higher than the original concentration of the buffer during exposure to SolBA-H³. As mentioned earlier Hokin, *et al.*,[2] have demonstrated the irreversible inhibitory action of alkylating cardiac steroids on brain Na-, K-ATPase. We have also reported similar irreversible inhibition of SinBA on rabbit heart Na-, K-ATPase in a preliminary report[5] (a detailed report will be published elsewhere). However, as indicated in the present study the positive inotropic effect of SinBA and SolBA are readily reversible and have a very short duration of action. Therefore, there appears to be a dissociation between inhibition of Na-, K-ATPase and the positive inotropic effect of SinBA. Thus, present indirect evidence suggests that inhibition of cardiac Na-, K-ATPase may not be responsible for the positive inotropic action of cardiac steroids. Furthermore, the long persistence of the drug in the myocardium after all positive inotropic effect has disappeared following washout suggests that the drug remaining in myocardial cells is bound to nonspecific sites.

Experimental Section[6]

Strophanthidin 3-bromoacetate (SinBA) was prepared as described by Kupchan, *et al.*[7] The SinBA prepared was chromatographically identical with a reference sample kindly supplied by Professor S. Morris Kupchan, mp 190–193°. *Anal.* ($C_{25}H_{33}BrO_7$): C, H, Br.

Strophanthidol 3-Bromoacetate (SolBA).—A solution of SinBA (0.500 g, 0.95 mmol) in purified dioxane (25 ml) was treated with $NaBH_4$ (0.32 mmol) and H_2O (0.5 ml). The mixture was then stirred at room temperature for 6 hr. Tlc was used to fractionate and identify the reaction products. The tlc consisted of silica gel G as the absorbent and EtOAc (system I) and $CHCl_3$–EtOH (6:1) (system II) as the solvent systems. Prior to use, the tlc plates were activated by heating for 30 min at 110°. The spots were identified by spraying the plates with a solution of 10% phosphomolybdic acid in MeOH and were heated for 5–10 min at 110° to locate the spots. Using the tlc systems the presence of four substances was noted and these were tentatively identified as strophanthidin 3-bromoacetate, strophanthidin, strophanthidol 3-bromoacetate, and strophanthidol. The reaction mixture was diluted with H_2O (25 ml) and the *dioxane was removed rapidly below 25°*. The crystalline product formed during the removal of the dioxane was collected and dried over P_2O_5 (yield 0.38 g). Tlc indicated that the material was a mixture of SinBA and SolBA with only a trace of the more polar decomposition products. Chromatography on silica gel followed by repeated crystallization from Me_2CO–petroleum ether gave 65 mg (13%) of SolBA, mp 206–208°. *Anal.* ($C_{25}H_{35}BrO_7$): C, H, Br.

Strophanthidol 3-Bromoacetate-19-H³ (SolBA-H³).—A solution of SinBA (25 mg, 0.048 mmol) in purified dioxane (2 ml) and H_2O (50 μl) was mixed with the contents of a vial of tritiated $NaBH_4$ (6.7 Ci/mmol, total activity 100 mCi, equivalent to 0.015 mmol $NaBH_4$). The mixture was shaken at room temperature for 5 hr, diluted with H_2O saturated with NaCl (10 ml), and quickly extracted with $CHCl_3$ (3 × 25 ml), and then dried (Na_2SO_4). The $CHCl_3$ was removed under reduced pressure and the resulting residue was redissolved in MeOH and induced to crystallize by the addition of H_2O. The crystalline product was dried and then applied, as a MeOH solution, to two 20 × 20 cm tlc plates. The chromatograms were developed with EtOAc. Autoradiography (2 hr) indicated the presence of one major band corresponding to SolBA as well as several minor more polar bands. The major band was eluted with MeOH and after crystallization gave 2.93 mg of radioactive material (specific activity 3.18 mCi/mg). The radioactive material was then dissolved in DMF and reserved for future use. An aliquot of this solution was then added to a methanolic solution of nonradioactive SolBA (20 mg) and crystallized to constant count to yield strophanthidol 3-bromoacetate-19-H³ (8.2 mg, specific activity 73 μCi/mg).

Acknowledgment.—The authors wish to express their sincere appreciation to Dr. S. Morris Kupchan of the University of Wisconsin for generously supplying us with a reference sample of strophanthidin 3-bromoacetate.

(5) G. T. Okita, F. Richardson, B. Roth-Schechter, and R. E. Thomas, *Fed. Proc.*, **28**, 607 (1969).

(6) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(7) S. M. Kupchan, M. Mokotoff, R. S. Sandhu, and L. E. Hokin, *J. Med. Chem.*, **10**, 1025 (1967).

Hypocholesteremic Agents. I. Substituted Stilbazoles and Dihydrostilbazoles

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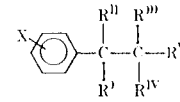
The clinical use of estrogens to lower serum cholesterol levels in the human male is limited because of the undesirable hormonal effects of this group of compounds. In attempts to chemically modify the structure of diethylstilbestrol, a series of substituted stilbazoles and dihydrostilbazoles were prepared and examined for their hypocholesterenic and estrogenic properties. Maximum separation of these biological properties was observed in the dihydrostilbazole series containing small alkyl groups on both carbons of the ethylene bridge. Other structure–activity relationships in this series are discussed.

Several groups of workers[1] have reported that estrogens lower serum or plasma cholesterol levels in humans. The clinical use of estrogens for lowering the elevated serum cholesterol levels in the human male is limited, however, because of the adverse endocrinological effects of these agents. In an attempt to synthesize compounds related to diethylstilbestrol in which the hypocholesteremic activity is dissociated from the estrogenic activity, a series of substituted stilbazoles (I) and dihydrostilbazoles (II) were prepared by the methods shown in Chart I.

2- or 3-pyridyllithium was added to a substituted ketone of type III to produce a racemic mixture of the *erythro* and *threo* forms of carbinol IV. In the majority of cases (Table I) the stereoisomers were not separated

(1) (a) M. L. Eilert, *Amer. Heart J.*, **38**, 472 (1949); (b) M. L. Eilert, *Metabolism*, **2**, 137 (1953); (c) E. M. Russ, H. H. Eder, and D. P. Barr, *Amer. J. Med.*, **11**, 468 (1951); (d) M. M. Gertler, P. B. Hudson, and H. Jost, *Geriatrics*, **8**, 500 (1953).

TABLE I

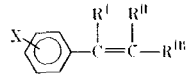


No.[a]	X	R^I	R^{II}	R^{III}	R^{IV}	R^V	Bp, °C (mm) or mp, °C	n_D (temp, °C)	Yield, %	Method	Formula	Anal.	Cholesterol lowering activity[b]
1A	H	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	98–99[c]		32	I	$C_{17}H_{21}NO$	C, H, N	+
1B	H	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	127–132 (2)	1.5564 (24)	12	I	$C_{17}H_{21}NO$	C, H, N	
2	*p*-OCH_3	H	H	OH	CH_3	2-C_5H_4N	189–191 (5)	1.5678 (24)	66	I	$C_{15}H_{17}NO_2$	C, H	
2·HCl							179–180[d]				$C_{15}H_{17}NO_2$·HCl	C, H	
3	*p*-OCH_3	H	H	OH	C_2H_5	2-C_5H_4N	170–174 (2)	1.5621 (25)	82	I	$C_{16}H_{19}NO_2$	C[e]	
4	*p*-OCH_3	H	CH_3	OH	CH_3	2-C_5H_4N	180–183 (25)		70	I	$C_{16}H_{19}NO_2$	C, H	
							97–98[c]						
4·HCl							198–200[d]				$C_{16}H_{19}NO_2$·HCl	C, H	
5	*p*-OCH_3	H	CH_3	OH	C_2H_5	2-C_5H_4N	155–160		98	I	$C_{17}H_{21}NO_2$	H[e]	
							77–78[c]						
5·HCl							178–180[d]				$C_{17}H_{21}NO_2$·HCl	C, H	
6A	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	175–180 (1)		62.5	I	$C_{18}H_{23}NO_2$	C, H	
							90–91[f,h]						
6A·HCl							204–205[d,e]				$C_{18}H_{24}NO_2$·HCl	C, H	+
6B	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	155–160 (1)	1.5520 (24)	20	I	$C_{18}H_{23}NO_2$	C, H	+
7	*o*-OCH_3	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	92–94[c]		66	I	$C_{18}H_{23}NO_2$	C[e]	
7·HCl							192–194[d]				$C_{18}H_{23}NO_2$·HCl	C, H	
8	*m*-OCH_3	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	160–165 (1)	1.5554 (24)	51	I	$C_{18}H_{23}NO_2$	C, H	
9	*p*-OCH_3	H	*i*-C_3H_7	OH	C_2H_5	2-C_5H_4N	190–195 (3)	1.5538 (26)	56	I	$C_{19}H_{25}NO_2$	C, H	-4
10	*p*-OCH_3	H	H	OH	*p*-$(OCH_3)C_6H_4$	2-C_5H_4N[i]	132–134[f]		34	I	$C_{21}H_{21}NO_3$	C, H	
10·HCl							185–187[d]				$C_{21}H_{21}NO_3$·HCl	C, H	
11	*p*-OCH_3	H	C_2H_5	OH	*p*-$(OCH_3)C_6H_4$	2-C_5H_4N[m]	127–128[c]		89	I	$C_{23}H_{25}NO_3$	C,H	
12	*p*-OCH_3	H	H	OH	*p*-OCH_2CH_2N-$Et_2C_6H_4$	2-C_5H_4N	91–93		52	II	$C_{26}H_{32}N_2O_3$	C, H	0
13	*p*-$(OCH_2$-CH_2NEt_2	H	C_2H_5	OH	C_2H_5	2-C_5H_4N	205–211 (1)	1.5380 (26)	49	I	$C_{29}H_{39}N_2O_2$	C, H, N	
14	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	2-$C_5H_{10}N$[n]	183–186 (3)	1.5335 (25)	93	III	$C_{18}H_{29}NO_2$	C, H	
15	H	OH	CH_3	H	H	2-C_5H_4N	135–138 (2)	1.5636 (28)	60	IV	$C_{14}H_{15}NO$	C, H	
15·HCl							184–185[d]				$C_{14}H_{15}NO$·HCl	C, H	0
16	H	OH	C_2H_5	H	H	2-C_5H_4N	144–147 (1)	1.5583 (23)	30		$C_{15}H_{17}NO$	o	
16·HCl							163–165				$C_{15}H_{17}NO$·HCl	C, H	
17	*p*-Cl	OH	CH_3	H	H	2-C_5H_4N	76–78[c]		53	IV	$C_{14}H_{14}ClNO$	C, H	
17·HCl							184–185[d]				$C_{14}H_{14}ClNO$·HCl		0
18	*p*-OCH_3	OH	CH_3	H	H	2-C_5H_4N	169–171 (2)		51	IV	$C_{15}H_{17}NO_2$	C, H, N	0
							63–64[c]						
19	*p*-CH_3	OH	CH_3	H	H	2-C_5H_4N	150–156 (3)	1.5572 (24)	59	IV	$C_{15}H_{17}NO$	C, H, N	0
19·HCl							163–165[d]				$C_{15}H_{17}NO$·HCl	C, H, N	0
20	*p*-SCH_3	OH	CH_3	H	H	2-C_5H_4N	78–80[c]		66	IV	$C_{15}H_{17}NOS$	C, H, N	
20·HCl							140–142[d]				$C_{15}H_{17}NOS$·HCl	C, H, N	0
21	*p*-OCH_3	OH	C_2H_5	H	H	2-C_5H_4N	52–53[c]		73	IV	$C_{16}H_{19}NO_2$	C, H	
21·HCl							150–152[d]				$C_{16}H_{19}NO_2$·HCl	H[e]	0

22	*p*-OH	OH	C_2H_5	H	H	2-C_5H_4N	89–90[a]		31	IV	$C_{15}H_{17}NO_2$	H[r]	0
23A	*p*-OCH_3	OH	CH_3	H	CH_3	2-C_5H_4N	91–93[c]		14	IV	$C_{16}H_{19}NO_2$	C, H, N	+
23B	*p*-OCH_3	OH	CH_3	H	CH_3	2-C_5H_4N	68–69[c]		47	IV	$C_{16}H_{19}NO_2$	C, H, N	+
24	*p*-OCH_3	OH	C_2H_5	H	CH_3	2-C_5H_4N	100–102[f]		18	IV	$C_{17}H_{21}NO_2$	C, H, N	+
25	*p*-OCH_3	OH	CH_3	H	C_2H_5	2-C_5H_4N	71–72[f]		15	IV	$C_{17}H_{21}NO_2$	C, H, N	0
26	*p*-Cl	OH	C_2H_5	H	C_2H_5	2-C_5H_4N	150–152 (2)	1.5351 (24)	29	IV	$C_{17}H_{20}ClNO_2$	C, H, N	0
27A	*p*-OCH_3	OH	C_2H_5	H	C_2H_5	2-C_5H_4N	101–102[c]		15	IV	$C_{18}H_{23}NO_2$	C[s]	+
27B	*p*-OCH_3	OH	C_2H_5	H	C_2H_5	2-C_5H_4N	162–167 (1)	1.5543 (25)	42	IV	$C_{18}H_{23}NO_2$	C, H	+
28	*p*-OH	OH	C_2H_5	H	C_2H_5	2-C_5H_4N	156–158		23	IV	$C_{17}H_{21}NO_2$	H, N[t]	+
29·HCl	*p*-OCH_3	OH	*n*-C_3H_7 CH / \ CH_2—CH_2	H	C_2H_5	2-C_5H_4N	170–175[d,u]		14	IV	$C_{19}H_{23}NO_2 \cdot HCl$	C, H, N	+
30	*p*-OCH_3	OH	CH_2—CH_2	H	C_2H_5	2-C_5H_4N	90–91[f]		17	IV	$C_{19}H_{23}NO_2$	C, H, N	+
31	*p*-OCH_3	OH	$C_6H_5CH_2$	H	C_2H_5	2-C_5H_4N[v]	120–121[f]		30	II	$C_{23}H_{25}NO_2$	C, H, N	0
32A	*p*-OCH_3	OH	CH_3	H	C_6H_5	2-C_5H_4N[w]	165–166[x,u]						+
33	3,4(OCH_3)$_2$	OH	CH_3	H	C_2H_5	2-C_5H_4N	164–180 (1)	1.5735 (25)	15	IV	$C_{18}H_{23}NO_3$	C, H, N	
33·HCl							108–110				$C_{18}H_{23}NO_3 \cdot HCl \cdot H_2O$	H, N[z]	0
34	OCH_3	H	H	OH	*p*-(OCH_2CH_2N-Et$_2$)C_6H_4	3-C_5H_4N	123–125[aa]		75	II	$C_{26}H_{32}N_2O_3$	C, H	
35A	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	3-C_5H_4N	105–106[x]		47	I	$C_{18}H_{23}NO_2$	C, H	
35A·HCl							190–191[bb]				$C_{18}H_{23}NO_2 \cdot HCl$	C, H	
35B	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	3-C_5H_4N	175–180 (1)		15	I	$C_{18}H_{23}NO_2$	C, H	
36	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	4-OH-3-C_5H_3N	234–235[bb]		57	I	$C_{18}H_{23}NO_3$	C, H	
37	*p*-OCH_3	H	*p*-(OCH_3)-C_6H_4	OH	*p*-(OCH_3)C_6H_4	3-C_5H_4N[cc]	100–104[x]		10	I	$C_{28}H_{27}NO_4$	C, H, N	0
38	*p*-OCH_3	OH	C_2H_5	H	H	4-C_5H_4N	165–170 (4)	1.5722 (26)	12	IV	$C_{16}H_{19}NO_2$	C, H	
39	*p*-OCH_3	OH	C_2H_5	H	C_2H_5	4-C_5H_4N	152–154[e]		14	IV	$C_{18}H_{23}NO_2$	C, H, N	+
40	*p*-$N(CH_3)_2$	OH	H	H	H	4-C_5H_4N	165–167[q]		46	*dd*	$C_{15}H_{17}N_2O$	C, H	
41	*p*-$N(CH_3)_2$	OH	C_6H_5	H	H	4-C_5H_4N	170–172[x]		21	*dd*	$C_{21}H_{22}N_2O$	C, H	
42	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	C_3H_2NS[ee]	99–100[c]		53	I	$C_{16}H_{21}NO_2S$	C, H	
42·HCl							203–204[d]				$C_{16}H_{21}NO_2S \cdot HCl$	H[ff]	
43	*p*-OCH_3	H	C_2H_5	OH	C_2H_5	$C_4H_5N_2$[gg]	95–97[c]		35	I	$C_{17}H_{24}N_2O_2$	C, H	
43·HCl							145–147[d]				$C_{17}H_{24}N_2O_2 \cdot HCl$	C, H	
44	*p*-OCH_3	OH	C_2H_5	H	C_2H_5	$C_4H_3N_2$[hh]	114–116		5	IV	$C_{17}H_{22}N_2O_2$	C, H, N	0/+

[a] The designations A and B represent stereoisomers only when isolated [b] Biological activity code: +, greater than 20% reduction in serum cholesterol; 0/+, borderline minimal activity; 0, no significant effect. [c] From hexane. [d] From EtOH–Et_2O. [e] H: calcd, 7.44; found, 6.96. [f] From petroleum ether (bp 30–60°). [g] C: calcd 75.24; found 76.13. [h] L. Gorum and W. L. Nobles report mp 94–95° (*J. Pharm. Sci.*, **57**, 1265 (1968)). [i] Reference *h* reports mp 204–205°. [j] H: calcd 8.12; found 7.56. [k] From 2-pyridyllithium and deoxyanisoin. [l] From *i*-Pr_2O. [m] From 2-pyridyllithium and α-ethyldeoxyanisoin. [n] 2-$C_5H_{10}N$ is 2-piperidyl. [o] This compound could not be obtained in analytical purity and was contaminated with starting ketone. [p] C: calcd 65.41; found 64.90. [q] From C_6H_6. [r] C: calcd 74.04; found 75.32. [s] H: calcd 8.12; found 7.35. [t] C: calcd 75.24, found 75.71. [u] Isolated as HCl salt. [v] From $PhCH_2MgCl$ and α-ethyl-*p*-methoxyphenacyl-2-pyridine. [w] From the Li derivative of 2-benzylpyridine and *p*-methoxyacetophenone. [x] From C_6H_6–hexane. [y] Mp reported 154–156° by W. D. Dixon, Ph.D. Dissertation, University of Kansas, Lawrence, Kansas (1960). [z] C: calcd 60.74; found 59.84. [aa] From *i*-PrOAc–petroleum ether. [bb] From EtOH. [cc] From *p*-methoxy-α,α-di(*p*-methoxyphenyl)acetophenone prepared by the method of K. Sisido, K. Okano, T. Isida, and H. Nozaki, *J. Amer. Chem. Soc.*, 77, 6580 (1953). [dd] From 4-picolyllithium prepared by the method of J. P. Wilbaut and J. W. Hey, *Rec. Trav. Chim. Pays-Bas*, **72,** 513 (1953). [ee] C_3H_2NS is 2-thiazolyl. [ff] C: calcd 58.61; found 59.22. [gg] $C_4H_5N_2$ is 1-Me-2-imidazyl. [hh] $C_4H_3N_2$ is 2-pyrazyl.

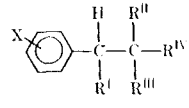
TABLE II



No.	X	R^I	R^{II}	R^{III}	Bp, °C (mm), or mp	n_D (temp, °C)	Yield, %	Method	Formula	Anal.	Cholesterol lowering activity[a]
45·HCl	H	C_2H_5	H	2-C_5H_4N	137–139[b]		50	V	$C_{15}H_{15}N$·HCl	C[c]	0
46	*p*-Cl	CH_3	H	2-C_5H_4N	62–64[d]		58	V	$C_{14}H_{12}ClN$	C, H	
46·HCl					179–181[b]				$C_{14}H_{12}ClN$·HCl	C, H, N	0
47	*p*-CH_3	CH_3	H	2-C_5H_4N	163–169 (2)	1.6161 (27)	41	V	$C_{15}H_{15}N$	C, H	
47·HCl					183–186[b]				$C_{15}H_{15}N$·HCl	C, H, N	0
48	*p*-OCH_3	CH_3	H	2-C_5H_4N	41–42[e]			V	$C_{15}H_{15}NO$	C, H	
49	*p*-OCH_3	C_2H_5	H	2-C_5H_4N	175–179 (2)	1.5937 (27)	60	V	$C_{16}H_{17}NO$	C, H, N	
50·HCl	*p*-SCH_3	CH_3	H	2-C_5H_4N	151–153[b]		66	V	$C_{15}H_{15}NS$·HCl	C, H	0
51·HCl	*p*-OCH_3	CH / CH_2—CH_2	H	2-C_5H_4N	255–256[b]		37	V	$C_{17}H_{17}NO$·HCl	C, H,	
52	*p*-OCH_3	C_2H_5	H	4-C_5H_4N	173–176 (1)	1.5984 (26)	71	V	$C_{16}H_{17}NO$	C, H	
52·HCl					134–136[b]				$C_{16}H_{17}NO$·HCl	C, H	
53	H	C_2H_5	C_2H_5	2-C_5H_4N	107–110 (1)	1.5660 (27)	47	VI	$C_{17}H_{19}N$	C, H	+
54	*p*-OCH_3	CH_3	CH_3	2-C_5H_4N	145–150 (1)	1.5827 (24)	60	VI	$C_{16}H_{17}NO$	C, H	0/+
55	*p*-OCH_3	CH_3	C_2H_5	2-C_5H_4N	172–174 (3)	1.5758 (24)	62	VI	$C_{17}H_{19}NO$	H[f]	0
56	*p*-OCH_3	C_2H_5	C_2H_5	2-C_5H_4N	169–170 (1)	1.5665 (24)	64	VI	$C_{18}H_{21}NO$	C, H	
56·HCl					154–156[b]				$C_{18}H_{21}NO$·HCl	C, H	0 +
57	*p*-OH	C_2H_5	C_2H_5	2-C_5H_4N	144–146[g]		47	*h*	$C_{17}H_{19}NO$	C, H	
58	*o*-OCH_3	C_2H_5	C_2H_5	2-C_5H_4N	152–155 (2)	1.5688 (24)	56	VI	$C_{18}H_{21}NO$	C, H	0
59	*p*-OCH_3	*i*-C_3H_7	C_2H_5	2-C_5H_4N	147–150 (1)	1.5639 (25)	67	VI	$C_{19}H_{23}NO$	C, H	+
60	*p*-OCH_2CH_2N·$(C_2H_5)_2$	C_2H_5	C_2H_5	2-C_5H_4N	204–206 (1)	1.5452 (26)	67	VI	$C_{23}H_{32}N_2O$	C, H, N	0
61	*p*-OCH_3	C_2H_5	C_2H_5	3-C_5H_4N	155–158 (1)	1.5645 (26)	64	VI	$C_{18}H_{21}NO$	C, H	0

[a] See footnote *b* in Table I. [b] From EtOH–Et_2O. [c] H: calcd 6.56; found 5.93. [d] From petroleum ether (bp 30–60°). [e] From hexane. [f] C: calcd 80.95; found 79.99. [g] From C_6H_6–petroleum ether. [h] By HBr demethylation of **56**.

TABLE III

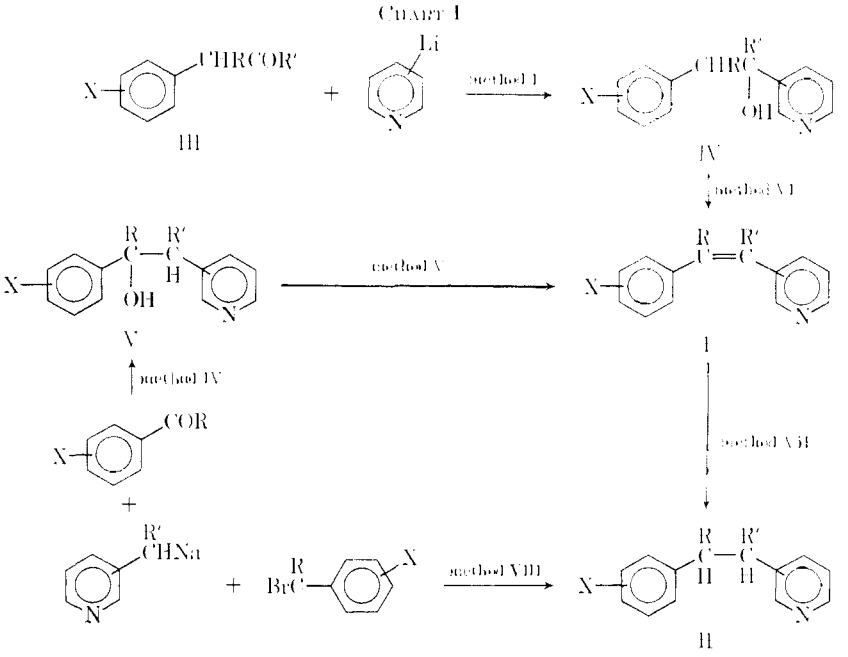


No.	X	R^I	R^{II}	R^{III}	R^{IV}	Bp, °C (mm), or mp, °C	n_D (t)	Yield, %	Method	Formula	Anal.	Cholesterol[a] lowering activity
62	*p*-Cl	CH_3	H	H	2-C_5H_4N	134–140 (1)	1.5676 (26)	69	*b*	$C_{14}H_{14}ClN$	C, H, N	0
63	*p*-Cl	C_2H_5	H	C_2H_5	2-C_5H_4N	154–158 (2)	1.5535 (25)	34	VIII	$C_{17}H_{20}ClN$	C, H	0
64	*p*-OCH_3	CH_3	H	H	2-C_5H_4N	128–132 (0.5)	1.5540 (27)	92	VII	$C_{15}H_{17}NO$	C, H, N	0
65	H	C_2H_5	H	C_2H_5	2-C_5H_4N	122–125 (2)	1.5425 (25)	89	VII	$C_{17}H_{21}N$	C, H, N	+
66	*p*-CH_3	C_2H_5	H	C_2H_5	2-C_5H_4N	149–153 (5)	1.5395 (24)	42	VIII	$C_{18}H_{23}N$	C, H	+
67	*p*-OCH_3	CH_3	H	CH_3	2-C_5H_4N	147–153 (4)	1.5508 (25)	97	VII	$C_{16}H_{19}NO$	C, H	+
68	*p*-OCH_3	CH_3	H	C_2H_5	2-C_5H_4N	165–170 (4)	1.5520 (26)	85	VII	$C_{17}H_{21}NO$	C, H, N	+

68A						50–51[c]			*d*	$C_{17}H_{21}NO$	C, H, N	
68A·HCl						170–171[e]				$C_{17}H_{21}NO \cdot HCl$	C, H	+
68B						147–152 (1)	1.5478 (25)		*d*	$C_{17}H_{21}NO$	C, H, N	+
69A	*p*-OH	CH_3	H	C_2H_5	2-C_5H_4N	163–165[g]		67	*f*	$C_{16}H_{19}NO$	C, H, N	
69A·HCl						208–211[e]			IX	$C_{16}H_{19}NO \cdot HCl$	C, H	+
69B						155–157[g]			IX	$C_{16}H_{19}NO$	C, H, N	
69B·HCl						213–216[d,e]			IX	$C_{16}H_{19}NO \cdot HCl$	C, H	+
70	*p*-OCH_3	C_2H_5	H	CH_3	2-C_5H_4N	149–154 (1)	1.5517 (24)	44	VIII	$C_{17}H_{21}NO$	C, H, N	+
71	*p*-OCH_3	C_2H_5	H	C_2H_5	2-C_5H_4N	145–150 (1)	1.5466 (24)	93	VII	$C_{18}H_{23}NO$	C, H	+
71A·HCl						237–239[d,e]			IX	$C_{18}H_{23}NO \cdot HCl$	C, H	+
71B						155–160 (3)			IX	$C_{18}H_{23}NO$	*h*	
71B·HCl						125–128[e]			IX	$C_{18}H_{23}NO \cdot HCl$	C, H	
72	*p*-OH	C_2H_5	H	C_2H_5	2-C_5H_4N	130–132[e]			*f*	$C_{17}H_{21}NO$	C, H	+
72A·HCl						253–256[e]				$C_{17}H_{21}NO \cdot HCl$	C, H, N	+
72B						126–128[i]				$C_{17}H_{21}NO$	C, H	
72B·HCl						103–104[e]				$C_{17}H_{21}NO \cdot HCl$	C, H	0/+
73	*p*-OCH_3	*i*-C_3H_7	H	C_2H_5	2-C_5H_4N	161–165 (1)	1.5473 (24)	87	VII	$C_{19}H_{25}NO$	C, H, N	
73·HCl						253–255				$C_{19}H_{25}NO \cdot HCl$	C, H	+
74	*o*-OCH_3	C_2H_5	H	C_2H_5	2-C_5H_4N	142–143 (1)	1.5504 (24)	94	VIII	$C_{18}H_{23}NO$	C, H	
74·HCl						176–179				$C_{18}H_{23}NO \cdot HCl$	C, H	0
75	*p*-OCH_3	C_2H_5	H	$CH_2CH_2N(Et)_2$	2-C_5H_4N	185–188 (1)	1.5333 (25)	30	*j*	$C_{22}H_{32}N_2O$	C, H	0
76	*p*-(OCH_2CH_2–N(Et)$_2$)	C_2H_5	H	C_2H_5	2-C_5H_4N	200–204 (1)	1.5328 (26)	89	VII	$C_{23}H_{34}N_2O$	C, H, N	0/+
77	*p*-OCH_3	CH_3	H	C_2H_5	3-C_5H_4N	155–156 (1)	1.5557 (24)	88	VII	$C_{17}H_{21}NO$	C, H	
77·HCl						150–155[e]				$C_{17}H_{21}NO \cdot HCl$	C, H	+
78	*p*-OCH_3	C_2H_5	H	C_2H_5	3-C_5H_4N	164–165 (2)	1.5531 (21)	86		$C_{18}H_{23}NO$	C, H	
						78–80[c]						
78·HCl						185–187[e]				$C_{18}H_{23}NO \cdot HCl$	C, H	+
79	*p*-OH	C_2H_5	H	C_2H_5	3-C_5H_4N	185–187[i]			*f*	$C_{17}H_{21}NO$	C, H	
79·HCl						201–203[e]				$C_{17}H_{21}NO \cdot HCl$	C, H	+
80	*p*-OC_2H_5	C_2H_5	H	C_2H_5	3-C_5H_4N	167–169 (1)		64	*k*	$C_{19}H_{25}NO$	C, H	
80·HCl						202–203[e]				$C_{19}H_{25}NO \cdot HCl$	C, H	+
81	*p*-OCH_3	C_2H_5	H	C_2H_5	4-C_5H_4N	175–178 (2)		70	VIII	$C_{18}H_{23}NO$	C, H	0
81A·HCl						205–206				$C_{18}H_{23}NO \cdot HCl$	C, H	0
81B·HCl						190–193				$C_{18}H_{23}NO \cdot HCl$	C, H	0
82	*p*-OCH_3	C_2H_5	CH_3	CH_3	4-C_5H_4N	169–170 (2)		21	VIII	$C_{18}H_{23}NO$	C, H	
82·HCl						167–168[e]				$C_{18}H_{25}NO \cdot HCl$	C, H	0
83	*p*-OCH_3	CH_3	C_6H_5	$CH_2CH_2N(CH_3)_2$	2-C_5H_4N	207–208 (1)		14	VIII	$C_{25}H_{30}N_2O$	C, H	+
84	*p*-OCH_3	C_2H_5	C_6H_5	$CH_2CH_2N(CH_3)_2$	2-C_5H_4N	210–217 (1)		39	VIII	$C_{26}H_{32}N_2O$	C, H	+
85	*p*-OCH_3	CH_3	H	C_6H_5	2-C_5H_4N	76–80[c]		50	VII	$C_{21}H_{21}NO$	H, N[l]	+
85A						106–110				$C_{21}H_{21}NO$	C, H, N	+
86	*p*-OCH_3	CH_3	C_2H_5	C_6H_5	2-C_5H_4N	206–208 (1)		31	VIII	$C_{29}H_{25}NO$	C, H	+
87	*p*-OCH_3	C_2H_5	H	C_2H_5	2-$C_5H_{10}N$[m]	152–154 (1)	1.5236 (26)	92	III	$C_{18}H_{29}NO$	C, H	+
88	*p*-OCH_3	C_2H_5	H	C_2H_5	2-$C_6H_{12}N$[n]	180–183 (4)	1.5225 (24)	80	*o*	$C_{19}H_{31}NO$	C, H	+
89	*p*-OCH_3	C_2H_5	H	C_2H_5	2-$C_4H_3N_2$[p]	147–150 (2)	1.5472 (26)	11	VIII	$C_{17}H_{22}N_2O$	H[q]	0

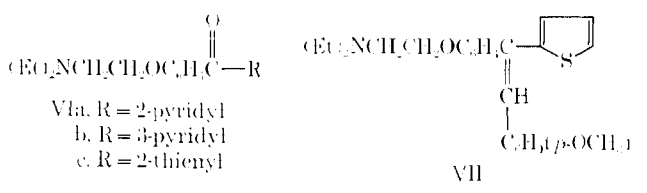
[a] See footnotes *a* and *b* of Table I. [b] P and I_2 in HOAc–H_2O reduction of **17**. [c] From hexane. [d] See alternate separation of isomers in Experimental Section. [e] From EtOH–Et_2O. [f] HBr demethylation. [g] From C_6H_6. [h] C, H: calcd 80.25, 8.61; found 79.81, 8.19. [i] From C_6H_6–petroleum ether. [j] $NaNH_2$–liquid NH_3 alkylation of 2-(2-pyridyl)-3-(*p*-methoxyphenyl)butane, bp 135–140° (1 mm), using $Et_2N(CH_2)_2Cl$. [k] Alkylation of **79** with NaOEt and EtI. [l] C: calcd 83.13; found 83.96. [m] 2-$C_5H_{10}N$ is 2-piperidyl. [n] 2-$C_6H_{12}N$ is *N*-Me-2-piperidyl. [o] Eschweiler–Clarke methylation of **87**. [p] 2-$C_4H_3N_2$ is pyrazyl. [q] C: calcd 75.52, found 76.01.

CHART I



In a few cases, the stereoisomeric carbinols were separated by fractional crystallization from petroleum ether or hexane. The solid form, designated as isomer A, was the predominant isomer in the mixture and on the basis of Cram's rule[2] is assumed to be the *erythro* form although definitive conformational studies were not attempted. The second minor component (isomer B) was obtained from the petroleum ether filtrates by distillation. The carbinols IV were resistant[3] to the conventional acid dehydrating agents, H_3PO_4, *p*-toluenesulfonic acid, Ac_2O, and/or H_2SO_4. However, fusion of the carbinol IV with potassium pyrosulfate[4] (method VI) gave good yields of the stilbazoles (I). Several attempts to separate the *cis* and *trans* olefins by physical or physical chemical methods failed. The stilbazoles (I) were hydrogenated (method VII) to the dihydrostilbazoles II. Separation of the stereoisomers was effected by the differences in solubility in petroleum ether, by solubility differences of the hydrochloride salts, and by column chromatography over alumina. As in the case of the carbinols, the higher melting form is designated as the A isomer.

The reaction of *p*-methoxybenzylmagnesium chloride (method II) with *p*-(diethylaminoethoxy-2- or -3-benzoyl)pyridine (VIa,b) gave the expected tertiary carbinols (IV) in good yield. However, a similar reaction with the 2-thienyl ketone VIc gave only the unsaturated compound VII.



VIa, R = 2-pyridyl
b, R = 3-pyridyl
c, R = 2-thienyl

VII

To prepare the isomeric carbinols V, the Na derivative of a 2- or 4-picoline was allowed to react with an aromatic ketone in liquid NH_3. In our laboratory these conditions gave consistently better yields and cleaner products than the corresponding reactions employing the picolyl-Li derivatives. In these latter cases considerable quantities of lower boiling fractions were obtained.

In contrast to carbinols IV, compounds V (R^1 = H) are easily converted into the stilbazoles by acid dehydrating agents (HCl and HOAc). However, when R^1 is lower alkyl, the tertiary carbinols are very labile and acid treatment results in a reverse aldolization with the isolation of the starting ketone and the substituted picoline. This may account for the poor yields of some of these compounds listed in Table I.

The desirable combination of biological activity, *i.e.*, high hypocholesteremic activity with minimum estrogenic activity, was observed in the dihydrostilbazoles II (R^1 and R = lower alkyl). Accordingly a direct synthesis of II was developed which would permit the synthesis of a maximum number of compounds. This simplified procedure (method VIII) involves the alkylation of a substituted 2- or 4-picoline with a secondary aromatic halide in the presence of $NaNH_2$. The resulting diastereomeric mixture could be separated into its components by the methods indicated. To further study structure–activity relationships in this series of compounds, the pyridyl ring was replaced by other heterocyclic systems, *e.g.*, 2-piperidyl, *N*-methyl-2-piperidyl, 1-methyl-2-imidazyl, 2-thiazolyl, and 2-pyrazyl. Details of the synthesis and the properties of the compounds are given in the accompanying tables (Tables I–III).

Biological Methods.—Male rats, Charles River CD strain, 6–8 weeks of age, were used to screen compounds for hypocholesteremic activity. All materials were suspended in peanut oil and injected subcutaneously for 4 days, generally at a daily dose of 10 mg/kg. On the fifth day, after a 24-hr fast, the animals were anesthetized with Et_2O and bled from the aorta to determine serum cholesterol levels. Total serum cholesterol was measured by the Zak method[5] initially

(2) D. J. Cram and F. A. Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).
(3) L. Goron and W. L. Nobles, *J. Pharm. Sciences*, **57**, 1265 (1968).
(4) F. V. Wessely, E. Kerschbaum, A. Kleedorfer, F. Pöllinger, and E. Jajic, *Monatsh. Chem.*, **73**, 127 (1940).
(5) B. Zak, *Tech. Bull. Registry Med. Tech.*, **27**, 71 (1957).

and later by the Technicon Autoanalyzer procedure.[6] Compounds that were active in the initial test in male rats were administered by gavage to 8-week old ovariectomized rats in order to determine the degree of separation of cholesterol-lowering and estrogenic activities and to obtain relative potency estimates. The treatment schedule was the same as in the male rats. Estrogenicity was determined by examining vaginal smears during the experimental period and weighing the uteri at autopsy.

Biological Results.—The hypocholesteremic activities of compounds **68A**·HCl and **78**·HCl, which had the most favorable separation of estrogenic and hypocholesteremic activities, were compared quantitatively with several standard estrogens in acute and chronic experiments. In ovariectomized rats the doses required to lower serum cholesterol by 50% were estimated to be 20 mg/kg for **68A**·HCl, and 24–30 mg/kg for **78**·HCl. Several dose-response curves of **68A**·HCl indicated that a dose of 5 mg/kg, which lowered serum cholesterol by 30% (ED_{30} cholesterol) produced no estrogenic stimulation of the uterus and vagina in ovariectomized female rats, and did not reduce seminal vesicle weights in male rats. Compound **68A**·HCl has approximately 0.002–0.004 times the hypocholesteremic activity of ethinylestradiol or stilbestrol. It was much less estrogenic than conjugated equine estrogen (Premarin), ethinylestradiol, and stilbestrol at comparable hypocholesteremic doses. A standard oral estrogen assay of **68A**·HCl by the rat vaginal smear technique indicated that **68A**·HCl had 0.0004 times the estrogenic potency of ethinylestradiol.

The acute oral toxicity (LD_{50}) of **78** was greater than 2500 mg/kg in mice. The oral LD_{50} of **68A**·HCl in mice was 1632 mg/kg and the intravenous LD_{50} was 94.5 mg/kg. Compound **68A**·HCl is undergoing clinical evaluation in man, and the results, when available, will be published in the appropriate medical journals.

Structure–Activity Relationships.—In this series of compounds the combination of maximum hypocholesteremic activity and minimal estrogenic potency is found in the dihydrostilbazole group (Table III). This desirable combination of biological properties is observed in those compounds wherein both C atoms in the ethylene bridge connecting the two rings are substituted by a small alkyl group (*e.g.*, Me or Et). The 2-pyridyldihydrostilbazoles were more active than the corresponding 3-pyridyl compounds, whereas the 4-pyridyl compounds were generally inactive at this screening dose. Reduction of the 2-pyridyl ring gave a compound of slight hypocholesteremic activity even at high doses.

Substitution of the *p*-OCH_3 by Cl, Me, or H gave compounds of lower activity. The *p*-OH compounds, **72A** and **72B**, were very active in the cholesterol lowering screen but were very estrogenic even at low doses (less than 1 mg/kg). The *p*-diethylaminoethoxy derivative **76** was inactive in male rats at a dose of 10 mg/kg.

In this series, the stilbazoles (Table II) were essentially inactive or of lower potency than the corresponding dihydro compounds. The presence of OH on either carbon of the bridge (Table I) gave variable results. Those carbinols which were active in the hypocholesteremic screen were also very estrogenic.

(6) Technicon Corp., Chauncey, N. Y.

Experimental Section[7]

Ketone Intermediates.—The following ketones were prepared by a standardized procedure involving Fe–HCl[8] reduction of the corresponding phenylnitroalkenes: 1-phenyl-2-propanone; 1-phenyl-2-butanone; 1-(*p*-methoxyphenyl)-2-propanone, and 1-(*p*-methoxyphenyl)-2-butanone. Similarly prepared were: 1-(*o*-methoxyphenyl)-2-butanone; yield 84%, bp 115–120° (3 mm), $n^{21}D$ 1.5215. *Anal.* ($C_{11}H_{14}O_2$) C, H. 1-(*m*-Methoxyphenyl)-2-butanone; bp 115–120° (3 mm), bp 138–139° (15 mm).[9] *Anal.* ($C_{11}H_{14}O_2$) C, H.

4-(*o*-Methoxyphenyl)-3-hexanone.—A mixture of 175 g (0.98 mol) of 1-(*o*-methoxyphenyl)-2-butanone and 160 g of commercial NaOMe was cooled in an ice bath while 500 g of EtI was added dropwise with stirring. After the addition (exothermic reaction) the mixture was heated under reflux on the steam bath for 3 hr; H_2O was added and extracted (Et_2O) and the solution was dried (Na_2SO_4) and distilled: bp 114–115° (1 mm); $n^{25}D$ 1.5074; yield 140 g (70%). *Anal.* ($C_{13}H_{18}O_2$) C, H.

4-(*m*-Methoxyphenyl)-3-hexanone was obtained in a similar manner: bp 107–112° (1 mm); $n^{25}D$ 1.5064; yield 90%. *Anal.* ($C_{13}H_{18}O_2$) C, H.

4-(*p*-Methoxyphenyl)-5-methyl-3-hexanone was obtained in 68% yield by the alkylation of 4-(*p*-methoxyphenyl)-3-butanone with isopropyl iodide and NaOMe: bp 133–136° (4 mm); $n^{27}D$ 1.5070. *Anal.* ($C_{14}H_{20}O_2$) C, H. This standardized alkylation procedure was used for the following ketones: 3-phenyl-2-butanone, 4-phenyl-3-hexanone, 3-(*p*-methoxyphenyl)-2-butanone, 2-phenyl-3-pentanone, 2-(*p*-methoxyphenyl)-3-pentanone, and 4-(*p*-methoxyphenyl)-3-hexanone.

4-(*p*-Hydroxyphenyl)-3-hexanone.—A mixture of 78 g (0.38 mol) of 4-(*p*-methoxyphenyl)-3-hexanone and 500 ml of 48% HBr was heated under reflux for 20 hr and allowed to cool, poured into water, and extracted with $CHCl_3$. The product was distilled, bp 160–165° (2 mm). On cooling the product solidified and was recrystallized from hexane: mp 63–65°; yield 45 g (62%). *Anal.* ($C_{12}H_{16}O_2$) C, H.

4-(*p*-2-Diethylaminoethoxyphenyl)-3-hexanone.—To a refluxing solution of 5 g of Na in 300 ml of EtOH was added 38 g (0.2 mol) of the above phenol followed by 27 g of diethylaminoethyl chloride. The mixture was refluxed with stirring for 12 hr. The EtOH was removed *in vacuo* on the steam bath and the residue was dissolved in H_2O and extracted with $CHCl_3$. The product was distilled: bp 165–170° (1 mm); $n^{25}D$ 1.5052; yield 27.5 g (48%). *Anal.* ($C_{18}H_{29}NO_2$) C, H. The hydrochloride, mp 134–135°, was recrystallized from EtOH–Et_2O. *Anal.* ($C_{18}H_{29}NO_2$·HCl) C, H, N.

***p*-(2-Diethylaminoethoxyphenyl 2-Pyridyl Ketone (VIa).**—This ketone was prepared from 47 g (0.23 mol) of *p*-hydroxyphenyl 2-pyridyl ketone, 5.8 g of Na, and 34 g of 2-diethylaminoethyl chloride in 300 ml of EtOH: bp 206–212° (1 mm); $n^{23}D$ 1.5835; yield 45.5 g (66%). *Anal.* ($C_{18}H_{22}N_2O_2$), C, H.

In the same manner, ***p*-(2-diethylaminoethoxyphenyl 3-pyridyl ketone** (VIb) was prepared in 43% yield: bp 207–215° (1 mm); $n^{26}D$ 1.5830. *Anal.* ($C_{18}H_{22}N_2O_2$) C, H.

***p*-Diethylaminoethoxyphenyl 2-thienyl ketone** (VIc) had bp 237–240° (2 mm); $n^{26}D$ 1.5955; yield 68%. *Anal.* ($C_{17}H_{21}NO_2S$) C, H.

Method I. 4-(*p*-Methoxyphenyl)-3-(2-pyridyl)-3-hexanol.—To an Et_2O (500 ml) solution of *n*-BuLi prepared under N_2 at −10° from 5.5 g (0.8 g-atom) of Li shot and 55 g of *n*-BuBr (0.4 mol) was added, at −40°, a solution of 63 g of 2-bromopyridine (0.4 mol) in 100 ml of Et_2O. The mixture was stirred for 20–30 min and an Et_2O solution of 41 g (0.2 mol) of 4-(*p*-methoxyphenyl)-3-hexanone was added dropwise, and, after 2 hr, the mixture was permitted to warm to room temperature and stirring was continued for 6 hr. Ice–H_2O was added and the organic

(7) Melting points are uncorrected and were obtained on a Thomas–Hoover melting point apparatus. Microanalytical results were obtained by the Physical-Analytical Department of the Schering Corp. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(8) F. W. Hoover, and H. B. Hass, *J. Org. Chem.*, **12**, 501 (1947); also B. R. Baker, *J. Amer. Chem. Soc.*, **65**, 1572 (1943).

(9) R. Royer and E. Bisagni, *Bull. Soc. Chim. Fr.*, 395 (1960).

material was extracted with Et_2O. The combined Et_2O solutions were extracted several times with 10% HCl and the acid extracts made basic (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ was removed and the brown oily residue was triturated with cold petroleum ether. The crude crystalline product (isomer A) was filtered and the petroleum ether filtrates were concentrated and distilled *in vacuo*. In several examples (Table I) the crude carbinol mixture was distilled prior to trituration and the distillate solidified on standing. The solid isomer A was obtained therefrom by crystallization from the designated solvent.

Similar metallation procedures were used with 3-bromopyridine, 2-bromothiazole,[10] and 1-methylimidazole.[11]

Method II. 1-(*p*-2-Diethylaminoethoxyphenyl)-1-(2-pyridyl)-2-(*p*-methoxyphenyl)ethanol.—*p*-Methoxybenzyl chloride (31 g, 0.2 mol) in 200 ml of Et_2O was added dropwise with stirring at reflux to 24 g (1 mol) of Mg and 200 ml of Et_2O over a period of 2–2.5 hr. The cloudy solution was decanted from the excess Mg, 20 g (0.067 mol) of *p*-(2-diethylaminoethoxyphenyl) 2-pyridyl ketone in an equal volume of Et_2O was added dropwise, and the mixture heated for 6 hr. A solution (20%) of NH_4Cl was added, the product was extracted with Et_2O, and the residue, after removal of solvent, was triturated with petroleum ether.

1-(*p*-2-Diethylaminoethoxyphenyl)-1-(2-thienyl)-2-(*p*-methoxyphenyl)ethylene (VII).—Using the procedure of method II from 25 g (0.08 mol) of *p*-(2-diethylaminoethoxyphenyl) 2-thienyl ketone, this compound was obtained as a viscous red oil which would not crystallize: yield 23 g (71%); bp 235–250° (0.8 mm). *Anal.* ($C_{25}H_{29}NO_2S$) C, H.

Method III. Reduction Procedure.—A solution of 0.03 mol of pyridylcarbinol in 150 ml of abs EtOH containing 4.0 ml of concd HCl was reduced in a Parr hydrogenator at room temperature in the presence of 0.5 g of PtO_2. The reduction was permitted to run overnight, the catalyst was filtered, and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in H_2O, neutralized (NH_4OH), and extracted with $CHCl_3$.

Method IV.—To a suspension of $NaNH_2$ prepared from 14 g (0.6 g-atom) of Na in about 800 ml of anhyd liquid NH_3 in the presence of $Fe(NO_3)_3$ catalyst was added an equivalent molar amount of the picoline in an equal volume of Et_2O, and the mixture was stirred for an additional hour. The ketone (0.3 mol) was added dropwise and stirring continued for 1 hr. NH_4Cl (45 g) was added cautiously followed by 400 ml of anhyd Et_2O, and the NH_3 was allowed to evaporate, usually overnight. Ice–H_2O was added, and the Et_2O layer was extracted (10% HCl) and discarded. The acid extracts were basified (NH_4OH) and extracted with $CHCl_3$. The solvent was removed and product isolated as in Table I.

Method V. Dehydration Procedure.—A mixture of 0.1 mol of carbinol, 60 ml of concd HCl, and 200 ml of glacial HOAc was heated under reflux for 4 hr. The solution was concentrated *in vacuo* on the steam bath. The HCl salt which often crystallized on standing was recrystallized. The free amine was obtained by neutralizing (NH_4OH) an aqueous solution of the HCl salt and extraction ($CHCl_3$). The solvent was removed and product isolated as indicated in Table II.

Method VI. Dehydration Procedure.—A mixture of tertiary carbinol and 4 times its weight of finely powdered potassium pyrosulfate was heated in a bath at an external temperature of 260–270° with occasional manual stirring until the mixture liquefied and then for an additional 2 min. The entire procedure required about 20 min. The dark green viscous solution was poured while still hot into a large volume of ice, and the solution made basic (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed (H_2O) and distilled.

Method VII.—A solution of 0.02 mol of the stilbazole (Table II) in 150 ml of EtOH was hydrogenated in a Parr hydrogenator at room temperature in the presence of freshly prepared Raney Ni catalyst. H_2 uptake was, in the majority of cases, very rapid and the reduction was permitted to run 2–3 hr. In those cases in which the reduction did not proceed readily, particularly in the 3-pyridyl series, the reaction was carried out at 50–55° for 15–20 hr. The catalyst was removed and the product isolated by distillation.

Method VIII. 1-(*p*-Methoxyphenyl)-1-bromopropane was prepared from the commercially available anethole by the following modified procedure.[12] To a cold (−35 to −40°) solution of 14.8 g (0.1 mol) of anethole in 50 ml of toluene was added 8.1 g of anhydrous HBr (requires 3–5 min). The solution was warmed to 0°, CO_2 gas was bubbled through the mixture for 15–20 min, and the system was then flushed with N_2 for 15–20 min. The solution was then diluted with an equal vol of dry Et_2O and kept at −40° until required in the next step. Similarly, a solution of 1-(*p*-methoxyphenyl)ethanol (15.2 g) in 100 ml of PhMe was saturated with HBr gas for 1 hr at 0°. The lower H_2O layer was removed and the PhMe solution was treated with CO_2 and N_2 as previously described. The solution was dried (Na_2SO_4) and stored at −10° until needed.

To a solution of $NaNH_2$ [from 2.3 g of Na in 1 l. of NH_3 [$Fe(NO_3)_3$ catalyst]] 12 g (0.1 mol) of 2-*n*-propylpyridine was added dropwise and stirring continued for 0.5 hr. The Et_2O–PhMe solution of *p*-methoxyphenyl-1-bromopropane was added dropwise and the mixture was stirred for an additional 4 hr. The NH_3 was then displaced by Et_2O, and the mixture was stirred overnight at room temperature, decomposed with H_2O, and extracted with Et_2O. The combined Et_2O solution was extracted (10% HCl), and the acid extracts were neutralized (NH_4OH), extracted with $CHCl_3$, and distilled.

Method IX. Separation of Stereoisomers.—A solution of 133 g of 3-(*p*-methoxyphenyl)-4-(2-pyridyl)hexane in 2.5 l. of anhydrous Et_2O was saturated with HCl until precipitation was complete. The Et_2O mixture was warmed on the steam bath for a few minutes to expel the excess HCl, Et_2O was decanted and the residue was dissolved in 1.3 l. of anhyd EtOH, clarified with charcoal, and filtered. The product was precipitated with 3.5 l. of anhyd Et_2O. The product, isomer A·HCl, was filtered and recrystallized several times from EtOH–Et_2O: mp 237–239°; yield 52 g (33%).

The filtrate from isomer A·HCl was concentrated *in vacuo* to dryness, dissolved in H_2O, basified (NH_4OH), extracted with $CHCl_3$, and distilled: bp 155–160° (3 mm); yield 66 g.

Alternate Separation of Isomers. Chromatography.—A solution of 28 g of 2-(*p*-methoxyphenyl)-3-(2-pyridyl)pentane in 300 ml of pentane was chromatographed on 840 g of alumina using pentane as eluent and collecting fractions of 1200–1500 ml. Isomer A (13 g) (mp 50–52°) was collected in the first 14–15 fractions, at which point the eluent was changed to Et_2O and 14.5 g of an oily residue was obtained in the next 5 fractions (isomer B).

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