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Analeptic Amides of d-α-Methylphenethylamine

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A series of amides of d-α-methylphenethylamine (I) have been synthesized and examined for excitant activity. Such activity has been found in the formamide and with selected α-oxyacylating groups. The structural parameters to which activity is confined are discussed, and a molecular model of the active form of the products proposed.

The noted cardiovascular side effects[1] of *d*- and *dl*-α-methylphenethylamine have detracted from the wider clinical application of these compounds in a variety of therapeutic indications.

With the premise that relatively small quantities of free *d*-α-methylphenethylamine (I) are required for pharmacologic response,[2,3] we have investigated the effect of acyl derivatives of I in the search for active structures which might be free of the noted cardiovascular side effects of the parent amine.

Since activity is associated largely with *d*-α-methylphenethylamine, our explorations were largely limited to derivatives of this substance.

A broad program of synthesis was undertaken and the compounds prepared are described in Tables I–III. In selected instances, parallel series of *dl*- and *l*-, as well as *d*-derivatives were studied.

As the work progressed, it became evident that activity was substantially confined to selected structures containing an α-oxy function on the acylating group and these were explored in more detail.

The role of the acylating groups containing an α-oxy function was explored with the sympathomimetic amines, *d*-N-methyl-α-methylphenethylamine (Table II, compounds 41, 53) and phenylpropanolamine (Table III), to establish whether desirable modification of the properties of these substances would also be obtained.

The synthesis of the compounds followed established procedures and the acylating component used, reflected in general, its commercial accessibility, and this was varied as esters, acid chlorides, free acids, lactides and lactones.

Although α-methylphenethylamine is a structurally hindered amine,[4] no complication occurred in the aminolysis of ethyl formate[5] though the higher boiling ethylene diformate[6] was more convenient and afforded a cleaner product.

By contrast, under parallel conditions, the hindered α-methylphenethylamine failed to react with ethyl acetate[7] although under forcing conditions under pressure, excellent yields of the acetamide were obtainable.[8] The compound (Table I, compound 3) also was prepared readily using acetyl chloride.

The aminolysis of the α-hydroxy esters such as ethyl glycolate, ethyl lactate and ethyl α-hydroxyisobutyrate proceeded readily. Here, reactivity was probably increased as a result of forms such as those postulated by Ratchford.[9]

An asymmetric α-carbon atom in the acylating moiety reflected the possibility of isolation of the *dd*- and *dl*-forms of the resultant amides. Such separation was effected in selected instances (Table II, compounds 59, 60 and 66, 67) by fractional crystallization procedures.

The aminolysis reaction with benzilic acid proceeded with difficulty and yielded the benzilic acid salt of the amine, and from the breakdown product, benzophenone,[10] a 34% yield of N-α-methylphenethylbenzhydrylimine. Reaction with methyl benzilate[11] (as above) afforded only the benzilic acid salt of *d*-α-methylphenethylamine.

The corresponding α-chlorodiphenylacetamide (Table I, compound 34) was prepared readily from α-chlorodiphenylacetyl chloride, but hydrolysis[12] and isolation of the desired benzilamide was unsuccessful.

The aminolysis with dibasic esters was effected readily in most instances. With the malonates, the required bisamide was obtained using diethyl malonate and diethyl ethyl malonate. With diethyl phenylmalonate, no reaction was noted,[13] and upon addition of sodium methoxide as a basic catalyst, the reactant ester suffered decarbethoxylation[14] and N-*d*-α-methylphenethylphenylacetamide (Table I, compound 31) and bis-N,N′-*d*-α-methylphenethylurea were obtained. Under similar conditions, diethyl ethylphenylmalonate afforded the urea and N-*d*-α-methylphenylethyl-α-phenylbutyramide (Table I, compound 32).

The noted decarbethoxylation of the substituted malonate esters[14] when treated with alkoxide to give the phenyl acetate and ethyl carbonate followed by reaction with I, would account for the product isolated. The amine I, however, yielded

(1) (a) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 516; (b) K. Soehring and G. Ergenzinger, *Arzneimittel-Forsch.*, **5**, 478 (1955).

(2) S. L. Shapiro and L. Freedman, *Arch. intern. pharmacodynamie*, **112**, 419 (1957).

(3) J. Axelrod, *J. Pharmacol. Exp. Therap.*, **110**, 315 (1954).

(4) For specific reaction rate constants for sympathomimetic amines with methyl acetate, see S. L. Jung, J. G. Miller and A. R. Day, THIS JOURNAL, **75**, 4664 (1953).

(5) W. H. Watanabe and L. R. DeFonso, *ibid.*, **78**, 4542 (1956).

(6) S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin and L. Freedman, *ibid.*, **79**, 5064 (1957).

(7) Failure of aminolysis of ethyl acetate by *t*-butylamine is noted; W. P. Ratchford and C. H. Fisher, *J. Org. Chem.*, **15**, 317 (1950); see ref. 4.

(8) For enhancement of the rate of another sterically unfavorable reaction through the use of forcing conditions, see I. S. Bengelsdorf, THIS JOURNAL, **80**, 1442 (1958).

(9) W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950).

(10) H. H. Wasserman, H. W. Ackerman, H. H. Wotiz and T. Liu, THIS JOURNAL, **77**, 973 (1955).

(11) A. Rahman and M. O. Farooq, *Naturwissenschaften*, **41**, 1 (1954).

(12) Possible complicating side products may be 2,2′-oxybis-(α-phenylphenylacetamides) similar to the bisamides reported by A. H. Schlesinger and E. J. Prill, THIS JOURNAL, **78**, 6123 (1956).

(13) S. B. Speck, *ibid.*, **74**, 2876 (1952).

(14) V. H. Wallingford, A. H. Homeyer and D. M. Jones, *ibid.*, **63**, 2056 (1941).

TABLE I

AMIDES OF α-METHYLPHENETHYLAMINE[a] $RCON(H)CH(CH_3)CH_2C_6H_5$[u]

Compound	R	M.p., °C.,[b,c] b.p. (mm.)	Yield,[d] %	Formula	Analyses[e] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1[f]	H	49–50	54	$C_{10}H_{13}NO$	73.6	73.7	8.0	7.9	8.6	8.8
2[g,q1]	H	104 (0.08)	57							
3	CH_3–	123–125	48	$C_{11}H_{15}NO$	74.5	75.0	8.5	8.6		
4[h,q1]	CH_3–	93–94	73							
5[i]	$ClCH_2$–	49–50[c1]	34	$C_{11}H_{14}ClNO$	62.4	62.4	6.7	6.7	6.6	6.7
6	$BrCH_2$–	102–114 (0.03)	41	$C_{11}H_{14}BrNO$					5.5	5.5
7[a2]	$BrCH_2$–	114–128 (0.1)	27	$C_{11}H_{14}BrNO$					5.5	5.3
8	Cl_2CH–	82–86[c6]	30	$C_{11}H_{13}Cl_2NO$	53.7	53.6	5.3	5.3	5.7	5.8
9	Cl_3C–	73–75	64	$C_{11}H_{12}Cl_3NO$	47.1	47.4	4.3	4.4	5.0	5.3
10	Cl_2FC–	92–93[c1]	90	$C_{11}H_{12}Cl_2FNO$	50.0	50.4	4.6	4.7	5.3	5.1
11	ClF_2C	79–80[c1]	78	$C_{11}H_{12}ClF_2NO$	53.3	53.9	4.9	4.9	5.7	5.6
12[a2]	ClF_2C–	79–81[c1]	77	$C_{11}H_{12}ClF_2NO$	53.3	53.6	4.9	5.4	5.7	5.8
13	F_3C–	79–81[c1]	57	$C_{11}H_{12}F_3NO$	57.2	56.9	5.2	5.7	6.1	5.8
14[a2]	F_3C–	82–84[c1]	67	$C_{11}H_{12}F_3NO$	57.2	57.3	5.2	5.5	6.1	6.4
15	CF_3CF_2–	76–78[c1]	71	$C_{12}H_{12}F_5NO$					5.0	5.0
16[a2]	CF_3CF_2–	78–80[c1]	73	$C_{12}H_{12}F_5NO$	51.3	51.7	4.3	4.6	5.0	4.8
17[a2]	$CF_3CF_2CF_2$–	75–76[c1]	72	$C_{13}H_{12}F_7NO$	47.1	47.4	3.7	3.8	4.2	4.1
18	$NCCH_2$–	74–75	61	$C_{12}H_{14}N_2O$	71.3	71.0	7.0	7.0	13.9	13.3
19	CH_3CHBr–	85	59	$C_{12}H_{16}BrNO$	53.3	53.3	6.0	5.6	5.2	5.1
20	$ClCH_2CH_2$–	64–65	65	$C_{12}H_{16}ClNO$	63.8	64.0	7.2	7.3	6.2	5.9
21	$HOCH_2CH_2O$–[p]	144–149 (0.2)	68	$C_{12}H_{17}NO_3$	64.6	65.0	7.7	8.2	6.3	5.7
22	$HOCH_2CHCH_3O$-	142 (0.17)	69	$C_{13}H_{19}NO_3$	65.8	66.5	8.1	8.3	5.9	5.6
23	OCH–	110–130 (0.2)	32	$C_{11}H_{13}NO_2$	69.1	67.3	6.9	7.2	7.3	6.7
24	$HOOCCH_2CH_2$–	87–89	44	$C_{13}H_{17}NO_3$	66.4	66.3	7.3	6.9	6.0	5.9
25	$C_2H_5OCH_2CH_2$–	120 (0.05)	43	$C_{14}H_{21}NO_2$					6.0	6.3
26	2-HOC_6H_4–	107–108	80	$C_{16}H_{17}NO_2$	75.3	75.3	6.7	6.8	5.5	5.1
27	C_4H_4O–[j]	103–104	80	$C_{14}H_{15}NO_2$	73.3	73.6	6.6	7.0	6.1	6.5
28[l]	C_4H_4S–[k]	142[c3]	79	$C_{14}H_{15}NOS$	68.6	69.1	6.2	6.1	5.7	5.8
29[n]	3-C_5H_5N–[m]	114–116[c4]	15	$C_{15}H_{16}N_2O$	75.0	74.9	6.7	6.7	11.7	11.7
30	4-C_5H_5N–[m]	138–140[c4]	16	$C_{15}H_{16}N_2O$	75.0	75.1	6.7	7.1	11.7	11.9
31	$C_6H_5CH_2$–	95	84	$C_{17}H_{19}NO$	80.6	80.8	7.6	7.7	5.5	5.7
32	$C_6H_5CH(C_2H_5)$–	89-90	72	$C_{19}H_{23}NO$	81.1	81.3	8.2	8.1	5.0	5.1
33	$C_4H_4OCH{=}CH$–[j]	112–114	2	$C_{16}H_{17}NO_2$	75.3	74.8	6.7	6.9	5.5	5.3
34	$(C_6H_5)_2CHCl$–	69–70[c1]	59	$C_{23}H_{22}ClNO$	75.9	76.4	6.1	6.1	3.9	3.9

BISAMIDES, $C_6H_5CH_2CH_3CHN(H)CRC(O)O(H)NCHCH_3CH_2C_6H_5$

35	[o]	204–205[c8]	51	$C_{29}H_{24}N_2O_2$	74.0	74.4	7.5	7.6	8.6	8.7
36	$-CH_2-$	132–133[c9]	86	$C_{21}H_{26}N_2O_4$	74.5	74.4	7.7	7.7	8.3	8.3
37	$-CH(C_2H_5)-$	148–149[c10]	40	$C_{23}H_{30}N_2O_2$	75.4	75.3	8.3	8.1	7.6	7.8
38	–CH(OH)–	108–112[c11]	33	$C_{21}H_{26}N_2O_3$	71.2	70.9	7.4	7.0	7.9	8.2
39	$-(CH_2)_4-$	164–165[c6]	71	$C_{22}H_{28}N_2O_2$	75.0	75.4	8.0	7.8	8.0	7.9

[a] The amine used was *d*-α-methylphenethylamine unless otherwise indicated; [a1] *dl*-α-methylphenethylamine; [a2] *l*-α-methylphenethylamine; [a3] *d*-N-methyl-α-methylphenethylamine. [b] Melting points are not corrected. [c] Recrystallizing solvent was hexane–ethyl acetate unless otherwise specified; [c1] hexane; [c2] methanol–ethyl acetate; [c3] benzene–hexane; [c4] ethanol–hexane; [c5] ether–hexane; [c6] ethyl acetate; [c7] ethanol–ether; [c8] butanol; [c9] heptane; [c10] acetone–water; [c11] ether; [c12] propanol–hexane; [c13] ethanol–water. [d] Yields are based on distilled product, or recrystallized product. In certain cases where the unrecrystallized material was of acceptable purity, the stated yield reflects the crude yield. [e] Analyses by Weiler and Strauss, Oxford, England. [f] Yield using ethylene diformate was 73%. [g] Reported, M. Sekuja, *J. Pharm. Soc., Japan*, **70**, 520 (1950). [h] Reported by J. J. Ritter and J. Kalish, THIS JOURNAL, **70**, 4048 (1948), as m.p. 88–89°. [i] The *dl*-analog of this compound is reported by S. Chiavarelli and G. B. Marini-Bettolo, *Gazz. chim. ital.*, **81**, 89 (1951), as m.p. 79–80°. [j] C_4H_4O = 2-furyl. [k] C_4H_4S = 2-thienyl. [l] Reported as *dl*-analog by N. D. Xuong, *Compt. rend.*, **244**, 138 (1957), as m.p. 126° [m] C_5H_5N = pyridyl. [n] Reported as *dl*-analog by S. Ya. Arbuzov, *Farmakologiya i Toksikologiya*, **19**, 16 (1956); cited in Abstracts of *J. Pharm. Pharmacol.*, **9**, 324 (1957). [o] Bis-oxamide. [p] Reported as *dl*-analog in reference 18. [q] R_3 = H unless otherwise indicated; [q1] R_3 = methyl. [r] C_3H_5 = allyl. [s] C_7H_{15} = 3-heptyl. [t] With C_4H_8O group the resultant compound is the pantoamide. The compound formed by reaction of pantoyllactone and *d*-α-methylphenethylamine and was a sirupy material which crystallized slowly. It has not been analyzed. [u] The derivatives of *d*-α-methylphenethylamine in this table and throughout this paper have been designated as "*d*"-form to reflect their origin from the dextrorotary form of the parent amine.

only trace amounts of the urea when treated with ethyl carbonate in the presence of sodium ethoxide.

An alternative mechanism which might account for the relatively large amounts of the urea obtained in the reactions with the phenyl malonates, involves initial amidation with a rapid reversible

TABLE II

α-OXYAMIDES OF α-METHYLPHENETHYLAMINE[a] $R_1OCR_2CONHCH(CH_3)CH_2C_6H_5$[g]

Compound	R_1	R_2	[M.p., °C.,[b,c] or b.p. (mm.)	Yield,[d] %	Formula	Analyses[e] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
40	H	H	159 (0.04)	100	$C_{11}H_{15}NO_2$	68.4	67.6	7.8	7.8	7.3	6.8
41[a3]	H	H	120 (0.1)	78	$C_{12}H_{17}NO_2$	69.5	69.6	8.3	7.9	6.8	6.8
42	C_2H_5OCO-	H	53–54[c1]	64	$C_{14}H_{19}NO_4$	63.4	63.6	7.2	7.9	5.3	4.8
43	CH_3-	H	40–44[c1]	83	$C_{12}H_{17}NO_2$	69.5	69.2	8.3	8.3	7.4	7.4
44	C_2H_5-	H	106–108 (0.08)	68	$C_{13}H_{19}NO_2$	70.6	70.6	8.7	8.8	6.3	6.3
45	$C_3H_5-^r$	H	132–136 (0.15)	51	$C_{14}H_{19}NO_2$	72.1	71.9	8.2	8.5	6.0	5.9
46	C_6H_5-	H	84–85[c1]	83	$C_{17}H_{19}NO_2$	75.8	76.1	7.1	7.3	5.2	5.4
47	$2\text{-}ClC_6H_4-$	H	83–85	56	$C_{17}H_{18}ClNO_2$	67.2	66.9	6.0	5.7	4.6	4.1
48	$C_6H_5CH_2-$	H	46–47[c1]	56	$C_{18}H_{21}NO_2$	76.3	76.3	7.5	7.3	4.9	5.3
49	CH_3-	CH_3O-	65–66		$C_{13}H_{19}NO_3$	65.8	66.2	8.1	8.0	5.9	6.1
50	H	CH_3-	52–53	64	$C_{12}H_{17}NO_2$	69.5	69.4	8.3	8.0	6.8	6.9
51[a1]	H	CH_3-	140 (0.2)	84	$C_{12}H_{17}NO_2$	69.5	69.0	8.3	8.2	6.8	6.9
52[a2]	H	CH_3-	149 (0.15)	87	$C_{12}H_{17}NO_2$					6.8	6.8
53[a3]	H	CH_3-	108 (0.03)	70	$C_{13}H_{19}NO_2$					6.3	5.9
54	CH_3CO-	CH_3-	130 (0.15)	69	$C_{14}H_{19}NO_3$	67.4	68.0	7.7	7.7		
55	C_2H_5OCO-	CH_3-	64–68		$C_{15}H_{21}NO_4$					5.0	4.8
56	CH_3-	CH_3-	110–112 (0.14)	62	$C_{13}H_{19}NO_2$	70.6	71.0	8.7	8.7		
57	C_2H_5-	CH_3-	98 (0.1)	55	$C_{14}H_{21}NO_2$	71.5	72.1	9.0	9.0	6.0	5.9
58	$C_3H_5-^r$	CH_3-	108 (0.12)	71	$C_{15}H_{21}NO_2$	72.9	73.0	8.6	8.7	5.7	5.8
59	C_6H_5-	CH_3-	124–126		$C_{18}H_{21}NO_2$	76.3	76.2	7.5	7.4	4.9	5.1
60	C_6H_5-	CH_3-	97–98		$C_{18}H_{21}NO_2$	76.3	75.9	7.5	7.7	4.9	4.9
61	$C_6H_5CH_2-$	CH_3-	30–60	81	$C_{19}H_{23}NO_2$	76.7	76.2	7.8	7.8	4.7	4.9
62	H	$C_7H_{15}-^s$	154–160 (0.03)	63	$C_{18}H_{19}NO_2$	74.2	74.2	10.0	10.1	4.8	4.9
63	H	$C_4H_9O-^t$		85	$C_{15}H_{23}NO_3$	67.9		8.7		5.3	
64[a1]	H	CH_3-	54–57	54	$C_{13}H_{19}NO_2$	70.6	70.4	8.7	8.5		
65	H	C_6H_5-	58–60[c5]	25	$C_{17}H_{19}NO_2$					5.2	5.3
66	CH_3-	C_6H_5-	70–76[c1]	21	$C_{18}H_{21}NO_2$	76.3	76.3	7.5	7.5		
67	CH_3-	C_6H_5-	55–56[c1]	13	$C_{18}H_{21}NO_2$	76.3	76.4	7.5	7.6	4.9	4.7

[a] Footnotes shown in Table I apply to this table.

TABLE III[a]

AMIDES OF PHENYLPROPANOLAMINE $R_1OCHCONHCH(CH_3)CHOHC_6H_5$ (R_2)

Compound	R_1	R_2	M.p., °C.,[b,c] or b.p. (mm.)	Yield,[d] %	Formula	Analyses[e] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3-	H	136–140 (0.03)	63	$C_{12}H_{17}NO_3$	64.6	64.6	7.7	7.7	6.3	5.7
2	C_2H_5-	H	138–142 (0.09)	65	$C_{13}H_{19}NO_3$					5.9	5.6
3	$C_6H_5CH_2-$	H	94	81	$C_{18}H_{21}NO_3$	72.2	72.5	7.1	6.9	4.7	5.1
4	CH_3-	CH_3O-	150–158 (0.06)	37	$C_{13}H_{19}NO_4$	61.6	61.2	7.6	7.7	5.5	5.4
5	H	CH_3-	180–186 (0.01)	56	$C_{12}H_{17}NO_3$	64.6	64.9	7.7	7.8		
6	CH_3-	CH_3-	138–142 (0.05)	82	$C_{13}H_{19}NO_3$					5.9	6.1
7	C_2H_5-	CH_3-	146–154 (0.05)	54	$C_{14}H_{21}NO_3$	66.9	66.7	8.4	8.6	5.6	5.3
8	$C_3H_5-^r$	CH_3-	152 (0.04)	67	$C_{15}H_{21}NO_3$	68.4	68.1	8.0	7.7	5.3	5.4
9	C_6H_5-	CH_3-	132–133[c13]	15	$C_{18}H_{21}NO_3$	72.2	72.3	7.1	7.2	4.7	4.9
10	$C_6H_5CH_2-$	CH_3-	187 (0.03)	74	$C_{19}H_{23}NO_3$	72.8	72.3	7.4	7.5	4.5	4.4
11	CH_3-	C_6H_5-	84–87	52	$C_{18}H_{21}NO_3$	72.2	72.3	7.1	7.2	4.7	4.7

[a] The footnotes shown in Table I apply to this table.

proton transfer between the methoxide ion and the N–H group[15] followed by formation of the isocyanate and the phenyl acetate as shown in Scheme I.[16] These in turn react with the amine I to give the noted products.

Condensation of *d*-α-methylphenethylamine[17] with glucuronolactone yielded a pure product which was not fully characterized but which is a

SCHEME I

$$C_6H_5\overset{\overset{R}{|}}{\underset{\underset{COOC_2H_5}{|}}{C}}(\ominus)-\overset{\overset{O}{\|}}{C}-N\overset{\oplus}{\leftarrow}-CH(CH_3)CH_2C_6H_5 \longrightarrow$$

$$C_6H_5\overset{\overset{R}{|}}{\underset{\ominus}{C}}COOC_2H_5 + C_6H_5CH_2CHCH_3NCO$$

(15) H. Heine, P. Love and J. Bove, THIS JOURNAL, **77**, 5420 (1955).

(16) For a related series of reactions, see M. M. Joullié, S. Násfay and L. Rypstat, *J. Org. Chem.*, **21**, 1358 (1956).

(17) J. F. Carson, THIS JOURNAL, **77**, 5957 (1955), obtained crystalline products from fructose and large excesses of aliphatic amines.

TABLE IV

SUMMARY OF PHARMACOLOGICAL FINDINGS[a,b]

Excitant response with compounds[c] of Tables I and II[d]					
4+ 300% and over 10 mg.	3+ 200–300%	2+ 100–299% 10 mg.	1+ 20–99% 10 mg.	Neg. 0–20% 10 mg.	Inhibits 10 mg.
1, 23, 40, 50	32 (100 mg.)	42, 54, 55	2, 25, 51, 65	3, 4, 5, 19, 20, 22, 24, 32, 34, 36, 38, 39, 41, 52, 53, 63	37, 62 64 (40 mg.) 27 (50 mg.)
20 mg.		20 mg.	20 mg.	20 mg.	
43, 44, 45, 48, 56, 58		61, 18 (100 mg).	29, 30, 46, 47, 49, 66	26, 28, 33, 67	

[a] The individual compounds were evaluated for their excitant effect in rats using activity cages. The excitory action is registered on a counter and kymograph responsive to motion and was established over a 16-hour test period. The compounds were administered at the indicated dosage levels in mg./kg. subcutaneously and evaluated in six rats, with six additional rats serving as controls during intervals from 5 P.M. to 9 A.M. the next day. The activity (excitant response) is expressed by the formula: A = % increase in activity = (activity increase of test group/activity control group) × 100. Four activity ranges were arbitrarily set up as shown in the table and expressed as 4+ through 0 (little or no activity). Several compounds showed depressant effects and these are grouped under the "Inhibits" column. Cardiovascular effects were investigated in the isolated guinea pig heart and in the anesthetized dog. [b] While toxicity of individual compounds is not listed, the range for the active structures indicated an $LD_{min.}$ in mice of 150–500 mg./kg. [c] As a control, benzedrine (*dl*-α-methylphenethylamine) hydrochloride at 10 mg./kg. showed a 4+ response. [d] Table III compounds 1 [1+(100)], 2, 3, 5, 7 and 9 were negative.

condensation of two moles of *d*-α-methylphenethylamine and one mole of glucuronolactone with elimination of one mole of water.

Additional syntheses of interest concerned the preparation of glycol carbonates from reaction of *d*-α-methylphenethylamine[18] with ethylene carbonate and propylene carbonate (Table I, compounds 21, 22).

Pharmacology.—The compounds herein described were assessed for their effects on increasing the motor activity of rats, and results have been noted in Table IV. The data obtained reflect the results of screening tests as established upon subcutaneous administration of the compounds. The more active derivatives were subsequently evaluated *per os*, and for indication of cardiovascular side effects.

Inspection of Table IV reflects a definite structure *vs.* activity relationship in that all compounds which retained the excitant effects of the parent amine upon acylation, with the exception of compound 1, contained an α-oxy function in the acylating function.

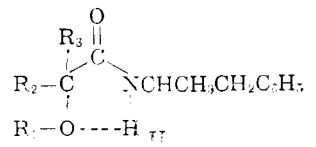
Within the active compounds a number of structural features were required for retention of activity. Thus, variation of the amine as *dl*-α-methylphenethylamine (compound 1 *vs.* 2, 50 *vs.* 51), or *l*-α-methylphenethylamine (compound 50 *vs.* 52), or *d*-N-methyl-α-methylphenethylamine (compound 40 *vs.* 41, 50 *vs.* 53), was associated with sharp diminution or disappearance of activity. While the presence of a hydroxy group, an alkoxy group or carbonyl oxygen on the α-carbon atom of the acylating group yielded compounds with high activity (compounds 40, 50; 43, 44, 45, 48, 56, 58, 61, and 23), this effect could be modified by other substituents on the α-carbon atom or on the α-oxy function. Thus, two methyl groups on the α-carbon (compound 64) or one phenyl group (compound 65) resulted in depressant effect and slight excitant effect, respectively, as did a larger alkyl group (compound 62). When derivatives of the active structures had substituents capable of withdrawing electrons from the α-oxy atom such as acetyl (compound 50 *vs.* 54), or carbethoxy (compound 50 *vs.* 55, 40 *vs.* 42) or phenyl (compound 40 *vs.* 46, 47), activity was reduced. An alkoxy group on the β-carbon atom yielded but slight activity (compound 25). Other compounds containing an α-oxy function which showed little or no response were the bisamide derived from tartronic acid (compound 38), the furoamide (compound 27) and the pantoamide (compound 63).

An indication of criticality dependent on the configuration at the α-carbon of the acyl group was reflected in the noted activity of compound 66 *vs.* 67. This factor is being explored further with optically active lactate as a reactant and will be reported at a later date.[19]

The body of data thus far presented is not consistent with a mechanism involving *in vivo* hydrolysis of the acylated amide to free *d*-α-methylphenethylamine. Although systematic studies of the hydrolysis of amides are scant, it is indicated[20,21] that the hydrolysis of amides parallels observations with esters. The use of the ester data cited by Hine[22] translated *per se* to the amides of this series would indicate that the order of increasing difficulty of hydrolysis would be compound 5, 1, 40, 3, which is clearly inconsistent with the pharmacological observations.

A structural parameter which is more conclusive is one associated with a hydrogen bonded cyclic structure.

It has been quite clearly established that in the simple amides a *trans* configuration is found between the carbonyl oxygen and the amide hydrogen.[23] A hydrogen bonded structure of the type II is proposed for the active structures noted herein.



(18) R. Hazard, J. Cheymol, P. Chabrier, Y. Gay and M. P. Muller, *Ann. pharm. franç.*, **9**, 390 (1951).

(19) S. L. Shapiro, I. M. Rose and L. Freedman, in preparation.

(20) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 298–299.

(21) M. L. Bender and R. D. Ginger, THIS JOURNAL, **77**, 348 (1955).

(22) Reference 20, p. 275.

(23) J. E. Worsham, Jr., and M. E. Hobbs, THIS JOURNAL, **76**, 206 (1954).

TABLE V

α-OXY ACIDS AND DERIVATIVES, $R_1OCHR_2COR_4$

Compound	R_1	R_2	R_4	B.p. °C.	B.p. Mm.	Yield, %	$n^{20}D$
1[a]	C_2H_5–	H	–OC_2H_5	56	17	74	
2[c]	C_3H_5–[b]	H	–OH	104–128	9	37	1.4538
3[d]	$C_6H_5CH_2$–	H	–OH	120–122	0.1	77	1.5280
4[e]	CH_3–	CH_3O–	–OCH_3	62	16	19	1.4056
5[f]	CH_3–	CH_3–	–OH	84	10	64	
6[g]	CH_3–	CH_3–	–Cl	38–58	90	95	
7[h]	C_2H_5–	CH_3–	–OC_2H_5	56	17	68	1.4014
8[i]	C_3H_5–	CH_3–	–OH	104–106	10	72	1.4384
9[j]	$C_6H_5CH_2$–	CH_3–	–OH	118–120	0.15	80	1.5140
10[k]	$C_6H_5CH_2$–	CH_3–	–Cl	68	0.12	81	1.5104

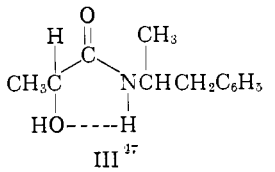
[a] S. M. McElvain and W. R. Davie, THIS JOURNAL, **73**, 1400 (1951), report b.p. 155–158°. [b] C_3H_5 is allyl. [c] R. M. Evans and L. N. Owen, *J. Chem. Soc.*, 244 (1949), report b.p. 120° at 13 mm. [d] B. Rothstein, *Bull. soc. chim.*, **51**, 691 (1932), report b.p. 180–182° at 15 mm., $n^{19}D$ 1.5250. [e] E. E. Royals and A. G. Robinson III, THIS JOURNAL, **78**, 4163 (1956), report b.p. 54° at 5 mm., $n^{25}D$ 1.4047. [f] C. Niemann, A. A. Benson and J. F. Mead, *J. Org. Chem.*, **8**, 397 (1943), report b.p. 87–89° at 10 mm. [g] Reference *f*, report b.p. 46–49° at 52 mm. [h] "Beilstein" Vol. III, p. 109, reports b.p. 153–155° at 755 mm., $n^{20}D$ 1.4013. [i] *Anal.* Calcd. for $C_7H_{14}O_3$: neut. equiv., 130.1. Found: neut. equiv., 135.4. [j] P. A. Levene and M. Kuara, *J. Biol. Chem.*, **113**, 153 (1936), report b.p. 123–128° at 0.2 mm. [k] Reference *j*, report b.p. 79–81° at 0.5 mm.

This structure is consistent with the effects of electron-attracting and electron-donating substituents on the hydroxy groups of compounds 40 and 50 discussed above. The compounds which could assume this structure, but had no excitant effect (compounds 64, 65), could conceivably exist in an alternate conformation[24] unfavorable for formation of the structure II.

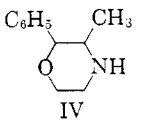
While a similar cyclic structure could be written for the pharmacologically inactive α-halo amides (compounds 5, 19), it is of interest that Katayama[25] in a crystal study of chloroacetamide, could find no evidence of hydrogen bond formation of the type shown in II.

Of the more active structures, compound 50, the N-(*d*-α-methylphenethyl)-lactamide, was shown to be orally effective without significant cardiovascular effects, and is under clinical trial.

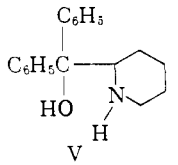
Inspection of the proposed structure for compound 50 (III) along with some of the newly described analeptic drugs[26] all bearing the important phenylisopropylamine group[26d] indicates an interesting parallelism.



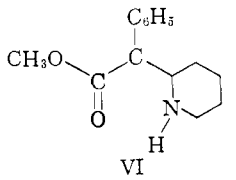
III[27]



IV



V



VI

(24) S. Mizushima, *et al.*, THIS JOURNAL, **78**, 2038 (1956).

(25) M. Katayama, *Acta Cryst.*, **9**, 986 (1956).

(26) (a) Structure IV, 3-methyl-2-phenylmorpholine hydrochloride, E. P. Galvin, T. H. McGavack and S. Kenigsberg, *Am. J. Dig. Dis.*, **1**, 155 (1956); (b) structure V, α-(2-piperidyl)-benzhydrol hydrochloride, B. B. Brown and H. W. Werner, *J. Pharmacol. Exp. Therap.*, **110**, 180 (1954); (c) structure VI, methyl α-(2-piperidyl)-phenylacetate hydrochloride, E. Sury and K. Hoffman, *Helv. Chim. Acta*, **37**, 2133 (1954); (d) F. Leuschner, A. Leuschner and F. Heim, *Arch. exp. Pathol. Pharmakol., Naunyn-Schmiedeberg's* **227**, 129 (1955).

(27) An interpretation of the infrared spectrum of this compound, received through the courtesy of Mr. E. S. Todero, Perkin-Elmer Corporation, indicates hydrogen bonding as shown.

Experimental[28]

Materials.—The *d*-, *l*- and *dl*-α-methylphenethylamines were purchased from True Synthetics, Long Island City, N. Y., and were of U.S.P. standard. Phenylpropanolamine hydrochloride was obtained from Hexagon Laboratories, N. Y., N. Y. The majority of the acylating agents were commercial materials; dimethyl tartronate was prepared as previously described,[29] and the α-oxy acids synthesized as intermediates have been gathered and described in Table V.

N-(*d*-α-Methylphenethyl)-lactamide (Table II, Compound 50 (from Ethyl Lactate).—A mixture of 135.2 g. (1.0 mole) of *d*-α-methylphenethylamine and 120 ml. (1.04 moles) of ethyl lactate were heated under reflux. After 15 hr. the initial internal reflux temperature of 159° had decreased to 115° by the formed ethanol of reaction. The condenser was replaced by a Vigreux column and after 41 ml. of ethanol had distilled, the internal temperature had increased to 183°. The column was replaced by a condenser and the reaction continued under reflux for 7 hr. The reaction mixture was then subjected to distillation. About 10 g. of unreacted amine was initially obtained and the product, the lactamide of *d*-α-methylphenethylamine, distilled 146–153° at 0.20–0.28 mm., there being obtained 186 g. (90%) which crystallized on seeding, m.p. 47–48°.

When lactide was heated with the amine for 4 hr. at 140°, the same product was obtained in 93% yield, m.p. 47–49°.

Unless specified below, the products of Tables I–III were obtained using the requisite ester by the procedure described above.

N-(*d*-α-Methylphenethyl)-α-allyloxypropionamide (Table II, Compound 58).—Over 16 hr., 1.4 ml. (theoretical amount) of water was removed by azeotropic distillation from a refluxing solution of 9.1 g. (0.07 mole) of *dl*-α-allyloxypropionic acid, 9.46 g. (0.07 mole) of *d*-α-methylphenethylamine and 100 ml. of xylene. The cooled xylene solution was washed with dilute hydrochloric acid, water, dilute sodium hydroxide solution, water and then filtered. The xylene was removed at 45° at 30 mm. and the residue was distilled *in vacuo*. After removal of low boiling materials and a small forerun, the product distilled at 108° at 0.12 mm. yielding 12.3 g. (71%).

The following compounds were also prepared from the acid and *d*-α-methylphenethylamine: 45, 48, 61, 62.

N-(*d*-α-Methylphenethyl)-salicylamide (Table I, Compound 26).—A solution of 6.6 g. (0.042 mole) of salicyloyl chloride in 25 ml. of benzene was added dropwise over 30 minutes with stirring, to a solution of 22 g. of *d*-α-methylphenethylamine in 125 ml. of benzene with the reaction

(28) Descriptive data shown in the tables are not herein reproduced

(29) S. L. Shapiro, K. Geiger and H. Soloway, Meeting-in-Miniature, Westchester Branch, American Chemical Society, April, 1956.

maintained at about 10° by external cooling. The benzene phase was separated and then washed with dilute hydrochloric acid, water, dilute sodium hydroxide and finally, water. After removal of the benzene, the residue crystallized yielding 8.45 g. (79.5%) of amide product, m.p. 89–97°.

The following products were similarly prepared from the acid chloride and *d*-α-methylphenethylamine: compounds 5–9, 19, 20, 25, 27, 28, 31, 32, 34, 35, 39, 46, 47, 56 and 65 of Tables I and II.

N-(*d*-α-Methylphenethyl)-acetamide from Ethyl Acetate under Pressure.—A mixture of 13.5 g. (0.1 mole) of *d*-α-methylphenethylamine and 11 ml. of ethyl acetate in a sealed steel bomb was immersed in an oil-bath at a temperature of 200°. After 12 hr., the bomb was allowed to cool to room temperature and the contents removed (methanol wash). The solvents were boiled off under vacuum and the crystalline solid obtained was washed with hexane. After trituration with 50 ml. of water containing 10 ml. of 3 *N* hydrochloric acid, and filtration, the crystals were washed with water, air-dried and finally dried *in vacuo*. The product 10.57 g. (60%), melted at 124–125°. A mixed m.p. with the acetamide prepared from acetyl chloride (Table I, compound 3) was 125–126°.

When ethyl acetate and *d*-α-methylphenethylamine were allowed to react under reflux at atmospheric pressure for 8 hr., no product was isolated.

Ethyl Carbonate Ester of N-(*d*-α-Methylphenethyl)-glycolamide (Table II, Compound 42).—N-(*d*-α-Methylphenethyl)-glycolamide (Table I, compound 40), 10.0 g., 0.05 mole) was dissolved in a mixture of 10 ml. of pyridine and 15 ml. of acetonitrile, the solution cooled in an ice-bath, and 7 ml. (excess) of ethyl chloroformate added dropwise over 10 minutes with stirring and cooling. After standing 1 hr. at 20°, the solvents were removed at reduced pressure and the residue dissolved in a mixture of 100 ml. of benzene and 100 ml. of 0.5 *N* hydrochloric acid. The benzene layer was washed with water and the benzene removed on the steam-bath. The residue of white needles was triturated with cold hexane, there being obtained 8.5 g.

Compound 55, the ethyl carbonate ester of N-(*d*-α-methylphenethyl)-lactamide was similarly prepared.

N-(*d*-α-Methylphenethyl)-α-acetoxypropionamide (Table II, Compound 54).—N-(*d*-α-Methylphenethyl)-lactamide (Table II, compound 50, 10.35 g., 0.05 mole), was dissolved in a mixture of 20 ml. of acetonitrile and 6 ml. of pyridine. This solution was cooled to 10° and 3 ml. (excess) of acetyl chloride was added dropwise over 15 minutes with continued cooling. After 2 hr. at 20° the solvents were removed. The residue was treated with 50 ml. of benzene and 15 ml. of 3 *N* hydrochloric acid, the benzene solution washed with water, filtered, and evaporated to a small volume on the steam-bath. Distillation of the residue gave 8.55 g. (69%) of the product, b.p. 128–130° at 0.15 mm.

N-(*d*-α-Methylphenethyl)-succinamic Acid (Table I, Compound 24).—To a refluxing suspension of 4.0 g. (0.04 mole) of succinic anhydride in 40 ml. of chloroform, a solution of 5.41 g. (0.04 mole) of *d*-α-methylphenethylamine in 10 ml. of chloroform was added dropwise over 1 hr. The anhydride dissolved slowly during addition, and heating was continued for 15 minutes after complete solution. The product was extracted into 5% sodium hydroxide, washed with ether, acidified and re-extracted into chloroform. Upon removal of the solvent, the oily residue obtained (7.65 g.) solidified when scratched and cooled under hexane.

N,N'-Di-(*d*-α-Methylphenethyl)-malonamide (Table I, Compound 36).—A mixture of 10.0 g. (0.0624 mole) of diethyl malonate and 20 ml. (excess) of *d*-α-methylphenethylamine was run through two cycles of reflux to constant internal temperature and removal of the formed ethanol. When cool, the reaction mixture crystallized. After trituration with dilute hydrochloric acid, there was obtained 20.0 g. (94%) of crude product, m.p. 124–125°.

N-(*d*-α-Methylphenethyl)-glyoxalamide (Table I, Compound 23).—A suspension of 2.37 g. (0.01 mole) of N-(*d*-α-methylphenethyl)-dimethoxyacetamide (Table II, compound 49) in 15 ml. of 5% sulfuric acid was treated under reflux for 3 hr. The solution so obtained was saturated with sodium chloride and the product extracted with seven 25-ml. portions of ether. The combined ether extracts were washed with aqueous sodium bicarbonate. The bicarbonate wash was extracted with two 25-ml. portions of ether which were combined with the main extract. The ether was removed on the steam-bath, the residue dissolved in benzene, the benzene removed on the steam-bath to dry the product and the residue distilled *in vacuo*, yielding 0.60 g. (31.4%) of an oil, b.p. 110–130° at 0.20 mm. The analyses indicated that the resultant compound was not analytically pure.[30]

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.9; N, 7.3. Found: C, 67.3; H, 7.2; N, 6.7.

Attempted Preparation of N-(*d*-α-Methylphenethyl)-benzilamide.—When 22.8 g. (0.1 mole) of benzilic acid and 13.48 g. (0.1 mole) of *d*-α-methylphenethylamine in xylene were heated as described above, 1.2 ml. of water was collected in 30 hr. The cooled xylene deposited a large quantity of crystals which were filtered, washed with benzene and dried; 15.35 g. (42%), m.p. 179–180°, on recrystallization (ethyl acetate) m.p. 181–182°.

Anal. Calcd. for $C_{23}H_{25}NO_3$: C, 76.0; H, 6.9; N, 3.9. Found: C, 76.3; H, 6.4; N, 3.8.

The compound proved to be the benzilic acid salt of *d*-α-methylphenethylamine, and did not depress the melting point of the authentic salt described below.

The *d*-α-methylphenethylamine salt of benzilic acid was prepared by mixing ethyl acetate solutions of the acid and base, m.p. 180–182°.

The xylene filtrate afforded an oily residue which yielded 10.12 g. (34%) of the N-(*d*-α-methylphenethyl)-benzhydrylimine, b.p. 148° at 0.08 mm.

Anal. Calcd. for $C_{22}H_{21}N$: C, 88.3; H, 7.1; N, 4.7. Found: C, 88.1; H, 7.5, N, 4.6.

N-(*d*-α-Methylphenethyl)-benzhydrylimine.—A solution of 9.1 g. (0.05 mole) of benzophenone and 6.8 g. (0.05 mole) of *d*-α-methylphenethylamine in 75 ml. of xylene was heated under reflux in a Dean–Stark apparatus for 24 hr. Only 0.5 ml. of water was obtained. Upon removal of the xylene, distillation of the residue after separation of unchanged reactants gave 2.53 g. (17%) of product, b.p. 134–144° at 0.04 mm.

Anal. Calcd. for $C_{22}H_{21}N$: C, 88.3; H, 7.1; N, 4.7. Found: C, 88.6; H, 7.7; N, 4.9.

Reaction of Methyl Benzilate and *d*-α-Methylphenethylamine.—A mixture of 9.0 g. (0.067 mole) of *d*-α-methylphenethylamine and 8.1 g. (0.033 mole) of methyl benzilate under an air-cooled condenser was heated in an oil-bath at 157–162° for 7.5 hr. Shortly after initiation, the internal temperature of the melt rose to 170° and then fell to 160°. On cooling, a semi-solid mass was produced which on trituration with hexane gave 10.95 g. (90%) of *d*-α-methylphenethylamine salt of benzilic acid, m.p. 181–182° alone, or mixed with authentic material prepared from *d*-α-methylphenethylamine and benzilic acid in ethyl acetate.

Reaction of *d*-α-Methylphenethylamine with Glucuronolactone.[31]—Addition of 14.85 g. (0.110 mole) of *d*-α-methylphenethylamine to a suspension of 9.68 g. (0.055 mole) of glucuronolactone in 55 ml. of methanol resulted in complete solution within a few minutes. After 2 hr., the solution had colored to an intense cherry red. Addition of 375 ml. of water gave a cloudy solution which after standing yielded 4.35 g. of product which after trituration with benzene weighed 3.75 g. (16%), m.p. 115–118°. Recrystallization (ethyl acetate) raised the m.p. to 121–123°.

Anal. Calcd. for $C_{24}H_{32}N_2O_5$: C, 67.3; H, 7.5; N, 6.5. Found: C, 66.5; H, 7.3; N, 6.8.

The analytical figure indicates two moles of *d*-α-methylphenethylamine reacting with one mole of glucuronolactone with elimination of one mole of water. The compound was not further investigated.

Hydroxyethyl Urethan of *d*-α-Methylphenethylamine (Table I, Compound 21).—A mixture of 6.75 g. (0.05 mole) of *d*-α-methylphenethylamine and 4.8 g. (10% excess) of ethylene carbonate was heated at 60° for 24 hr. and then at 0.2 mm. and 100° for 1.5 hr. On distillation of the residue there was obtained 68% yield of product, b.p. 144–149° at 0.2 mm.

Compound 22, Table I was similarly prepared.

(30) The compound has been described herein in view of the pharmacological activity as isolated.

(31) The authors appreciate the sample of glucuronolactone provided by Dr. D. M. Rathmann, Corn Products Refining Co., New York, N. Y.

The Diastereoisomers of N-(d-α-Methylphenethyl)-α-methoxyphenylacetamide (Table II, Compounds 66 and 67).—When 8.3 g. (0.05 mole) of *dl*-α-methoxyphenylacetic acid and 6.76 g. (0.05 mole) of *d*-α-methylphenethylamine in 100 ml. of xylene were treated as above, 0.9 ml. of water was collected in 15 hr. After the removal of the xylene, the residue of 12.5 g. crystallized on cooling. The solid was dissolved in 100 ml. of boiling hexane and five 20-ml. portions of hexane added as the solution cooled. On standing for 4 hr., 5.9 g. (m.p. 50–68°) separated, called fraction I. The filtrate stored at 10° for 72 hr. afforded 4.0 g. (m.p. 58–60°), called fraction II. Fraction I was dissolved in 150 ml. of boiling hexane and after standing 4 hr., 2.3 g. (compound 66), m.p. 70–76°, was obtained, α_D ($CHCl_3$) −24.6°. Fraction II was dissolved in 100 ml. of hexane. On standing for several hours, the hard needles of compound 66 formed. These were separated and on standing for 20 hr., 1.8 g. of fluffy needles of compound 67 was obtained, m.p. 55–56°, α_D ($CHCl_3$) −55.1°.

The Diastereoisomers of N-(d-α-Methylphenethyl)-α-phenoxypropionamide (Table II, Compounds 59 and 60). A solution of 9.23 g. (0.05 mole) of *dl*-α-phenoxypropionyl chloride in 25 ml. of benzene was added to a stirred cooled solution of 13.85 g. (0.015 mole) of *d*-α-methylphenethylamine in 75 ml. of benzene at 15°. The stirred suspension was allowed to warm to room temperature over 30 minutes. The amine hydrochloride was separated and the benzene solution was washed with dilute hydrochloric acid, water, dilute sodium hydroxide and finally water. Upon removal of the benzene, there was obtained 13.1 g. (92%) of the mixture of isomers, m.p. 80–110°.

Compound 59, Table II.—The crude mixture was stirred with 1 liter of hexane at room temperature and filtered. The insoluble material, 4 g. melting about 123°, was recrystallized from a mixture of 110 ml. of hexane and 20 ml. of ethyl acetate, yielding 3.2 g. (22%) of needles, m.p. 124–125.5°.

Compound 60, Table II.—To the filtrate above, hexane was added to a total volume of 1.5 liters and a small additional crude crop of compound 59 was separated and discarded. On cooling at 10° for 48 hr., an additional 0.6 g. of mixed product, m.p. 87–94°, was obtained and discarded. The filtrate was concentrated to 250 ml., carbon added and the solution filtered. After several hours, the formed crystals of compound 60 were separated, washed with hexane and dried; yield 4.0 g. (28%), m.p. 97–98°.

Reaction of d-α-Methylphenethylamine with Diethyl Phenylmalonate in the Presence of Sodium Methoxide.—A mixture of 11.8 g. (0.05 mole) of diethyl phenylmalonate, 20 ml. (excess) of *d*-α-methylphenethylamine and 1.0 g. of sodium methoxide was heated under reflux. After 1.25 hr. the formed ethanol was removed (4.0 ml.). When cool, the solid residue was triturated successively with 1 *N* hydrochloric acid, water and hexane, yielding 20.2 g. of a mixture of products, m.p. 80–90°.

Isolation of N,N'-Bis-(d-α-methylphenethyl)-urea.—A solution of 2.0 g. of the above material in 15 ml. of hot ethanol (charcoal) was filtered, diluted with water (5.0 ml.) till just cloudy, and seeded. After standing overnight, the crystals which had formed were filtered, washed with 50% ethanol and dried over phosphorus pentoxide at 80° giving 0.53 g. of the urea, m.p. 147–151°. A mixed m.p. with an authentic sample of the urea (m.p. 149–151°) was 148–151°.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2; N, 9.5. Found: C, 77.6; H, 8.0; N, 9.7.

Isolation of N-(d-α-Methylphenethyl)-phenylacetamide.—The product mixture, 2.0 g., was extracted with 100 ml. of boiling hexane. On cooling, the filtrate deposited 0.42 g. of a mixture, m.p. 88–91°. After several recrystallizations from hexane, most of the urea was removed and the m.p. of the needles (0.12 g.) was raised to 89–96°. The mixed melting point with authentic amide (Table I, compound 31) was 92–96°.

N,N'-Bis-(d-α-methylphenethyl)-urea.—A solution of 8.0 g. (0.059 mole) of *d*-α-methylphenethylamine, 2.0 g. (0.033 mole) of urea and 10.0 g. of glacial acetic acid was heated in an oil-bath until 4.0 ml. of acetic acid distilled out.[32] The cool, still liquid residue was diluted with 70 ml. of methanol and 30 ml. of water was added to the cloud point. The product crystallized and was separated, 0.76 g. (8.5%), m.p. 149–151°.

(32) R. H. Wiley, P. Beasley and L. H. Knabeschuh, THIS JOURNAL, **76**, 311 (1954).

Reaction of d-α-Methylphenethylamine with Diethyl Ethylphenylmalonate in the Presence of Sodium Methoxide.—A solution of 13.2 g. (0.05 mole) of diethyl ethylphenylmalonate and 20 ml. (excess) of *d*-α-methylphenethylamine heated under reflux showed no reaction, with the internal temperature remaining at 214° for 2 hr. Upon addition of 1.1 g. of sodium methoxide, the internal temperature fell to 116° after 2 hr. under reflux. Distillation at atmospheric pressure up to 190° yielded 3.7 ml. of formed alcohol. Upon additional heating under reflux, the internal temperature fell from 185 to 173° after 3.5 hr. When cool, the solid residue was washed successively with 1 *N* hydrochloric acid, water and hexane to give 19.8 g. of a mixture of products which was dissolved (charcoal) in a mixture of 700 ml. of heptane and 65 ml. of ethyl acetate, and filtered. On standing 5 hr., 6.1 g. (41%) of N,N'-bis-(*d*-α-methyl-β-phenethyl)-urea, m.p. 148–149°, was obtained. Upon recrystallization (ethyl acetate), the m.p. was 151–152°. A mixed melting point with an authentic sample of the urea (m.p. 149–151°) was 150–151°.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2; N, 9.5. Found: C, 77.0; H, 7.9; N, 9.1.

The heptane mother liquor, stored at 10°, gave 6.62 g. (47%) of material, m.p. 80–85°, still containing some of the urea. Recrystallization (hexane–ethyl acetate) gave 4.3 g. of N-(*d*-α-methylphenethyl)-α-phenylbutyramide, m.p. 89–90°. A mixed melting point with authentic material (Table I, Compound 32) was 89–90°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.1; H, 8.2; N, 5.0. Found: C, 81.5; H, 8.1; N, 4.8.

N-(dl-α-Methyl-β-hydroxyphenethyl)-lactamide (Table III, Compound 5).—A mixture of 7.2 g. (0.05 mole) of lactide and 17.5 g. (0.16 mole) of phenylpropanolamine was heated at 140° for 4 hr. When cool, 50 ml. of water was added, the solution acidified with hydrochloric acid and the product extracted with nine 100-ml. portions of ether. After removal of the ether, the residue was distilled *in vacuo* yielding 12.5 g. (56%) of amide, b.p. 180–186° at 0.1 mm.

N-(dl-α-Methyl-β-hydroxyphenethyl)-α-ethoxypropionamide (Table III, Compound 7).—A solution of 8.0 g. (0.053 mole) of phenylpropanolamine and 7.32 g. (0.050 mole) of ethyl α-ethoxypropionate was heated under reflux to a constant internal temperature and the formed ethanol then was distilled out until the internal reaction temperature reached 180°. The reflux step was repeated. The residue, after cooling, was dissolved in ether and the solution washed with dilute hydrochloric acid. On removal of the ether, the residue was dried by boiling with benzene, the benzene removed on the steam-bath and the residue distilled. There was obtained 6.8 g. (54%) of amide, b.p. 146–154° at 0.05 mm.

Compounds 1, 2 and 4 in Table III were prepared in a similar manner.

N-(dl-α-Methyl-β-hydroxyphenethyl)-α-benzyloxypropionamide (Table III, Compound 10).—A solution of 7.8 g. (0.0393 mole) of *dl*-α-benzyloxypropionyl chloride in 25 ml. of acetonitrile was added dropwise over 30 minutes with stirring to a solution of 12.48 g. (0.0825 mole) of phenylpropanolamine in 500 ml. of acetonitrile while maintaining the reaction temperature below 25°. Stirring was continued for 30 minutes after addition was complete, the phenylpropanolamine hydrochloride was separated and the acetonitrile removed from the filtrate *in vacuo*. The residue was dissolved in 300 ml. of benzene and 100 ml. of 0.5 *N* hydrochloric acid. The benzene layer was washed with water, dilute sodium hydroxide solution, water, and then the benzene was evaporated on the steam-bath. The residue on distillation yielded 9.17 g. (74%) of product boiling at 187–189° at 0.03 mm.

Compounds 3, 6, 8, 9 and 11 in Table III were prepared in a similar manner.

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