.93	73.22	5.78	5.84	4.73	4.66	14 (5)	>4
88		23	95–97	A	$C_{13}H_{18}N_2O$	78.58	78.68	6.25	6.36	9.65	9.61	0 (5)	2.19
89		11	118–119	A	$C_{13}H_{18}N_2O$	78.58	78.20	6.25	6.26	9.65	10.17	0 (5)	1.20
90		34	115–118	B	$C_{13}H_{21}NO$	81.68	81.71	7.58	7.67	5.01	4.90	0 (25)	...
91		7	115–116	B	$C_{20}H_{19}NOS$	74.73	74.67	5.96	6.17	4.36	4.24	0 (10)	...
92		5	137–139	B	$C_{20}H_{19}NOS$	74.73	74.78	5.96	6.08	4.36	4.28	0 (5)	...
93		20	146–152	B	$C_{20}H_{23}NO$	81.87	81.64	7.90	8.06	4.78	4.62	23 (25)	>4
94		47	133–139	B	$C_{20}H_{25}NO$	81.31	81.18	8.53	8.55	4.74	4.70	14 (25)	...
95		33	89.5–92	B	$C_{21}H_{21}NO$	83.13	83.27	6.98	7.00	4.62	4.44	0 (25)	..

96		60	107–112	C	$C_{22}H_{21}NO$	83.77	83.85	6.72	6.93	4.45	4.61	0 (25)	0.85
97		18	174–176	B	$C_{24}H_{24}N_2O$	80.86	80.50	6.79	6.92	7.86	7.86	0 (25)	...
98		51	126–127	D	$C_{24}H_{28}N_2O$	80.40	80.50	7.31	7.27			0 (25)	...
99		5.6	130–131	F	$C_{25}H_{18}NO$	85.93	85.99	5.47	5.56			0 (5)	>4
100		1.4	235–237	E	$C_{25}H_{19}NO_2$	82.18	82.40	5.25	4.63			0 (25)	...

[a] A, CCl_4; B, EtOH; C, heptane; D, EtOH–H_2O; E, benzene; F, benzene–petroleum ether.

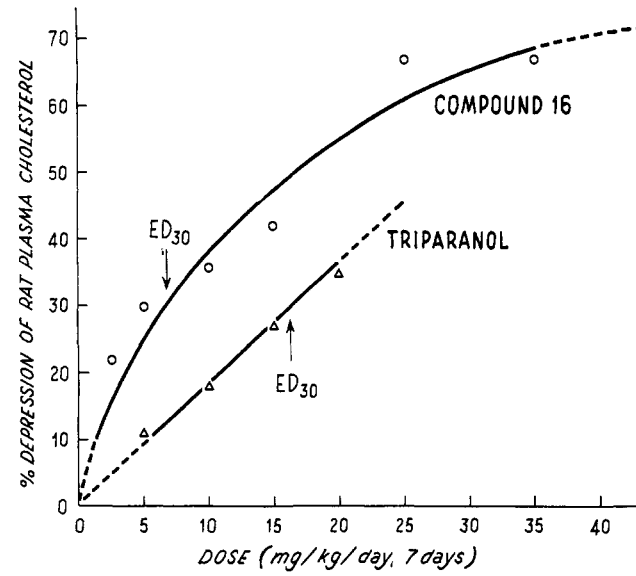


Figure 1.—Comparative dose–response curves for **16** and triparanol.

phenyl-1-phenylvinyl]thiophene, directly. This material did not lower serum cholesterol when administered at 25 mg/kg.

α-(*p*-Methoxy-α-methylbenzyl)-α-phenyl-2-pyridinemethanol (III), prepared from the lithium derivative of 2-bromopyridine and 4′-methoxy-α-methyldeoxybenzoin, produced 36% lowering of serum cholesterol at a dose of 25 mg/kg.

α′-4-Pyridyl-4-stilbenol, obtained from 4-benzylpyridine and 4-hydroxybenzaldehyde, lowered serum cholesterol 16% at a dose of 25 mg/kg.

Structure–activity relationships within the series are rather erratic, but several generalizations may be drawn: ring substitution of the pyridine moiety or the adjacent phenyl ring does not appear to enhance hypocholesteremic potency; linkage of the pyridine ring at positions other than 2 abolishes the activity; similarly, reduction of the pyridine ring abolishes the activity. The data suggest other correlations, but these are too vague and undocumented to permit further comment.

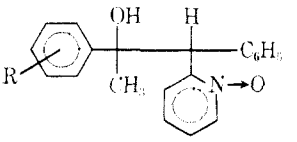
Compound **16** (I, $R_1 = CH_3$; $R_2 = H$; $R_3 = 3\text{-Cl}$) was selected for clinical evaluation. Some of the preliminary biochemical studies leading to this choice will be presented in the following paragraphs. Compound **16**, the higher melting DL pair, is soluble in water at 25° at less than 1 μg/ml and unstable to aqueous base, and its hydrochloride salt is extensively hydrolyzed in water solution. Presumably the latter is due to a stronger tendency for internal hydrogen bonding than for simple salt formation. It has an $ED_{30} \sim 7$ mg/kg/day, an ES ~ 2.9 μg of diethylstilbestrol (DES)/mg, and an $LD_{50} > 4$ g/kg (acute, orally, or intraperitoneally in mice and rats).

Figure 1 represents the dose–response curve for **16** compared with that of a reference drug, triparanol.[8] The effects shown there are reached after 4 days of treatment and indicate, by comparison of ED_{30} values, that **16** is two to three times more active than triparanol. A plateau at about 67% depression of plasma cholesterol is suggested by the data. No drug refractoriness develops upon treatment for 6 weeks. The

(8) F. P. Palopoli, *Progr. Cardiovascular Diseases*, **2**, 489 (1960).

TABLE III

2-(2-PYRIDYL 1-OXIDE)-1,2-DIARYLALKANOLS

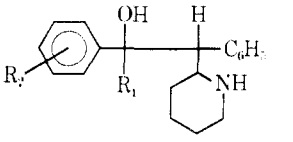


No.	R	Yield purified, %	Mp, °C	Purifen solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Decrease in serum cholesterol, % (mg/kg/day)	Estrogenicity
101	2,4-Cl_2	25	159–160	A	$C_{20}H_{17}Cl_2NO_2$	64.18	64.07	4.58	4.58			15 (5)	...
102	2,5-Cl_2	26	166–167	B	$C_{20}H_{17}Cl_2NO_2$	64.18	64.07	4.58	4.72	3.75	3.75	0 (5)	...
103	4-Br	18	163–165	D	$C_{20}H_{18}BrNO_2$	62.50	62.26	4.72	4.89			0 (5)	...
104	3-Cl	71	168–170	B	$C_{20}H_{18}ClNO_2$	70.69	70.80	5.34	5.56			18 (5)	1.60
105	H	9.4	156–158	C	$C_{20}H_{19}NO_2$	78.65	78.77	6.27	6.40	4.59	4.58	39 (5)	1.68
106	H	29	148	B	$C_{20}H_{19}NO_2$	78.65	78.96	6.27	6.41	4.59	4.47	0 (25)	...
107	4-OCH_3	51	143–145	B	$C_{21}H_{21}NO_3$	75.20	75.50	6.31	6.43	4.18	3.96	20 (5)	21
108	3-OCH_3	32	156–157	B	$C_{21}H_{21}NO_3$	75.20	74.85	6.31	6.46	4.18	4.33	27 (5)	1.30

[a] A, benzene–cyclohexane; B, $CHCl_3$–Et_2O; C, heptane–EtOH; D, benzene–$CHCl_3$.

TABLE IV

2-(2-PIPERIDINE)-1,2-DIARYLALKANOLS



No.	R_1	R_2	Yield purified, %	Mp, °C	Purifen solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Decrease in serum cholesterol, % (mg/kg/day)	Estrogenicity
109	CH_3	4-Cl	68	265–267 dec	A	$C_{20}H_{24}NOCl \cdot HCl$	65.58	65.37	6.88	6.73				
110	CH_3	H	61	128–130	B	$C_{20}H_{23}NO$	81.31	81.20	8.53	8.60			0 (25)	1.0
111	CH_3	4-OCH_3	74	230–232 dec	C	$C_{21}H_{25}NO_2 \cdot HCl$	69.70	69.85	7.80	7.82				
112	CH_3	4-OCH_3	76	252–254 dec[b]	D	$C_{21}H_{25}NO_2 \cdot HCl$	69.70	69.78	7.80	7.93				
113	CH_3	4-OCH_3	58	118–120[b]	B	$C_{21}H_{25}NO_2$	77.50	77.21	8.36	8.28			B (25)	0.83
114	C_2H_5	H	90	232–234 dec	A	$C_{21}H_{27}NO \cdot HCl$	72.91	72.82	8.16	8.23				
115	C_2H_5	4-OCH_3	82	251–253 dec	D	$C_{22}H_{29}NO_2 \cdot HCl$	70.28	69.93	8.01	7.57			0 (25)	15.1
116	C_3H_7	H	79	269–271 dec	E	$C_{22}H_{29}NO \cdot HCl$	73.42	73.67	8.36	8.45			0 (25)	0.67
117	C_6H_5	H	92	255–256 dec	D	$C_{25}H_{27}NO \cdot HCl$	76.23	75.88	7.17	7.11			0 (25)	1.20
118	CH_3	4-C_6H_5	57	137–139	F	$C_{26}H_{29}NO$	84.05	84.11	7.87	7.86				

[a] A, acetonitrile; B, EtOH–H_2O; C, acetone–Et_2O; D, EtOH–Et_2O; E, acetone; F, MeOH. [b] The low-melting racemate of the corresponding pyridylalkanol was used to prepare this compound. The starting material used to prepare the free base **112** may have been contaminated with some high-melting isomer.

animals consumed a normal diet, but the effects are identical, relative to pair-fed controls, when the diet is mildly atherogenic[9] and treatment is begun simultaneously.

Compound **16** does not affect the cholesterol levels of most tissues studied. The only significant effects are a 14% depression in total carcass cholesterol and a 60% depression in adrenal cholesterol at a dose of 25 mg/kg. Despite its effect on adrenal cholesterol, **16** does not impair adrenal sufficiency in ACTH-stressed animals.

The mechanism of action of **16** is not yet known. It does not affect, *in vivo* or *in vitro*, the rate of conversion of acetate-^{14}C to cholesterol or intermediate sterol concentration patterns[10] in the liver, so the compound cannot be a synthesis inhibitor. Studies of the effect of **16** on the excretion of radioactivity after injection of cholesterol-4-^{14}C show no increased excretion rate of ^{14}C-labeled compounds. In normal animals, the excretion of these metabolites, chiefly bile acids, is accompanied by reabsorption and recycling of part of the ^{14}C-bile acids as micelles containing exogenous cholesterol (a requirement for cholesterol absorption). The fact that there was no change in final fecal excretion rate, together with the knowledge that the known absorption inhibitors, β-sitosterol[11] and cholestyramine,[12] do increase excretion would tend to rule out absorption inhibition as a mechanism of action.

A comparison, shown in Figure 2, of the estrogenicity and hypocholesteremic effects of the more active DL pairs of five compounds (**69**, **16**, **115**, **107**, **86**) shows a steady rise of estrogenic activity and a completely erratic rise and fall of the hypocholesteremic values. This demonstrates rather conclusively the lack of a necessary correlation between the two types of activity

(9) This diet is basically that used by L. C. Fillios, S. B. Andrus, G. V. Mann, and F. J. Stare, *J. Exptl. Med.*, **104**, 539 (1956), but with 10% corn oil, 1.5% cholesterol, and 0.5% cholic acid instead of the concentrations they used.

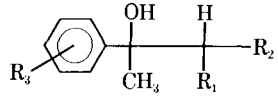
(10) The lack of effect of **16** on sterol accumulation patterns was demonstrated by the gas chromatographic procedure described by Rodney and co-workers.[5]

(11) L. Swell, E. C. Trout, Jr., G. V. Vahouny, H. Field, Jr., S. von Schuching, and C. R. Treadwell, *Proc. Soc. Exptl. Biol. Med.*, **97**, 337 (1958).

(12) R. W. Harkins, L. M. Hagerman, and H. P. Sarett, *J. Nutr.*, **87**, 85 (1965).

TABLE V

MISCELLANEOUS 2-(PYRIDYL)ALKANOLS

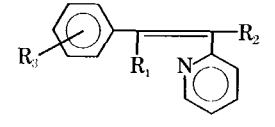


No.	R_1	R_2	R_3	Yield purified, %	Mp, °C	Purifen solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Decrease in serum cholesterol, % (mg/kg/day)	Estrogenicity
119	2-Pyridyl	H	4-OCH_3	45	52–53.5	A	$C_{15}H_{17}NO_2$	74.05	74.24	7.04	7.23	5.75	5.72	0 (25)	...
120	3-Pyridyl	H	4-OCH_3	3.7	90–91	B	$C_{15}H_{17}NO_2$	74.05	74.13	7.04	7.02			0 (25)	...
121	2-Pyridyl	CH_3	4-OCH_3	5.8	100–101	C	$C_{16}H_{19}NO_2$	74.67	74.84	7.44	7.60			0 (5)	0.33
122	4-Pyridyl	C_6H_5	4-Cl	12	150–158	D	$C_{20}H_{18}ClNO$	74.18	74.47	5.60	5.79	4.32	4.25	0 (5)	0.67
123	4-Pyridyl	C_6H_5	4-OCH_3	12	128–130	E	$C_{21}H_{21}NO_2$	78.96	78.78	6.63	6.42	4.39	4.39	0 (5)	0.42

[a] A, cyclohexane–heptane; B, EtOH–H_2O; C, EtOH; D, cyclohexane–benzene; E, CCl_4.

TABLE VI

2-(2-PYRIDYL)-1-ARYLALKENES



No.	R_1	R_2	R_3	Yield purified, %	Mp, °C	Purifen solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Decrease in serum cholesterol, % (mg/kg/day)	Estrogenicity
124	CH_3	H	4-OCH_3	3	151–154	A	$C_{15}H_{15}NO \cdot HCl$	68.82	68.96	5.77	6.01	5.35	5.39	0 (25)	...
125	CH_3	C_6H_5	H	17	72–83	B	$C_{20}H_{17}N$	88.52	88.32	6.32	6.37	5.16	5.21	39 (5)	4.88
126	CH_3	C_6H_5	4-SH	72	130–132	C	$C_{20}H_{17}NS$	79.17	79.32	5.52	5.52	4.62	4.36	72 (5)	>4
127	CH_3	C_6H_5	4-OCH_3	74	99–101	D	$C_{21}H_{19}NO$	83.69	83.64	6.35	6.41				...
128	CH_3	C_6H_5	4-OCH_3	71	165–167	E	$C_{21}H_{19}NO \cdot HCl \cdot 0.5H_2O$	72.72	72.96	6.10	6.34			85 (25)	>4
129	CH_3	C_6H_5	4-SCH_3	44	77–79	F	$C_{21}H_{19}NS$	79.47	79.53	6.03	5.91	4.41	4.27	83 (5)	>4
130	CH_3	C_6H_5	4-SCH_3	11	103–105	F	$C_{21}H_{19}NS$	79.47	79.26	6.03	6.11	4.41	4.20	92 (5)	>4
131	H	C_6H_5	4-$N(CH_3)_2$		165.5–166.5		$C_{21}H_{20}N_2$	83.96	84.03	6.71	6.70	9.33	9.30	0 (25)	...
132	CH_3	C_6H_5	H	14	171–171.5	A	$C_{20}H_{13}NO$[b]	83.58	83.50	5.96	5.88	4.87	4.94	29 (10)	0.81
133	CH_3	C_6H_5	H	Trace	177–180	A	$C_{20}H_{17}NO$[b]	83.58	83.87	5.96	5.93	4.87	5.00	...	...

[a] A, $CHCl_3$–Et_2O; B, heptane; C, MeOH; D, EtOH–H_2O; E, EtOH–Et_2O; F, ethyl acetate–petroleum ether. [b] These are N-oxides.

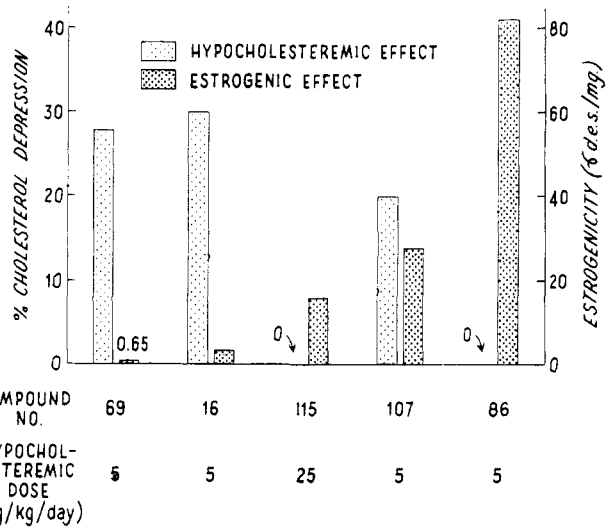


Figure 2.—Dissociation of estrogenic and hypocholesteremic effects in the rat for five of the compounds described in the tables.

and shows that the hypocholesteremic activity of a given compound could not result entirely from its estrogenicity. Although no compound of this series is completely nonestrogenic, the data suggest that a complete dissociation of the two types of activity should be possible.

Compound **16** is remarkably nontoxic in several laboratory animals. In mice and rats, for example, the acute LD_{50} is greater than 4 g/kg, either orally or intraperitoneally. Subacute studies in dogs and monkeys showed no effects referable to drug toxicity, including estrogenicity, either grossly or histologically. These studies included, in the dog, a daily oral dose regimen rising from 10 to 1000 mg/kg in 24 days and, in the monkey, a daily oral dose rising in 26 days from 5 to 2400 mg/kg. The same was true when monkeys were given 400 mg/kg/day orally for 12 weeks. Estrogen-equivalent doses of diethylstilbestrol in either of these species would produce unmistakable signs of estrogenicity, so the absence of these signs in **16**-treated animals supports further the view that the drug is not simply an attenuated estrogen.

The toxicologic studies afforded, at the same time, an opportunity to study the effect of **16** on blood cholesterol levels in the larger laboratory species under a variety of dosage conditions. The drug is ineffective in this respect in both the dog and the monkey.

Despite the inactivity of **16** in these species, a brief study of this agent in man still seemed essential as a means of assessing the trustworthiness of the rat alone as a screening animal for hypocholesteremic agents. Doses of **16** (three per day) ranging from 25 to 200 mg were thus administered orally for 29 successive days to a group of 12 human males between 21 and 50 years of age.[13] A control group of six male subjects of the same age distribution was given placebo capsules for the same period. All subjects had serum total-cholesterol concentrations in excess of 250 mg/100 ml, but were otherwise normal and healthy by a number of clinical laboratory criteria. Periodic determinations of serum cholesterol concentrations during treatment showed variations of less than two standard deviations from the individual subject's pretreatment average. It was therefore concluded that **16** is of no value as a human hypocholesteremic agent.

(13) The clinical trial was performed under the supervision of Dr. A. Z. Lane. Data are on file in the Department of Clinical Investigation, Parke, Davis and Company, under the code designation, CI-573.

Experimental Section[14]

2-(2-Pyridyl)-1,2-diarylalkanols. Table I. General Method. DL-α-(*m*-Chlorophenyl)-α-methyl-β-phenyl-2-pyridineethanol (16, 17).—To 22.2 g (3.2 g-atoms) of finely cut lithium ribbon overlaid with 500 ml of dry ether was slowly added with vigorous stirring and under N_2, 251 g (1.6 moles) of bromobenzene in 1 l. of ether. The addition was controlled to maintain rapid refluxing of the ether. The mixture was stirred for 1 hr after the addition was complete, and then 256 g (1.5 moles) of 2-benzylpyridine in 500 ml of ether was added rapidly, while cooling the reaction flask in ice. The resulting red mixture was stirred for 1 hr at room temperature. A solution of 223 g (1.44 moles) of *m*-chloroacetophenone in 500 ml of ether was added slowly with external cooling. The mixture was allowed to warm to room temperature and to stir at this temperature for 2 hr.[15] About 500 ml of saturated aqueous NH_4Cl solution was added cautiously with efficient cooling. The ether layer was separated, washed with water, and extracted with 1 l. of cold 2 *N* HCl.[16] The hydrochloride salt of the product separated as a dense oil, insoluble in both the ether and aqueous phases. The crude oily salt was separated, washed with a small volume of water, and overlaid with a mixture of water and ether. Dilute NaOH solution was added with cooling until the aqueous layer was strongly basic. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined ether extracts were dried ($MgSO_4$), treated with charcoal, filtered, and concentrated to about 1 l. Crystallization from the ether solution gave a first crop of 177 g, mp 94–130°, and a second crop of 40 g, mp 94–121°. Addition of petroleum ether (bp 32–59°) to the residue yielded a third crop of 55 g of low-melting material. The original aqueous acid layer was made basic and extracted with ether to give 8.5 g of additional solid, mp 115–130°. The total crude yield was 60%. The first and second crops were combined and allowed to crystallize slowly from a mixture of benzene and petroleum ether to give two distinct crystalline forms: prisms, mp 131–134°; needles, mp 114–116°. The two forms were separated mechanically.[9] The prisms were recrystallized from a mixture of benzene–petroleum ether to give 61 g of nearly pure product, mp 128–135°. Three additional recrystallizations from the same solvent provided 33 g of the product, mp 134–136°. The needles also were recrystallized from benzene–petroleum ether to give 42 g of solid, mp 85–89°. Three additional recrystallizations from the same solvent followed by a recrystallization from ethyl acetate–heptane gave 5 g of the other DL pair, mp 108–110°.

α-Methyl-α-(*p*-methylsulfonylphenyl)-β-phenyl-2-pyridineethanol (62).—A mixture of 3.3 g (0.01 mole) of α-methyl-α-(*p*-methylthiophenyl)-β-phenyl-2-pyridineethanol (**53**) and 15 ml of acetone was treated at 5° with 4 ml of 40% peracetic acid in acetic acid. After refrigeration overnight at 5°, the mixture was diluted with water. The solid (3.3 g) was recrystallized from a mixture of acetone–water to yield 3.0 g of product as colorless needles, mp 148–150°.

4-Acetylphenyl-2-tetrahydropyranyl Ether.—During 1.75 hr, 96.5 g of dihydropyran was added dropwise to a well-stirred mixture of 142.5 g of *p*-hydroxyacetophenone, 400 ml benzene, and 7 drops of concentrated H_2SO_4. The resulting solution was diluted with an equal volume of ether and washed in a separatory funnel with aqueous K_2CO_3. The organic layer was dried over

(14) Melting points were determined with various Thomas–Hoover melting point apparatus and are uncorrected.

(15) Often the mixture was heated under reflux for 0.5–1 hr or allowed to stir overnight at room temperature.

(16) This extraction is generally unnecessary, but for cases in which the hydrochloride salt of the product is only slightly soluble in H_2O, this procedure served to separate product hydrochloride from unreacted acetophenone and 2-benzylpyridine hydrochloride.

(17) This is obviously a tedious process even though only a rough separation was performed. A separate experiment provided separation of isomers after repeated crystallizations from 95% ethanol.

anhydrous K_2CO_3 and concentrated to dryness, and the residue was dissolved in hot isooctane. Treatment of the hot solution with activated charcoal and decantation of the filtrate from the gummy deposit that first separated on cooling gave, on further cooling, 146.7 g (85.5%) of the desired material, mp 87.5–89.5°. Two further crystallizations from isooctane gave material of mp 89.5–91.0°.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.72; H, 7.50.

DL-**α-Methyl-β-phenyl-α-[*p*-(tetrahydropyran-2-yloxy)phenyl]-2-pyridineethanol (83, 84).**—The condensation and isolation of the crude material was effected by the standard procedure, but because of the instability of the tetrahydropyranyl ring in an acidic environment, the solution of O-lithium salt was decomposed by quenching with water instead of aqueous NH_4Cl. Isolation of the desired material was very laborious owing to the presence of diastereoisomers with quite different melting points but with nearly identical solubilities in the more common organic solvents. Repeated crystallizations of the crude product from acetone and methanol (alternately) finally gave, however, 2.5 g of the DL pair with mp 134.5–135° and 21.4 g of the DL pair with mp 165.5–166°.

DL-**α-(*p*-Hydroxyphenyl)-α-methyl-β-phenyl-2-pyridineethanol (28).**—A solution of 21 g (0.054 mole) of **84** in 0.5 *N* HCl was stirred at room temperature for 1.5 hr. The solution was filtered and the filtrate was made basic with dilute NH_4OH. The solid separating was collected, washed with water, and redissolved in aqueous NaOH. The resulting solution was filtered and the filtrate was acidified with dilute acetic acid. The solid separating was collected, washed with water, and after drying, recrystallized from acetone–isooctane. The 5.67 g (42%) of product melted at 135.5–137°. Another recrystallization from the same solvent pair gave material melting at 139–140°, $pK_a' = 4.3$ and 11.4.

3-Acetylphenyl 2-Tetrahydropyranyl Ether.—The crude product resulting from a procedure identical with that described for the 4-isomer (intermediate for **83, 84**) was a viscous oil requiring fractionation by vacuum distillation. The tendency of the product to dismutate thermally required short-path distillation with some sacrifice in quality of the distillate, as indicated by the presence of a faint phenolic hydroxyl band in the infrared spectrum. The desired product, of purity suitable for conversion to the pyridineethanol, was obtained in 38% yield after two distillations [bp 114–120° (0.25 mm)].

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.57; H, 7.31.

DL-*p*-[**α-(2-Diethylaminoethoxy)-α-methyl-β-2-pyridylphenethyl]phenol. Isomers, mp 140–141° and mp 156°.**—β-Diethylaminoethyl chloride hydrochloride (61.9 g, 0.36 mole) was dissolved in ~500 ml of water in a separatory funnel. Aqueous 10 *N* NaOH (45 ml) was added and the resulting mixture was extracted three times with 200-ml portions of benzene. The benzene extract was dried ($CaSO_4$), filtered into a dropping funnel, then added dropwise to a well-stirred and refluxing solution of the lithium pyridineethoxide previously prepared in ether by the standard procedure from 57.9 g of 2-benzylpyridine, 5.75 g of lithium ribbon, 59.1 g of bromobenzene, and 75.5 g 4-acetylphenyl 2-tetrahydropyranyl ether. The resulting solution was stirred under reflux for 18 hr, then cooled and extracted with aqueous HCl. The aqueous extract was stirred at room temperature for 1 hr, then extracted three times with ether and the ether layer was discarded. The pH was raised to 11.5–12 (aqueous NaOH) and the solution was extracted three times with ether (organic layer discarded). Addition of glacial acetic acid to give a solution of pH 9.5–10 caused separation of a tan crystalline product weighing, when dry, 24.5 g. Fractionation of this material by repeated crystallization from acetone gave 8.0 g of the DL pair with mp 156° (serum cholesterol lowered 10% at 25 mg/kg) and 2.9 g of the DL pair with mp 140–141° (serum cholesterol lowered 19% at 25 mg/kg). Titration of each of the isomers gave pK_a' values of 3.5–3.6 (pyridine nitrogen), 9.1 (aliphatic nitrogen), and 11.0–11.5 (phenolic hydroxyl).

Anal. Calcd for $C_{26}H_{32}NO_2$: C, 77.18; H, 7.97; N, 6.93. Found for isomer, mp 140–141°: C, 77.10; H, 7.87; N, 6.91. Found for isomer, mp 156°: C, 76.94; H, 7.78; N, 7.14.

β-(*p*-Chlorophenyl)-α-(*p*-methoxyphenyl)-α-4-dimethyl-2-pyridineethanol.—To an ether solution of phenyllithium prepared from 21 g (0.13 mole) of bromobenzene and 1.85 g (0.26 g-atom) of lithium was added 26 g (0.12 mole) of 2-*p*-chlorobenzyl-4-methylpyridine (Reilly) in ether. Reaction of this reagent with 20 g (0.12 mole) of *p*-methoxyacetophenone and subsequent work-up were similar to that described above for **16** and **17**. An oily crude product was obtained which was crystallized from hexane to give 8 g of solid, mp 97–103°. Two additional recrystallizations from hexane gave 4.5 g (10%) of product, mp 104–106.5°. This compound at 25 mg/kg did not lower serum cholesterol.

Anal. Calcd for $C_{22}H_{22}ClNO_2$: C, 71.82; H, 6.03. Found: C, 71.86; H, 6.03.

1,2,3,4-Tetrahydro-1-(α-2-pyridylbenzyl)-1-naphthol (96).—Reaction of 40 g (0.24 mole) of 2-benzylpyridine as the lithium salt with 34.4 g (0.24 mole) of α-tetralone was effected as for **16** and **17**. The reaction mixture was decomposed with water and the dark ether layer was separated, dried, treated with charcoal, and concentrated. The residual oil crystallized on addition of heptane to give 60 g of crude product, mp 103–106°. Two additional recrystallizations from heptane gave 38.5 g (52%) of product, mp 107–112°.

2-[α-(3,4-Dihydro-1-naphthyl)benzyl]pyridine.—A mixture of 5 g (0.016 mole) of 1,2,3,4-tetrahydro-1-(α-2-pyridylbenzyl)-1-naphthol (**96**) and 25 ml of 85% orthophosphoric acid was warmed on the steam bath for 3 hr. The mixture was cooled and diluted with water, and the resulting solution was washed with ether. The aqueous layer was made basic with concentrated NH_4OH and extracted with ether. The ether solution was washed with saturated NaCl solution, dried, and concentrated. The 4 g of residue was recrystallized from heptane to give 2.1 g (45%) of the olefin, mp 100–104°, λ_{max}^{EtOH} 262 mμ (ε 12,500), $\lambda_{max}^{EtOH-HCl}$ 261 mμ (ε 14,700). The nmr spectrum showed absorption at δ 5.4–5.75 (2 H, olefinic H and HC<). The product has therefore been assigned the structure with the endocyclic double bond. The material at 25 mg/kg did not lower serum cholesterol.

Anal. Calcd for $C_{22}H_{19}N$: C, 88.84; H, 6.44; N, 4.71. Found: C, 89.14; H, 6.29; N, 4.63.

α-Methyl-α,β-diphenyl-2-pyridineethanol 1-Oxide (105).—A mixture of 100 g (0.35 mole) of **25**, 300 ml of glacial acetic acid, and 85 ml of 40% peracetic acid (in acetic acid) was warmed gently until solution was effected. After standing for 2.5 days at room temperature the solution was diluted with water and ice and extracted portionwise with a total of 1.5 l. of $CHCl_3$. The combined extracts were washed twice with dilute NaOH solution and once with water. The $CHCl_3$ solution was dried and concentrated to about 300 ml, and crystallization then was induced by the addition of 900 ml of ether. There was obtained 57 g (54%) of solid product, mp 156–158°.

α-Methyl-α,β-diphenyl-2-piperidineethanol (110).—To a suspension of 5.8 g (0.02 mole) of **25** in 200 ml of alcohol there was added 1.6 ml (0.02 mole) of concentrated HCl. The solution was hydrogenated at 4.2 kg/cm² of hydrogen using 0.5 g of PtO_2 catalyst. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the alcohol was evaporated in a stream of air. The viscous residue was dissolved in 50 ml of water and neutralized with 10% NH_4OH solution. The solution was cooled and extracted with ether. The ethereal extract was evaporated and a solid obtained. Recrystallization from an alcohol–water mixture gave 3.6 g (61%) of a white crystalline solid, mp 125–128°. Two further recrystallizations from an alcohol–water mixture gave an analytical sample, mp 128–130°.

α-(*p*-Methoxyphenyl)-α,β-dimethyl-2-pyridineethanol (121).—To a solution of 0.22 mole of phenyllithium was added 21.4 g (0.2 mole) of 2-ethylpyridine at reflux temperature. The solution was refluxed for 1 hr and 30 g (0.2 mole) of *p*-methoxyacetophenone was added. The mixture was allowed to stand overnight and decomposed by the cautious addition of 250 ml of water. The water layer was extracted twice with ether and the combined ether layer was dried ($MgSO_4$) and evaporated. The small quantity of crystals collected by filtration was washed with petroleum ether and recrystallized from ethanol and water to give 12 g of product, mp 96–100°. An additional recrystallization from ethanol gave an analytical sample, mp 100–101°.

α-(*p*-Methoxyphenyl)-α-methyl-3-pyridineethanol (120).—To a solution of KNH_2 prepared from 8 g (0.2 g-atom) of potassium in about 500 ml of liquid NH_3 and a trace of $Fe(NO_3)_3$ was added 19 g (0.2 mole) of β-picoline (Riley) in 50 ml of ether. To the bright red solution which had been stirred for 55 min was added 30 g (0.2 mole) of *p*-methoxyacetophenone and 75 ml of ether. The mixture, which turned light brown after being stirred for 15 min, was decomposed by adding 22 g of NH_4Cl. The NH_3 was allowed to evaporate and the residue was taken up in 800 ml

of 5% HCl and 1 l. of ether. The ether layer was separated and the acid layer was washed thoroughly with ether. The combined ether layer was dried ($MgSO_4$) and evaporated. There was a 90% recovery of unreacted *p*-methoxyacetophenone from this residue. The aqueous layer was made strongly basic by adding Na_2CO_3 and extracted three times ($CHCl_3$). The organic layer was dried ($MgSO_4$) and evaporated to a brown oil. Trituration with petroleum ether gave a solid which was collected by filtration and recrystallized from alcohol–water, giving 1.8 g of white crystals, mp 90–91°.

2-[2-[*p*-(Methylthio)phenyl]-1-phenylpropenyl]pyridine (129, 130).—A mixture of 6.7 g (0.02 mole) of **53** and 25 ml of 85% phosphoric acid was heated on the steam bath for 2.5 hr. The solution was diluted with 200 ml of water and made strongly basic with concentrated NH_4OH. The oil was extracted into $CHCl_3$. After drying ($MgSO_4$) and evaporation of the solvent, the oil was crystallized from 15 ml of ethyl acetate and *ca.* 100 ml of petroleum ether to give 3.4 g of solid, mp 97–101°. This was recrystallized from ethyl acetate–petroleum ether to give 2.7 g (43%) of **130**: mp 103–105°; λ_{max}^{EtOH} 297 mμ (ε 14,700) and 253 mμ (ε 12,300); nmr peaks ($CDCl_3$) at δ 2.11 (3 H, $=CCH_3$) and 2.39 (3 H, SCH_3). The mother liquors afforded 1.5 g of solid, mp 60–70°. This lot was recrystallized from ethyl acetate–petroleum ether to give 1.0 g (16%) of the geometric isomer **129**, mp 77–79°, and nmr peaks ($CDCl_3$) at δ 2.17 (3 H, $=CCH_3$) and 2.42 (3 H, SCH_3). These spectral data do not allow configurational assignment of the two geometric forms.

A mixture of 6.7 g (0.02 mole) of **52**, 40 ml of glacial acetic acid, 10 ml of concentrated HCl, and 25 ml of 57% HI was heated under reflux for 2 min. The mixture was poured into 200 ml of ice–water containing 12 g of sodium sulfite and made strongly basic by the addition of 50% NaOH solution. The mixture was extracted ($CHCl_3$), the $CHCl_3$ extracts were dried ($MgSO_4$), and the filtrate was evaporated *in vacuo*. The oil was crystallized from ethyl acetate–petroleum ether to yield 5.6 g (88%) of solid, mp 75–95°. This was separated into its diastereoisomeric components by repeated recrystallization from petroleum ether: **129**, mp 75–77° (2.8 g, 44%), and **130**, mp 103–105° (0.7 g, 11%).

α-Methyl-α′-2-pyridyl-4-stilbenethiol (126).—A mixture of 8 g *p*-(α-hydroxy-α-methyl-β-2-pyridylphenethyl)-*N*,*N*-dimethylbenzenesulfonamide (**75**), 40 ml of glacial acetic acid, 10 ml of concentrated HCl, and 30 ml of 57% HI was heated under reflux for 4 hr. The mixture was poured into 200 ml of ice–water containing 14 g of sodium sulfite. The mixture was made strongly basic with 50% aqueous NaOH and the oil was extracted into warm $CHCl_3$. After evaporation of the solvent, the oil was crystallized from 20 ml of methanol to give 4.4 g (72%) of **126**: mp 129–131°; λ_{max}^{EtOH} 285 mμ (ε 14,100), 271 (14,050), and 234 (15,700). The nmr signal in $CDCl_3$ for $=CCH_3$ was split at δ 2.12 and 2.17, indicating a mixture of isomers.

2-(1,2-Diphenylpropenyl)pyridine 1-Oxide, *cis* and *trans* Forms.—A mixture of 30 g (0.1 mole) of **105** and 250 ml of 85% H_3PO_4 was warmed on the steam bath for 3 hr and then allowed to stand at room temperature overnight. The mixture was poured into ice-water and extracted ($CHCl_3$). The combined $CHCl_3$ extracts were washed with dilute NaOH solution and water. The $CHCl_3$ solution was dried and concentrated to give 4.5 g of solid, mp 168–171°; second and third crops amounting to 6 g also were obtained. The 4.5-g crop was recrystallized twice from chloroform–ether to give 2.5 g of pure material, mp 170–171°, and λ_{max}^{EtOH} 264 mμ (ε 28,500). At 10 mg/kg serum cholesterol was lowered 29%.

Anal. Calcd for $C_{30}H_{19}NO$: C, 83.58; H, 5.96; N, 4.87. Found: C, 83.50; H, 5.88; N, 4.94.

The aqueous reaction mixture was further extracted with $CHCl_3$ to give 15 g of solid; total yield, 25 g (77%). This crop was recrystallized from $CHCl_3$–ether to give 11 g of the above product, mp 168–171°, and a second crop of 3 g, mp 159–177°. This second crop was recrystallized from $CHCl_3$–ether to give a small quantity of the geometric isomer as needles, mp 177–180°. Another recrystallization from the same solvent gave no change in melting point; λ_{max}^{EtOH} 262 mμ (ε 27,000).

Anal. Calcd for $C_{30}H_{19}NO$: C, 83.58; H, 5.96; N, 4.87. Found: C, 83.87; H, 5.93; N, 5.00.

2-[2-(*p*-Chlorophenyl)-1-phenylvinyl]thiophene.—The Grignard reagent was prepared in ether from 3.5 g (0.146 g-atom) of magnesium turnings and 26 g (0.161 mole) of *p*-chlorobenzyl chloride in the usual manner. To the stirred suspension was added a solution of 18.8 g (0.10 mole) of phenyl 2-thienyl ketone in 300 ml of ether. The reaction mixture was heated under reflux for 2–3 hr, cooled, and decomposed with aqueous NH_4Cl. Additional water was added, the ether layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residual brown oil was distilled to give 13.1 g (44%) of product, bp 187° (0.6 mm), and an additional 7.0 g (23.6%) of slightly impure material, bp 181–188° (0.6 mm). The product at 25 mg/kg did not lower serum cholesterol.

Anal. Calcd for $C_{18}H_{13}ClS$: C, 72.84; H, 4.41. Found: C, 72.92; H, 4.78.

α-(*p*-Methoxy-α-methylbenzyl)-α-phenyl-2-pyridinemethanol.—To 50 ml of anhydrous ether under N_2 was added 0.18 g (0.025 g-atom) of finely divided lithium wire. A solution of 1.7 g (0.0125 mole) of butyl bromide in 20 ml of anhydrous ether was added over a 10-min period. The mixture was vigorously stirred for 4 hr. After the lithium had reacted, 2.0 g (0.0125 mole) of 2-bromopyridine in 20 ml of anhydrous ether was added and the solution was stirred for an additional 1 hr. To this solution was added 2.4 g (0.01 mole) of 4′-methoxy-α-methyldeoxybenzoin[18] in 25 ml of anhydrous ether. The solution was stirred for 2 hr and then allowed to warm to room temperature. The solution was treated with 100 ml of water containing 1.8 g of NH_4Cl. The ether layer was separated and the aqueous layer was extracted twice with 100-ml portions of ether. The ether extracts were combined and evaporated to give a solid. The solid was recrystallized from alcohol to give 2.9 g (91%) of product, mp 83–86°. A sample was recrystallized twice from alcohol: mp 86–88°. At 25 mg/kg this compound produced 36% lowering of serum cholesterol.

Anal. Calcd for $C_{21}H_{21}NO$: C, 78.97; H, 6.63. Found: C, 78.76; H, 6.61.

α′-4-Pyridyl-4-stilbenol.—A mixture of 3.4 g (0.02 mole) of 4-benzylpyridine, 2.4 g (0.02 mole) of 4-hydroxybenzaldehyde, and 4.1 g (0.04 mole) of acetic anhydride was heated at reflux temperature for 4 hr. After distillation of the acetic acid which had formed, the solution was poured over ice and 200 ml of 5% HCl was added. The solution was heated on the steam bath for 1 hr and then neutralized with 10% NH_4OH. The aqueous layer was extracted with several 100-ml portions of ether. The ethereal extracts were combined and dried (K_2CO_3), and the ether was evaporated. The oily residue, dissolved in a methanol–water mixture and allowed to stand overnight, gave a yellow crystalline solid. The yield was 2.3 g (41%) of product, mp 187–191°. The product, after two recrystallizations from a methanol–water mixture, melted at 189–191°. At 25 mg/kg, serum cholesterol was lowered 16%.

Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53. Found: C, 83.31; H, 5.75.

1,2,3,4-Tetrahydro-3,3,6,8-tetramethyl-1-(2-pyridylmethyl)-1-naphthol.—A solution of 4.7 g (0.05 mole) of 2-picoline in 50 ml of ether was slowly added at 0° to an ether solution (250 ml) of phenyllithium from 0.7 g (0.1 g-atom) of lithium wire and 7.9 g (0.05 mole) of bromobenzene. The solution was then stirred for 1 hr at 0°. With the reaction mixture still maintained at 0°, 10.1 g (0.05 mole) of 3,3,6,8-tetramethyl-1-tetralone[19] was added as a solid. The solution was slowly warmed to room temperature, stirred for an additional 30 min, and hydrolyzed with 100 ml of water containing 2.8 g of NH_4Cl. The aqueous and ethereal layers were separated and the aqueous layer was extracted with two 100-ml portions of ether. The ethereal layers were combined and evaporated to give a light yellow solid. After recrystallization from an alcohol–water mixture, the compound was air dried for 2 days. The yield was 7.8 g (53%) of a white crystalline solid, mp 106–109°. Two recrystallizations from an alcohol–water mixture raised the melting point to 108–110°. This compound at 25 mg/kg did not lower serum cholesterol.

Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53. Found: C, 81.15; H, 8.30.

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Imidazoline Derivatives with Antiarrhythmic Activity[1]

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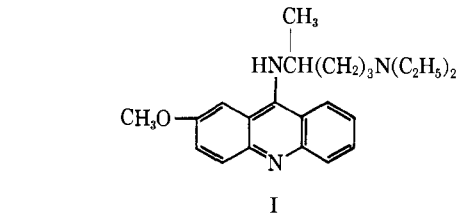
Imidazolinylmethyl derivatives of a number of bicyclic and tricyclic ring systems were prepared and studied for their effect on experimental cardiac arrhythmias. One of the bicyclic compounds, 3-phenyl-2,3,4,5-tetrahydro-1-benzazepine, obtained by means of a Schmidt reaction on 2-phenyl-3,4-dihydro-1-naphthalenone followed by reduction with $LiAlH_4$, yielded imidazoline derivatives of particular interest and was studied in greater detail. Numerous analogs were prepared.

It has been found that many chemical drug groups have the ability to suppress cardiac arrhythmias. In general these drugs belong to the group of local anesthetics, antispasmodics, antihistamines, and β-adrenergic receptor blockers, *e.g.*, quinidine, quinacrin (I), procainamide (II), antazoline[2] (III), and propranolol (IV).[3] All have in common the property of depressing the physiological functions of the cardiac muscle in such a way as to affect favorably the course of an arrhythmia. None, however, are uniformly successful.[4]



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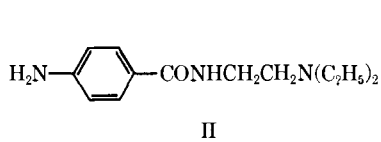

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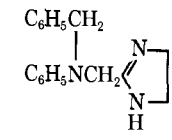

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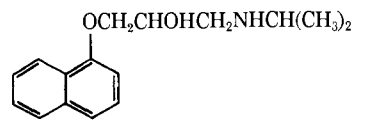
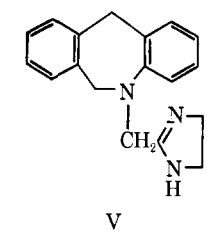


IV



V

In a previous paper[5] we had reported that 5-(2-imidazolinylmethyl)-5,6-dihydromorphanthridine (V) had shown interesting antifibrillatory effects on aconitine-induced cardiac arrhythmias. The present report is an extension of our previous work and describes a number of bicyclic and tricyclic ring systems to which a 2-imidazolinylmethyl group has been attached in an attempt to find compounds with improved antifibrillatory activity. Derivatives of 3-phenyl-2,3,4,5-tetrahydro-1-benzazepine were of particular interest and were studied in greater detail. In Tables I and II are shown a variety of tricyclic ring systems attached to a 2-imidazolinylmethyl group. The ring systems employed as starting materials in this part of the study are 10,11-dihydrodibenz[*b*,*f*][1,4]thiazepine,[6] 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine,[7] 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine,[8] 10,11-dihydrodibenz[*b*,*f*]azepine (iminodibenzyl), phenoxazine, phenothiazine, acridan, dihydrophenanthridine, carbazole, tetrahydrocarbazole, 6,7-dihydrobenz[*c*,*e*]azepine,[9] thioxanthene, anthrone, and 10,11-dihydrodibenz[*a*,*d*]cyclohepten-5-one.[10] The resulting imidazoline derivatives and their relative activity are shown in Tables I and II. A number of previously reported compounds have been included in these tables for comparative purposes. Four procedures were used to attach the imidazolinylmethyl group to the above described bicyclic and tricyclic ring systems. As shown in Chart I, the nature of the ring system determined the method employed.

Derivatives of the bicyclic 3-, 4-, and 5-phenyl-2,3,4,-5-tetrahydrobenzazepines were included in the second part of this study. It is possible to visualize these compounds as being formed from a tricyclic structure merely by separating one of the benzene rings and attaching it to the remaining bicyclic ring system by a single bond. The 3-, 4-, and 5-phenyl-3,4-dihydrobenzazepinones were obtained by means of a Schmidt reaction on the corresponding 2-, 3-, or 4-phenyl-3,4-dihydro-1-naphthalenone (VIa–d). This reaction can lead to the isomeric benzazepinones VII and VIII,

(1) Presented in part before the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) L. D. Dreifus, T. F. McGarry, Y. Watanabe, S. R. Kline, M. Waldman, and W. Likoff, *Am. Heart. J.*, **65**, 607 (1963).

(3) W. M. Ginn, Jr., G. V. Irons, Jr., and E. S. Orgain, *Circulation*, **32**, Supp. II. 97 (1965); J. P. Payne and R. M. Senfield, *Brit. Med. J.*, **1**, 603 (1964). See also Symposium on β-Adrenergic Receptor Blockade, *Am. J. Cardiol.*, **18**, 303 (1966).

(4) J. R. DiPalma in "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 624.

(5) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, **8**, 74 (1965).

(6) R. Jaques, A. Rossi, E. Urech, H. J. Bein, and K. Hoffmann, *Helv Chim. Acta*, **42**, 1265 (1959).

(7) J. O. Jilek, J. Pomikacek, and M. Protiva, Czechoslovakian Patent 111,215 (June 15, 1964); *Chem. Abstr.*, **62**, 14707 (1965).

(8) A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, **6**, 255 (1963).

(9) W. Wenner, *J. Org. Chem.*, **16**, 1475 (1951).

(10) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951).