Synthesis and Adrenocortical-Inhibiting Activity of Substituted 2,2-Diphenethylamines

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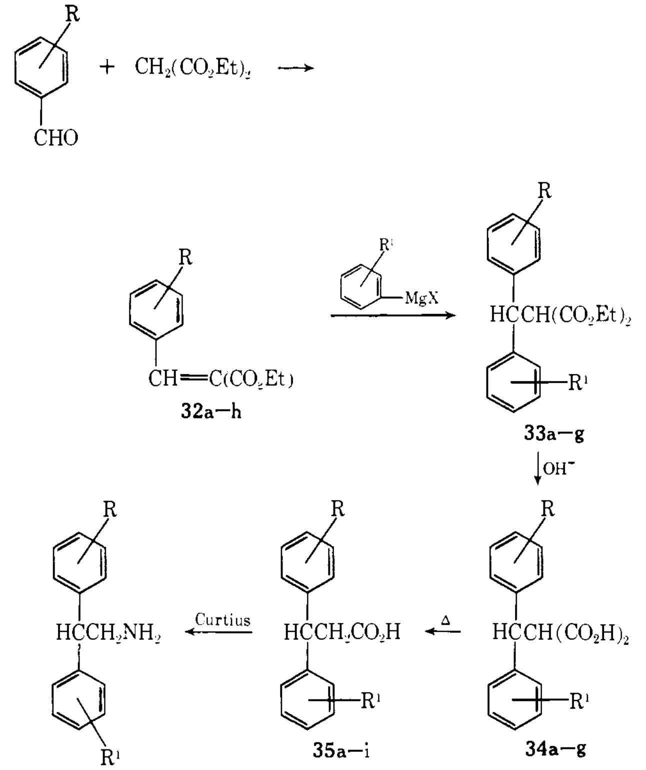
The synthesis and adrenal-inhibitory effects of a series of substituted 2,2-diphenethylamines are described. Most of the analogs appear to suppress adrenal steroidogenesis by inhibition of the 11-hydroxylation reaction. The introduction of methyl at C-2 of the aliphatic side chain of **2** appears to inhibit enzymatic reactions occurring early in the biosynthetic pathway, while the introduction of methyl at C-1 of **1** is followed by a highly selective inhibition of aldosterone biosynthesis.

A number of compounds possess the ability to inhibit adrenal corticogenesis by a direct action on adrenal steroidogenic enzyme systems.[2-6] Among these compounds, 2-(*p*-aminophenyl)-2-phenethylamine (**2**)[7] has been shown to suppress adrenal steroid biosynthesis in the rat, dog, guinea pig, and human, presumably by inhibition of the hydroxylation reactions occurring at C-11, C-17, and C-18.[6,8] Because minor modifications in chemical structure can produce significant alterations in the spectrum and intensity of the adrenal inhibition,[9-11] we have attempted to correlate the structure of analogous diphenethylamines with the intensity and character of the adrenal inhibition, in an effort to develop an agent which would inhibit the synthesis of all the principal adrenal corticosteroids, or which would selectively inhibit aldosterone biosynthesis. This report summarizes the results of our studies of the synthesis of a series of substituted diphenethylamines and of their adrenal-inhibitory activity.

The compounds prepared for testing (**1**–**31**) are listed in Table I and their testing results are shown in Table II. Compounds **4**, **6**–**9**, **11**, and **12** were prepared using the sequence of reactions shown in Scheme I. The intermediates **32**–**35** are listed in Tables III–VI and were prepared using the well-established procedures described in the Experimental Section. The sulfone and sulfoxide (**35h**, **i**) were prepared by the oxidation of the methylthio compound **35f**. Compounds **35h** and **i** were converted to amines **13** and **14** as were **35a**–**g**.

SCHEME I



Compounds **3**, **5**, **10**, and **15**–**18** were prepared using specific syntheses. The acid-catalyzed condensation of 2-nitro-1-(*m*-nitrophenyl)ethan-1-ol with benzene gave 2-nitro-1-(*m*-nitrophenyl)-1-phenethane, which was reduced catalytically to **3**. Similarly, the condensation of benzene and the cyanohydrin of *o*-chlorobenzaldehyde gave (*o*-chlorophenyl)phenylacetonitrile which was reduced to **5**. The cyanohydrin of *p*-tolualdehyde was converted to α-bromo-(*p*-tolyl)acetonitrile. This with benzene, under Friedel–Crafts conditions, gave phenyl(*p*-tolyl)acetonitrile, which on hydrogenation yielded **10**. Compound **15** was derived simply by hydriodic acid hydrolysis of **4**. Condensation of thiophenol with 2-amino-1-phenethan-1-ol produced the thio analog **16**. The *p*-acetyl compound **17** was prepared by acetylating N-acetyl-2,2-diphenethylamine with 1 mole of acetyl chloride in the presence of $AlCl_3$ and by then hydrolyzing the amide. The synthesis of **18** is shown in Scheme II.

The alkylated amines **19**–**22** were derived from (*p*-aminophenyl)phenylacetonitrile (**36**) as shown in Scheme II. The intermediates **37** and **38** are listed in Table VII together with appropriate physical constants.

The symmetrically substituted bis compounds, **23** and **24**, were obtained by reduction of amides or nitriles derived from appropriate diphenylacetic acid precursors. The analogs **25**–**27** resulted from the reduction of 4-oxo-α-phenyl-2,5-cyclohexadiene-$\Delta^{1,\alpha}$-acetonitrile oximes (or more simply phenylcyanomethyl-

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(1) Author to whom inquiries should be addressed.

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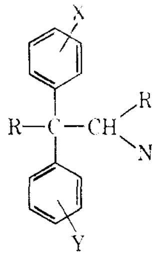
(10) F. W. Kahnt and R. Neher, *Experientia*, **18**, 499 (1962).

(11) R. Neher and F. W. Kahnt, *ibid.*, **21**, 310 (1965).

TABLE I

2,2-DIPHENETHYLAMINES



No.	X	Y	R	R¹	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
1	H	H	H	H	258–260[a]	EtOH–Et_2O	71	$C_{14}H_{15}N \cdot HCl$	C, H, Cl
2	p-NH_2	H	H	H	324–325[b,c]	MeOH–EtOAc	61	$C_{14}H_{16}N_2 \cdot 2HCl$	Cl
3	m-NH_2	H	H	H	200–201	MeOH–EtOAc	27	$(C_{14}H_{16}N_2)_2 \cdot C_4H_4O_4$[d]	C, H, N
4	p-OCH_3	H	H	H	199–201[e]	EtOH–Et_2O	60	$C_{15}H_{17}NO \cdot HCl$	C, H, Cl
5	o-Cl	H	H	H	281–282	EtOH–Et_2O	52	$C_{14}H_{14}ClN \cdot HCl$	C, H, N
6	m-Cl	H	H	H	263–265	EtOH–Et_2O	39	$C_{14}H_{14}ClN \cdot HCl$	C, H, Cl, N
7	p-Cl	H	H	H	220–222[f]	EtOH–Et_2O	46	$C_{14}H_{14}ClN \cdot HCl$	C, H, Cl, N
8	o-CH_3	H	H	H	271–273	EtOH–Et_2O	48	$C_{15}H_{17}N \cdot HCl$	C, H, Cl, N
9	m-CH_3	H	H	H	257–260	$CHCl_3$–petr ether	67	$C_{15}H_{17}N \cdot HCl$	C, H, Cl, N
10	p-CH_3	H	H	H	232–234[g]	Me_2CO–Et_2O	45	$C_{15}H_{17}N \cdot HCl$	C, H, N
11	p-CF_3	H	H	H	211–213	EtOAc–Et_2O	50	$C_{15}H_{14}F_3N \cdot HCl$	C, H, Cl, N
12	p-SCH_3	H	H	H	184–186[h]	Me_2CO–Et_2O	16	$C_{15}H_{17}NS \cdot HCl$	C, H, Cl, N
13	p-SO_2CH_3	H	H	H	200[i]	EtOH–Et_2O	13	$C_{15}H_{17}NO_2S \cdot HCl$	j
14	p-$SOCH_3$	H	H	H	k	EtOH–Et_2O	31	$C_{15}H_{17}NOS \cdot HCl$	C, H, Cl, N
15	p-OH	H	H	H	220–221	n-BuOH–Et_2O	12	$C_{14}H_{15}NO \cdot HCl$	C, H, N
16	p-SH	H	H	H	191–192	MeOH–Et_2O	10	$C_{14}H_{15}NS \cdot HCl$	C, H, Cl, N
17	p-$COCH_3$	H	H	H	152–154	EtOH–EtOAc	39	$C_{16}H_{17}NO \cdot HCl$[l]	C, H, Cl, N
18	p-$NHCOCH_3$	H	H	H	k	EtOH–Et_2O	33	$C_{16}H_{18}N_2O \cdot HCl$[l]	C, H, Cl, N
19	p-$N(CH_3)_2$	H	H	H	241[b]	MeOH	66	$(C_{16}H_{20}N_2)_2 \cdot C_4H_4O_6$[m]	C, H, N
20	p-$NHCH_3$	H	H	H	254–256[b]	MeOH–EtOAc	48	$C_{15}H_{17}N_2 \cdot 2HCl$	C, H, Cl, N
21	p-NHC_2H_5	H	H	H	177–178	MeOH–Et_2O	65	$(C_{16}H_{20}N_2)_2 \cdot C_4H_4O_4$[d]	C, H, N
22	p-NH-n-C_4H_9	H	H	H	160–162	MeOH–Et_2O	66	$(C_{18}H_{24}N_2)_2 \cdot C_4H_4O_4$[d]	C, H, N
23	p-Cl	p-Cl	H	H	230–231[n]	EtOH–Et_2O	46	$C_{14}H_{13}Cl_2N \cdot HCl$	C, H, Cl
24	p-CH_3	p-CH_3	H	H	245–246[o]	i-PrOH–Et_2O	31	$C_{16}H_{19}N \cdot HCl$	C, H, N
25	p-NH_2	p-OCH_3	H	H	p				
26	p-NH_2	p-Cl	H	H	293–295[b,q,r]	MeOH–EtOAc		$C_{14}H_{15}ClN_2 \cdot 2HCl$	C, H, Cl
27	p-NH_2	p-CH_3	H	H	279–282	MeOH–Et_2O	58	$C_{15}H_{18}N_2 \cdot 2HCl$	C, H, Cl, N
28	p-NH_2	H	CH_3	H	278–280[b]	MeOH–EtOAc	52	$C_{15}H_{18}N_2 \cdot 2HCl$	C, H, Cl, N
29	p-NH_2	H	n-C_4H_9	H	272–273[b]	EtOH–Et_2O	64	$C_{18}H_{24}N_2 \cdot 2HCl$	C, H, Cl, N
30	p-NH_2	H	$CH_2C_6H_5$	H	339–340[b,q]	MeOH–EtOAc	67	$C_{21}H_{22}N_2 \cdot 2HCl$[l]	C, H, Cl, N
31	H	H	H	CH_3	279–281[s]	EtOH–Et_2O	87	$C_{15}H_{17}N \cdot HCl$	Cl

[a] C. R. Harington and W. McCartney [*J. Chem. Soc.*, 892 (1929)] reported mp 259°. [b] With decomposition. [c] The free base has been reported.[7] [d] Fumarate. [e] Lit.[17] mp 191–194°. [f] Lit.[17] mp 212–215°. [g] Lit.[17] mp 228–231° dec. [h] V. S. Deshpande and K. S. Nargund [*J. Karnatak Univ.*, **1**, 7 (1956); *Chem. Abstr.*, **52**, 7183*f* (1958)] give mp 184°. [i] Deshpande and Nargund[h] report compound is unstable; we find it is hygroscopic. [j] Analyses consistently check for aquarter hydrate. *Anal.* ($C_{15}H_{17}NO_2S \cdot HCl \cdot 0.25H_2O$) C, H. [k] Very hygroscopic. [l] Hemihydrate. [m] Tartrate. [n] E. J. Skerrett and D. Woodcock [*J. Chem. Soc.*, 3308 (1952)] give mp 227–228°. [o] Lit.[17] mp 244–246° dec. [p] Material supplied by R. B. Davis, University of Notre Dame.[7] [q] Melting point taken in a metal block and is uncorrected. [r] Lit.[7] mp 291–294° dec. [s] E. B. Hodge, M. C. Bachman, and M. B. Neher [*J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 205 (1951)] give mp 276–278°.

enequinone oximes) following the procedure of Davis and Benigni.[7]

The compounds **28–30**, resulting from substitution on the benzhydryl carbon atom of **2**, were prepared from the phthaloyl derivative (**39**) of **36** (Scheme II). The intermediates **39** and **40** are listed in Table VII. The analog **31** with a branched methyl side chain was made conveniently by reduction of the oxime of 1,1-diphenylacetone.

Experimental Section[12]

Diethyl benzalmalonates (32) (Table III) were prepared from diethyl malonate and an appropriately substituted benzaldehyde according to the method of Allen and Spangler.[13]

Diethyl Benzhydrylmalonates (33) (Table IV).—A suitably substituted phenyl Grignard reagent was added to **32** using the method of Newman and Flanagan.[14] The reaction mixture was stirred 18–22 hr prior to hydrolysis.

Benzhydrylmalonic Acids (34) (Table V).—To a stirred solution of 0.22 mole of KOH in 250 ml of H_2O was added 0.05 mole of **33** in a small volume of EtOH. The mixture was stirred and heated on a steam bath overnight. The cooled mixture was extracted with Et_2O and the aqueous layer was cooled and acidified with 28 ml of concentrated HCl. The resulting solid was filtered, washed with H_2O, and recrystallized.

3-Phenyl-3-(substituted phenyl)propionic Acids (35) (Table VI).—**34** was heated to 190° in an oil bath. The melt was kept at this temperature for 20 min after the evolution of CO_2 had

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(12) Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected unless otherwise specified. All compounds containing an asymmetric carbon atom were isolated and tested as the racemates. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(13) C. F. H. Allen and F. W. Spangler, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 377.

(14) M. S. Newman and H. R. Flanagan, *J. Org. Chem.*, **23**, 796 (1958).

TABLE II

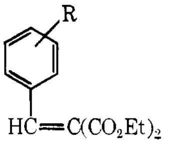
RELATIVE ANTIADRENAL ACTIVITIES

No.	Rat cold-stress test[a]	Rat antialdosterone assay[a]	Isolated rat adrenal % change in steroid levels from controls B[b]	DOC[c]	Aldosterone
1	20	100	−87	+542	−94
2	100	100	−84	+755	−94
3	20				
4	5				
5	10				
6	10				
7	20				
8	8				
9	6				
10	6	70	−94	+124	
11	20		−84	+122	−90
12	90	50			
13	100	50	−67	+778	*d*
14	100				
15	8				
16	10				
17	40				
18	*e*				
19	100		−49	+415	
20	80	50			
21	80		−46		
22	50		−50		
23	8				
24	6				
25	6				
26	30				
27	6				
28	40	70	−86	+90	−91
29	4		−54	+367	*d*
30	50		−22	−455	*d*
31	1	250	−9	+67	−79

[a] Activity expressed in terms of **2** having an arbitrary value of 100. [b] Corticosterone. [c] 11-Desoxycorticosterone. [d] Below limits of detection. [e] Preliminary data indicated an activity less than that shown by **2**.

TABLE III

DIETHYL BENZALMALONATES



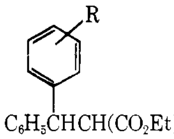
$HC{=}C(CO_2Et)_2$

No.	R	Bp (mm), °C	% yield	Formula	Analyses
32a	*p*-OCH$_3$	185–190 (2)[a]	97	$C_{15}H_{18}O_5$	C, H
b	*o*-Cl	160–165 (2)	73	$C_{14}H_{15}ClO_4$	C, H, Cl
c	*m*-Cl	160–167 (3)	76	$C_{14}H_{15}ClO_4$	H, Cl; C[b]
d	*p*-Cl	162–167 (1–2)[c]	56	$C_{14}H_{15}ClO_4$	
e	*o*-CH$_3$	145 (2)[d]	57	$C_{15}H_{18}O_4$	
f	*m*-CH$_3$	155–165 (2)	69	$C_{15}H_{18}O_4$	C, H
g	*p*-SCH$_3$	210–215 (6)	82	$C_{15}H_{18}O_4S$	C, H, S
h	H	131–132 (2)[e]	74	$C_{14}H_{16}O_4$	

[a] A. Horeau and J. Jacques [*Compt. Rend.*, **228,** 1873 (1949)] reported bp 215–217° (12 mm). [b] C: calcd, 59.47; found, 60.00. [c] E. F. Pratt and E. Werble [*J. Am. Chem. Soc.*, **72,** 4638 (1950)] reported bp 156–158° (1.5 mm). [d] M. S. Newman and M. Wolf [*ibid.*, **74,** 3225 (1952)] reported bp 128° (0.6–0.7 mm). [e] Lit.[13] bp 140–142° (4 mm).

TABLE IV

DIETHYL BENZHYDRYLMALONATES



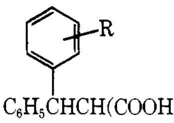
$C_6H_5CHCH(CO_2Et)_2$

No.	R	Mp or bp (mm), °C	Recrystn solvent	% yield	Formula	Analyses
33a	*p*-OCH$_3$	198 (3)		73	$C_{21}H_{24}O_5$[a]	
b	*m*-Cl	48–49	EtOH–H$_2$O	43	$C_{21}H_{21}ClO_4$	C, H, Cl
c	*p*-Cl	58–59	EtOH–H$_2$O	33	$C_{20}H_{21}ClO_4$	C, H, Cl
d	*o*-CH$_3$	132–195 (3)[b]		44	$C_{21}H_{24}O_4$	
e	*m*-CH$_3$	53–54	Hexane	72	$C_{21}H_{24}O_4$	C, H
f	*p*-SCH$_3$	54–56	Et$_2$O–petr ether	51	$C_{21}H_{24}O_4S$	C, H, S
g	*p*-CF$_3$	83–84	Petr ether	64	$C_{21}H_{21}F_3O_4$	C, H

[a] Subsequent thin layer chromatography showed this material to contain another component. [b] Lit. (footnote *d* in Table III) bp 182–186° (0.9–1.5 mm).

TABLE V

BENZHYDRYLMALONIC ACIDS



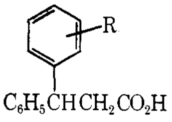
$C_6H_5CHCH(COOH)_2$

No.	R	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
34a	*p*-OCH$_3$	177–180[a]	CHCl$_3$	50	$C_{17}H_{16}O_5$	
b	*m*-Cl	162–164	EtOH–H$_2$O	94	$C_{16}H_{13}ClO_4$	C, H, Cl
c	*p*-Cl	180–181	EtOH–H$_2$O	32	$C_{16}H_{13}ClO_4$	C, H, Cl
d	*o*-CH$_3$	182[b]	EtOH–H$_2$O	67	$C_{17}H_{16}O_4$	
e	*m*-CH$_3$	173–174	EtOH–H$_2$O	64	$C_{17}H_{16}O_4$	C, H
f	*p*-SCH$_3$	181–182	EtOH–H$_2$O	98	$C_{17}H_{16}O_4S$	C, H, S
g	*p*-CF$_3$	174–176	EtOH–H$_2$O	66	$C_{17}H_{13}F_3O_4$	C, H

[a] L. Baillon [*Ann. Chim.* (Rome), **15,** 61 (1921)] reported mp 178°. [b] Lit. (footnote *d* in Table III) mp 182.4–182.8°.

TABLE VI

3,3-DIPHENYLPROPIONIC ACIDS



$C_6H_5CHCH_2CO_2H$

No.	R	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
35a	*p*-OCH$_3$	123–125[a]	EtOH–H$_2$O	96	$C_{16}H_{16}O_3$	
b	*m*-Cl	99.5–100	CCl$_4$–petr ether	79	$C_{15}H_{13}ClO_2$	C, H, Cl
c	*p*-Cl	105–106	EtOH–H$_2$O	59	$C_{15}H_{13}ClO_2$	C, H, Cl
d	*o*-CH$_3$	126–129	EtOH–H$_2$O	53	$C_{16}H_{16}O_2$	C, H
e	*m*-CH$_3$	111–112	EtOH–H$_2$O	95	$C_{16}H_{16}O_2$	C, H
f	*p*-SCH$_3$	142–143[b]	EtOH–H$_2$O	91	$C_{16}H_{16}O_2S$	C, H, S
g	*p*-CF$_3$	99–100	EtOH–H$_2$O	96	$C_{16}H_{13}F_3O_2$	C, H
h	*p*-SO$_2$CH$_3$	150–154[c]	EtOH–H$_2$O	94	$C_{16}H_{16}O_4S$	
i	*p*-SOCH$_3$	161–163	MeOH	90	$C_{16}H_{16}O_3S$	C, H, S

[a] Lit. (footnote *a* in Table V) mp 123–125°. [b] This compound has been prepared by the acid-catalyzed addition of thioanisole to cinnamic acid, mp 122°: V. N. Deshpande and K. S. Nargund, *J. Karnatak Univ.*, 1, 1 (1956). This method when used in our laboratories gave **35f** in 65% yield, mp 135–137°. [c] Lit. (reference in footnote *b*) mp 116°.

stopped. The cooled melt was crystallized and recrystallized from EtOH–H$_2$O or MeOH.

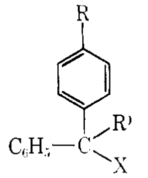
3-(*p*-Methylsulfonylphenyl)-3-phenylpropionic Acid (35h).—To a solution of **35f** in HOAc (10 ml/g of **35f**) was added slowly 30% H$_2$O$_2$ (5 ml/g of **35f**). The solution was stirred and heated on a steam bath for 2–4 hr. The product was isolated by pouring the reaction solution into several volumes of cold H$_2$O and filtering the resulting solid. The solid was washed with H$_2$O and recrystallized.

3-(*p*-Methylsulfinylphenyl)-3-phenylpropionic Acid (35i).—A solution of 5 g (0.018 mole) of **35f**, 2.04 ml (0.018 mole) of 30% H$_2$O$_2$, and 30 ml of HOAc was stirred overnight at room temperature. The solution was diluted with H$_2$O and cooled; the resulting solid was filtered, washed (H$_2$O), and recrystallized; yield 4.6 g.

2-Phenyl-2-(substituted phenyl)ethylamines (4, 6-9, 11-14) (Table I).—Compound **35** was converted to an acid chloride or

TABLE VII

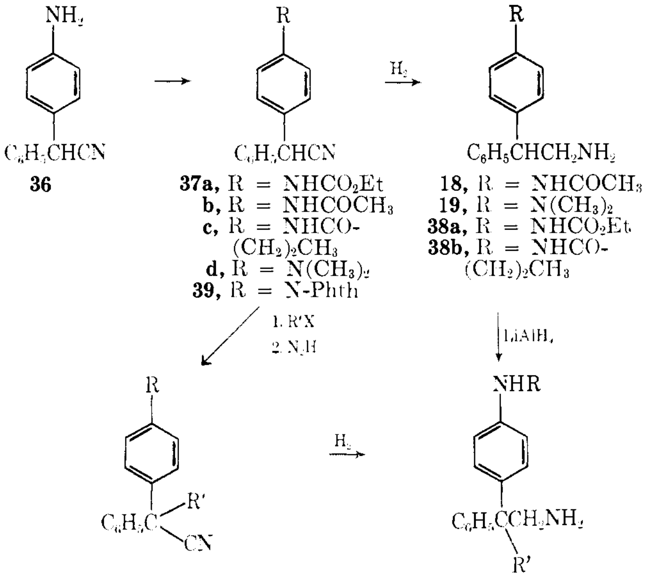
SUBSTITUTED DIPHENYLALKYLAMINES AND NITRILES



No.	R	R¹	X	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
37a	$NHCO_2Et$	H	CN	95.5–97[a]	EtOH–H_2O	70	$C_{17}H_{16}N_2O_2$	C, H, N
b	$NHCOCH_3$	H	CN	*b*				
c	$NHCO(CH_2)_2CH_3$	H	CN	105–107	C_6H_6–petr ether	72	$C_{18}H_{18}N_2O$	C, H, N
d	$N(CH_3)_2$	H	CN	100–102	EtOH	50	$C_{16}H_{16}N_2$	C, H, N
38a	$NHCO_2Et$	H	CH_2NH_2	96–99	C_6H_6–petr ether	64	$C_{17}H_{20}N_2O_2$	C, H, N
b	$NHCO(CH_2)_2CH_3$	H	CH_2NH_2	94–96	C_6H_6–petr ether	87	$C_{18}H_{22}N_2O$	C, H, N
39	N-Phth	H	CN	224–225	DMF–H_2O	91	$C_{22}H_{14}N_2O_2$	C, H, N
40a	N-Phth	CH_3	CN	147–149	EtOH	74	$C_{23}H_{16}N_2O_2$	C, H, N
b	N-Phth	*n*-C_4H_9	CN	*c*				
c	N-Phth	$CH_2C_6H_5$	CN	193–198[c]				
d	NH_2	CH_3	CN	204–206[d]	*n*-BuOH–petr ether	100	$C_{15}H_{14}N_2 \cdot HCl$	C, H, N
e	NH_2	*n*-C_4H_9	CN	196–198[d]	EtOAc	64	$C_{18}H_{20}N_2 \cdot HCl$	H, N, Cl; C[e]
f	NH_2	$CH_2C_6H_5$	CN	167–168	EtOH	*c*	$C_{21}H_{18}N_2$	C, H, N

[a] R. B. Davis, R. T. Buckler, and D. D. Carlos [*J. Chem. Eng. Data*, **13,** 132 (1968)] reported mp 69°. [b] Reference 25. [c] See Experimental Section. [d] With decomposition. [e] C: calcd, 71.87; found, 71.30.

SCHEME II



36

37a, R = $NHCO_2Et$
b, R = $NHCOCH_3$
c, R = NHCO-$(CH_2)_2CH_3$
d, R = $N(CH_3)_2$
39, R = N-Phth

18, R = $NHCOCH_3$
19, R = $N(CH_3)_2$
38a, R = $NHCO_2Et$
38b, R = NHCO-$(CH_2)_2CH_3$

40a, R = N-Phth; R' = CH_3
b, R = N-Phth; R' = *n*-C_4H_9
c, R = N-Phth; R' = $CH_2C_6H_5$
d, R = NH_2; R' = CH_3
e, R = NH_2; R' = *n*-C_4H_9
f, R = NH_2; R' = $CH_2C_6H_5$

20, R = CH_3; R' = H
21, R = C_2H_5; R' = H
22, R = *n*-C_4H_9; R' = H
28, R = H; R' = CH_3
29, R = H; R' = *n*-C_4H_9
30, R = H; R' = $CH_2C_6H_5$

mixed anhydride. Using the "wet NaN_3" method of Kaiser, *et al.*,[15] the acyl derivatives were converted to acyl azides. The azides were subsequently rearranged and hydrolyzed to the amines. These procedures have been described fully.[15]

2-Nitro-1-phenyl-1-(*m*-nitrophenyl)ethane was prepared from 9.7 g (0.046 mole) of 2-nitro-1-(*m*-nitrophenyl)ethan-1-ol,[16] 15 ml of C_6H_6, and 31.1 ml of 3% oleum using the method of Hass, *et al.*[17] The isolated oil was chromatographed on a silica gel (100-200 mesh) column with cyclohexane–EtOAc (4:1 by volume). A yellow oil was obtained from the eluates; it weighed 11.1 g (89%). The oil was homogeneous when studied by thin layer chromatography (silica gel G, R_f 0.6, cyclohexane–EtOAc 2:1 by volume). *Anal.* ($C_{14}H_{12}N_2O_4$) C, H, N.

2-(*m*-Aminophenyl)-2-phenethylamine Fumarate (3).—A solution of 17.1 g (0.063 mole) of the above dinitro compound in EtOH was hydrogenated with Ra(Ni) as described by Hass and coworkers.[17] The resulting product was distilled to give a brown oil, bp 160–165° (2 mm). The oil was dissolved in EtOAc, diluted with Et_2O, and then diluted again with a saturated ethereal solution of fumaric acid. The precipitated salt was filtered and recrystallized twice, yield 4.6 g.

Substituted Benzaldehyde Cyanohydrins.—Using the directions of Alford and Schofield[18] the benzaldehydes were converted to their corresponding cyanohydrins: *o*-chlorobenzaldehyde cyanohydrin, mp 50.5–52° (C_6H_6–petroleum ether (bp 30–60°)), 71% (*Anal.* (C_8H_6ClNO) C, H, N); *p*-tolualdehyde cyanohydrin, mp 63.5–64° (C_6H_6–petroleum ether), 81% (*Anal.* (C_9H_9NO) C, H, N).

***o*-(Chlorophenyl)phenylacetonitrile.**—To a solution of 37.2 g (0.22 mole) of *o*-chlorobenzaldehyde cyanohydrin in 80 ml of dry C_6H_6 was added dropwise 45.2 ml (0.33 mole) of 47% BF_3 in Et_2O. The reaction mixture was kept at 70° for 3 hr and stirred at room temperature for 66 hr. The mixture was washed (H_2O, 400 ml of 10% Na_2CO_3, twice with 400 ml of 10% $NaHSO_3$, twice with 400 ml of H_2O). The organic phase was dried (Na_2SO_4) and concentrated. The residue was distilled to give 8.2 g (16%) of product, bp 156–161° (2 mm) [lit.[19] bp 139° (0.75 mm)].

2-(*o*-Chlorophenyl)-2-phenethylamine Hydrochloride (5).—A solution of 8.2 g (0.035 mole) of (*o*-chlorophenyl)phenylacetonitrile in MeOH saturated with NH_3 was reduced at 55° and 70 kg/cm² of H_2 in the presence of (Ra)Ni. The catalyst was removed and the filtrate was evaporated. The residue was dissolved in Et_2O and the hydrochloride was precipitated with HCl. Recrystallization of the salt gave 4.7 g of **5**.

Phenyl(*p*-tolyl)acetonitrile.—A mixture of 69 g (0.47 mole) of *p*-tolualdehyde cyanohydrin and PBr_3 in dry C_6H_6 was allowed to react using the procedure described by Shirley.[20] The resulting α-bromo-*p*-tolylacetonitrile, without purification, was treated with C_6H_6 and $AlCl_3$ as reported by Shapiro[21] to give 49.9 g (80%) of product, mp 59–61° (lit.[21] 61°).

2-Phenyl-2-(*p*-tolyl)ethylamine Hydrochloride (10).—Phenyl-(*p*-tolyl)acetonitrile (20.7 g, 0.1 mole) was added to a stirred suspension of $LiAlH_4$ and $AlCl_3$ (1.1 moles/mole of nitrile) in Et_2O.

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(19) Q. F. Soper, U. S. Patent 3,063,822 (Sept 15, 1960).

(20) D. A. Shirley, "Preparation of Organic Intermediates," John Wiley & Sons, Inc., New York, N. Y., 1951, p 136.

(21) D. Shapiro, *J. Org. Chem.*, **14**, 839 (1949).

The conditions used were reported by Nystrom.[22] The purified amine salt weighed 11.5 g.

2-(*p*-Hydroxyphenyl)-2-phenethylamine Hydrochloride (**15**).—A solution of 2.4 g (9 mmoles) of **4**, 12.5 ml of HI, and 12.5 ml of HOAc was refluxed and stirred for 6 hr. The solution was poured over ice, made basic with 10% NaOH, and extracted with EtOAc. The combined organic layers were washed with H_2O, dried (Na_2SO_4), and saturated with gaseous HCl. The precipitated salt was filtered and recrystallized, yield 230 mg.

2-(*p*-Mercaptophenyl)-2-phenethylamine Hydrochloride (**16**).—Using the reaction conditions and method of isolation reported by Kappe and Armstrong,[23] a mixture of 11 g (0.08 mole) of 2-amino-1-phenylethan-1-ol, 9.9 g (0.09 mole) of thiophenol, and 58 ml of 6 *N* HCl led to the eventual isolation of 2.2 g of pure **16**.

N-Acetyl-2-(*p*-acetylphenyl)-2-phenethylamine.—A solution of 20 g (0.1 mole) of 2,2-diphenethylamine in H_2O, containing sufficient HCl to keep the amine dissolved, was treated at 0° with 20 ml of Ac_2O and enough NaOAc to bring the pH to 5–6. The mixture was stirred for 2 hr at 0° and overnight at room temperature. Additional NaOAc was added to keep the pH at 5–6. The mixture was diluted with (H_2O) and cooled. The solid N-acetyl-2,2-diphenethylamine was filtered, washed with H_2O, and dried, mp 85–87° (lit.[24] mp 88°), yield 10.4 g (43%).

To a stirred mixture of 9.5 g (0.04 mole) of N-acetyl-2,2-diphenethylamine, 16 g (0.12 mole) of $AlCl_3$, and 50 ml of CS_2 below 0° was added dropwise 2.6 ml (0.036 mole) of AcCl. The solution was stirred for 2 hr in the cold, warmed to room temperature, and poured into a mixture of ice and concentrated HCl. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with H_2O until neutral, dried (Na_2SO_4), and concentrated to a brown oil, which crystallized when triturated with C_6H_6–petroleum ether. Recrystallization from the same solvents yielded 8.2 g (89%) of white crystals, mp 142–144°. *Anal.* ($C_{18}H_{19}NO_2$) C, H, N.

2-(*p*-Acetylphenyl)-2-phenethylamine Hydrochloride Hemihydrate (**17**).—A mixture of 2.6 g (9.3 mmoles) of N-acetyl-2-(*p*-acetylphenyl)-2-phenethylamine and 30 ml of 6 *N* H_2SO_4 was stirred and refluxed for 2.5 hr. The mixture was diluted with H_2O, made basic, and extracted with C_6H_6. The extracts were washed (H_2O), dried, and saturated with dry HCl to precipitate crude **17**. Recrystallization gave 980 mg of pure product.

N-Acyl-(*p*-aminophenyl)phenylacetonitriles (37a and c).—A slight excess of the requisite acylating agent was added to a stirred mixture of **36**[7] in Et_2O and saturated aqueous Na_2CO_3. The mixture was stirred at room temperature for 4–6 hr. The layers were separated and the Et_2O was washed (H_2O), dried, and evaporated. The residue was recrystallized.

(*p*-Dimethylaminophenyl)phenylacetonitrile (**37d**).—To a suspension of 0.4 g of prereduced PtO_2 in 200 ml of EtOH was added 25 g (0.12 mole) of **36**,[7] 10 ml of concentrated HCl, and 19.5 g (0.24 mole) of 37% aqueous CH_2O. The dark red solution was reduced under 3 atm of H_2, the catalyst was filtered, and the filtrate was evaporated. The residue was diluted (H_2O), made basic, and extracted with C_6H_6. The extracts were washed (H_2O), dried (K_2CO_3), and concentrated to an oil. The oil was acetylated by refluxing for 30 min with 28 ml of HOAc, 24 ml of Ac_2O, and a trace of zinc dust. The resulting mixture, which contained the product and the amides of any contaminating primary or secondary amines, was decanted from the zinc into a beaker of ice-H_2O. The mixture was extracted with C_6H_6 and the extracts were washed (10% NaOH, H_2O, dilute HCl). The acidic washes were extracted with Et_2O to give a clear, yellow aqueous phase. The aqueous phase was made alkaline with 10% NaOH and the resulting mixture was extracted (CH_2Cl_2). The CH_2Cl_2 phases were washed (H_2O), dried, and evaporated to a solid residue weighing 19.6 g. Recrystallization of the solid from EtOH gave 14 g (50%) of product, mp 100–102°.

Substituted Diphenethylamines (18, 19, 24, 27, 38a and b).—Compounds **37b**[25] and **d** were hydrogenated in MeOH saturated with NH_3 at 80° and 70 kg/cm² of H_2 in the presence of (Ra)Ni. After the catalyst and solvent were removed, **18** was solidified by trituration with Et_2O. Crude **19** was obtained as an oil which distilled at 170° (1 mm). The distillate solidified and melted at 72–75°.

Compound **37a** and **c** were hydrogenated under the same conditions as **37b** and **d** except that THF was used as a solvent. After suitable acid extractions, the crude products were induced to crystallize by trituration with petroleum ether.

Bis(*p*-tolyl)acetonitrile[26] (12.6 g) and (*p*-aminophenyl)-*p*-tolylacetonitrile (0.1 mole) were reduced in a similar fashion. Compound **24** was converted directly to a hydrochloride with ethereal HCl. Crude **27** was distilled at 200–205° (1 mm) to give 13.1 g (58%) of oil which was converted to a dihydrochloride.

2-(*p*-Alkylaminophenyl)-2-phenethylamines (20–22).—A solution of the N-acylaminodiphenethylamine (**18, 38a,** or **38b**) in a mixture of Et_2O and THF was added dropwise to a stirred suspension of $LiAlH_4$ in Et_2O (containing 5 moles of hydride/mole of amide or carbamate being reduced). The mixture was stirred under reflux overnight and cooled. The excess hydride was decomposed with H_2O and 10% NaOH and the resulting granular precipitate was filtered and washed with Et_2O. The combined filtrates were evaporated and the residual oil was distilled giving **20**, bp 160–170° (1 mm); **21**, bp 190–200° (1 mm); and **22**, bp 215–220° (0.5 mm).

2,2-Bis(*p*-chlorophenyl)ethylamine Hydrochloride (**23**).—A solution of 8 g (0.0286 mole) of 2,2-bis(*p*-chlorophenyl)acetamide[27] in 75 ml of dry Et_2O was added dropwise to a stirred suspension of $LiAlH_4$ and $AlCl_3$ (prepared by adding 4.5 g of $AlCl_3$ in 50 ml of Et_2O to 1.5 g of $LiAlH_4$ in 35 ml of Et_2O). The mixture was stirred overnight at room temperature and the complex was decomposed with 5 ml of H_2O and enough 40% NaOH to make the mixture basic. After being stirred for 1 hr, the solid was filtered and washed with Et_2O. The Et_2O was washed (H_2O), dried (K_2CO_3), and evaporated to an oil. The oil was dissolved in Et_2O and the hydrochloride was precipitated with ethereal HCl.

2-(*p*-Aminophenyl)-2-(*p*-chlorophenyl)ethylamine Dihydrochloride (**26**).—A methanolic solution of *p*-chlorophenylcyanomethylene quinone–oxime[28] saturated with NH_3 was hydrogenated at 70 kg/cm² in the presence of (Ra)Ni at 55° until the uptake of H_2 was complete. Higher temperatures led to loss of Cl. The catalyst was filtered and the filtrate was evaporated. The gummy residue was dried by azeotropic distillation of absolute EtOH and was dissolved in EtOAc. This solution was saturated with dry HCl. The salt was filtered and dissolved in H_2O. The aqueous solution was basified to precipitate a semisolid, which was dissolved in EtOAc. The EtOAc was washed with H_2O, dried, and concentrated. The concentrate was saturated with HCl. The salt was filtered, suspended in hot *n*-BuOH, and cooled. The resulting pale yellow solid was filtered and recrystallized to give off-white crystals. Concentration of the butanolic filtrate followed by dilution with Et_2O or EtOAc yielded a very hygroscopic solid.

4-Oxo-α-(*p*-tolyl)-2,5-cyclohexadiene-$\Delta^{1,\alpha}$-acetonitrile Oxime.—Using the procedure of Davis, *et al.*,[28,29] 0.19 mole of *p*-tolylacetonitrile was converted to the corresponding quinone oxime in 87% yield, mp 170–171.5° dec (C_6H_5Me). *Anal.* ($C_{15}H_{12}N_2O$) C, H, N.

(*p*-Aminophenyl)-*p*-tolylacetonitrile.—Reduction of 34.2 g (0.14 mole) of *p*-tolylcyanomethylene quinone oxime with Zn–Hg in aqueous HOAc[7] gave 22 g (71%) of the aminonitrile, mp 100–102° (EtOH). *Anal.* ($C_{15}H_{14}N_2$) C, H, N.

N-Phthaloyl(*p*-aminophenyl)phenylacetonitrile (**39**).—A mixture of 140 g (0.5 mole) of **36**,[7] 74 g (0.5 mole) of phthalic anhydride, and 2500 ml of C_6H_5Me was heated and stirred so that the H_2O formed during the reaction was removed by azeotropic distillation (*ca.* 18 hr). The solution was cooled to room temperature and the precipitate was filtered. The filtrate was taken to dryness and the combined solids were recrystallized (DMF–H_2O) to give 154 g (91%) of **39**, mp 221–222°.

N-Phthaloyl-2-(*p*-aminophenyl)-2-phenylpropionitrile (**40a**).—To a stirred suspension of 6.8 g (0.02 mole) of **39** in 75 ml of dry DMF was added 1 g of a 53.3% mineral oil dispersion of NaH. The suspension was immediately converted to a dark brown solution (slightly exothermic). A solution of 4 ml of MeI in 15 ml of dry DMF was added fairly rapidly, whereupon the brown color was discharged and a pale yellow solution was pro-

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[22] R. F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955).

[23] T. Kappe and M. D. Armstrong, *J. Org. Chem.*, **29**, 826 (1964).

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duced (temperature rose to 40–55°). The solution was stirred for 15 min at room temperature and for 20 min on a steam bath. The solution was poured into several volumes of ice-H_2O to precipitate a yellow gum. The aqueous solution was decanted and the gum was triturated with EtOH to produce white crystals. The crystals were recrystallized (EtOH), mp 147–149°, yield 5.2 g (74%).

2-Phenyl-2-(*p*-phthalamidophenyl)propionitrile.—A suspension of 3.5 g (0.01 mole) of **40a**, 2.4 g (0.06 mole) of KOH, 150 ml of EtOH, and 5 ml of H_2O was stirred under reflux for 1 hr. The solution was cooled, diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ was washed once with H_2O and the aqueous phases were combined and acidified. The solid was filtered, washed (H_2O), and recrystallized (EtOH–H_2O), mp 180–182°, yield 2.5 g (68%). *Anal.* ($C_{23}H_{18}N_2O_3$) C, H, N.

N-Phthaloyl-2-(*p*-aminophenyl)-2-phenylcapronitrile (40b).—An equivalent amount of NaH was added to a suspension of 13.5 g (0.04 mole) of **39** in 125 ml of dry DMF. *n*-BuBr (6 ml) in 15 ml of DMF was added and the solution was treated as described in the preparation of **40a**. The aqueous mixture of product, H_2O, DMF, and unreacted **39** was extracted with $CHCl_3$. The $CHCl_3$ was washed (H_2O), dried, and evaporated. The residual oil was stirred with a small volume of MeOH for several hours. The resulting solid was filtered and the filtrate was cooled to give additional solid. The combined solids (4 g) were extracted with Et_2O and the Et_2O was filtered. The Et_2O was evaporated and the residue was dissolved in hot MeOH. The MeOH was filtered and cooled to give a mixture of gum and crystals. Trituration of the gum with fresh MeOH caused it to solidify. The total solids were recrystallized from CCl_4–petroleum ether to give 2.5 g of solid with an indefinite melting point. A small sample was recrystallized further (MeOH), mp 125–127°. However, when examined by tlc (silica gel, cyclohexane–EtOAc, 2:1) this material still showed the presence of several impurities. The material was subjected to hydrazinolysis without further purification.

N-Phthaloyl-2-(*p*-aminophenyl)-2,3-diphenylpropionitrile (40c).—A suspension of 20.3 g (0.06 mole) of **39**, 3 g of a 53.4% mineral oil dispersion of NaH, and 20 ml of dry DMF was treated with 7 ml of benzyl chloride in DMF as described in the preparation of **40a**. The product was isolated by diluting the DMF with H_2O and extracting the aqueous mixture with $CHCl_3$. The $CHCl_3$ was washed (H_2O), dried ($MgSO_4$), and evaporated. When the residue was diluted with a small volume of EtOH, crystals precipitated. These were filtered and dried; mp *ca.* 193–198°, yield 20 g. The crystals were shown by tlc to contain unreacted **39**.

2-(*p*-Aminophenyl)-2-phenylalkylnitriles (40d–f).—A mixture of 0.035 mole of **40a**, **b**, or **c**, 200 ml of EtOH, and 12 ml of 85% $N_2H_4 \cdot H_2O$ was stirred and heated to reflux. In a short time solution was effected. This was followed quickly by the formation of a thick white precipitate. Enough H_2O was added through the top of the condenser to dissolve the solid and heating was continued for 1 hr. The heating bath was removed and stirring was continued for an additional 1 hr. The solution was diluted with H_2O and the EtOH was removed *in vacuo*. The aqueous residue was extracted with Et_2O three times and the combined Et_2O phases were washed (H_2O) until neutral. The Et_2O was dried and removed. In the case of **40d**, the residual yellow oil weighed 8 g. A 400-mg sample was converted to the hydrochloride with ethereal HCl. The remainder of the free base was hydrogenated without further purification.

Compound **40e** was isolated as an oil which was converted to a hydrochloride. During the Et_2O extraction of the aqueous reaction mixture containing **40f** solid precipitated in the aqueous phase. This was filtered and combined with **40f** obtained from concentration of the ether extracts.

2-(*p*-Aminophenyl)-2-phenylalkylamines (28–30).—The nitriles **40d–f** were reduced in MeOH saturated with NH_3 in the presence of (Ra)Ni at 70° and 70 kg/cm² of H_2 for 4 hr. The catalyst was filtered, the filtrate was evaporated, and the residue was dried and dissolved in EtOAc. The EtOAc was filtered from a small amount of insoluble material and the dihydrochlorides were precipitated with dry HCl.

2-Amino-1,1-diphenylpropane Hydrochloride (31).—The oxime of 1,1-diphenylacetone, mp 162–164° (lit.[30] 164.5°), was prepared according to the method of Wright and Gutsell.[31] The oxime (72.3 g, 0.23 mole) was reduced with (Ra)Ni alloy, EtOH, and 2 *N* NaOH according to Staskun and van Es.[32] The spent metal alloy was filtered, the EtOH was removed *in vacuo*, and the aqueous residue was extracted with Et_2O. The Et_2O was washed (H_2O), dried, and saturated with dry HCl. The salt was filtered and recrystallized.

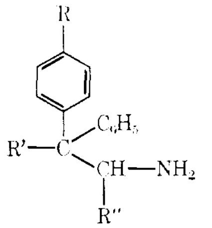
Biological Testing.—The antiadrenal activity of the title compounds was evaluated in the rat cold-stress test[6] (which estimates the ability of compounds to decrease peripheral plasma corticosterone). Representatives of this series with high, low, and intermediate activity in the cold-stress assay were evaluated further in the rat antialdosterone assay,[6] in which a natriuretic response may indicate a decreased aldosterone secretion, and in the isolated rat adrenal preparation[33] (which provides a profile of the adrenal inhibition). Briefly, the *in vitro* studies were carried out as follows. Adrenals from Na^+-depleted rats were halved and preincubated in 2 ml of Hanks medium containing ACTH (Armour) (0.005 U/mg of adrenal) and the test compound at a concentration of 5×10^{-4} *M*. After 2 hr of incubation, the adrenals were washed once with 1 ml of Hanks solution, and the washing and incubation media were combined and acidified. The combined media were extracted once with 5 ml of isooctane. The isooctane extract, which contained the 11-desoxycorticosterone, was evaporated to dryness under vacuum. The aqueous phase was extracted once with 5 ml of $CHCl_3$. The $CHCl_3$ extract, which contained corticosterone and aldosterone, was washed once with 0.5 ml of 0.1 *N* NaOH. Corticosterone levels were measured in an aliquot of the $CHCl_3$ extract using the fluorescence method of Sweat.[34] Aldosterone was converted to its γ-lactone by periodate oxidation[35] and measured using glpc. Desoxycorticosterone was converted to its acetate according to the method of Bush,[36] and the resulting acetate was measured using glpc (Table II).

Adrenal vein cannulation studies in the dog were carried out using the method of Hume and Nelson.[37] Thoracic vena caval constriction was done by the method of Davis, *et al.*[38]

Discussion

In the rat cold-stress assay the most active compounds, **2**, **12–14**, **19–21**, were monosubstituted in the *para* position of one phenyl ring. Neither the electronic character nor the size of the substituent seemed related to the biological activity, because **13** and **14** with electron-withdrawing sulfone and sulfoxide groups were as active as **2**, **12**, and **19–21** with electron-releasing amino, substituted amino, or methylthio substituents. The unimportance of the electronic character of the substituent was further demonstrated by the poor activity shown by other compounds with strong electron-releasing and -withdrawing groups (*e.g.*, **4**, **11**, **15**, and **16**).

When the aromatic amino group in **2** was moved from a position *para* to the alkyl side chain to a position *meta* to the side chain (**3**), there was a marked decrease in activity. Replacing the benzhydryl hydrogen of **2** with an alkyl or aralkyl group (**28–30**) also decreased activity; the decrease depended upon the nature of the group.



2, R = NH_2; R' = R'' = H
28, R = NH_2; R' = CH_3; R'' = H
31, R = R' = H; R'' = CH_3

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Except for **2**, **12–14**, and **19**, aromatic substitution of diphenethylamine (**1**) did not intensify the *in vivo* inhibition or alter the character of the *in vitro* suppression. These analogs of **1** were approximately five times more potent than **1** in preventing the increase in peripheral plasma corticosterone in rats exposed to cold. Although **2**, **13**, and **19** depressed corticosterone synthesis in the isolated rat adrenal preparation, they also caused a compensatory increase in 11-desoxycorticosterone (DOC). These findings suggest an inhibitory effect on 11-hydroxylation similar to that produced by a known 11-hydroxylase inhibitor, 2-methyl-1,2-bis(3-pyridyl)-1-propanone (methopyrapone).[39,40] **10** was one-third as active as **1** in the cold-stress test, but was almost as active as **1** in the antialdosterone assay. This relationship persisted in the isolated rat adrenal system where minimal DOC accumulation was found at inhibitor concentrations of **10** that maximally suppressed corticosterone. Thus, the introduction of a *p*-methyl group into **1** appeared to minimize the 11-hydroxylase inhibition without adversely affecting other enzyme-inhibiting activities.

Introduction of a methyl group at C-2 of the aliphatic side chain of **2** (**28**) decreased potency *in vivo* and altered the profile of inhibition *in vitro*. Compound **28** decreased corticosterone and aldosterone, but did not significantly affect DOC. Amphenone has been found[40,41] to produce similar changes *in vitro*. These changes are consistent with an inhibitory action occurring early in the biosynthetic pathway. Preliminary adrenal vein studies in the dog with **28** indicated a similar inhibitory action because the secretion rates of Porter–Silber positive material and DOC were significantly reduced. In contrast, the *n*-butyl (**29**) and benzyl (**30**) analogs resembled **2**, because the decrease in corticosterone was invariably accompanied by an increase in DOC *in vitro*.

Introduction of a methyl group at C-1 of the aliphatic side chain of **1** (**31**) caused a highly selective inhibition of aldosterone *in vitro*. At concentrations which maximally suppressed aldosterone, no significant decrease in corticosterone or increase in DOC was evident. These *in vitro* observations could be correlated to the *in vivo* findings. **31** was essentially devoid of activity in the rat cold-stress test at oral doses as high as 100 mg/kg, suggesting minimal effects on corticosterone production. The enhanced activity of **31** in the antialdosterone assay is also consistent with aldosterone inhibition. Compound **31** caused a marked natriuresis in the sodium-depleted rat at oral doses as low as 20 mg/kg; it did not increase sodium excretion in saline-loaded adrenalectomized rats. Adrenal vein cannulation studies in dogs with aldosteronism secondary to constriction of the thoracic vena cava showed that **31** decreased aldosterone secretion rates, but did not alter cortisol or DOC secretion rates. However, **31** did not evoke a natriuretic response in the caval dog at doses which produced side effects. In other studies, **31** did not alter corticosterone levels in dexamethasone-blocked, ACTH-treated rats, and it did not suppress the peripheral plasma levels of Porter–Silber positive material in ACTH-treated intact guinea pigs.[42] Finally, **31** was without effect in the metacorticoid hypertensive rat.[43]

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(42) These data suggest that **31** has a minimum inhibitory effect on 11- and 17-hydroxylation.

(43) Because aldosterone secretion is reduced in these animals, it would appear that **31** has minimal direct natriuretic activity and no hypotensive activity.