ethyl)propionanilide-*d*-tartrate, m.p. 194–197°, was 30.7 g. Three recrystallizations from ethanol resulted in a 71% yield of pure product, m.p. 204.5–205.5° and $[\alpha]_D^{25}$ +23.7 (2% in water).

Anal. Calcd. for $C_{21}H_{32}N_2O_7$: C, 59.4; H, 7.6; N, 6.6. Found: C, 59.2; H, 7.8; N, 6.6.

This product was converted to the hydrochloride by the procedure described above for the *l* isomer. The over-all yield of *d*-*N*-(1-methyl-2-piperidinoethyl)propionanilide hydrochloride, m.p. 202–203° and $[\alpha]_D^{25}$ +18.9 (2% in water) was 8.1 g. (35%).

Anal. Calcd. for $C_{17}H_{27}ClN_2O$: C, 65.7; H, 8.8; Cl, 11.4; N, 9.0. Found: C, 65.6; H, 8.8; Cl, 11.2; N, 9.4.

Acknowledgment. We are indebted to Mr. L. Brancone and associates for the microanalyses, to Dr. J. H. Clark and co-workers for the preparation of some of the intermediates, and to Dr. A. C. Osterberg and associates for the pharmacological data.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Synthetic Analgesics. III. Basic Anilides and Carbanilates Containing the Phenalkyl Moiety[1]

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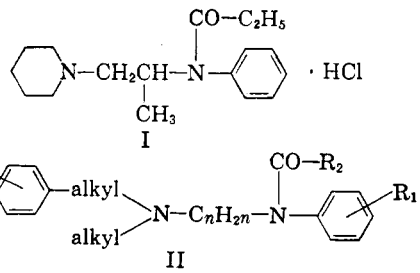
A series of *N*-(*tert*-aminoalkyl)anilides and -carbanilates containing the phenalkyl moiety has been prepared. Some of these compounds show analgesic potency in the codeine to morphine range. *N*-[2-(Methylphenethylamino)propyl]propionanilide sulfate, diampromid, has been chosen for clinical trial in man.

N-(1-Methyl-2-piperidinoethyl)propionanilide hydrochloride (I), phenampromid, which may be considered a nitrogen analog of isomethadone, was reported in the previous papers of this series[2] to have analgesic activity similar to meperidine.

Other investigators[3] have shown that replacement of the *N*-methyl group by a phenalkyl group in analgesics such as meperidine, racemorphan, and α-prodine often results in increased activity. We, therefore, were interested in determining whether increased potency could be obtained by introducing



I

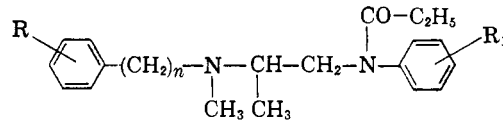
II

phenalkyl groups in our series of *N*-(*tert*-aminoalkyl)anilides and -carbonilates. Such compounds are represented by formula II.

One general procedure used for these compounds is that described in our previous paper.[2] This consisted of acylation of the appropriate alkylenediamines with an acid chloride or anhydride (Tables IV, V, VI). Conventional alkylation of an aniline with a *tert*-aminoalkyl halide gave the straight chain diamines[4] (Tables III and V). Lith-

TABLE I

ANALGESIC ACTIVITY



R	*n*	R_1	AD_{50}[a] Mg./Kg.
H	1	H	8
m-CH_3	1	H	2
p-CH_3	1	H	3
p-Cl	1	H	6
p-F	1	H	6
H	2	H	4
m-CH_3	2	H	14
p-NH_2	2	H	16
H	2	*m*-CH_3O	15
H	3	H	17
[b]		H	4
Meperidine			11
Morphine			3

[a] AD_{50} = The subcutaneous dose which elevates the rat tail radiant heat response time by 100% in 50% of the animals. [b] *N*-[2-(Cinnamylmethylamino)propyl]propionanilide.

(1) (a) Presented in part at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959; (b) W. B. Wright, Jr., R. A. Hardy, Jr., and H. J. Brabander, U. S. Patent 2,944,081, July, 1960.

(2) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, 81, 1518 (1959); *J. Org. Chem.*, 26, 476 (1961).

(3) (a) T. D. Perrine and N. B. Eddy, *J. Org. Chem.* 21, 125 (1956); (b) E. L. May, *J. Org. Chem.* 21, 899 (1956); (c) J. Weijlard, P. D. Orahovats, A. P. Sullivan, G. Purdue, F. D. Heath, and K. Pfister, *J. Am. Chem. Soc.*, 78, 2342 (1956); (d) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, 79, 1951 (1957); (e) B. Elpern, W. Wetterau, P. Carabateas, and L. Grumbach, 133rd Meeting of the American Chemical Society, April, 1958, Abstracts of Papers, p. 11M., Abs. No. 19.

TABLE II

2-AMINO- AND 2-BROMOPROPIONAMIDES

R	R_1	R_2	Yield, %	M.P.	B.P., Mm.	n_D^{25}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Br	CH_3	Anilino	53	98–101[a]			$C_9H_{11}BrNO$	47.4	47.3	4.4	4.6	35.0	35.1	6.1	6.2
Br	CH_3	Benzylmethylamino	65		120–123(0.4)	1.557	$C_{11}H_{14}BrNO$	51.6	51.6	5.5	5.7	31.2	31.5	5.5	5.3
Br	CH_3	Methylphenethylamino	80		140–145(0.5)		$C_{12}H_{16}BrNO$	53.4	54.0	6.0	6.3	29.6	28.0	5.2	5.3
Anilino	CH_3	Benzylmethylamino	34	90–92			$C_{17}H_{20}N_2O$	76.1	76.0	7.5	7.7			10.4	10.5
Anilino	CH_3	Methylphenethylamino	55	92–93			$C_{18}H_{22}N_2O$	76.6	76.8	7.9	8.0			9.9	10.0
Benzylmethylamino	CH_3	Anilino	80	72–74			$C_{17}H_{20}N_2O$	76.1	76.4	7.5	7.7			10.4	10.6
Methylphenethylamino	CH_3	Anilino	87	65–67			$C_{18}H_{22}N_2O$	76.6	76.6	7.9	8.0			9.9	10.0
Methylphenethylamino	CH_3	*m*-Chloroanilino	28[b]		174–178(0.2)	1.575	$C_{18}H_{21}ClN_2O$	68.2	67.5[c]	6.7	6.7	11.2	11.5	8.8	9.0
Methylphenethylamino	CH_3	*m*-Anisidino	62[b]		184–190(0.3)	1.568	$C_{19}H_{24}N_2O_2$	73.0	72.0[c]	7.7	7.8			9.0	8.7
Methylphenethylamino	C_2H_5	Anilino	80[d]		180–185(0.5)	1.564	$C_{19}H_{24}N_2O$	77.0	76.8	8.2	8.2			9.5	9.4
Ethylphenethylamino	CH_3	Anilino	77		195–198(0.8)	1.564	$C_{19}H_{24}N_2O$	77.0	76.8	8.2	8.4			9.5	9.4

[a] E. K. Harvill *et al.*, *J. Org. Chem.*, **17**, 1597 (1952) reports m.p. 101–102°. [b] Over-all yield from 2-bromopropionylbromide. [c] These compounds were reduced without further purification. [d] Over-all yield from 2-bromobutyryl chloride.

ium aluminum hydride reduction of the appropriate propionamide gave the desired branched chain diamines (Table III) of unequivocal structure.[2]

A second general procedure was also used, which allowed for the preparation of many end products containing a variety of phenalkyl groups from a common intermediate. Compound III was reductively debenzylated to IV in nearly quantitative yield and converted to V by reductive alkylation or by reaction with an aralkyl halide.

Pharmacological results indicated that introduction of the phenalkyl group in the basic moiety of the *N*-(*tert*-aminoalkyl)anilide series significantly increased analgesic activity in many cases. These compounds were tested by a sequential modification[5] of the mouse hot plate method of Woolfe and Macdonald[6] and Eddy *et al.*[7] and the rat tail radiant heat procedure of D'Amour and Smith.[8] *N*-[2-(Methylphenethylamino)propyl]propionanilide sulfate, diampromid, was found to approximate the potency of meperidine in mice and morphine in rats.[9] Extensive pharmacological evaluation led to the selection of this compound for trial in man. Clinical results indicate that diampromid is a narcotic-type analgesic.

Structure-activity relationships in this series

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(5) A. C. Osterberg, J. D. Haynes, and C. E. Rauh, *J. Pharmacol. Exptl. Therap.*, **122**, 59A (1958).

(6) G. Woolfe and A. D. Macdonald, *J. Pharmacol. Exptl. Therap.*, **80**, 300 (1944).

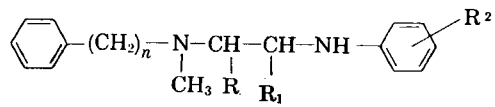
(7) N. B. Eddy, C. F. Touchberry, and J. E. Lieberman, *J. Pharmacol. Exptl. Therap.*, **98**, 121 (1950).

(8) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(9) A. C. Osterberg and C. E. Rauh, *The Pharmacologist*, 1 (No. 2), 78 (1959): Abstracts of Papers, Fall Meeting, *Am. Soc. Pharmacol. Exptl. Therap.*, Aug.–Sept., 1959, Coral Gables, Fla.

TABLE III

Diamine Intermediates

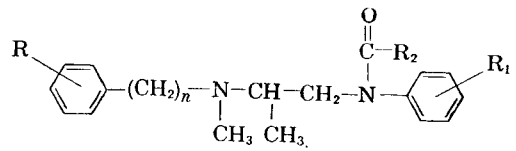


n	R	R_1	R_2	Yield,[a] %	B.P., mm.	n_D^{25}	Hydrochloride, M.P.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	H	72[c]	164–167(1.8)	1.575	121–123	$C_{16}H_{21}ClN_2$	69.4	69.3	7.6	7.8	12.8	12.9	10.1	10.3
1	H	H	*m*-Cl	64[c]	154–160(0.3)	1.581	113–116	$C_{16}H_{20}Cl_2N_2$	61.7	61.5	6.5	6.4	22.8	22.9	9.0	8.9
1	H	H	*m*-OCH_3	23[c]	186–194(1)	1.574	110–112	$C_{17}H_{23}ClN_2O$	66.5	66.5	7.6	7.9	11.6	11.9	9.1	9.4
1	H	H	*m*-OH	51[d]	176–182(0.2)	1.595		$C_{16}H_{20}N_2O$	75.0	75.0	7.9	8.1			10.9	10.3
1	H	CH_3	H	84[e]	140–144(0.4)	1.566	150–151	$C_{17}H_{23}ClN_2$	70.2	69.9	8.0	8.1	12.2	12.5	9.6	9.6
1	CH_3	H	H	86[e]	145–150(0.3)	1.590		$C_{17}H_{22}N_2$	80.3	80.4	8.7	8.9			11.0	11.0
2	H	CH_3	H	86[e]	145–150(0.4)		171–172	$C_{18}H_{25}ClN_2$	70.9	70.5	8.3	8.5	11.6	12.1	9.2	9.6
2	CH_3	H	H	80[e]	138–142(0.2)	1.565		$C_{18}H_{24}N_2$	80.6	80.2	9.0	9.4			10.4	10.5
2	CH_3	H	*m*-Cl	75[e]	175–180(0.3)	1.572		$C_{18}H_{23}ClN_2$	71.4	71.2	7.7	7.8	11.7	11.9	9.3	9.5
2	CH_3	H	*m*-OCH_3	72[e]	188–192(0.5)	1.567		$C_{19}H_{26}N_2O$	76.5	76.6	8.8	8.9			9.4	9.4
2	CH_3	H	*m*-OH	54[d]	205–216(0.2)			$C_{18}H_{24}N_2O$	76.0	76.1	8.5	8.8			9.9	10.3
2	C_2H_5	H	H	75[e]	162–166(0.3)	1.559		$C_{19}H_{26}N_2$	80.8	80.7	9.3	9.5			9.9	10.1
3	CH_3	H	H	52[f]	158–164(0.2)	1.559		$C_{19}H_{26}N_2$	80.8	80.6	9.3	9.5			9.9	10.2
4	CH_3	H	H	59[g]	158–162(0.08)	1.555		$C_{20}H_{28}N_2$	81.0	80.7	9.5	9.7			9.5	9.6
2[h]	CH_3	H	H	75[e]	158–162(0.3)	1.556		$C_{19}H_{26}N_2$	80.8	80.7	9.3	9.6			9.9	10.1

[a] Distilled base. [b] Formulas and analyses are for salt if reported, otherwise for the base. [c] Reaction of 2-benzylmethylaminoethyl chloride hydrochloride with the aniline derivative. [d] Hydrolysis of the methoxy analog, using 48% hydrobromic acid. [e] Lithium aluminum hydride reduction of the amide. [f] Prepared from 3-phenylpropyl bromide and N^2-methyl-N^1-phenyl-1,2-propanediamine. [g] Lithium aluminum hydride reduction of *N*-(2-anilino-1-methylethy-1)-*N*-methyl-4-phenylbutyramide. [h] *N*-Ethyl-N^2-phenethyl-N^1-phenyl-1,2-propanediamine.

TABLE IV

N-[2-(PHENALKYLMETHYLAMINO)PROPYL]ANILIDES AND -CARBANILATES (METHADONE ANALOGS)

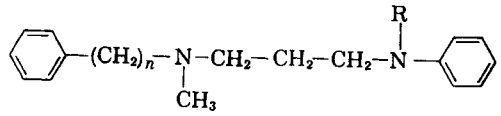


				Yield,[a]						Carbon, %		Hydrogen, %		Chlorine, %		Nitrogen, %	
n	R	R_1	R_2	%	B.P., Mm.	n_D^{25}	Salt	M.P., Salt	Formula[b]	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	H	H	C_2H_5	90[c]	166–170(0.4)	1.548	HCl	150–151[d]	$C_{20}H_{27}ClN_2O$	69.2	69.4	7.8	7.9	10.2	10.4	8.1	8.3
1	*o*-Cl	H	C_2H_5	54[e]	165–170(0.1)	1.557	HCl	136–138	$C_{20}H_{26}Cl_2N_2O$	63.0	63.3	6.9	7.0	18.6	18.3	7.3	7.3
1	*p*-Cl	H	C_2H_5	72[e]	183–188(0.1)	1.555	HCl	169–171	$C_{20}H_{26}Cl_2N_2O$	63.0	63.3	6.9	7.1	18.6	18.6	7.3	7.3
1	*o*-F	H	C_2H_5	74[e]	160–165(0.1)	1.541	HCl	146–148	$C_{20}H_{26}ClFN_2O$	65.8	66.2	7.2	7.3	9.7	9.9	7.7	7.7
1	*p*-F	H	C_2H_5	43[e]	152–156(0.2)	1.538	HCl	161–163	$C_{20}H_{26}ClFN_2O$	65.8	65.5	7.2	7.4	9.7	9.4	7.7	7.6
1	*m*-CH_3	H	C_2H_5	41[e]	170–176(0.2)		HCl	150–151	$C_{21}H_{29}ClN_2O$	69.9	70.1	8.1	7.9	9.8	10.0	7.8	7.8
1	*p*-CH_3	H	C_2H_5	67[e]	160–164(0.1)	1.546			$C_{21}H_{28}N_2O$	77.7	77.3	8.7	8.7			8.6	8.7
1	*p*-OCH_3	H	C_2H_5	26[e]	165–175(0.2)	1.549			$C_{21}H_{28}N_2O_2$	74.1	73.7	8.3	8.5			8.2	8.6
1	H	H	OC_2H_5	37[f]	155–163(0.2)	1.540	HCl	125–127	$C_{20}H_{27}ClN_2O_2$	66.2	66.3	7.5	7.8	9.8	9.9	7.7	7.9
2	H	H	CH_3	81[c]	144–150(0.08)	1.549	HNO_3	142–143	$C_{20}H_{27}N_3O_4$	64.3	64.0	7.3	7.1			11.3	11.3
2	H	H	C_2H_5	83[c]	174–178(0.5)	1.547	H_2SO_4	110–111	$C_{21}H_{30}N_2O_5S$	59.7	59.6	7.2	7.4			6.6	6.4
2	H	H	C_3H_7	78[c]	165–170(0.2)	1.540	H_2SO_4	90–92	$C_{22}H_{32}N_2O_5S$	60.5	60.2	7.4	7.9			6.4	6.4
2	H	H	*i*-C_3H_7	76[c]	148–155(0.08)	1.541	H_2SO_4	158–159	$C_{22}H_{32}N_2O_5S$	60.5	60.6	7.4	7.6			6.4	6.4
2	H	H	C_4H_9	81[c]	156–162(0.08)	1.538	H_2SO_4	117–119	$C_{23}H_{34}N_2O_5S$	61.3	61.2	7.6	7.9			6.2	6.3
2	H	*m*-Cl	C_2H_5	81[c]	180–185(0.2)	1.552	HCl	121–123	$C_{21}H_{28}Cl_2N_2O$	63.8	63.4	7.1	7.3	17.9	17.7	7.1	7.2
2	H	*m*-OCH_3	C_2H_5	80[c]	195–196(0.1)	1.547	HCl	134–135[d]	$C_{22}H_{31}ClN_2O_2$	67.6	67.4	8.0	8.1	9.1	8.9	7.2	7.3
2	H	*m*-$OCOC_2H_5$	C_2H_5	84[c]	200–205(0.1)				$C_{24}H_{32}N_2O_3$	72.7	72.1	8.1	8.3			7.1	7.3
2	*m*-CH_3	H	C_2H_5	45[e]	170–175(0.1)	1.543			$C_{22}H_{30}N_2O$	78.1	78.0	8.9	9.2			8.2	8.2
2	*p*-NH_2	H	C_2H_5	10[g]	190–200(0.1)				$C_{21}H_{29}N_3O$	74.3	74.1	8.6	9.0			12.4	12.4
3	H	H	C_2H_5	84[c]	165–170(0.3)	1.544			$C_{22}H_{30}N_2O$	78.1	77.8	8.9	9.2			8.3	8.3
4	H	H	C_2H_5	63[c]	170–175(0.1)	1.538[h]			$C_{23}H_{32}N_2O$	78.4	78.1	9.2	9.3			7.9	7.9
h	H	H	C_2H_5	29[e,i]	170–176(0.2)	1.564			$C_{22}H_{28}N_2O$	78.5	78.2	8.4	8.8			8.3	8.1
2[j]	H	H	C_2H_5	79[c]	180–185(0.2)	1.541	H_2SO_4	156–157	$C_{22}H_{32}N_2O_5S$	60.5	60.4	7.4	7.6			6.4	6.6
2[k]	H	H	C_2H_5	79[c]	170–175(0.1)	1.541			$C_{22}H_{30}N_2O$	78.1	77.8	8.9	9.0			8.3	8.5

[a] Distilled base. [b] Formulas and analyses are for the salt if reported, otherwise for the base. [c] Reaction of the base with the anhydride. [d] Recrystallized from acetone. [e] Reaction of the phenalkyl halide with *N*-[2-(methylamino)propyl]propionanilide. [f] Reaction of the amine with ethyl chloroformate. [g] See experimental section. [h] *N*-[2-(Cinnamylmethylamino)-propyl]propionanilide. [i] From 3-chloropropenylbenzene and *N*-[2-(methylamino)propyl]propionanilide. [j] *N*-[2-(Ethylphenethylamino)propyl]propionanilide. [k] *N*-[2-(Methyl-phenethylamino)butyl]propionanilide.

TABLE V

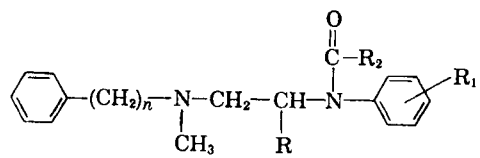
1,3-PROPANEDIAMINE DERIVATIVES



n	R	Yield,[a] %	B.P., mm.	n_D^{25}	Hydrochloride, M.P.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	65	160–165(0.5)	1.569		$C_{17}H_{22}N_2$	80.3	80.0	8.7	8.7			11.0	11.4
1	Propionyl	72	160–165(0.3)		150–152	$C_{20}H_{27}ClN_2O$	69.2	69.1	7.8	8.0	10.2	10.2	8.1	8.0
1	Carbethoxy	51	150–155(0.1)	1.533	124–126	$C_{20}H_{27}ClN_2O_2$	66.2	65.9	7.5	7.7	9.8	10.2	7.7	7.7
2	H	71	175–180(0.8)	1.564		$C_{18}H_{24}N_2$	80.5	80.0	9.0	9.2			10.4	10.4
2	Propionyl	80	200–205(1.0)	1.545	99–101	$C_{21}H_{29}ClN_2O$	69.9	69.5	8.1	8.3	9.8	10.2	7.8	7.6
2	Carbethoxy	52	170–175(0.2)	1.538		$C_{21}H_{28}N_2O_2$	74.1	73.5	8.3	8.4			8.2	8.2

[a] Distilled base. [b] Formulas and analyses are for salt if reported, otherwise for base.

TABLE VI. MISCELLANEOUS ANILIDES[a]



n	R	R_1	R_2	Yield,[b] %	B.P., Mm.	n_D^{25}	Hydrochloride, M.P.	Formula[c]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	CH_3	96	146–150(0.1)	1.556	203–205	$C_{18}H_{23}ClN_2O$	67.8	67.5	7.3	7.7	11.1	11.1	8.8	9.0
1	H	H	C_2H_5	92	150–155(0.3)	1.551	179–181	$C_{19}H_{25}ClN_2O$	68.6	68.2	7.6	7.7	10.7	11.0	8.4	8.2
1	H	H	C_3H_7	74	166–170(0.4)		117–118[d]	$C_{20}H_{27}ClN_2O$	69.2	68.8	7.8	8.3	10.2	10.1	8.1	8.1
1	H	H	i-C_3H_7	72	140–144(0.3)		200–202	$C_{20}H_{27}ClN_2O$	69.2	69.6	7.8	7.6	10.2	10.2	8.1	8.1
1	H	m-Cl	C_2H_5	74	165–170(0.1)	1.558	166–168	$C_{19}H_{24}Cl_2N_2O$	62.1	61.8	6.6	6.6	19.3	19.2	7.7	7.5
1	H	m-OCH_3	C_2H_5	80	182–186(0.4)	1.553	123–125[e]	$C_{20}H_{27}ClN_2O_2$	66.2	66.2	7.5	7.6	9.8	10.0	7.7	8.2
1	H	m-OH	C_2H_5	24[f]	190–200(0.08)	1.572		$C_{19}H_{24}N_2O_2$	73.0	73.3	7.7	7.9			9.0	9.3
1	CH_3	H	C_2H_5	86	160–162(0.4)	1.546	163–164	$C_{20}H_{27}ClN_2O$	69.2	69.0	7.8	8.2	10.2	10.4	8.1	7.9
2	CH_3	H	C_2H_5	84	155–160(0.2)		125–127	$C_{21}H_{29}ClN_2O$	69.9	69.9	8.1	8.3	9.8	10.0	7.8	7.8
2	CH_3	H	C_3H_7	91	165–170(0.2)	1.537	103–105[g]	$C_{22}H_{31}N_3O_4$	65.8	65.8	7.8	8.0			10.5	10.2

[a] Prepared by the reaction of the diamine with the anhydride, unless otherwise noted. [b] Distilled base. [c] Formulas and analyses are for the salt if reported, otherwise for the distilled base. [d] Recrystallized from ethyl acetate. [e] Recrystallized from acetone. [f] Reaction of the diamine with propionyl chloride. [g] Nitrate.

are generally similar to those described in our previous paper.[2] However, the greatest activity in the phenalkyl series was found when the alkylene chain between the two nitrogens was analogous to that of methadone. A variety of phenalkyl groups gave active compounds with a considerable range of potency as illustrated in Table I.

EXPERIMENTAL

The salts, 2-bromopropionamides (Table II), 2-aminopropionamides (Table II), alkylenediamines (Tables III and V), carbanilates (Tables IV and V), and some of the anilides (Tables IV–VI) were prepared by the methods described in the previous paper of this series.[2] New procedures are described below.

N-[2-(Methylamino)propionanilide. A mixture of 31 g. (0.1 mole) of *N*-[2-(benzylmethylamino)propyl]propionanilide, 25 ml. of 4*N* hydrochloric acid, 175 ml. of ethanol, and 2 g. of 10% palladium-on-carbon catalyst was shaken in a Parr hydrogenator under about 3 atm. of hydrogen pressure until the theoretical amount of hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated to a sirup and treated with aqueous sodium hydroxide. The product was extracted into ether and distilled. The yield of *N*-[2-(methylamino)propyl]propionanilide, b.p. 112–116° (0.2 mm.) and n_D^{25} 1.521, was 71%.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.9; H, 9.1; N, 12.7. Found: C, 70.5; H, 9.3; N, 13.1.

N-[2-(Phenalkylmethylamino)propyl]propionanilides. A mixture of 0.025 mole of the appropriate phenalkyl halide, 0.05 mole of *N*-[2-(methylamino)propyl]propionanilide, and 40 ml. of ethanol was heated on the steam bath overnight, concentrated to remove the solvent, and diluted with 10 ml. of water. The reaction mixture was extracted with ether and the combined ether extracts were dried over magnesium sulfate and distilled.

N-[2-(p-Aminophenethylmethylamino)propyl]propionanilide. A mixture of 23.0 g. (0.1 mole) of *p*-nitrophenethyl bromide, 18.0 g. (0.11 mole) of N^2-methyl-N^1-phenyl-1,2-propanediamine, 150 ml. of toluene, and 21.2 g. of sodium carbonate was heated at reflux for 48 hr. and then cooled. Enough water was added to dissolve the solids and the toluene layer was separated. The aqueous layer was extracted with ether. The organic layers were combined, dried over magnesium sulfate, and concentrated to a syrup. Propionic anhydride (50 ml.) was added and the reaction mixture was heated on the steam bath for 3 hr. and then concentrated to remove the propionic acid and excess propionic anhydride. A solution of 10 ml. of concd. hydrochloric acid and 100 ml. of water was added and the mixture was extracted with ether to remove non-basic products. The aqueous layer was treated with 30 ml. of 5*N* sodium hydroxide and extracted with ether to remove the crude *N*-[2-(methyl-*p*-nitrophenethylamino)propyl]propionanilide (9.8 g.). A mixture of the above crude intermediate with 100 ml. of ethanol, 5 ml. of water, 5 ml. of concd. hydrochloric acid, and 1 g. of palladium-on-carbon catalyst was reduced in the Parr hydrogenator until 4.7 lb. of hydrogen was absorbed. The catalyst was filtered and the solvent was evaporated. The residue was made alkaline with dilute sodium hydroxide and extracted with ether. The ether layer was concentrated and distilled. *N*-[2-*p*-Aminophenethylmethylamino)propyl]propionanilide was collected at 190–200° (0.1 mm.).

4-Phenylbutyryl chloride. A solution of 16.4 g. (0.1 mole) of 4-phenylbutyric acid in 100 ml. of cold chloroform was slowly added to a cooled solution of 30 ml. of thionyl chloride in 100 ml. of chloroform. The reaction mixture was refluxed for 90 min. and distilled. The yield of 4-phenylbutyryl chloride, b.p. 80–85° (0.2 mm.), was 8.6 g. (47%). This compound was not analyzed.

N^2-Methyl-N^1-phenyl-1,2-propanediamine. A mixture of 12.7 g. (0.05 mole) of N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine, 50 ml. of 1*N* hydrochloric acid, 50 ml. of ethanol, and 1 g. of 10% palladium-on-carbon catalyst was shaken in a Parr hydrogenator under about 3 atm. of hydrogen pressure until the theoretical amount of hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated. The residue was triturated with ether until crystallization occurred and the product was filtered. The yield of N^2-methyl-N^1-phenyl-1,2-propanediamine, hydrochloride, m.p. 96–99°, was 9.3 g. (93%). Recrystallization from ethanol by the addition of ether raised the melting point to 100–102°.

Anal. Calcd. for $C_{10}H_{17}ClN_2$: C, 59.8; H, 8.5; Cl, 17.7; N, 14.0. Found: C, 59.7; H, 8.9; Cl, 17.7; N, 13.9.

The base was obtained by treating the hydrochloride with aqueous alkali, extracting the product with ether, and distilling, b.p. 90–96° (0.1 mm.) and n_D^{25} 1.547.

N-(2-Anilino-1-methylethyl)-N-methyl-4-phenylbutyramide. A solution of 8.6 g. (0.05 mole) of 4-phenylbutyryl chloride in ether was added to a cooled solution of 16.4 g. (0.1 mole) of N^2-methyl-N^1-phenyl-1,2-propanediamine in 100 ml. of ether. The reaction mixture was refluxed for 2 hr. and then cooled overnight. The salt was filtered and washed with ether. The organic layers were combined and shaken with 50 ml. of 1*N* sodium hydroxide. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined and distilled. *N*-(2-Anilino-1-methylethyl)-*N*-methyl-4-phenylbutyramide, b.p. 195–200° (0.4 mm.), was obtained in 60% yield.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.4; H, 8.4; N, 9.0. Found: C, 77.1; H, 8.6; N, 9.4.

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