Synthesis and Adrenocortical Inhibiting Activity of Substituted Diphenylalkylamines

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A number of diphenylpropylamines and diphenylbutylamines with and without branched side chains were prepared as specific inhibitors of aldosterone biosynthesis. The adrenal corticosteroid inhibiting activity of the compounds was measured in one or more bioassay systems. Many of the compounds were found to be moderately potent, specific inhibitors of aldosterone biosynthesis.

In a previous study,[1] we found it difficult to correlate the structure of 2,2-diphenethylamines with their ability to inhibit adrenal corticosteroid biogenesis. Simple changes in aromatic substituents profoundly affected the profile of biological activity. One compound, 2-amino-1,1-diphenylpropane (**28**), appeared to be a potent and specific inhibitor of aldosterone biosynthesis.

The diphenylalkylamines (**1–23**) listed in Table I were prepared to study the relationship between side-chain length and branching and the ability to selectively inhibit aldosterone biosynthesis (Table II).

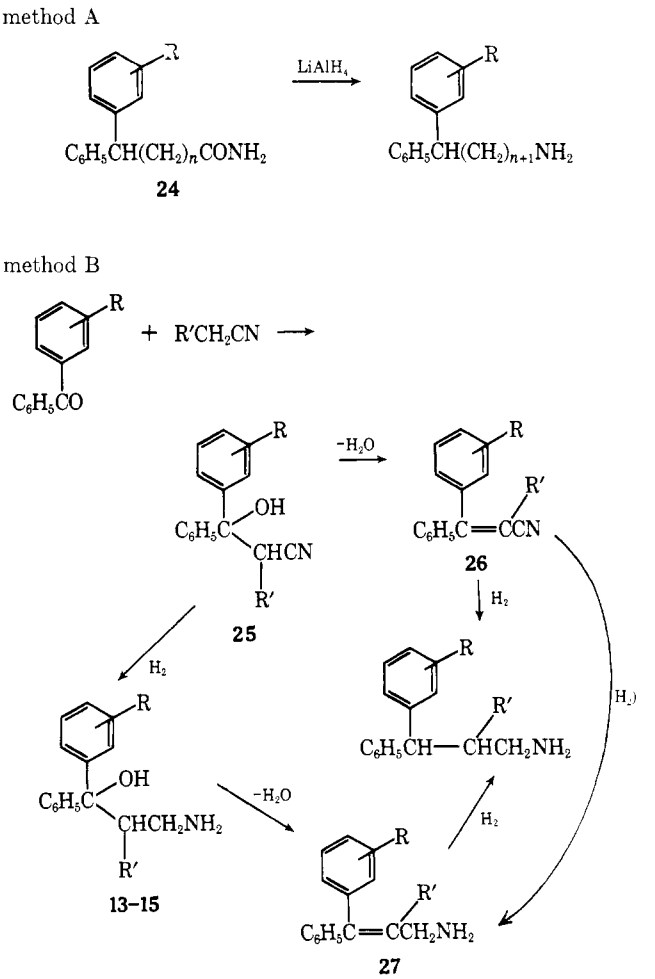
The diphenylalkylamines **1–3**, **5**, **7–9**, and **18–20** were prepared by lithium aluminum hydride reduction of a suitable amide precursor (Chart I, method A). Preparation of the *m*- and *p*-chloro analogs in a similar fashion from **24i** and **j** was unsuccessful because of the concomitant loss of ring chlorine. Compounds **4**, **6**, and **13–17** were prepared from benzophenones and alkylnitriles as outlined in Chart I (method B); **5** and **8** were prepared by both methods, and **10** and **11** were prepared by oxidizing the N-acetyl derivative of **9** and hydrolyzing the amide.

Repeated attempts were made to prepare **12** using a sequence of reactions comparable to those shown in method B. *p*-Acetamidobenzophenone did not react with acetonitrile for us under conditions identical with those which produced the hydroxynitriles **25**. Attempts to form the same intermediate using Reformatsky conditions were also unsuccessful. However, the Reformatsky reaction was successful when ethyl bromoacetate was used. The hydroxy ester was hydrolyzed with base to the hydroxy acid and dehydrated to the cinnamic ester. Hydrolysis of the unsaturated ester or dehydration of the hydroxy acid yielded the cinnamic acid in very poor yield. To some extent, the poor yield was the result of decarboxylation of the cinnamic acid, as evidenced by the isolation of (*p*-acetamidophenyl)phenylethene. Similar results have been noted by others.[2] The ethene was identical with material obtained from the reactions described below.

Alternatively, the synthesis of **12** was attempted starting with (*p*-aminophenyl)phenylacetic acid and using the following sequence of reactions. The acid was esterified, the ester was reduced with hydride to the amino alcohol, the amino alcohol was N-acetylated, and the amido alcohol was tosylated. Attempts to displace the tosyl group with cyanide in refluxing acetone or EtOH or in DMF at room temperature yielded unchanged starting material. Heating the cyanation mixture in DMF caused the tosylate to disappear (followed by tlc). The resulting product was predominantly (*p*-acetamidophenyl)phenylethene formed by the intramolecular loss of tosylate.

The desired 3-(*p*-acetamidophenyl)cinnamonitrile was finally obtained from the Wittig-type reaction of *p*-acetamidobenzophenone with diethyl cyanomethylphosphonate in the presence of sodamide. Hydrogenation and hydrolysis of the cinnamonitrile gave **12**.

CHART I

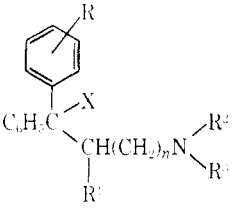


(1) W. A. Zuccarello, B. Blank, G. J. Frishmuth, S. R. Cohen, D. Scaricaciottoli, and F. F. Owings, *J. Med. Chem.*, **12**, 9 (1969).

(2) D. S. Noyce, S. K. Brauman, and F. B. Kirby, *J. Am. Chem. Soc.*, **87**, 4335 (1965).

TABLE I

DIPHENYLALKYLAMINES



No.	R	R^1	R^2	R^3	X	n	Mp, °C	Recrystn solvent	Method	% yield	Formula	Analyses
1	H	H	H	H	H	1	217–218[a]	EtOH–Et_2O	A	74	$C_{15}H_{17}N \cdot HCl$	Cl
2	H	H	C_2H_5	H	H	1	162–163	EtOH–Et_2O	A	60	$C_{17}H_{21}N \cdot HCl$	C, H, Cl, N
3	H	H	CH_3	CH_3	H	1	169–170[b]	EtOH–Et_2O	A	62	$C_{17}H_{21}N \cdot HCl$	C, H
4	*p*-CH_3	H	H	H	H	1	178–180	Me_2CO–EtOH–Et_2O	B	50	$C_{16}H_{19}N \cdot HCl$	C, H, Cl, N
5	*m*-CH_3	H	H	H	H	1	188–190[c]	EtOH–Et_2O	A	35	$C_{16}H_{19}N \cdot HCl$	C, H, Cl, N
							192–194		B	86		
6	*o*-CH_3	H	H	H	H	1	192–194	EtOH–Et_2O	B	58	$(C_{16}H_{19}N)_2 \cdot C_4H_6O_6$[d]	C, H, N
7	*p*-CF_3	H	H	H	H	1	191–192	EtOAc–PE[e]	A	49	$C_{16}H_{16}F_3N \cdot HCl$	C, H
8	*p*-OCH_3	H	H	H	H	1	178–179[c]	EtOH–Et_2O	A	56	$C_{16}H_{19}NO \cdot HCl$	C, H, Cl, N
									B	68		
9	*p*-SCH_3	H	H	H	H	1	179–181	EtOH–Et_2O	A	100	$C_{16}H_{19}NS \cdot HCl$	C, H, Cl, N
10	*p*-$SOCH_3$	H	H	H	H	1	*f*	EtOH–Et_2O			$(C_{16}H_{19}NOS)_2 \cdot C_4H_6O_6$[d,g]	C, H, N
11	*p*-SO_2CH_3	H	H	H	H	1	*f*	EtOH–Et_2O		22	$C_{16}H_{19}NO_2S \cdot HCl$[g]	C, H, Cl, N
12	*p*-NH_2	H	H	H	H	1	207[h]	MeOH–EtOAc		55	$C_{15}H_{18}N_2 \cdot 2HCl$	C, H, Cl, N
13	*m*-CH_3	H	H	H	OH	1	205–207	MeOH–Et_2O	B	79	$(C_{16}H_{19}NO)_2 \cdot C_4H_6O_6$[d]	C, H, N
14	*o*-CH_3	H	H	H	OH	1	116–117	MeOH–H_2O	B	67	$C_{16}H_{19}NO$	C, H, N
15	H	C_2H_5	H	H	OH	1	132–133	MeOH–H_2O	B	84	$C_{17}H_{21}NO$	C, H, N
16	H	CH_3	H	H	H	1	248–250	*n*-C_4H_9OH	B	62	$C_{16}H_{19}N \cdot HCl$	C, H, Cl, N
17	H	C_2H_5	H	H	H	1	233–235	EtOH–Et_2O	B	74	$C_{17}H_{21}N \cdot HCl$	C, H, Cl, N
18	H	H	H	H	H	2	197–198	EtOH–Et_2O	A	71	$C_{16}H_{19}N \cdot HCl$	C, H, Cl, N
19	H	H	CH_3	H	H	2	162–163	EtOH–Et_2O	A	73	$C_{17}H_{21}N \cdot HCl$	C, H, Cl, N
20	H	H	CH_3	CH_3	H	2	153–154[i]	EtOH–Et_2O	A	74	$C_{18}H_{23}N \cdot HCl$	Cl
21	*p*-OH	CH_3	H	H	H	0	324–326[j]	*i*-C_3H_7OH–Et_2O		2	$C_{15}H_{17}NO \cdot HCl$	C, H, Cl, N
22	*p*-CF_3	CH_3	H	H	H	0	267	EtOAc–PE		14	$C_{16}H_{16}F_3N \cdot HCl$	C, H, Cl, N
23	H	CH_3	H	H	CH_3	0	227–228[k]	EtOH–Et_2O		10	$C_{26}H_{29}N \cdot HCl$	C, H

[a] W. J. Gensler and J. C. Rockett [*J. Am. Chem. Soc.*, **77**, 3262 (1955)] report mp 218–219.5°. [b] J. Klosa and H. Starke [East German Patent 33,285 (Dec 5, 1964); *Chem. Abstr.*, **63**, 11579*f* (1965)] report mp 166–168°. [c] The free base has been reported by K. Harsanyi, D. Korbonits, P. Kiss, L. Tardos, and G. Leszkovszky, Hungarian Patent 151,020 (Dec 1963); *Chem. Abstr.*, **60**, P9197*e* (1964). [d] Tartrate. [e] H. Lettré and K. Wick [*Ann.*, **603**, 189 (1957)] report mp 178–179°. [f] Too hygroscopic to be taken. [g] Hemihydrate. [h] With decomposition. [i] V. Seidlova, J. Metysova, F. Hradil, Z. Votava, and M. Protiva, *Cesk. Farm.*, **14**, 75 (1965); *Chem. Abstr.*, **62**, 1170*gh* (1965)] report mp 153–154.5°. [j] Taken in a metal block and is uncorrected. [k] H. Zaugg, M. Freifelder, and B. W. Horrom [*J. Org. Chem.*, **15**, 1191 (1950)] report mp 224–225°. [l] PE = petroleum ether (bp 40–60°).

TABLE II

ANTIADRENAL ACTIVITIES

No.	Rat cold stress test[a]	Rat anti-aldosterone assay[a]	Isolated rat adrenal, % change in steroid level from control: B[b]	DOC[c]	Aldosterone
1	−	+	−59	+400	−91
2	−	+	−44	*d*	−84
4		−			
5	−	±	−34[e]	−12[e]	−90
6		+			
7		+	−47	+267[e]	−95
8	−	+	−42	+267[e]	−92
9	−	+	−57	+433	−93
11		±	+17[e]	+200[e]	−53
12		±			
16		+	−70	+58[e]	−94
17		+			
18		+			
19		−			
20		±			
21	−	−			
23		−			
24a		±	−14[e]	−43[e]	−22[e]
27a	−	−			
28	−	++	−9[e]	+67[e]	−79
29	++	−	−87	+542	−94

[a] −, inactive; ±, weak activity; +, moderate activity; ++, potent activity. [b] Corticosterone. [c] 11-Deoxycorticosterone. [d] Not detectable. [e] No statistically significant ($P < 0.05$) difference from control.

Compound **21** was obtained by the acid-catalyzed condensation of phenol with 2-amino-1-phenylpropan-1-ol, using the conditions described by Kappe and Armstrong.[3] 2-Amino-1-phenyl-1-(*p*-trifluoromethylphenyl)propane (**22**) was obtained in four steps from α-phenoxypropiophenone, using a method described by Wright and Gutsell.[4] The propiophenone, when treated with *p*-trifluoromethylphenylmagnesium bromide, gave 2-phenoxy-1-phenyl-1-*p*-trifluoromethylphenylpropan-1-ol. Dehydration of this tertiary alcohol with acid yielded the phenyl enol ether of a diphenylpropanone, which was simultaneously hydrolyzed to 1-phenyl-1-*p*-trifluoromethylphenylpropan-2-one. The propanone was converted to the oxime which was hydrogenated in poor yield to **22**. 3-Amino-2,2-diphenylbutane (**23**) was obtained by catalytic reduction of the oxime derived from 2,2-diphenylbutan-3-one. Reduction of this oxime proceeded poorly also, and much unchanged starting material was recovered. We feel that the conditions developed by Staskun and van Es,[5] which we used previously[1] to prepare **28**, would have been more satisfactory for the preparation of **22** and **23**.

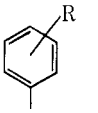
(3) T. Kappe and M. D. Armstrong, *J. Org. Chem.*, **29**, 826 (1964).

(4) J. B. Wright and E. S. Gutsell, *J. Am. Chem. Soc.*, **81**, 5193 (1959).

(5) B. Staskun and T. van Es, *J. Chem. Soc., C*, 531 (1966).

TABLE III

DIPHENYLALKYLAMIDES



$C_6H_5CHCH_2-A$

No.	R	A	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
24a	H	$CH_2NHCOCH_3$	101–102[a]	C_6H_6–PE[g]	64	$C_{17}H_{19}NO$	C, H
b	*m*-CH_3	$CONH_2$	64–65	Et_2O–PE	50	$C_{16}H_{17}NO$[b]	C, H, N
c	*p*-CF_3	$CONH_2$	91–93	C_6H_6–PE	83	$C_{16}H_{14}F_3NO$	C, H, N
d	*p*-OCH_3	$CONH_2$	140[c]	EtOH	99	$C_{16}H_{17}NO_2$	
e	*p*-SCH_3	$CONH_2$	136–138	EtOH–H_2O	60	$C_{16}H_{17}NOS$	C, H, N, S
f	*p*-SCH_3	$CH_2NHCOCH_3$	87–89	MeOH–H_2O	53	$C_{18}H_{21}NOS$	C, H, N, S
g	*p*-$SOCH_3$	$CH_2NHCOCH_3$	*d*		35	$C_{18}H_{21}NO_2S$[b]	C, H, N
h	*p*-SO_2CH_3	$CH_2NHCOCH_3$	*e*		89	$C_{18}H_{21}NO_3S$	
i	*m*-Cl	$CONH_2$	71–73	Et_2O–PE	48	$C_{15}H_{14}ClNO$	C, H, Cl, N
j	*p*-Cl	$CONH_2$	112–113	MeOH–H_2O	42	$C_{15}H_{14}ClNO$	C, H, Cl, N
k	H	$CON(CH_3)_2$	113–114[f]	Hexane	80	$C_{17}H_{19}NO$	
l	H	CH_2CONH_2	76–78	C_6H_5Me–PE	76	$C_{16}H_{17}NO$	C, H, N
m	H	$CH_2CONHCH_3$	99–100	C_6H_5Me–PE	65	$C_{17}H_{19}NO$	C, H, N
n	H	$CH_2CON(CH_3)_2$	100–101	C_6H_5Me–PE	51	$C_{18}H_{21}NO$	C, H, N
o	H	$(CH_2)_2NHCOCH_3$	100–102	C_6H_6–PE	62	$C_{18}H_{21}NO$	C, H, N

[a] K. Harsanyi, K. Takaco, D. Korbonits, L. Tardos, G. Leszkovszky, and J. Erdelyi [Hungarian Patent 151,255 (March 1964); *Chem. Abstr.*, **60**, P14431*g* (1964)] report mp 104°. [b] Hemihydrate. [c] V. N. Deshpande and K. S. Nargund, *J. Karnatak Univ.*, **1**, 7 (1956); *Chem. Abstr.*, **52**, 7183*f* (1958)] report mp 140°. [d] An oil which was purified by chromatography. [e] An oil which was used without further purification. [f] G. Gilbert [*J. Am. Chem. Soc.*, **77**, 4413 (1955)] report mp 114–114.2°. [g] PE = petroleum ether (bp 40–60°).

Experimental Section[6]

4,4-Diphenylbutanoic Acid.—4,4-Diphenylbut-3-enoic acid was prepared in good yield using the procedure reported by Johnson, *et al.*[7] Reduction according to the method of Wawzonek and Kozikowski[8] gave a mixture of product and starting material. When this mixture was reduced a second time in EtOH using PtO_2 as a catalyst, the saturated acid was the sole product, mp 104° (lit.[8] mp 103–106°), yield 78%; its nmr spectrum contained no vinyl protons.

Diphenylalkylamides (24b–e and l–n) (Table III).—The appropriate propionic or butyric acid was refluxed for 3 hr with excess $SOCl_2$. The excess $SOCl_2$ was removed *in vacuo*, and the residual acid chloride was evaporated twice with fresh portions of C_6H_6. Alternatively, the acids were converted to mixed anhydrides using the method of Kaiser, *et al.*[9] The acyl derivative, dissolved in dry Me_2CO, was added to a stirred solution of NH_3 or amine in ice water. The resulting solid was cooled, filtered, washed (H_2O), dried, and recrystallized.

N-Acetyldiphenylalkylamines (24a, f, and o) (Table III).—A mixture of amine, Ac_2O (1.1 ml/0.01 mole of amine), HOAc (2.5 ml/0.01 mole of amine), and NaOAc was heated on a steam bath for 30 min to 2 hr. The resulting solution was poured into several volumes of ice water. The product, if solid, was filtered, washed, dried, and recrystallized; if an oil, it was extracted into Et_2O. The Et_2O was washed (H_2O, 5% $NaHCO_3$, H_2O). The dried extract (Na_2SO_4) was evaporated, and the residue was triturated with Et_2O and hexane to give a solid which was filtered and recrystallized.

N-Acetyl-3-(*p*-methylsulfinylphenyl)-3-phenylpropylamine Hemihydrate (24g).—A solution of 5.5 g (0.018 mole) of **24f**, 10 ml of HOAc, and 2.1 ml (0.018 mole) of 30% H_2O_2 was stirred at room temperature overnight. The mixture was diluted with H_2O, and the resulting gum was extracted with EtOAc. The EtOAc extract was washed (H_2O, 5% $NaHCO_3$, H_2O) and dried (Na_2SO_4). The solvent was removed, and the residue was dissolved in C_6H_6 and chromatographed on a silica gel column. The column was washed successively with C_6H_6, C_6H_6–$CHCl_3$, $CHCl_3$–EtOAc, EtOAc, and EtOAc–EtOH, each mixture 1:1 by volume. The final mixture (1000 ml) on evaporation gave 2 g (35%) of **24g** as a yellow oil which was analytically pure.

N-Acetyl-3-(*p*-methylsulfonylphenyl)-3-phenylpropylamine (24h).—A solution of 5.5 g (0.018 mole) of **24f** and 70 ml of HOAc was stirred and heated on a steam bath. To this solution was added dropwise 40 ml of 30% H_2O_2. Heating was continued for 2 hr, the solution was diluted with ice water, and the resulting oil was extracted into EtOAc. The organic phase was washed (H_2O, 5% $NaHCO_3$), dried (Na_2SO_4), and evaporated. The residual oil was hydrolyzed directly without further purification.

3-Hydroxy-3,3-diphenylpropionitriles (25a–f) (Table IV).—Equimolar quantities of the appropriate benzophenone, alkylnitrile, and $NaNH_2$ were allowed to react in Et_2O, using the conditions described by Runti and Sindellari.[10] The solid products were filtered and worked up as usual.

3-Substituted Phenylcinnamonitriles (26a–c).—A solution of 10 g (0.042 mole) of **25** in 150 ml of 98–100% HCO_2H was refluxed for 30 min and poured into ice water. The mixture was extracted with Et_2O; the extract was washed (H_2O), dried (Na_2SO_4), and concentrated. The residue was distilled, recrystallized, or used directly without further purification.

3,3-Diphenylprop-2-enylamines (27a, b, and d) (Table IV). A.—A solution of **14**, **15**, or 3-hydroxy-3-(*p*-methoxyphenyl)-3-phenylpropylamine (0.04 mole) in 50 ml of HOAc was saturated with dry HCl and refluxed for 3 hr. The solvent was removed *in vacuo*, and the residue was evaporated with dry EtOH.

Compound 27c. B.—A solution of 0.1 mole of **26c** in MeOH saturated with NH_3 was hydrogenated with shaking at 60° and under a pressure of 4.2 kg/cm² of H_2 for 3 hr in the presence of Ra(Ni). The catalyst and solvent were removed and the residue was dissolved in Et_2O. The Et_2O solution was extracted with dilute HCl whereupon solid separated. The addition of more HCl and H_2O dissolved the solid. The aqueous layer was made basic and extracted with Et_2O. The ethereal extract was worked

(6) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected unless otherwise specified. All compounds containing asymmetric centers were isolated and tested as racemates. All materials and extracts were washed, dried, and evaporated.

(7) W. S. Johnson, J. W. Petersen, and W. P. Schneider, *J. Am. Chem. Soc.*, **69**, 74 (1947).

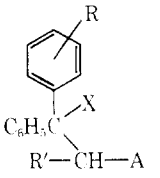
(8) S. Wawzonek and J. Kozikowski, *ibid.*, **76**, 1641 (1954).

(9) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *J. Med. Pharm. Chem.*, **5**, 1243 (1962).

(10) C. Runti and L. Sindellari, *Boll. Chim. Farm.*, **99**, 499 (1960); *Chem. Abstr.*, **55**, 10468*a* (1961).

TABLE IV

DIPHENYLALKYL- AND -ALKENYLNITRILES AND -AMINES



No.	R	R′	X	A	Mp or bp (mm), °C	Recrystn solvent	% yield	Formula	Analyses
25a	*p*-CH_3	H	OH	CN	133–135[a]	C_6H_5Me–PE[b]	15	$C_{16}H_{15}NO$	
b	*m*-CH_3	H	OH	CN	106	C_6H_6–PE	91	$C_{16}H_{15}NO$	C, H, N
c	*o*-CH_3	H	OH	CN	151–152	C_6H_5Me–PE	30	$C_{16}H_{15}NO$	C, H, N
d	*p*-OCH_3	H	OH	CN	127–129[b]	CCl_4	27	$C_{16}H_{15}NO_2$	
e	H	CH_3	OH	CN	125–126[c]	C_6H_5Me–PE	32	$C_{16}H_{15}NO$	
f	H	C_2H_5	OH	CN	164–166[d]	C_6H_5Me	25	$C_{17}H_{17}NO$	
26a	*p*-CH_3	H	—[e]	CN	Oil		95	$C_{16}H_{13}N$	
b	*m*-CH_3	H	—	CN	142–143 (1)		75	$C_{16}H_{13}N$	C, H, N
c	H	CH_3	—	CN	59–61[f]	Hexane	91	$C_{16}H_{13}N$	
27a	*o*-CH_3	H	—	CH_2NH_2	172–174	EtOH–Et_2O	98	$C_{16}H_{17}N \cdot HCl$	C, H, Cl, N
b	*p*-OCH_3	H	—	CH_2NH_2	170–173[g]	EtOH–Et_2O	97	$C_{16}H_{17}NO \cdot HCl$	C, H, Cl, N
c	H	CH_3	—	CH_2NH_2	233–235	MeCOEt	60	$C_{16}H_{17}N \cdot HCl$	C, H, Cl, N
d	H	C_2H_5	—	CH_2NH_2	224–225	EtOH–Et_2O	83	$C_{17}H_{19}N \cdot HCl$	C, H, Cl, N

[a] W. Chodkiewicz, P. Cadiot, and A. Willemart [*Bull. Soc. Chim. France*, 1586 (1958)] report mp 137°. [b] H. Lettré and K. Wick [*Ann.*, **603**, 189 (1957)] report mp 135–137°. [c] Lit.[a] mp 126°. [d] Lit.[a] mp 164°. [e] Double bond. [f] Lit.[a] mp 63°. [g] Lit.[b] mp 171–173°. [h] PE = petroleum ether (bp 40–60°).

up[6] and the concentrate was diluted with ethereal HCl. The resulting salt was filtered and recrystallized.

Diphenylalkylamines (1, 3, 5, 7–9, and 18–20) (Table I). A.—A solution of **24** (0.0235 mole) in 100 ml of dry THF was added dropwise to a stirred suspension of 4.5 g (0.118 mole) of $LiAlH_4$ in 100 ml of Et_2O. The mixture was stirred under reflux for 5 hr and at room temperature overnight. The complex was decomposed by adding successively 4.5 ml of H_2O, 4.5 ml of 10% NaOH, and 13.4 ml of H_2O, and stirring for 45 min. The granular precipitate was filtered and washed with Et_2O. The filtrates[6] were converted to appropriate salts.

Compounds 6, 8, and 13–17. B.—A solution of 0.02 mole of **25b, c,** or **f** or **27a–d** in 250 ml of EtOH containing 0.5 g of PtO_2 was hydrogenated under an initial pressure of 3.2 kg/cm² of H_2. The catalyst and solvent were removed and the residue was converted to an appropriate salt.

Compounds 4 and 5. C.—A solution of **26a** or **b** in MeOH saturated with NH_3 was hydrogenated as described for **27c**. The products were isolated and purified as described there.

N-Ethyl-3,3-diphenylpropylamine Hydrochloride (2).—A solution of 5.1 g (0.02 mole) of **24a** in Et_2O was added dropwise to a stirred suspension of 4.2 g (0.11 mole) of $LiAlH_4$ in 300 ml of Et_2O. The mixture was stirred under reflux overnight. The complex was decomposed and **2** was isolated as described under A above.

3-(*p*-Methylsulfinyl- and -Methylsulfonylphenyl)-3-phenylpropylamines (10 and 11).—Compounds **24g** and **h** were stirred and refluxed with 6 *N* H_2SO_4 for 3–6 hr. The mixtures were diluted with ice water, neutralized, and extracted with C_6H_6. The C_6H_6 extract[6] was treated with the appropriate acid to give the salt reported.

Methyl (*p*-Aminophenyl)phenylacetate Hydrochloride.—A solution of 55.1 g (0.265 mole) of (*p*-aminophenyl)phenylacetic acid[11] in 810 ml of MeOH was stirred, cooled, and saturated with dry HCl. The solution was refluxed for 3 hr, cooled, and poured into several volumes of Et_2O. The layers were separated, and the lower layer yielded crystals which were filtered and recrystallized from MeOH. When dry, the crystals weighed 44.5 g (61%), mp 203–204°. A second recrystallization raised the melting point to 217–218°. *Anal.* ($C_{15}H_{15}NO_2 \cdot HCl$) C, H, Cl, N.

2-(*p*-Aminophenyl)-2-phenylethan-1-ol Hydrochloride.—A solution of 50.7 g (0.21 mole) of the preceding ester (the free base was prepared by dissolving the hydrochloride in H_2O, stirring for 1 hr, filtering, basifying the filtrate with $NaHCO_3$, extracting with Et_2O, and washing and drying the Et_2O) was added dropwise at room temperature to a stirred suspension of 24 g (0.62 mole) of $LiAlH_4$ in 1100 ml of THF. The reaction mixture was stirred at room temperature for 30 min and under reflux for 3 hr. The complex was cooled and decomposed by adding 84 ml of H_2O. The mixture was stirred for 1 hr and filtered, and the residue was washed with THF. The combined filtrates were evaporated to dryness, and the residue was evaporated several times with fresh portions of C_6H_6. The hydrochloride was prepared and recrystallized from EtOH–Et_2O (Darco), mp 204–205°, yield 42 g (80%). *Anal.* ($C_{14}H_{15}NO \cdot HCl$) C, H, Cl, N.

2-(*p*-Acetamidophenyl)-2-phenylethan-1-ol.—2-(*p*-Aminophenyl)-2-phenylethan-1-ol hydrochloride (42 g, 0.17 mole) was dissolved in 310 ml of H_2O and cooled, while 35.4 ml of Ac_2O was added dropwise together with enough NaOAc to keep the mixture at pH 5–6. The mixture was stirred vigorously for 2 hr at 0° and 1 hr at room temperature. The solid was filtered[6] and recrystallized from $CHCl_3$–petroleum ether (bp 40–60°) to give 40.8 g (96%) of white crystals, mp 111–112°. *Anal.* ($C_{16}H_{17}NO_2$) C, H, N.

2-(*p*-Acetamidophenyl)-2-phenylethan-1-ol Tosylate Hemihydrate.—A mixture of 40.8 g (0.16 mole) of 2-(*p*-acetamidophenyl)-2-phenylethan-1-ol, 30.7 (0.175 mole) of *p*-toluenesulfonyl chloride, and 400 ml of dry pyridine was swirled until solution was complete and was left at room temperature overnight. The mixture was heated on a steam bath for 1.5 hr, cooled, poured into 2 l. of ice H_2O, stirred, and extracted with $CHCl_3$. The extracts were washed with 1500 ml of 5% H_3PO_4 and twice with H_2O. The dried $CHCl_3$ extract (Na_2SO_4) was distilled, and the residue was evaporated three times with C_6H_5Me. The residual oil was dissolved in MeOH, and the methanolic solution was treated with Darco, filtered, diluted with H_2O, and cooled to give white crystals. Recrystallization from MeOH–H_2O gave 33 g (56%) of crystals, mp 97–99°. *Anal.* ($C_{23}H_{23}NO_4S \cdot 0.5H_2O$) C, H, S.

1-(*p*-Acetamidophenyl)-1-phenylethene.—A mixture of 27.8 g (0.068 mole) of the preceding tosylate, 5.5 g (0.085 mole) of KCN, and 200 ml of DMF was heated and stirred for 1 hr on a steam bath and then refluxed for 2 hr. The solution was cooled and poured into ice H_2O, and the solid which formed was filtered. The solid was recrystallized from EtOH–H_2O (Darco) to give 9.2 g (57%) of white solid, mp 147–149°. Two recrystallizations from C_6H_5Me raised the melting point to 151–153°; nmr ($CDCl_3$), δ 5.5 (s, 2, C=CH_2), 2.1 (s, 3, $NHCOCH_3$). *Anal.* ($C_{16}H_{15}NO$) C, H, N.

1-(*p*-Aminophenyl)-1-phenylethene Sulfate.—A suspension of 7 g (0.029 mole) of 1-(*p*-acetamidophenyl)-1-phenylethene in 75 ml of 6 *N* H_2SO_4 was stirrred and refluxed overnight. The mixture was cooled and poured into H_2O to give an off-white solid.

(11) R. B. Davis and J. D. Benigni, *J. Chem. Eng. Data*, **8**, 578 (1963).

This was filtered and recrystallized from EtOH, mp 212–214°, yield 5 g (70%). *Anal.* [$(C_{14}H_{13}N)_2 \cdot H_2SO_4$] C, H, N, S.

Ethyl 3-(*p*-Acetamidophenyl)-3-hydroxy-3-phenylpropionate.—A mixture of 22.7 g (0.095 mole) of *p*-acetamidobenzophenone[12] and 31.7 g (0.285 mole) of ethyl bromoacetate was stirred in 200 ml of THF; 18.7 g (0.288 mole) of activated Zn[13] and a crystal of I_2 were added. After heating for 30 min, the mixture changed from orange to green and began to reflux violently. It was cooled until the exothermic reaction subsided and was then refluxed for 4 hr. The hot solution was decanted from unreacted Zn and was diluted with several volumes of H_2O. The resulting red oil was extracted into EtOAc. The organic phase was washed with H_2O, dried (Na_2SO_4), and concentrated to give a pale yellow solid, mp 125–127°. After recrystallization from EtOH–H_2O, the solid weighed 19.6 g (63%), mp 130–132°. *Anal.* ($C_{19}H_{21}NO_4$) C, H, N.

Ethyl 3-(*p*-Acetamidophenyl)-3-phenylprop-2-enoate.—The preceding alcohol (6.5 g, 0.02 mole) was heated to 170° in an oil bath and kept at this temperature for 2 hr. After cooling, the melt was dissolved in MeOH and an oil was precipitated with H_2O. The oil was extracted into EtOAc; the EtOAc extract was dried (Na_2SO_4) and concentrated to a brown gum. The gum solidified after standing for several days. The solid was stirred with Et_2O, filtered, and recrystallized three times from CCl_4 to give 4.8 g (80%) of white solid, mp 141–143°. *Anal.* ($C_{19}H_{19}NO_3 \cdot 0.25H_2O$) C, H, N.

3-(*p*-Acetamidophenyl)-3-phenylprop-2-enoic Acid.—A solution of 3.9 g (0.0126 mole) of ethyl 3-(*p*-acetamidophenyl)-3-phenylprop-2-enoate, 0.78 g (0.014 mole) of KOH, and 30 ml of EtOH was refluxed for 3 hr. It was diluted with H_2O and acidified to give a brown solid. This solid was collected and recrystallized from EtOH–H_2O, mp 197–199°. *Anal.* ($C_{17}H_{15}NO_3$) C, H, N.

3-(*p*-Acetamidophenyl)-3-hydroxy-3-phenylpropionic Acid.—A solution of 37.7 g (0.115 mole) of ethyl 3-(*p*-acetamidophenyl)-3-hydroxy-3-phenylpropionate in 300 ml of MeOH and 75 ml of 40% NaOH was stirred for 1 hr at room temperature, diluted with H_2O, acidified, and cooled. The resulting white solid weighed 24 g (90%). A sample recrystallized twice from THF–petroleum ether melted at 168–169°. *Anal.* ($C_{17}H_{17}NO_4$) C, H, N.

3-(*p*-Acetamidophenyl)cinnamonitrile.—A solution of 24.8 g (0.14 mole) of diethyl cyanomethylphosphonate in 50 ml of dry DMF was added dropwise below 20° to a stirred suspension of 6.3 g (0.14 mole) of a 53.4% mineral oil dispersion of NaH in 125 ml of dry DMF. After the suspension was stirred for 1 hr at room temperature, 31.2 g (0.14 mole) of *p*-acetamidobenzophenone[12] in 100 ml of dry DMF was added dropwise. Stirring was continued at room temperature for 2 hr, and the mixture was poured into several volumes of H_2O. The precipitated gummy solid was extracted into EtOAc. The EtOAc extract was washed (H_2O), dried (Na_2SO_4), and evaporated. The residual semisolid was triturated with Et_2O to give about 20 g of sticky solid. A portion was recrystallized from C_6H_5Me for analysis, mp 182–183° (single spot on tlc). Tlc of the crude product showed two components of the same color and almost identical R_f (*cis–trans* isomers). One of the spots corresponded to the analytically pure product. *Anal.* ($C_{17}H_{14}N_2O$) C, H, N.

Evaporation of the ethereal filtrates gave 39 g of gum.

3-(*p*-Aminophenyl)-3-phenylpropylamine Dihydrochloride Hemihydrate (12).—The preceding crude cinnamonitrile was reduced in the same way as **4** and **5**. The catalyst and solvent were removed and the residue was dissolved in EtOAc. The EtOAc solution was extracted with dilute HCl and H_2O until neutral. The aqueous extracts were cooled and made basic with 40% NaOH. The resulting gum and solid were dissolved in EtOAc. The solution was washed (H_2O) and evaporated. The residue (*ca.* 27 g) was hydrolyzed without further purification. The crude amino amide in 100 ml of HOAc and 50 ml of concentrated HCl was stirred and refluxed for 4 hr. The solvents were removed *in vacuo*, and the residue was evaporated twice with absolute EtOH and twice with C_6H_5Me. The solid residue was recrystallized from MeOH–EtOAc.

2-Amino-1-(*p*-hydroxyphenyl)-1-phenylpropane Hydrochloride (21).—A mixture of 38.8 g (0.21 mole) of 2-amino1-phenylpropan-1-ol hydrochloride, 21 g (0.224 mole) of phenol, and 150 ml of 6 *N* HCl was refluxed for 24 hr. It was then diluted with 240 ml of H_2O and extracted with four 100-ml portions of Et_2O. The aqueous layer was made basic with 40% NaOH (pH 12) and extracted with Et_2O. The basic aqueous layer was adjusted to pH 8.5 with 10% HCl and extracted five times with Et_2O. These ethereal extracts were combined, dried ($MgSO_4$), and concentrated to a pink oil which weighed 8.7 g. The oil was dissolved in Et_2O and treated with dry HCl. The salt was filtered and dried *in vacuo*. The dried salt was suspended in hot Me_2CO and filtered to give a white solid, mp 312–320°. The solid was recrystallized twice from *i*-PrOH–Et_2O to give 1.3 g of white crystals.

2-Phenoxy-1-phenyl-1-(*p*-trifluoromethylphenyl)propan-1-ol.—A solution of 10 ml (0.05 mole) of *p*-bromobenzotrifluoride in 10 ml of Et_2O was added dropwise to 1.2 g (0.05 g-atom) of Mg turnings in 20 ml of Et_2O. The mixture refluxed spontaneously and was stirred under reflux until all of the Mg dissolved. A solution of 11.3 g (0.05 mole) of α-phenoxypropiophenone[14] in 50 ml of Et_2O was added dropwise to the stirred Grignard reagent, and the mixture was stirred under reflux for 3 hr and at room temperature overnight. A 20% solution of NH_4Cl was added dropwise to the stirred reaction mixture. A few milliliters of 10% HCl was added and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined ethereal layers were washed (H_2O), dried (Na_2SO_4), and concentrated to a brown solid. The solid was recrystallized once from MeOH and once from Skellysolve L to give 9 g (48%) of tan solid, mp 132–135°; a sample recrystallized twice from Skellysolve L melted at 137–138°. *Anal.* ($C_{22}H_{19}F_3O_2$) C, H.

1-Phenyl-1-(*p*-trifluoromethylphenyl)propan-2-one.—A mixture of 7.2 g (0.0194 mole) of 2-phenoxy-1-phenyl-1-(*p*-trifluoromethylphenyl)propan-1-ol in 35 ml of concentrated H_2SO_4 was stirred for 2 hr and poured into ice water, and the resulting brown solid was filtered. The filtrate was extracted several times with Et_2O, and the ethereal extract was washed (10% NaOH). A third layer formed. The two layers were removed and the ethereal extract was washed (H_2O) until the washings were neutral. Evaporation of the Et_2O left 2.2 g (41%) of a pale yellow oil; ir (Nujol mull), λ 5.8 μ (C=O). The product was used without further purification.

Oxime of 1-Phenyl-1-(*p*-trifluoromethylphenyl)propan-2-one.—A suspension of 5 g (0.019 mole) of the preceding ketone in 20 ml of EtOH was warmed until it dissolved. To this solution was added a solution of 2.5 g (0.036 mole) of $H_2NOH \cdot HCl$ and 3.5 g (0.036 mole) of KOAc in 20 ml of H_2O. The mixture was refluxed on a steam bath while sufficient EtOH was added through the condenser to form a clear solution. The solution was refluxed for 15 min and concentrated. The residue was extracted with EtOAc, and the EtOAc extract was worked up[6] to give 4 g (80%) of an orange oil. The oil solidified when triturated with petroleum ether. Recrystallization from Skellysolve L gave white crystals, mp 129–130°. *Anal.* ($C_{16}H_{14}F_3NO$) C, H, N.

2-Amino-1-phenyl-1-(*p*-trifluoromethylphenyl)propane Hydrochloride (22).—A mixture of 4 g (0.014 mole) of oxime, 1 g of PtO_2, and 200 ml of HOAc was shaken on a Parr shaker for 3 hr under an initial pressure of 3.2 kg/cm² of H_2. The mixture was left overnight under H_2 without shaking. The catalyst was filtered and washed (HOAc). The combined filtrates were concentrated to a brown gum. The gum was dissolved in Et_2O and the ethereal solution was washed (H_2O, 10% HCl, H_2O). The ethereal solution was dried and evaporated, and the residue was hydrogenated again.

The combined acid phases from the two hydrogenations were neutralized and extracted with Et_2O. The ethereal extracts were washed, dried, and added to ethereal HCl. The solution was concentrated, and the residue was evaporated several times with absolute EtOH and C_6H_5Me. The residue, weighing 2.5 g, was recrystallized from EtOAc–petroleum ether to give 630 mg of white crystals.

3-Amino-2,2-diphenylbutane Hydrochloride (23).—A mixture of 9.6 g (0.04 mole) of the oxime of 2,2-diphenylbutan-3-one,[15] 1.5 g of PtO_2, and 200 ml of HOAc was hydrogenated as described in the preparation of **22**. After standing overnight, the spent catalyst was removed and replaced with 0.5 g of fresh PtO_2. After reduction for an additional 6 hr, the catalyst and solvent were

(12) O. Döbner, *Ann.*, **210**, 246 (1881).

(13) Prepared as described by L. F. Fieser and W. S. Johnson, *J. Am. Chem. Soc.*, **62**, 575 (1940).

(14) C. K. Bradsher and R. Rosher, *ibid.*, **61**, 1524 (1939).

(15) K. Shishido, H. Nozaki, and O. Kurihara, *ibid.*, **72**, 2270 (1950).

removed. The solid residue was dissolved in H_2O; the aqueous solution was made basic and extracted with Et_2O. The ethereal extract was worked up and diluted with ethereal HCl. The precipitated salt was filtered and recrystallized.

Biological Testing.—Adrenal inhibition was studied in the rat cold stress test, the rat antialdosterone assay, and in an isolated adrenal preparation.[1,16]

As a result of earlier studies,[1] we concluded that the most interesting type of adrenal corticosteroid inhibitors would be that which specifically inhibited aldosterone biosynthesis. Such compounds would have no effect on peripheral plasma corticosterone levels (cold stress assay), would increase Na^+ excretion (antialdosterone assay), and would produce an appropriate steroid shift, that is, a decrease in aldosterone levels with no change in corticosterone (B) and deoxycorticosterone (DOC) levels. With the establishment of these criteria, the antialdosterone assay became a primary screen, while the cold stress and *in vitro* assays were used for further evaluation. The results of these studies are summarized in Table II; the quantities of **10** and **22** obtained were too small to permit adequate testing and therefore, these compounds are not included in Table II.

Reproducible estimates of natriuretic activity in the antialdosterone assay, based on the relative potencies of the compounds studied, could not be obtained because of the variability inherent in this test method. However, those compounds which caused a statistically significant increase in urinary Na^+ levels were arbitrarily ranked as follows: weak (±), urinary Na^+ between 1–2 mg; moderate (+), 2–4 mg; and strong (++), >4 mg. Compounds were given orally to sodium-depleted rats at doses of 50 mg/kg or less because our potent standard inhibitors of 11-hydroxylation were marginally active at this dose. In the *in vitro* assay, statistical significance ($P < 0.05$) was achieved when the levels of B and aldosterone differed from the controls by at least 30%, and when DOC increased by more than 300%.

Discussion

The diphenethylamines investigated earlier appeared to exert an inhibitory effect predominantly on 11-hydroxylation because of their potent activity in the rat cold stress test, which is very sensitive to agents of this type. This type of inhibition was also indicated in *in vitro* studies when DOC increased at the same time that corticosterone and aldosterone decreased (*e.g.*, 2,2-diphenethylamine, **19**, Table II). In the present study we found that the effect on 11-β-hydroxylase decreased as the length of the side chain was increased by one or two methylene groups, for none of the compounds were active at doses from 10 to 50 mg/kg when studied in the cold stress assay. On the other hand, **29**, a potent inhibitor of 11-hydroxylation, was very active at 5 mg/kg. In addition, *in vitro*, only **1** and **9** were like **29** in producing a definite accumulation of DOC.

Most of the compounds in this study were active in the rat antialdosterone assay. The active compounds were less potent than **28**, but were more potent than **29** (no natriuresis was observed with **29** at 50 mg/kg, the highest dose used in this study). A homolog of **28**, **16**, markedly inhibited both aldosterone and corticosterone synthesis *in vitro* without elevating DOC. Thus, **16** exhibited a profile of activity *in vitro* similar to amphenone, which suggested that inhibition occurred early in corticogenesis.[17] Another homolog of **28**, **23**, in which the benzhydryl H of **28** was replaced with CH_3, was inactive in the antialdosterone screen.

In summary, except for **1** and **9**, the compounds studied had a minimal effect on 11-β-hydroxylation together with a moderate but specific antialdosterone effect (**2**, **5**, **7**, **8**, and **11**). Compound **16** appeared to cause a generalized inhibition similar to that produced by amphenone,[17] suggesting steroid inhibition early in the biosynthetic pathway. As we reported in our previous study,[1] small structural changes markedly affected the character of adrenal inhibition. For example, when the length of the side chain was increased from Et to Pr to Bu (**29**, **1**, and **18**), activity in the antialdosterone assay increased concurrently. However, the most significant changes occurred when the side chain had a methyl substituent on the carbon bearing the amino group (compare **1** with **28** and **29** with **28**). Compound **28** had no effect on the *in vitro* levels of B or DOC but depressed aldosterone production significantly. The effects of increasing the distance between the amino group and the methyl branch (compare **28** with **16**) and of replacing the benzhydryl proton of **28** with CH_3 (compare **28** with **23**) have been noted above.

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(16) H. L. Saunders, B. Steeiw, V. Kostos, and J. Tomaszewski, *Steroids*, **7**, 513 (1966).

(17) W. A. Zuccarello and G. Frismuth, unpublished observations.