residue was dissolved in about 10 ml. of dioxane. A hot, freshly filtered solution of 4 g. (0.02 mole) of cupric acetate in 37 ml. of water was added. The resulting mixture was heated several min. and shaken intermittently while cooling to room temperature. The precipitated copper salt was collected and air dried, weight 7 g. (83%). The copper chelate was not decomposed by shaking with 10% sulfuric acid and only very slightly with 25% sulfuric acid. Shaking with 50% ice cold sulfuric acid and ethyl acetate decomposed most of the copper compound. The organic layer was separated, washed with water and dilute sodium bicarbonate, dried over magnesium sulfate, and filtered. After removing the solvent, the residue was distilled. The distillate collected 163–172° (0.2 mm.) was cloudy and redistillation at 165–170° (0.2 mm.) did not improve the quality of the product.

Anal. Calcd. for $C_{19}H_{17}O_3Cu_{1/2}$: C, 70.15; H, 5.28; Cu, 9.78. Found: C, 70.60; H, 5.49; Cu, 9.48.

Difficulties were also encountered when the cyclization was attempted with metallic sodium or potassium *t*-butoxide in toluene according to established procedures.[21]

5-(2-Diethylaminoethyl)-2,2-diphenylcyclopentanone Hydrochloride.—The cyclization of methyl 2,2-diphenyladipate with sodium hydride in oil was effected as described above. The reaction mixture was cooled in ice while a solution of β-diethylaminoethyl chloride in xylene, prepared according to Meltzer and Lewis,[22] was added. After being stirred at room temperature for 2 hr., the mixture was heated on a boiling water bath for 2 hr. The mixture was cooled, treated with a few ml. of ethanol, and a large volume of water followed by a few drops of acetic acid. The organic layer was separated, and the organic solution was extracted twice with 10% hydrochloric acid. The acid solution was made strongly basic and extracted with ether. After removal of the solvent, the residue was refluxed with 30 ml. of 30% sulfuric acid and 20 ml. of acetic acid for 6 hr. The cooled mixture was poured into ice cold sodium hydroxide and the strongly basic solution was extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and saturated with hydrogen chloride at 0°. The oil which separated crystallized upon standing in the refrigerator overnight. The precipitate was separated and recrystallized three times by dissolving in a minimum amount of absolute ethanol, cooling, and adding anhydrous ether. The pure product (1 g.) melted at 164.5–165.5.

Anal. Calcd. for $C_{25}H_{30}ClNO$: C, 74.27; H, 8.13; Cl, 9.53. Found: C, 74.10; H, 8.43; Cl, 9.65.

5-(2-Dimethylaminoethyl)-2,2-diphenylcyclopentanone Hydrochloride.—This compound was prepared as described above for the diethylamino homolog. The white solid melted at 206.5–208.5° dec.

Anal. Calcd. for $C_{21}H_{26}ClNO$: C, 73.25; H, 7.62; Cl, 10.30. Found: C, 73.00; H, 7.59; Cl, 10.55.

5-Dimethylaminomethyl-2,2-diphenylcyclopentanone Hydrochloride.—To 2,2-Diphenylcyclopentanone (1 g.), melted on the steam bath,[23] were added 0.25 g. of paraformaldehyde, 0.25 g. of dimethylamine hydrochloride, and 5 drops of 1:1 hydrochloric acid. The mixture was heated on the steam bath with occasional shaking until complete solidification had occurred. The solid was washed with ether, dissolved in water, filtered, and made basic. The mixture was extracted with isopropyl ether. The ether solution was dried over magnesium sulfate, filtered, and saturated with hydrogen chloride at 0°. The precipitate which formed was separated and after air drying for 12 hr. weighed 0.4 g. It melted at 173°.

Anal. Calcd. for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.33; Cl, 10.75; N, 4.25. Found: C, 72.80; H, 7.50; Cl, 10.85; N, 4.21.

5-Methyl-2,2-diphenylcyclopentanone.—Prepared by cyclization, alkylation, and hydrolysis as described above. The product, b.p. 143° (2 mm.), m.p. 52–54°, was easily recrystallized from methanol. This procedure is better than alkylation of the cyclopentanone.[24] Attempted alkylation with β-dimethylaminoethyl chloride was unsuccessful.

(21) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956).

(22) R. I. Meltzer and A. D. Lewis, *J. Org. Chem.*, **22**, 615 (1957).

(23) J. M. Sprague and E. M. Schultz, Brit. Patent 733,406; *Chem. Abstr.*, **50**, 7867*e* (1956).

(24) S. Nelson, Ph.D. Thesis, Lehigh University, 1951.

Anorexigenic Agents: Aromatic Substituted 1-Phenyl-2-propylamines

GERALD F. HOLLAND,[1] CARL J. BUCK, AND ALBERT WEISSMAN

Medical Research Laboratories, Chas. Pfizer and Co., Inc., Groton, Connecticut

Received March 30, 1963

A number of aromatic substituted 1-phenyl-2-propylamines (Table I) have been prepared by three general routes. The anorectic activities of these compounds are listed in Table IV. Although none are as active as (+)-amphetamine, a number are more potent than phenmetrazine or diethylpropion. The most active compounds are 1-(4-dimethylaminophenyl)-2-propylamine and 1-(3-trifluoromethylphenyl)-2-propylamine. Unexpectedly, 1-(3-trifluoromethylphenyl)-2-propylamine is more potent than 1-(4-trifluoromethylphenyl)-2-propylamine. Both the 3- and 4-trifluoromethylamphetamines depress food intake in the rat and dog without observable central nervous sytem stimulation.

1-Phenyl-2-propylamine (amphetamine)[2] was studied by Alles in 1927.[3,4] Since the initial investigations, dealing with the vasopressor effects of amphetamine in man[5] and the dog,[6] a vast literature on this important sympathomimetic amine has appeared.[3] The majority of these reports are concerned with either more detailed pharmacological studies or clinical applications of this drug.[7]

Although amphetamine has found a number of clinical applications it is most widely used as an adjunct in the treatment of obesity.[8] Concomitant with the anorectic effect are some undesirable side effects, which are related to central nervous system stimulation, such as insomnia, nervousness, and hyperactivity. Some consider that this central sympathomimetic stimulation is the general mechanism by which amphetamine and its congeners depress appetite.[9–11] If this is so then

(1) Presented before the Division of Medicinal Chemistry, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 3, 1961, Abstracts, p. 5-O.

(2) In this report 1-phenyl-2-propylamine (amphetamine) and its derivatives are related to (±)-1-phenyl-2-propylamine, unless stated otherwise.

(3) C. D. Leake, "The Amphetamines," Charles C Thomas, Springfield, Ill., 1958, p. 4.

(4) G. A. Alles, *J. Am. Chem. Soc.*, **54**, 271 (1932); amphetamine was first prepared by L. Edeleano, *Ber.*, **20**, 616 (1887).

(5) G. Piness, H. Miller, and G. A. Alles, *J. Am. Med. Assoc.*, **94**, 790 (1930).

(6) G. A. Alles, *J. Pharmacol. Exptl. Therap.*, **47**, 339 (1933).

(7) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Company, New York, N. Y., 1958, p. 52.

(8) S. C. Harris, *Ann. N. Y. Acad. Sci.*, **63**, 121 (1955).

(9) W. Modell, *J. Am. Med. Assoc.*, **173**, 1131 (1960).

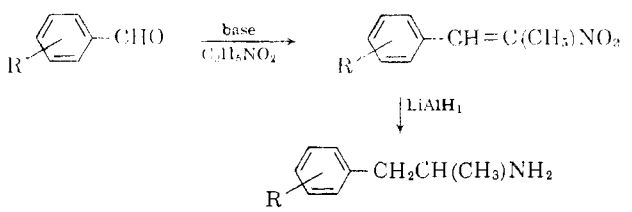
(10) W. Modell, "Drugs of Choice," The C. V. Mosby Company, St. Louis, Mo., 1960, Chapter 21.

the divorcement of the undesired stimulation from the therapeutically useful anorectic effect should not be possible.[9,10] Fineberg partially objects to this stimulation–anorexia hypothesis because it does not explain the anorexia observed in some patients in the complete absence of central sympathomimetic stimulation.[12] Others have considered that since certain hypothalamic centers are important in the regulation of food intake,[13,14] these centers might be the site of action of amphetamine. Brobeck has shown that amphetamine excites the medial region of the hypothalamus (satiety center), and he suggests stimulation of the satiety center as a possible mechanism.[15] Stowe and Miller, however, favor the view that amphetamine acts at the lateral nuclei of the hypothalamus (feeding center), and they believe that amphetamine inhibits this feeding center.[16] Only further studies will decide whether any of these mechanisms, either individually or collectively, are sufficient to explain the anorectic properties of amphetamine.

During the course of a search for new anorexigenic agents that would not only be of clinical interest, but would also be useful in mechanism studies, we have synthesized and screened a number of aromatic substituted 1-phenyl-2-propylamines.

Synthesis.—Three methods were employed for the preparation of the aromatic substituted 1-phenyl-2-propylamines. The first (method A) involved the condensation of a substituted benzaldehyde with nitroethane followed by lithium aluminum hydride reduction of the intermediate 1-aryl-2-nitropropene. This well known sequence of reactions is convenient for the preparation of those amphetamines in which the required aldehydes are either available or readily accessible. The aldehydes which were not commercially available were prepared by the following routes.

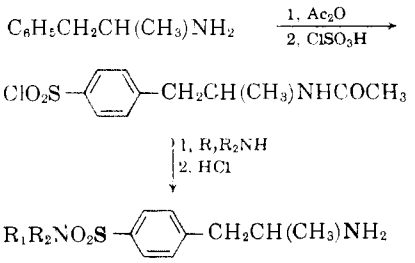
METHOD A



R	X	Method
CF_3(2, 3, and 4)	Cl	Grignard (Mg, DMF)
SCH_3 (2 and 3)	COOH	McFadyen–Stevens
$SCH_2C_6H_5$ (2 and 4)	COOH	McFadyen-Stevens
4-SCH_3	CH_2Cl	Sommelet
3-CH_3-4-SCH_3	CH_2Cl	Sommelet
4-SO_2CH_3	CH_3	CrO_3–Ac_2O

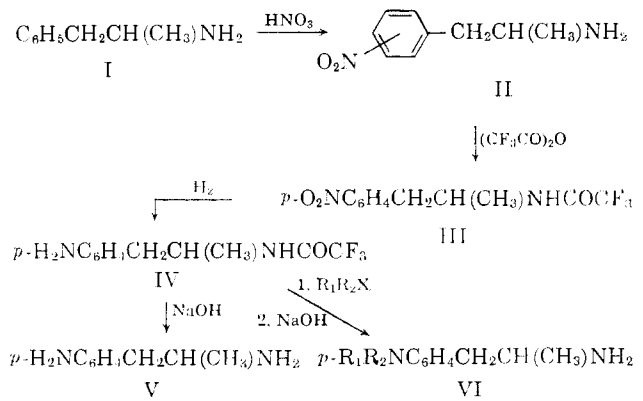
Chlorosulfonation of N-acetyl-1-phenyl-2-propylamine followed by amination and deacetylation was found to be a general route for the synthesis of 1-(4-sulfamylphenyl)-2-propylamines (method B). By this procedure both 1-(4-sulfamylphenyl)-2-propylamine and 1-(4-N,N-dimethylsulfamylphenyl)-2-propylamine were prepared. This same sequence of reactions could also, of course, be used with (+)-1-phenyl-2-propylamine to give the optically active 1-(4-sulfamylphenyl)-2-propylamines.

METHOD B



A general route to the (+)-1-(4-aminophenyl)-2-propylamines was developed (Method C). Nitration of (+)-amphetamine (I) produces position isomers.[17] Trifluoroacetylation of this mixture gives pure (+)-N-trifluoroacetyl-1-(4-nitrophenyl)-2-propylamine (III). Catalytic reduction of III yields (−)-N-trifluoroacetyl-1-(4-aminophenyl)-2-propylamine (IV). (+)-1-(4-Aminophenyl)-2-propylamine (V) was prepared by detrifluoroacetylation of IV with dilute base. The valuable intermediate IV can be alkylated or acylated, etc., to compounds represented by structure VI. By this latter procedure IV and methanesulfonylchloride form (+)-N-trifluoroacetyl-1-(4-methylsulfamidophenyl)-2-propylamine. Detrifluoroacetylation gives (+)-1-(4-methylsulfamidophenyl)-2-propylamine (VI, R_1 = H,R_2 = CH_3SO_2). Also the reaction between IV and benzoyl chloride leads to (+)-N-trifluoroacetyl-1-(4-benzamidophenyl)-2-propylamine. Removal of the trifluoroacetyl group gives (+)-1-(4-benzamidophenyl)-2-propylamine (VI, R_1 = H, R_2 = C_6H_5CO). The 1-phenyl-2-propylamine hydrochlorides are described in Table I. The intermediates of method A, 1-phenyl-2-nitropropenes and 1-phenyl-2-propylamines, are listed in Tables II and III, respectively.

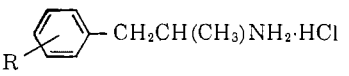
METHOD C



(11) J. F. Fazekas, W. R. Ehrmantraut, K. D. Campbell, and M. C. Negron, *J. Am. Med. Assoc.*, **170**, 1018 (1959).
(12) S. K. Fineberg, *ibid.*, **175**, 680 (1961).
(13) J. R. Brobeck, *Ann. N. Y. Acad. Sci.*, **63**, 44 (1955).
(14) B. Andersson and S. Larsson, *Pharmacol. Rev.*, **13**, 1 (1961).
(15) J. R. Brobeck, S. Larsson, and E. Reyes, *J. Physiol.*, **132**, 358 (1956).
(16) F. R. Stowe, Jr., and A. T. Miller, Jr., *Experientia*, **13**, 114 (1957).
(17) T. M. Patrick, Jr., E. T. McBee, and H. B. Hass, *J. Am. Chem. Soc.*, **68**, 1153 (1946).

TABLE I

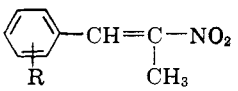
AROMATIC SUBSTITUTED 1-PHENYL-2-PROPYLAMINE HYDROCHLORIDES



R	Method	M.p., °C.	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
4-CF_3	A	200–201	$C_{10}H_{12}F_3N \cdot HCl$	50.11	5.47	5.85	50.40	5.47	5.97
3-CF_3	A	163–164	$C_{10}H_{12}F_3N \cdot HCl$	50.11	5.47	5.85	50.06	5.56	5.93
2-CF_3	A	207–208	$C_{10}H_{12}F_3N \cdot HCl$	50.11	5.47	5.85	49.82	5.60	5.47
4-SCH_3	A	190–191	$C_{10}H_{15}NS \cdot HCl$	55.15	7.41	6.43	55.22	7.54	6.48
3-SCH_3	A	136–137	$C_{10}H_{15}NS \cdot HCl$	55.15	7.41	6.43	55.07	7.53	6.35
2-SCH_3	A	146–147	$C_{10}H_{15}NS \cdot HCl$	55.15	7.41	6.43	54.96	7.45	6.53
3-CH_3-4-SCH_3	A	202–203	$C_{11}H_{17}NS \cdot HCl$	57.00	7.83	6.04	57.31	7.85	5.98
4-SO_2CH_3	A	260–261	$C_{10}H_{15}NO_2S \cdot HCl$	48.09	6.46	5.60	47.41	6.50	5.59
2-$SCH_2C_6H_5$	A	157–158	$C_{16}H_{19}NS \cdot HCl$	65.39	6.86	4.77	64.95	6.79	4.51
4-$SCH_2C_6H_5$	A	173–174	$C_{16}H_{19}NS \cdot HCl$	65.39	6.86	4.77	65.80	6.93	4.97
4-$CH(CH_3)_2$	A	200–202	$C_{12}H_{19}N \cdot HCl$	67.42	9.43	6.55	67.08	9.48	6.45
4-$N(CH_3)_2$	A	220–221	$C_{11}H_{18}N_2 \cdot 2HCl$	52.59	8.03	11.15	52.88	8.12	11.44
4-SO_2NH_2	B	227–228	$C_9H_{14}N_2O_2S \cdot HCl$	43.11	6.03	11.17	42.87	6.11	11.02
4-$SO_2N(CH_3)_2$	B	215–216	$C_{11}H_{18}N_2O_2S \cdot HCl$	47.39	6.87	10.05	47.24	7.13	9.64
(+)-4-NH_2	C	296	$C_9H_{14}N_2 \cdot 2HCl$	48.63	7.26	12.61	48.64	7.10	12.55
(+)-4-$NHSO_2CH_3$	C	260–261	$C_{10}H_{16}N_2O_2S \cdot HCl$	45.36	6.47	10.58	44.98	6.45	10.84
(+)-4-$NHCOC_6H_5$	C	294–295	$C_{16}H_{18}N_2O \cdot HCl$	66.08	6.59	9.64	66.02	6.87	9.29

TABLE II

AROMATIC SUBSTITUTED 1-PHENYL-2-NITROPROPENES

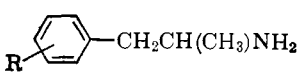


R	B.p. range, °C. (mm.) or M.p., °C.	n_D range (°C.)	Yield, %	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
4-CF_3[a]	114–120 (0.5) m.p. 37–39	1.5029–1.5100 (33)	63	$C_{10}H_8F_3NO_2$	51.95	3.49	6.06	52.45	3.49	5.79
3-CF_3[a]	104–118 (0.6–1.0)	1.5043–1.5099 (24.5)	63	$C_{10}H_8F_3NO_2$	51.95	3.49	6.06	52.77	3.96	5.72
2-CF_3[a]	92 (0.07)	1.5010–1.5060 (26)	75	$C_{10}H_8F_3NO_2$	51.95	3.49	6.06	52.02	4.01	5.83
3-SCH_3[b]	98–126 (0.1–0.7)	1.6021–1.6113 (25)	40							
2-SCH_3	110 (0.07)	1.6285 (25.5)	72							
4-$CH(CH_3)_2$[c]	126–134 (1)	1.5801 (25.5)	36							
4-SCH_3[d]	m.p. 76–77		34	$C_{10}H_{11}NO_2S$	57.39	5.30	6.69	57.12	5.50	6.39
4-$SCH_2C_6H_5$[e]	m.p. 74–75		35	$C_{16}H_{15}NO_2S$	67.34	5.30		66.87	5.22	
2-$SCH_2C_6H_5$	m.p. 70–71		59	$C_{16}H_{15}NO_2S$	67.34	5.30	4.91	67.62	5.49	4.70
4-SO_2CH_3[f]	m.p. 131–132		70	$C_{10}H_{11}NO_4S$	49.78	4.60	5.81	49.63	4.80	5.80

[a] The 2-, 3-, and 4-trifluoromethylbenzaldehydes were kindly supplied to us by Dr. Charles E. Maxwell of these Laboratories. [b] The 3-methylthiobenzaldehyde was prepared according to J. W. Baker, G. F. C. Barrett, and W. T. Tweed, *J. Chem. Soc.*, 2831 (1952). [c] The 4-isopropylbenzaldehyde was purchased from Eastman Kodak Co., Rochester 3, N. Y. [d] The 4-methylthiobenzaldehyde was prepared according to N. P. Buu-Hoi and N. Hoan, ref. 27. [e] The 4-benzylthiobenzaldehyde was prepared according to D. F. Elliott and C. Harington, *J. Chem. Soc.*, 1374 (1949). [f] The 4-methylsulfonylbenzaldehyde was prepared according to T. Momose, Japanese Patent 3073 (1951); *Chem. Abstr.*, **47**, 5439 (1953).

TABLE III

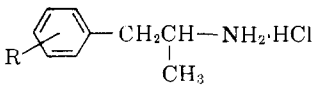
AROMATIC SUBSTITUTED 1-PHENYL-2-PROPYLAMINES



R	B.p. range, °C. (mm.)	n_D range (°C.)	Yield, %	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
3-CF_3	60–74 (0.4–0.7)	1.4564–1.4584 (28.5)	66	$C_{10}H_{12}F_3N$	59.10	5.95	6.89	59.02	6.26	6.04
2-CF_3	59 (0.3–0.4)	1.4650–1.4665 (24.5)	65	$C_{10}H_{12}F_3N$	59.10	5.95	6.89	59.41	6.34	6.60
4-SCH_3	108–118 (0.6)	1.5710–1.5761 (27)	78	$C_{10}H_{15}NS$	66.24	8.34	7.73	65.56	8.49	7.11
4-$SCH_2C_6H_5$[a]	160 (0.7)	1.6051–1.6068 (25)	46	$C_{16}H_{19}NS$	74.66	7.44		74.29	7.65	
2-$SCH_2C_6H_5$[a]	148 (0.5)	1.5951–1.6034 (24)	53	$C_{16}H_{19}NS$	74.66	7.44		74.40	7.70	
4-$CH(CH_3)_2$	78–84 (0.7–0.8)	1.5071–1.5082 (24.5)	70							
4-$N(CH_3)_2$[a,b]	104–108 (0.2–0.3)	1.5500–1.5512 (23)	79							

[a] In a number of cases where the compound to be reduced was insoluble in ether, tetrahydrofuran was used. After decomposing the excess lithium aluminium hydride with water, the tetrahydrofuran was removed by distillation and the aqueous solution then extracted with ethyl acetate. [b] The 1-(4-dimethylaminophenyl)-2-nitropropene was prepared according to D. E. Worrall and L. Cohen, *J. Am. Chem. Soc.*, **66**, 842 (1944).

TABLE IV
ANORECTIC ACTIVITY OF 1-PHENYL-2-PROPYLAMINE HYDROCHLORIDES



R	Rat[a]	Dog[b]
(+)-amp.	+++	++++
4-CF_3	++	+
3-CF_3	+++	++
2-CF_3	+	+
4-SCH_3	++	++
3-SCH_3	+	+
2-SCH_3	−	+
3-CH_3-4-SCH_3	+	+
2-$SCH_2C_6H_5$	+	+
4-$SCH_2C_6H_5$	±	+
4-SO_2CH_3	+	−
4-$N(CH_3)_2$	+++	++ to +++
4-$CH(CH_3)_2$	+	++
4-SO_2NH_2	±	
4-$SO_2N(CH_3)_2$	+	+
(+)-4-NH_2	+	++
(+)-4-$NHCOC_6H_5$	±	+
(+)-4-$NHSO_2CH_3$	±	±
Phenmetrazine	+	+
Diethylpropion	+	++
Benzphetamine		±

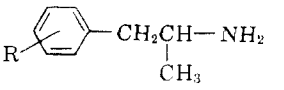
[a] Activity indicated as follows: +++ (5 mg./kg.), ++ (5–10 mg./kg.), + (10–30 mg./kg.), ± (inactive at 30 mg./kg.). [b] Activity indicated as follows: ++++ (0.2 mg./kg.), +++ (0.2–1.0 mg./kg.), ++ (1.0–2.0 mg./kg.), + (2–5 mg./kg.), ± (inactive at 5 mg./kg.).

Results and Discussion

The report by Marsh and Herring[18] represents one of the few systematic studies concerning the appetite depressing effects of aromatic substituted amphetamines. They found that in the dog amphetamine is more active than 1-(4-methylphenyl)-2-propylamine which in turn is more active than 1-(3-methylphenyl)-2-propylamine. The 2-methyl, 3,4-dimethyl, and 2,5-dimethyl derivatives are inactive.

The 1-phenyl-2-propylamine hydrochlorides described in Table I were screened for their anorectic activity in both the rat and dog, after oral administration. (+)-Amphetamine was used as the standard and in our assay it significantly depresses food intake in the rat at approximately 5 mg./kg. and in the dog at about 0.2 mg./kg. It is more potent than any of the compounds listed in Table I. The anorectic activities are listed in Table IV. A number of compounds (Table IV: R = 4-$N(CH_3)_2$, 3-CF_3, 4-SCH_3, (+)-4-NH_2, and 4-CF_3) are either more active or approximately as active as phenmetrazine, diethylpropion, or benzphetamine. 1-(4-Dimethylaminophenyl)-2-propylamine and 1-(3-trifluoromethylphenyl)-2-propylamine are the most active compounds.

The trifluoromethylamphetamines were studied further. The comparative potencies of (+)-amphetamine and these compounds were determined using a standard bioassay procedure.[19] As reported earlier,[20] 1-(4-trifluoromethylphenyl)-2-propylamine is approximately 0.08 as potent as (+)-amphetamine in the dog and about 0.5 as potent as (+)-amphetamine in the rat. 1-(3-Trifluoromethylphenyl)-2-propylamine is approximately 0.2 as potent as (+)-amphetamine in the dog and equipotent to (+)-amphetamine in the rat. In both the rat and dog, the 3-trifluoromethylamphetamine is about 2–3 times more potent than the 4-trifluoromethylamphetamine. The greater activity of the 3-trifluoromethylamphetamine in comparison to the 4-trifluoromethylamphetamine was unexpected in the light of the results of Marsh and Herring.[18]



Rat (+)-Amphetamine = 3-CF_3 > 4-CF_3 > 2-CF_3
Dog (+)-Amphetamine > 3-CF_3 > 4-CF_3 and 2-CF_3
vs. D. F. Marsh and D. A. Herring[18]
Dog Amphetamine > 4-CH_3 > 3-CH_3 > 2-CH_3

It is of interest that 1-(4-trifluoromethylphenyl)-2-propylamine[20,21] and 1-(3-trifluoromethylphenyl)-2-propylamine in both the rat and dog show significant depression of food intake without observable CNS stimulation. Also, in the rat both compounds depress food intake without behavioral stimulation, as measured by operant conditioning techniques.[22,23] These anorectic activities, in both the rat and dog, without central sympathomimetic stimulation would seem to cast doubt, at least in these species, on the hypothesis that CNS stimulation and anorexia are indivisible. Whether the mechanism of anorectic action for both the 3 and 4-trifluoromethylamphetamine is by a specific effect upon some area of the hypothalamus is not known. Further studies will be required to elucidate the mode of this anorectic effect.

Experimental

Chemical.[24] **1-(2-Trifluoromethylphenyl)-2-nitropropene.**—A solution of 10 g. (0.058 mole) of 2-trifluoromethylbenzaldehyde, 4.12 ml. (0.058 mole) of nitroethane, and 24 drops of *n*-butylamine in 30 ml. of absolute ethanol was heated to reflux for 18 hr. The solution was concentrated *in vacuo* to a yellow liquid which was distilled. The following fractions were collected: (1) 3.3 g., b.p. 92° (0.07 mm.), $n^{26}D$ 1.5010, and (2) 6.7 g., b.p. 92° (0.07 mm.), $n^{26}D$ 1.5060. The yield was 75%.

Anal. Calcd. for $C_{10}H_8F_3NO_2$: C, 51.95; H, 3.49; N, 6.06. Found: C, 52.02; H, 4.01; N, 5.83.

All of the 1-phenyl-2-nitropropenes were prepared by essentially the same method.

1-(2-Trifluoromethylphenyl)-2-propylamine Hydrochloride.—To a suspension of 14 g. (0.36 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether was added an ethereal solution containing 13.7 g. (0.06 mole) of 1-(2-trifluoromethylphenyl)-2-nitropropene. The mixture was refluxed for 2 hr., cooled, and the excess lithium aluminum hydride decomposed by the careful addition of water. The heavy suspension was extracted with three 200-ml. portions of ethyl acetate. The dried solvent was removed by concentration and the free base distilled. The follow-

(18) D. F. Marsh and D. A. Herring, *J. Pharmacol. Exptl. Therap.*, **100**, 298 (1950).

(19) D. J. Finney, "Statistical Method in Biological Assay," Hafner, New York, N. Y., 1952, Chapters 4 and 5.

(20) A. Weissman and J. A. Schneider, *Pharmacologist*, **2**, 71 (1960).

(21) More recently it was reported that 1-(4-trifluoromethylphenyl)-2-propylamine is approximately 0.14 as potent as (+)-amphetamine in the dog and 0.36 as potent as (+)-amphetamine in the rat: C. A. Leonard, T. Fujita, D. H. Tedeschi, and E. J. Fellows, *ibid.*, **3**, 79 (1961). A. Kandel, R. B. Miller, C. A. Leonard, and E. J. Fellows, *ibid.*, **3**, 78 (1961), have also shown that this compound causes anorexia without stimulation.

(22) A. Weissman, *Federation Proc.*, **18**, 168 (1959).

(23) A. Weissman, *J. Exptl. Anal. Behav.*, **2**, 271 (1959).

(24) All melting points are corrected.

ing fractions were collected: (1) 4.3 g., b.p. 59° (0.3 mm.), $n^{24.5}D$ 1.4650, and (2) 3.5 g., b.p. 59° (0.4 mm.), $n^{24.5}D$ 1.4665. The yield was 65%.

Anal. Calcd. for $C_{10}H_{12}F_3N$: C, 59.10; H, 5.95; N, 6.89. Found: C, 59.41; H, 6.34; N, 6.60.

The hydrochloride was prepared by bubbling dry hydrogen chloride into an ethereal solution of the base. The analytical sample was prepared by recrystallization from ethanol–ether.

All of the 1-phenyl-2-propylamine hydrochlorides were prepared by this procedure, unless otherwise stated.

1-(4-Trifluoromethylphenyl)-2-propylamine.—The free base was not purified by distillation; instead the hydrochloride was prepared from the crude base. A 68% over-all yield of the hydrochloride from 1-(4-trifluoromethylphenyl)-2-nitropropene was obtained.

1-(3-Methylthiophenyl)-2-propylamine.—The hydrochloride was prepared from the crude base. A 36% over-all yield of hydrochloride was obtained from the 1-(3-methylthiophenyl)-2-nitropropene.

1-(4-Toluenesulfonyl)-2-(2-methylthiobenzoyl)hydrazide.—To a solution of 14.5 g. (0.08 mole) of 2-methylthiobenzoic acid hydrazide[25] in 175 ml. of pyridine at 0° was added 17 g. (0.089 mole) of 4-toluenesulfonyl chloride. After the addition was complete the mixture was warmed on the steam bath for 10 min. and then poured into 600 ml. of water containing 300 ml. of concentrated hydrochloric acid. The solution was cooled and 23.8 g. (88%) of product was collected by suction filtration. An analytical sample was prepared by recrystallization from ethanol–water, m.p. 132–133°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3S_2$: C, 53.57; H, 4.80; N, 8.33. Found: C, 53.60; H, 4.76; N, 9.06.

2-Methylthiobenzaldehyde.—A mixture of 91.5 g. (0.272 mole) of 1-(4-toluenesulfonyl)-2-(2-methylthiobenzoyl)hydrazide and 33 g. (0.31 mole) of sodium carbonate in 620 ml. of ethylene glycol containing a small amount of powdered soft glass[26] was heated at 160° for 4 min. The mixture was poured into hot water which was then cooled and the oil that separated was extracted into ether and distilled. There was obtained 20.2 g. (50%) of product, b.p. 92° (0.09 mm.), $n^{24}D$ 1.6270.

Anal. Calcd. for C_8H_8OS: C, 63.15; H, 5.30. Found: C, 62.98; H, 5.29.

1-(2-Methylthiophenyl)-2-propylamine.—The hydrochloride was prepared from the crude base. This hydrochloride was synthesized in 70% over-all yield from 1-(2-methylthiophenyl)-2-nitropropene.

1-(3-Methyl-4-methylthiophenyl)-2-propylamine.—The hydrochloride (Table I) was prepared in 62% yield from 1-(3-methyl-4-methylthiophenyl)-2-nitropropene. The latter was formed in 28% yield from 3-methyl-4-methylthiobenzaldehyde.[27]

2-Benzylthiobenzaldehyde.—The McFadyen–Stevens reaction was employed for the preparation of this aldehyde. 2-Benzylthiobenzoic acid hydrazide, m.p. 165–166°, was synthesized in 86% yield from ethyl-2-benzylthiobenzoate.[28]

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.49; H, 5.52; N, 10.55.

The reaction between this hydrazide and 4-toluenesulfonyl chloride gave a 78% yield of 1-(4-toluenesulfonyl)-2-(2-benzylthiobenzoyl) hydrazide, m.p. 144–145°.

Anal. Calcd. for $C_{21}H_{20}N_2O_3S_2$: C, 61.14; H, 4.89; N, 6.79. Found: C, 60.75; H, 4.80; N, 6.87.

The decomposition of 1-(4-toluenesulfonyl)-2-(2-benzylthiobenzoyl) hydrazide with sodium carbonate at 160° yielded 2-benzylthiobenzaldehyde in 88% yield, m.p. 73–74°.

Anal. Calcd. for $C_{14}H_{12}OS$: C, 73.67; H, 5.30. Found: C, 73.33; H, 5.65.

1-(4-Methylsulfonylphenyl)-2-propylamine.—The hydrochloride (Table I) was prepared from the crude free base. It was synthesized in a 22% over-all yield from 1-(4-methylsulfonylphenyl)-2-nitropropene.

1-(4-Sulfamylphenyl)-2-propylamine Hydrochloride.—N-Acetyl-1-phenyl-2-propylamine (16 g., 0.091 mole) was chlorosulfonated with 210 g. (1.8 moles) of chlorosulfonic acid according to a general procedure.[29] The crude sulfonyl chloride was treated with excess aqueous ammonia and N-acetyl-1-(4-sulfamylphenyl)-2-propylamine was obtained as a crude oil after the excess ammonia was removed. Deacetylation using a mixture of 100 ml. of water and 33 ml. of concentrated hydrochloric acid gave 7.8 g. (35%) of product. The analytical sample was prepared from ethanol–ether.

1-(4-N,N-Dimethylsulfamylphenyl)-2-propylamine Hydrochloride.—This was prepared in 16% yield by the same method as 1-(4-sulfamylphenyl)-2-propylamine hydrochloride, except that dimethylamine was substituted for the ammonia.

1-(Nitrophenyl)-2-propylamine (II).—(+)-1-Phenyl-2-propylamine ((+)-amphetamine) was nitrated by a procedure similar to the one used for (±)-1-phenyl-2-propylamine.[17] The product, obtained in 80% yield, was a mixture of position isomers, b.p. 115° (0.6 mm.), $n^{20}D$ 1.5588.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.42; H, 6.94; N, 15.18.

(+)-N-Trifluoroacetyl-1-(4-nitrophenyl)-2-propylamine (III).—To a solution of 232 g. (1.29 moles) of 1-(nitrophenyl)-2-propylamine (II) in 1 l. of benzene was added dropwise 300 g. (1.43 moles) of trifluoroacetic anhydride. The mixture was then heated to reflux for 3 hr., cooled, and the product collected by suction filtration. The white solid was washed well with *N* hydrochloric acid and water; yield 198 g. (56%), m.p. 172–173°. An analytical sample was prepared by recrystallization from chloroform, m.p. 172–173° $[\alpha]^{24}D$ +35.5 (*c* 1.0, tetrahydrofuran).

Anal. Calcd. for $C_{11}H_{11}F_3N_2O_3$: C, 47.83; H, 4.01; N, 10.14. Found: C, 47.85; H, 4.30; N, 10.26.

The structure of compound III was proven as follows: the hydrochloride of II was prepared and the pure 1-(4-nitrophenyl)-2-propylamine position isomer was isolated by fractional recrystallizations.[17] It gave, after trifluoroacetylation, material which was identical by melting point, mixture melting point, and paper chromatography with III.

(−)-N-Trifluoroacetyl-1-(4-aminophenyl)-2-propylamine (IV).—(+)-N-Trifluoroacetyl-1-(4-nitrophenyl)-2-propylamine (III) (59 g., 0.214 mole) in 500 ml. of tetrahydrofuran with 1 g. of platinum dioxide was hydrogenated at a pressure of 3 atm. After the theoretical amount of hydrogen had been taken up the catalyst was filtered off and the tetrahydrofuran removed by distillation. Crystallization of the oily residue from ether–hexane yielded 42.8 g. (81%) of product, m.p. 76–77°, $[\alpha]^{24}D$ −13.9 (*c* 1.0, ethyl acetate).

Anal. Calcd. for $C_{11}H_{13}F_3N_2O$: C, 53.65; H, 5.32; N, 11.38. Found: C, 53.46; H, 5.48; N, 11.89.

(+)-1-(4-Aminophenyl)-2-propylamine Dihydrochloride (V).—Under nitrogen, 40 ml. of *N* sodium hydroxide was added dropwise to a solution of 50 ml. of dimethoxyethane containing 10 g. (0.04 mole) of (−)-N-trifluoroacetyl-1-(4-aminophenyl)-2-propylamine (IV). After 2 hr. at 25° the dimethoxyethane was removed *in vacuo* and the aqueous extracted 3 times with 40 ml. of methylene chloride. The dried solution was concentrated under reduced pressure to an oil. The dihydrochloride was prepared by dissolving the oil in ether and bubbling in dry hydrogen chloride. The crude dihydrochloride was recrystallized from ethanol–ether, 4.8 g. (100%), $[\alpha]^{24}D$ +16.5 (*c* 1.0, water).

(+)-N-Trifluoroacetyl-1-(4-methylsulfamidophenyl)-2-propylamine.—To a cooled solution of 5.6 g. (0.02 mole) of (−)-N-trifluoroacetyl-1-(4-aminophenyl)-2-propylamine in 30 ml. of methylene chloride was added dropwise with stirring 1.67 ml. (0.022 mole) of methanesulfonyl chloride in 20 ml. of methylene chloride and 3 ml. (0.022 mole) of triethylamine in 20 ml. of methylene chloride. The mixture was allowed to come to 25° and then stirred for 12 hr. The reaction mixture was washed with *N* hydrochloric acid and water and the methylene chloride removed under reduced pressure. There was obtained 3.9 g. (60%) of product, m.p. 171–172°. An analytical portion was prepared by recrystallization from ethyl acetate–ether, m.p. 172°, $[\alpha]^{24}D$ +13.5° (*c* 2.0, dimethylacetamide).

Anal. Calcd. for $C_{12}H_{15}F_3N_2O_3S$: C, 44.44; H, 4.66; N, 8.64. Found: C, 44.62; H, 4.75; N, 9.39.

(+)-1-(4-Methylsulfamidophenyl)-2-propylamine Hydrochloride.—A mixture of 4.3 g. (0.0133 mole) of (+)-N-trifluoroacetyl-1-(4-methylsulfamidophenyl)-2-propylamine and 33 ml. of *N* sodium hydroxide in 30 ml. of dimethoxyethane was stirred at 25° for 2 hr. The dimethoxyethane was removed *in vacuo* and

(25) L. Katz, L. S. Karger, W. Schroeder, and M. S. Cohen, *J. Org. Chem.*, **18**, 1380 (1953).

(26) M. S. Newman and E. G. Caflisch, Jr., *J. Am. Chem. Soc.*, **80**, 862 (1958).

(27) N. P. Buu-Hoi and N. Hoan, *J. Org. Chem.*, **17**, 350 (1952).

(28) W. J. Barry and I. L. Finar, *J. Chem. Soc.*, 138 (1954).

(29) E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Am. Chem. Soc.*, **62**, 2099 (1940).

the aqueous solution was adjusted to pH 1.5 with *N* hydrochloric acid. After removal of the water *in vacuo*, a colorless solid was obtained, 2.4 g. (69%), m.p. 260–261°. The analytical sample was prepared by recrystallization from ethanol–ether, $[\alpha]^{24}D$ +15.1° (*c* 2.0, water).

(+)-N-Trifluoroacetyl-1-(4-benzamidophenyl)-2-propylamine.—To a cooled solution of 10 g. (0.035 mole) of (−)-N-trifluoroacetyl-1-(4-aminophenyl)-2-propylamine in 50 ml. of methylene chloride, was added dropwise with stirring 4.1 ml. (0.035 mole) of benzoyl chloride in 20 ml. of methylene chloride and 4.8 ml. (0.035 mole) of triethylamine in 20 ml. of methylene chloride. The mixture was stirred at 25° for 12 hr., water added, and the white solid that formed was removed by suction filtration. There was obtained 11.7 g. (96%), m.p. 219–220°. An analytical sample was prepared by recrystallization from ethanol–water, m.p. 220–221°, $[\alpha]^{23}D$ +15.7° (*c* 2.0, dimethylacetamide).

Anal. Calcd. for $C_{18}H_{17}F_3N_2O_2$: C, 61.71; H, 4.89; N, 8.00. Found: C, 61.77; H, 5.20; N, 7.97.

(+)-1-(4-Benzamidophenyl)-2-propylamine Hydrochloride.—A mixture of 3.0 g. (0.0086 mole) of (+)-N-trifluoroacetyl-1-(4-benzamidophenyl)-2-propylamine and 8.7 ml. of *N* sodium hydroxide in 25 ml. of ethyl alcohol was stirred at 25° for 16 hr. The alcohol was removed *in vacuo* and the aqueous solution acidified with *N* hydrochloric acid. The water was removed *in vacuo* and the residue recrystallized from ethanol–ether, 1.8 g. (70%), $[\alpha]^{24}D$ +17.8° (*c* 2.0, water).

Pharmacology. Rat.[30]—Food (Purina lab chow in spill-proof cups) was presented to mature Sprague–Dawley male rats for 1 hr. at the same time each day. *Ad libitum* watering was permitted. An aqueous solution of the compound was administered *via* stomach tube to randomly selected groups of 6 rats. Compounds were given twice weekly. Control groups received only water. Food intake was measured for 1 hr., beginning 1 hr. after the compound was administered. Compounds were active if there were significant (t-test, 5% level of confidence) reductions in food intake compared with controls. Compounds were tested at 30, 10, and 5 mg./kg. If inactive at one dose they were not tested at a lower dose.

For a selected group of compounds, potency determinations were made. A three-point parallel line bioassay design was superimposed on the usual testing procedure. Twelve rats were employed at each point for standard (usually (+)-amphetamine) and test compounds. The potencies were calculated after suitable statistical analysis.[19]

Dog.—Food (canned meat) was presented to mongrel dogs, weighing 2.74–5.48 kg., for 1 hr. at the same time each day. Each compound was administered by means of a capsule to randomly selected groups of 4 dogs. Compounds were given 2 or 3 times each week. Food intake was measured for 1 hr., beginning 1 hr. after the compound was administered. Compounds were considered to be active when food intake for each of the 4 treated dogs was at least 100 g. less than under control conditions. On control days, the same 4 dogs received only empty capsules. Borderline and procedurally suspect results were repeated.

Potency determinations for a selected group of compounds were made. The parallel line assays, employing groups of 12 dogs in crossover designs[19] were superimposed on the usual preliminary testing procedures.

(30) Recently, J. A. Gylys, J. J. D. Hart, and M. R. Warren, *J. Pharmacol. Exptl. Therap.*, **137**, 365 (1962), reported that chlorphentermine causes anorexia in rats without any increase in motor activity.

The Synthesis of 8-D-Phenylalanine-, 8-*p*-Fluoro-L-phenylalanine-, and 8-*p*-Fluoro-D-phenylalanine-bradykinin

E. D. NICOLAIDES, M. K. CRAFT, AND H. A. DEWALD

The Research Division, Parke, Davis and Company, Ann Arbor, Michigan

Received April 25, 1963

Three new analogs of bradykinin have been prepared in which the penultimate amino acid phenylalanine has been replaced by D-phenylalanine, *p*-fluoro-L-phenylalanine, and *p*-fluoro-D-phenylalanine. The synthetic approaches used to obtain the three analogs were identical and consisted mainly of the stepwise lengthening of the peptide chain with the appropriate protected amino acid *p*-nitrophenyl ester.

The replacement of one amino acid by another of similar or diverse structure in a peptide which has been found to possess a profound biological effect has been a favored approach used by many investigators to obtain either compounds with enhanced activity, *e.g.*, desamino-oxytocin and 1-desamino-8-lysine-vasopressin[1] or inhibitors of the parent compound, *e.g.*, 3-homotyrosine-oxytocin.[2] Although this approach in the angiotensin area has not yielded analogs with enhanced, prolonged, or antagonistic properties, useful information has been obtained about structure–activity relationships.[3,4]

This report describes three new analogs of bradykinin in which phenylalanine in position 8 of the molecule has been replaced by D-phenylalanine, *p*-fluoro-L-phenylalanine, and *p*-fluoro-D-phenylalanine. The variation of a peptide structure by changing the optical configuration is a device that has not been greatly explored. Some interest in this direction has been reported[5,6] with the peptide antibiotics, the change being from D to L rather than L to D and an oxytocin analog containing a D-amino acid recently has been described.[7] The influence of such a change or of introducing *p*-fluorophenylalanine on the activity of a peptide was believed to be unpredictable, but recent experiences with angiotensin analogs[8] have indicated that in the bradykinin series activity might be retained.

The synthetic scheme used to prepare the three nonapeptides was identical with that used in the preparation of bradykinin[9] and is shown in Chart I.

The *p*-fluorophenylalanine was resolved into its optical antipodes using purified carboxypeptidase on

(1) D. B. Hope, V. V. S. Murti, and V. du Vigneaud, *J. Biol. Chem.*, **237**, 1563 (1962); W. Y. Chan and V. du Vigneaud, *Endrocrinology*, **71**, 977 (1962).

(2) S. Guttmann, P. A. Jaquenoud, and R. A. Boissonnas, *Naturwissenschaften*, **44**, 632 (1957).

(3) R. Schwyzer, *Helv. Chim. Acta*, **44**, 667 (1961).

(4) F. M. Bumpus, P. A. Khairallah, K. Arakawa, I. H. Page, and R. S. Sneby, *Biochim. Biophys. Acta*, **46**, 38 (1961).

(5) B. F. Erlanger, W. V. Curran, and N. Kokowsky, *J. Am. Chem. Soc.*, **81**, 3055 (1959).

(6) E. D. Nicolaides and M. E. Munk, to be published.

(7) C. H. Schneider and V. du Vigneaud, *J. Am. Chem. Soc.*, **84**, 3965 (1962).

(8) E. D. Nicolaides, M. E. Munk, H. A. DeWald, and D. F. Hylander, unpublished results.

(9) E. D. Nicolaides and H. A. DeWald, *J. Org. Chem.*, **26**, 3872 (1961).