In the preparation of the monomethylene derivative 30 g. (0.5 mole) of methylene chloride and 15 g. (0.1 mole) of sodium iodide replaced the α,ω-dibromoalkane and a reflux time of 68 hr. was used.

4,4'-Dicarboxy-α,ω-diphenoxy alkanes. Method A. In a 500 ml. three neck flask, fitted with a condenser and mechanical stirrer, were placed 0.02 mole of a pure 4,4'-diformyl-α,ω-diphenoxyalkane and 100 ml. of absolute ethanol. The mixture was heated until all solid had dissolved and 13.6 g. (0.08 mole) of silver nitrate in 28 ml. of water and 4.8 g. (0.12 mole) of sodium hydroxide in 10 ml. of water were added. At the end of a 30-min. heating period the mixture was placed into 500 ml. of hot water and filtered while hot. When necessary the extraction was repeated using another 500 ml. of hot water. The filtrate was acidified to congo red with 6*N* hydrochloric acid. When the white precipitate was filtered, washed thoroughly with water, and dried at 110°, a product of high purity was obtained. One recrystallization from ethylene glycol monomethyl ether gave an analytically pure product.

Method B. After dissolving 0.02 mole of a 4,4'-dicarbethoxy-α,ω-diphenoxyalkane in hot absolute ethanol or its recrystallization solvent, the solution was cooled to 60° and 500 ml. of a saturated solution of potassium hydroxide in absolute methanol were added. The mixture was refluxed for 30 min. If no precipitation occurred within the first 10 min. of refluxing, solid potassium hydroxide was added until precipitation began. At the end of the reflux period the mixture was cooled in an ice bath for 15 min. and the precipitate was collected. The precipitate was dissolved in 500 to 1000 ml. of hot water and acidified to congo red with 6*N* hydrochloric acid. When the white solid was filtered, washed thoroughly with water, and dried at 110° an acid of high purity was obtained. Recrystallization from ethylene glycol monomethyl ether gave analytically pure crystals.

Preparation of sodium salts of 4,4'-dicarboxy-α,ω-diphenoxyalkanes. A 4,4'-dicarboxy-α,ω-diphenoxyalkane (5 g.) was placed in a 500 ml. flask and 25–50 ml. of hot water containing a very slight excess of the equivalent amount of sodium hydroxide were added. The mixture was boiled until solution was complete, more water being added when necessary After filtering, the solution was placed in an ice bath for 20 min. At the end of the cooling period, 250 ml. of absolute ethanol was added to the cold solution to initiate or complete precipitation of the sodium salt. The solution was kept in an ice bath for 1 hr. before filtering. The excess of sodium hydroxide was removed by washing the salt with 25 ml. portions of absolute ethanol until the washings were neutral to litmus. The salt was dried at 110°. The yield was nearly quantitative.

St. Louis 4, Mo.
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[Contribution from the Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Co.]

Synthetic Analgesics. II. Basic Anilides and Carbanilates[1]

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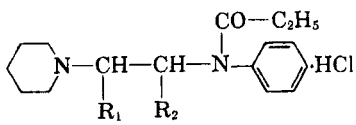
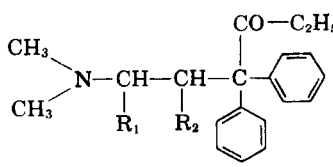
N-(*tert*-Aminoalkyl)anilides and *N*-(*tert*-aminoalkyl)carbanilates were synthesized for analgesic testing. *N*-(1-Methyl-2-piperidinoethyl)propionanilide hydrochloride, phenampromid, was chosen as an analgesic worthy of clinical investigation in man. This compound was resolved, and analgesic activity was shown to reside largely in the *l*-enantiomorph.

In the previous paper of this series[2] a new potent analgesic, *N*-(1-methyl-2-piperidinoethyl)propionanilide hydrochloride, phenampromid[3] (Ia), was described. This compound may be considered an analog of isomethadone (IIa), in which the dimethylamino moiety has been replaced by the piperidino group and the quaternary carbon atom and one of its attached phenyl groups has been replaced by nitrogen.



Ia. $R_1 = H$, $R_2 = CH_3$
b. $R_1 = CH_3$, $R_2 = H$



IIa. $R_1 = H$, $R_2 = CH_3$
b. $R_1 = CH_3$, $R_2 = H$

Such a compound retains the steric requirements of a potent analgesic as set forth by Beckett and Casy and others,[4] and would be expected to fit the same receptor surface as active analgesics such as meperidine, methadone, and morphine.

The basic anilides studied in this program were prepared by acylation of the appropriate ethylenediamines and propanediamines with an acid halide or anhydride. The straight chain ethylenediamine (Table III) and 1,3-propanediamine (Table VII) intermediates were obtained by the well known procedure[5] of reacting a *tert*-aminoalkyl chloride with an aniline derivative (Method A). This reaction was not useful for the preparation of branched

(1) Presented in part at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

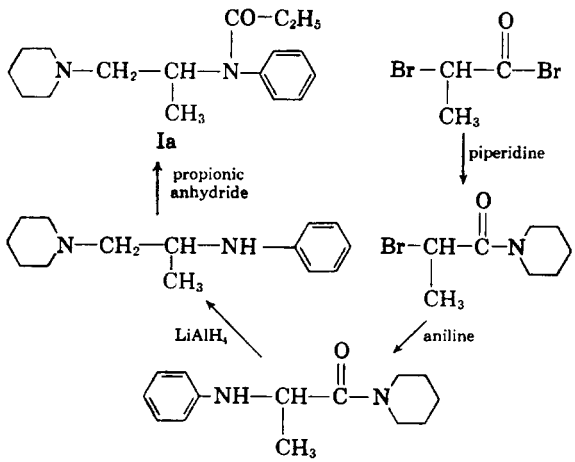
(2) Preliminary communication, W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(3) The generic name "phenampromid" has been proposed for this compound.

(4) (a) A. H. Beckett and A. F. Casy, *J. Pharm. and Pharmacol.*, **6**, 986 (1954); (b) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

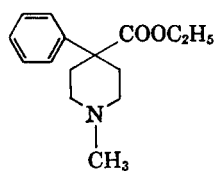
chain 1,2-propanediamines since branched chain *tert*-aminoalkyl chlorides rearrange through a cyclic imonium structure and form mixtures of the isomeric diamines.[5a,6]

Branched chain alkylenediamines of unequivocal structure (Table III) were obtained by lithium aluminum hydride reduction of amides of known structure (Method B). This reaction scheme is illustrated below for the preparation of compound Ia (isomethadone series, Table V):

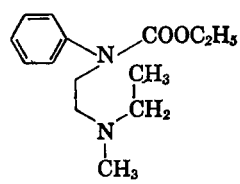


The other position isomers (methadone series, Table VI) were obtained when the amines were allowed to react in the opposite order.

A series of basic carbanilates (Table VIII) which may be considered as nitrogen analogs of ethyl 1-methyl-4-phenylisonipecotate, meperidine (III), was also prepared by the reaction of ethylenediamines and propanediamines with alkylchloroformates. The structural relationship between meperidine (III) and one of these compounds, ethyl *N*-(2-ethylmethylaminoethyl)carbanilate (IV), is illustrated below.



III



IV

These compounds were tested for analgesic activity by two methods. A sequential modification[7] of the mouse hot plate method of Woolfe and Macdonald[8] and Eddy *et al.*[9] and the rat-tail radiant heat procedure of D'Amour and Smith[10] were used. Phenampromid (Ia) was found to approximate the potency of codeine in mice and meperidine in rats.[11] Extensive pharmacological evaluation led to the selection of this compound for trial in man. Clinical results indicate that phenampromid is a narcotic-type analgesic in man and also possesses antitussive activity.

Structure-activity relationships in this series of *N*-(*tert*-aminoalkyl)anilides formed a consistent pattern. Good activity was particularly sensitive to changes in the alkylene chain between the two nitrogens. For example, phenampromid (Ia), with an alkylene chain analogous to isomethadone, was a potent analgesic while the isomeric methadone analog, *N*-(2-piperidinopropyl)propionanilide (Ib), was virtually devoid of analgesic activity. When the acyl portion of the anilide moiety was varied, optimum activity was obtained with the propionyl group. Substituents in the aromatic ring generally reduced analgesic activity. The aliphatic *tert*-amino group could be varied somewhat with retention of activity, but the piperidino radical gave the best results. The corresponding *N*-(*tert*-aminoalkyl)carbanilates (Table VIII) showed poor analgesic activity compared to codeine, meperidine, and the anilide series.

When analgesics containing an asymmetric center are resolved, one enantiomorph is usually much more active than the other.[4] A similar relation was found with phenampromid. The *l*-enantiomorph was more active and the *d*-enantiomorph was much less active than the racemic form (Table I).

TABLE I

RELATIVE ACTIVITIES OF ENANTIOMORPHS

Compound	AD_{50} (Mg./Kg.)[a]
dl-Phenampromid	13
l-Phenampromid	9
d-Phenampromid	36
Morphine sulfate	3
Meperidine	11

[a] AD_{50} = the subcutaneous dose which elevates the rat-tail radiant heat response time by 100% in 50% of the animals.

Resolution was accomplished by treating an ethanol solution of phenampromid with *l*-malic acid. *l*-*N*-(1-Methyl-2-piperidinoethyl)propionanilide-*l*-malate, m.p. 178–179.5°, $[\alpha]_D^{25}$ − 16.3

(5) (a) F. Leonard and U. V. Solmssen, *J. Am. Chem. Soc.*, **70**, 2064 (1948); (b) S. G. Fridman, *Zhur. Obshcheĭ Khim.*, **23**, 278 (1953); (c) M. A. Stahmann and A. C. Cope, *J. Am. Chem. Soc.*, **68**, 2494 (1946); (d) M. W. Goldberg and S. Teitel, U. S. Patent **2,746,992**, May 22, 1956.

(6) (a) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, p. 357; (b) J. F. Kerwin, G. E. Ullyot, R. C. Fuson, and C. L. Zirkle, *J. Am. Chem. Soc.*, **69**, 2961 (1947); (c) E. M. Schultz, C. M. Robb, and J. M. Sprague, *J. Am. Chem. Soc.*, **69**, 2454 (1947).

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

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

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

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

(11) 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 II

2-AMINOPROPIOMAMIDES $R_1—CH(CH_3)—C(=O)—R$

R	R_1	Yield,[a] %	M.P.	B.P., Mm.	n_D^{25}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	Anilino	27[b]	127–129			$C_{11}H_{16}N_2O$	68.7	68.7	8.4	8.6	14.6	14.7
Diethylamino	Anilino	63	78–80			$C_{13}H_{20}N_2O$	70.9	70.6	9.2	9.3	12.7	12.6
Pyrrolidino	Anilino	62	113–115			$C_{13}H_{18}N_2O$	71.5	71.9	8.3	8.2	12.8	12.8
Piperidino	Anilino	81	90–91			$C_{14}H_{20}N_2O$	72.4	72.2	8.7	8.6	12.1	12.1
Piperidino	*m*-Chloroanilino	58	140–142			$C_{14}H_{19}ClN_2O$[c]	63.0	62.8	7.2	7.3	10.5	10.7
Piperidino	*m*-Anisidino	84	143–145			$C_{15}H_{22}N_2O_2$	68.7	68.7	8.5	8.7	10.7	10.5
Hexamethyleneimino	Anilino	22	69–70[d]			$C_{15}H_{22}N_2O$	73.1	72.9	9.0	9.2	11.4	11.3
Morpholino	Anilino	41	158–160			$C_{13}H_{18}N_2O_2$	66.6	66.3	7.7	7.9	12.0	11.7
Anilino	Dimethylamino	86[e]		112–118(0.5)	1.542	$C_{11}H_{16}N_2O$	68.7	68.4	8.4	8.6	14.6	14.3
Anilino	Diethylamino	91		184–186(7)	1.527	$C_{13}H_{20}N_2O$	70.9	70.8	9.2	9.2	12.7	13.3
Anilino	Piperidino	93		138–142(0.4)	1.548	$C_{14}H_{20}N_2O$	72.4	72.5	8.7	8.8	12.1	12.1
Anilino	Morpholino	83		212–214(7)	1.557	$C_{13}H_{18}N_2O_2$	66.6	66.4	7.7	7.7	12.0	12.2
Anilino	4-Methylpiperazino	74	85–86			$C_{14}H_{21}N_3O$	68.0	67.7	8.6	8.7	17.0	17.3
m-Chloroanilino	Piperidino	38[b]	67–68	176–180(1)		$C_{14}H_{19}ClN_2O$[f]	63.0	62.4	7.2	7.1	10.5	10.7
m-Anisidino	Piperidino	72[b]		154–160(0.2)		$C_{15}H_{23}ClN_2O_2$[g]	60.3	60.5	7.8	8.0	9.4	9.4

[a] The yield is calculated from the distilled 2-bromopropionamide unless otherwise noted. [b] The yield is calculated from bromopropionyl bromide. [c] Chlorine: calcd. 13.3; found 13.4. [d] Recrystallized from dilute ethanol. [e] H. Erdtman and N. Löfgren, *Svensk. Kem. Tidskr.* **49**, 163 (1937), reported b.p. 140–144° (0.44 mm.), [f] Chlorine: calcd. 13.3; found 13.5. [g] Hydrochloride, m.p. 164–166°. Chlorine: calcd. 11.9; found, 12.0.

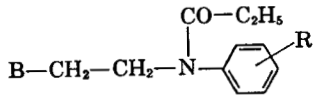
TABLE III. ETHYLENEDIAMINES B—CH(R)—CH(R$_1$)—NH—C$_6$H$_4$—R$_2$

R	R	R$_1$	R$_2$	Method	Yield,[a] %	B.P., Mm.	n_D^{25}	Salt	M.P.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	H	H	H	A	41[c,d]	100–103(2)	1.537	HCl	138–140	$C_{10}H_{17}ClN_2$	59.7	60.0	8.5	8.6	17.7	17.8	14.0	14.2
Dimethylamino	H	H	*p*-CH$_3$	A	27[c,e]	83–88(0.7)	1.530	2HCl	177–179	$C_{11}H_{20}Cl_2N_2$	52.6	52.9	8.0	8.1	28.2	28.4	11.1	11.1
Dimethylamino	H	H	*m*-Cl	A	39[c,f]	120–125(1.8)		HCl	135–137	$C_{10}H_{16}Cl_2N_2$	51.0	51.2	6.8	7.2	30.2	30.4	11.9	12.3
Dimethylamino	CH$_3$	H	H	B	67[c]	90–95(0.6)	1.526	HNO$_3$	111–113	$C_{11}H_9N_3O_3$	54.8	54.9	7.9	7.9			17.4	17.2
Ethylmethyl-amino	H	H	H	B	74[g]	86–90(0.2)	1.533			$C_{11}H_{18}N_2$[b]	74.1	73.6	10.2	10.2			15.7	16.0
Diethylamino	H	H	H	A	62	100–105(0.3)	1.529	HCl[i]	120–121	$C_{11}H_{19}ClN_2$	61.5	61.9	8.9	9.1	16.5	16.2	13.1	12.9
Diethylamino	H	H	H	A	65[j]	135–147(12)	1.525	HCl	135–136	$C_{12}H_{21}ClN_2$	63.0	63.1	9.2	9.1	15.5	15.8	12.2	12.1
Diethylamino	H	H	*m*-OCH$_3$	A	45[k]	134–138(1.6)	1.530	HCl	130–132	$C_{13}H_{23}ClN_2O$	60.3	59.9	9.0	9.1	13.7	13.8	10.8	10.8
Diethylamino	H	H	*o*-CH$_3$	A	68	153–156(12)	1.520	HCl	124–126	$C_{13}H_{23}ClN_2$	64.3	64.2	9.6	9.6	14.6	14.7	11.5	11.7
Diethylamino	H	H	*m*-Cl	A	76[l]	130–133(1.2)	1.539	HCl	162–163	$C_{12}H_{20}Cl_2N_2$	54.8	55.0	7.7	7.8	26.9	26.9	10.6	10.9
Diethylamino	H	H	2.4-diCl	A	65[m]	136–144(1.4)	1.544	HCl	138–139	$C_{12}H_{19}Cl_3N_2$	48.4	48.1	6.4	6.6	35.7	35.9	9.4	9.3
Diethylamino	H	H	*p*-OC$_2$H$_5$[c]	A	47[n]	142–146(0.3)		2HCl	128–131	$C_{14}H_{26}Cl_2N_2O$	54.4	54.7	8.5	8.8	22.9	22.5	9.1	8.9
Diethylamino	H	H	*m*-Br	A	58	137–140(0.6)	1.554	HCl	175–177	$C_{12}H_{20}BrClN_2$	46.8	46.8	6.6	6.6	11.5	11.7	9.1	9.5
Diethylamino	H	CH$_3$	H	B	82[o]	87–88(0.5)	1.518	HCl[p]	97–99	$C_{13}H_{23}ClN_2$	64.3	64.2	9.5	9.8	14.6	14.6	11.5	11.4
Diethylamino	CH$_3$	H	H	B	80[q]	100–105(0.4)	1.518	HNO$_3$	88–90	$C_{13}H_{22}N_3O_3$	58.0	58.0	8.6	8.7			15.6	15.6
Dibutylamino	H	H	H	A	85	141–145(3)	1.507	HCl	88–91	$C_{18}H_{29}ClN_2$	67.4	67.1	10.3	10.4	12.5	12.7	9.8	10.2
Dibutylamino	H	H	*m*-Cl	A	87	163–165(3)	1.518	HCl	108–109	$C_{16}H_{28}Cl_2N_2$	60.2	59.9	8.9	8.7	22.2	22.4	8.8	9.0
Pyrrolidino	H	H	H	A	55[c,r]	142–144(2)	1.555	HCl	149–150	$C_{12}H_{19}ClN_2$	63.6	63.6	8.5	8.7	15.6	15.8	12.4	12.4
Pyrrolidino	H	H	*m*-Cl	A	59	156–159(2)	1.561	HCl	160–162	$C_{12}H_{18}Cl_2N_2$	55.2	55.0	7.0	7.3	27.2	26.9	10.7	10.9
Pyrrolidino	H	CH$_3$	H	B	68	110–112(0.8)	1.541	HNO$_3$	95–96	$C_{13}H_{21}N_3O_3$	58.4	58.4	7.9	8.0			15.7	15.9
Piperidino	H	H	H	A	80[c,s]	146–149(2)	1.549	HCl	185–186	$C_{13}H_{21}ClN_2$	64.8	64.7	8.8	8.9	14.7	14.7	11.6	11.7
Piperidino	H	CH$_3$	H	B	85	108–112(0.4)	1.537	2HCl	178–180	$C_{14}H_{24}Cl_2N_2$	57.7	57.4	8.3	8.2	24.4	24.1	9.6	9.9
Piperidino	H	CH$_3$	*m*-Cl	B	78	130–133(0.4)		HCl	129–131	$C_{14}H_{22}Cl_2N_2$	58.1	58.7	7.7	7.9	24.5	24.1	9.7	9.8
Piperidino	H	CH$_3$	*m*-OCH$_3$	B	79	127–130(0.3)	1.542	HCl	108–110	$C_{15}H_{25}ClN_2O$	63.2	62.9	8.8	8.9	12.5	12.2	9.8	9.6
Piperidino	CH$_3$	H	H	B	81[t]	110–112(0.4)	1.542	2HCl	202–204	$C_{14}H_{24}Cl_2N_2$	57.7	57.4	8.3	8.2	24.4	24.1	9.6	9.9
Piperidino	CH$_3$	H	*m*-OCH$_3$	B	74	146–150(0.3)	1.544	HCl	165–168	$C_{15}H_{25}Cl\,N_2O$	63.3	62.9	8.8	8.9	12.4	12.8	9.8	9.7
Piperidino	CH$_3$	H	*m*-OH	C	25[u]	190–195(0.2)												
Morpholino	H	H	H	A	47	156–161(0.8)	1.555	HCl	171–173	$C_{12}H_{19}ClN_2O$	59.4	59.4	7.9	7.6	14.6	14.6	11.5	11.7
Morpholino	H	H	*m*-Cl	A	58	174–178(0.8)	1.566	HCl	155–157	$C_{12}H_{18}Cl_2N_2O$	52.0	52.1	6.6	6.8	25.6	25.7	10.1	10.4
Morpholino	H	CH$_3$	H	B	90	108–116(0.2)	1.546	2HCl	176–178	$C_{13}H_{22}Cl_2N_2O$	53.3	53.0	7.6	7.8	24.2	24.0	9.6	9.6
Morpholino	CH$_3$	H	H	B	70	150–152(1.4)	1.548	HCl	173–175	$C_{13}H_{21}ClN_2O$	60.8	60.6	8.3	8.4	13.8	13.8	10.9	11.1
Hexamethylene-imino	H	CH$_3$	H	B	68	130–132(0.7)	1.540	Base		$C_{15}H_{24}N_2$	77.5	77.5	10.4	10.5			12.1	11.9
Methyl-piperazino	CH$_3$	H	H	B	70	156–158(1.6)	1.543	Base		$C_{14}H_{23}N_3$	72.0	71.6	9.9	9.9			18.0	17.8

[a] The yields are for the distilled base. [b] Formulas and analyses are for salts unless otherwise noted. [c] Analysis of the base was unsatisfactory. [d] F. J. Villani, N. Sperber, J. Lang, and D. Papa, *J. Am. Chem. Soc.*, 72, 2724(1950), reported b.p. 90–98° (1 mm.) and n_D 1.535. [e] Ref. d reported b.p. 100–103° (1 mm.) and n_D 1.530. [f] Ref. d reported b.p. 105–110° (1 mm.). [g] Ref. 3a reported b.p. 97–102° (3 mm.). [h] Analysis of the base. [i] Recrystallized from acetone. [j] Ref. 3c reported b.p. 126–127° (3 mm.) and n_D^{25} 1.525. [k] J. P. Fourneau and Y. de Lestrange, *Bull. soc. chim. France* 827, 1947, reported b.p. 198° (27 mm.). [l] Ref. 3c reported b.p. 151–153° (3 mm.) and n_D^{25} 1.537. [m] Ref. 3c reported b.p. 158–159° (3 mm.). [n] K. Tsuda, et al., *Chem. Abstr.*, 58, 2114f(1954). [o] Ref. k reported b.p. 149° (14 mm.) and n_D^{23} 1.519. [p] Recrystallized from chloroform and ether. [q] J. P. Fourneau, *Bull. soc. chim. France*, 11, 141 (1944), reported b.p. 150° (18 mm.) and n_D^{23} 1.521. [r] E. H. Lincoln, R. V. Heinzelman, and J. H. Hunter, *J. Am. Chem. Soc.*, 71, 2902(1949), reported b.p. 128–129° (0.15 mm.). [s] Ref. 3b reported b.p. 165–174° (4 mm.). [t] Ref. g reported b.p. 174–176° (17 mm.). [u] Not analyzed.

TABLE IV

N-(2-*tert*-AMINOETHYL)PROPIONANILIDES[a]

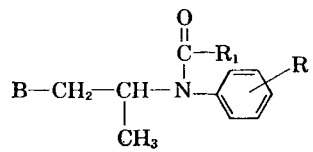


B	R	Yield,[b] %	B.P., Mm.	n_D^{25}	Salt[c]	M.P.	Formula[d]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	H	58	115–118(1.7)	1.514	HCl	138–141	$C_{13}H_{20}N_2O$	70.9	70.6	9.1	9.0			12.7	12.5
Dimethylamino	*p*-CH_3	74	118–123(0.5)	1.512	HCl	144–145	$C_{14}H_{22}N_2O$	71.8	71.7	9.5	9.5			12.0	12.0
Dimethylamino	*m*-Cl	57	142–144(2.5)		HCl	125–127	$C_{13}H_{19}ClN_2O$	61.4	60.9	7.5	7.7	14.0	13.8	11.0	11.1
Diethylamino	H	70	130–133(1.5)	1.507			$C_{15}H_{24}N_2O$	72.5	72.1	9.7	9.3			11.3	11.5
Diethylamino	*m*-OCH_3	68	152–156(1)	1.513			$C_{16}H_{26}N_2O_2$	69.0	68.6	9.4	9.6			10.1	9.6
Diethylamino	*o*-CH_3	45	116–120(0.2)	1.507			$C_{16}H_{26}N_2O$	73.2	73.3	10.0	10.1			10.7	10.8
Diethylamino	*m*-Cl	51	140–144(0.9)	1.519			$C_{15}H_{23}ClN_2O$	63.7	64.0	8.2	8.5	12.5	12.5	9.9	9.9
Diethylamino	2,4-diCl	50	138–144(0.4)	1.528			$C_{15}H_{22}Cl_2N_2O$	56.8	56.4	7.0	7.2	22.4	22.5	8.8	8.7
Diethylamino	*p*-OC_2H_5	41	144–148(0.3)	1.509			$C_{17}H_{28}N_2O_2$	69.8	69.5	9.7	9.7			9.6	9.7
Diethylamino	*m*-Br	48	138–142(0.3)	1.533			$C_{15}H_{23}BrN_2O$	55.0	54.9	7.1	7.1	24.4	24.6	8.6	8.9
Dibutylamino	H	84	132–134(0.3)	1.498			$C_{19}H_{32}N_2O$	75.0	74.7	10.6	10.6			9.2	9.6
Dibutylamino	*m*-Cl	84	140–144(0.3)	1.511			$C_{19}H_{31}ClN_2O$	67.3	67.0	9.2	9.3	10.5	10.5	8.3	8.4
Pyrrolidino	H	66	132–136(0.5)	1.528	HCl	128–130	$C_{15}H_{22}N_2O$	73.1	72.8	9.0	8.9			11.4	11.5
Pyrrolidino	*m*-Cl	68	146–150(0.7)[e]	1.538	HCl	129–131	$C_{15}H_{22}Cl_2N_2O$[f]	56.8	56.4	7.0	7.1	22.4	22.4	8.8	9.2
Piperidino	H	63	150–152(1)	1.526	HCl	125–127	$C_{16}H_{24}N_2O$	73.8	73.6	9.3	9.2			10.8	11.0
Morpholino	H	75	154–160(0.8)	1.527	HNO_3	143–144	$C_{15}H_{22}N_2O_2$	68.7	68.4	8.5	8.6			10.7	10.9
Morpholino	*m*-Cl	62	154–160(0.2)	1.539	HCl	189–191	$C_{15}H_{21}ClN_2O_2$	60.7	60.6	7.1	7.3	12.0	11.9	9.4	9.3

[a] All compounds were prepared by Method D. [b] Distilled base. [c] The microanalyses for these salts were within the usually accepted limits. [d] Formulas and analyses are for the bases unless otherwise noted. [e] Analysis was unsatisfactory. [f] Hydrochloride.

TABLE V

N-(2-*tert*-AMINO-1-METHYLETHYL)ANILIDES[a]
(Isomethadone Analogs)

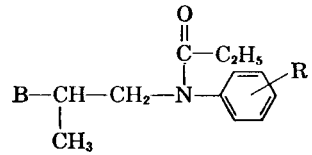


B	R	R_1	Yield,[b] %	B.P., Mm.	n_D^{25}	Salt	M.P.	Formula[c]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	H	C_2H_5	72[d]	118–122(0.05)	1.509	HNO_3	105–106	$C_{14}H_{23}N_3O_4$	56.5	56.5	7.8	7.8			14.1	14.1
Diethylamino	H	CH_3	77[d]	108–112(0.1)	1.507	HCl	186–188	$C_{15}H_{25}ClN_2O$	63.3	63.4	8.8	8.9	12.5	12.1	9.8	9.9
Diethylamino	H	C_2H_5	73[d]	115–118(0.2)	1.505	HCl	160–162	$C_{16}H_{27}ClN_2O$	64.3	64.4	9.1	9.3	11.9	11.5	9.4	9.1
Diethylamino	H	C_3H_7	60	110–112(0.2)	1.501	HCl	146–148	$C_{17}H_{29}ClN_2O$	65.3	65.4	9.3	9.2	11.3	11.2	8.9	8.9
Diethylamino	H	*i*-C_3H_7	36	95–100(0.2)	1.506	HCl	164–166[f]	$C_{17}H_{29}ClN_2O$	65.3	65.0	9.3	9.3	11.3	11.2	8.9	9.0
Pyrrolidino	H	C_2H_5	72[d]	122–126(0.4)	1.527	HCl	197–198[g]	$C_{16}H_{25}ClN_2O$	64.7	64.4	8.5	8.4	12.0	11.9	9.4	9.5
Pyrrolidino	H	C_3H_7	68	124–128(0.3)	1.517	HCl	168–170	$C_{17}H_{27}ClN_2O$	65.7	65.6	8.8	8.9	11.4	11.1	9.0	9.2
Piperidino	H	CH_3	63[d]	116–120(0.3)	1.523	HCl	174–176	$C_{16}H_{25}ClN_2O$	64.7	64.5	8.5	8.4	12.0	11.7	9.5	9.5
Piperidino	H	C_2H_5	88	124–128(0.2)	1.520	HCl	201–202	$C_{17}H_{27}ClN_2O$	65.8	65.6	8.8	9.0	11.4	11.7	9.0	9.1
Piperidino	H	C_3H_7	55	116–120(0.2)	1.517	HCl	180–182	$C_{18}H_{29}ClN_2O$	66.5	66.7	9.0	9.0	10.9	11.0	8.6	8.9
Piperidino	H	*i*-C_3H_7	58[d]	110–115(0.2)		HCl	167–169	$C_{18}H_{29}ClN_2O$	66.5	66.4	9.0	9.0	10.9	11.2	8.6	8.9
Piperidino	H	C_4H_9	73[d]	140–145(0.8)		HCl	164–165[h]	$C_{19}H_{31}ClN_2O$	67.3	67.4	9.2	9.3	10.5	10.4	8.3	8.1
Piperidino	*m*-OCH_3	C_2H_5	75	140–145(0.3)		HCl	193–194	$C_{18}H_{29}ClN_2O_2$	63.4	63.4	8.6	9.0	10.4	10.2	8.2	8.2
Piperidino	*m*-$OCOC_2H_5$	C_2H_5	82	155–160(0.2)	1.514			$C_{20}H_{30}N_2O_3$[e]	69.3	69.0	8.7	9.0			8.1	8.4
Piperidino	*m*-Cl	C_2H_5	79	146–150(0.4)	1.530			$C_{17}H_{25}ClN_2O$[e]	66.1	66.0	8.2	8.4	11.5	11.3	9.1	9.0
Morpholino	H	C_2H_5	91	144–148(0.7)	1.523	HCl	189–190	$C_{16}H_{25}ClN_2O_2$	61.4	61.4	8.1	8.2	11.3	11.3	9.0	9.1
Hexamethyleneimino	H	C_2H_5	75	146–148(0.3)	1.522	HCl	187–188	$C_{18}H_{29}ClN_2O$	66.5	66.3	9.0	9.2	10.9	10.7	8.6	9.1

[a] All compounds were prepared by Method D. [b] Yields are for the distilled base. [c] Formulas and analyses are reported for the salts unless otherwise noted. [d] Microanalyses on these bases were unsatisfactory due to low carbon. [e] Formulas and analyses are for the base. [f] Recrystallized from ethyl acetate. [g] Recrystallized from methanol and ether. [h] Recrystallized from acetone.

TABLE VI

N-(2-*tert*-AMINOPROPYL)PROPIONANILIDES[a]
(Methadone Analogs)

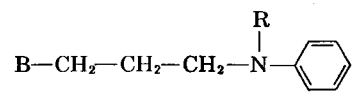


B	R	Yield, %	B.P., Mm.	n_D^{25}	Salt[b]	M.P.	Formula[c]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	H	68	115–120(0.1)	1.512	HNO_3	134–136	$C_{14}H_{22}N_2O$	71.7	71.0	9.5	9.4	12.0	12.1
Diethylamino	H	60	116–120(0.3)	1.506			$C_{16}H_{26}N_2O$	73.2	72.0[d]	10.0	10.0	10.7	10.7
Piperidino	H	76	120–123(0.2)	1.524			$C_{17}H_{26}N_2O$	74.4	74.3	9.6	9.6	10.2	10.4
Piperidino	*m*-OH[e]	43	210–215(0.1)				$C_{17}H_{26}N_2O_2$	70.3	70.3	9.0	9.1	9.7	9.8
Piperidino	*m*-OCH_3	74	168–172(0.2)	1.527	HCl[f]	124–127	$C_{18}H_{28}N_2O_2$	71.0	70.6	9.3	9.4	9.2	9.3
Piperidino	*m*-$OCOC_2H_5$	81	175–180(0.1)	1.516			$C_{20}H_{30}N_2O_3$	69.3	68.8	8.7	8.7	8.1	8.2
Morpholino	H	81	146–150(0.3)		HCl[g]	156–158	$C_{16}H_{24}N_2O_2$	69.5	69.5	8.7	8.6	10.1	10.4
4-Methylpiperazino	H	79	150–153(0.1)	1.525	2HCl	225–227	$C_{17}H_{27}N_3O$	70.5	70.0	9.4	9.2	14.5	14.4

[a] Compounds were prepared by Method D unless otherwise noted. [b] Analyses on these salts were within the usually accepted limits. [c] Formulae and analyses are for the bases. [d] Redistillation did not improve the analysis. [e] Method E. [f] Recrystallized from ethyl acetate. [g] Recrystallized from methanol and ether.

TABLE VII

DERIVATIVES OF 1,3-PROPANEDIAMINES

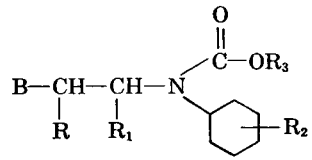


B	R	Yield,[a] %	B.P., mm.	Salt	M.P.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	H	65[c]	145–150(10)	2HCl	180–182	$C_{11}H_{20}Cl_2N_2$	52.6	52.2	8.0	7.8	28.2	28.2	11.2	11.0
Dimethylamino	Propionyl	72[d]	121–124(6)	HCl	170–172	$C_{14}H_{23}ClN_2O$	62.1	62.4	8.6	8.7	13.1	13.0	10.4	10.4
Dimethylamino	Butyryl	60[d]	117–122(0.1)	HCl	160–161	$C_{15}H_{25}ClN_2O$	63.3	62.8	8.8	9.1	12.5	12.6	9.8	9.9
Diethylamino	H	45[c]	119–121(2)	HCl	124–126[e]	$C_{13}H_{23}ClN_2$	64.3	64.3	9.6	9.9	14.6	14.5	11.5	11.4
Diethylamino	Propionyl	66[d]	145–150(2)	HCl	153–154	$C_{16}H_{27}ClN_2O$	64.3	64.2	9.1	9.2	11.9	12.0	9.4	9.5
Piperidino	H	64[c]	117–120(0.5)	HCl	178–181[f]	$C_{14}H_{23}ClN_2$	66.0	66.0	9.1	9.3	13.9	14.1	11.0	10.9
Piperidino	Propionyl	64[d]	140–144(0.3)	HCl	197–199[g]	$C_{17}H_{27}ClN_2O$	65.7	65.8	8.8	8.9	11.4	11.4	9.0	8.9

[a] The yield is for the distilled base. [b] The formulas and analyses are for the salts. [c] Method A. [d] Method D. [e] British patent 604,363 (1948) reported m.p. 122–123°. [f] Reference 3b reported b.p. 143–145° (3 mm.). [g] Recrystallized from ethanol and acetone.

TABLE VIII

N-(*tert*-AMINOALKYL)CARBANILATES
(Meperidine Analogs)



B	R	R_1	R_2	R_3	Yield,[a] %	B.P., Mm.	n_D^{25}	Hydrochloride, M.P.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylamino	H	H	H	C_2H_5	42	106–110(1.6)	1.508	135–138	$C_{13}H_{21}ClN_2O_2$	57.2	57.3	7.8	8.0	13.0	13.0	10.3	10.3
Dimethylamino	H	H	*p*-CH_3	C_2H_5	46	112–117(0.5)	1.504	145–147	$C_{14}H_{23}ClN_2O_2$	58.6	59.0	8.1	8.1	12.4	12.6	9.8	9.9
Dimethylamino	H	H	*m*-Cl	C_2H_5	44	118–124(1.0)	1.519	172–174	$C_{13}H_{20}Cl_2N_2O_2$	50.8	50.7	6.5	6.4	23.1	23.4	9.1	9.2
Ethylmethylamino	H	H	H	C_2H_5	73[c]	115–118(0.4)	1.497		$C_{14}H_{22}N_2O_2$	67.2	67.0	8.9	9.0			11.2	11.3
Diethylamino	H	H	H	CH_3	27	120–125(2.0)	1.509	68–70	$C_{14}H_{23}ClN_2O_3$	58.6	58.4	8.1	8.3	12.4	12.5	9.8	9.8
Diethylamino	H	H	H	C_2H_5	52	126–131(1.7)	1.498		$C_{15}H_{24}N_2O_2$	68.3	68.0	9.1	9.0			10.6	10.5
Diethylamino	H	H	H	C_3H_7	33	130–133(1.8)	1.515		$C_{16}H_{26}N_2O_2$	69.0	69.0	9.4	9.5			10.1	10.3
Diethylamino	H	H	H	C_4H_9	59	152–156(1.8)	1.493		$C_{17}H_{28}N_2O_2$	69.8	69.7	9.6	9.9			9.6	9.4
Diethylamino	H	H	*m*-OCH_3	C_2H_5	49	142–146(0.6)	1.505	125–126	$C_{16}H_{27}ClN_2O_3$	58.2	58.2	8.3	8.1	10.7	11.0	8.5	8.4
Piperidino	H	H	H	C_2H_5	62	138–140(0.8)		100–102	$C_{16}H_{25}ClN_2O_2$	61.4	61.3	8.1	8.3	11.3	11.2	9.0	9.2
Piperidino	H	CH_3	H	C_2H_5	71[c,d]			183–185	$C_{17}H_{27}ClN_2O_2$	62.5	62.2	8.3	8.5	10.8	11.0	8.6	8.6
Piperidino	CH_3	H	H	C_2H_5	62[c]	134–140(0.3)	1.513	124–126	$C_{17}H_{27}ClN_2O_2$	62.5	62.3	8.3	8.3	10.8	10.6	8.6	8.8
Morpholino	H	H	H	C_2H_5	66[c]	136–140(0.3)	1.519	123–125	$C_{15}H_{22}ClN_2O_3$	57.2	57.0	7.4	7.6	11.3	11.3	8.9	9.0
Morpholino	CH_3	H	H	C_2H_5	66	160–162(0.8)	1.516		$C_{16}H_{24}N_2O_3$	65.7	66.1	8.2	8.2	8.4		9.6	9.6

[a] Yield of distilled base. [b] The formulas and analyses are given for the hydrochloride when prepared, otherwise for the base. [c] These compounds were prepared in benzene, the others were prepared using ethanol as solvent. [d] Isolated from the reaction mixture as the hydrochloride.

(2% in water), precipitated. This salt was easily converted to *l*-*N*-(1-methyl-2-piperidinoethyl)propionanilide hydrochloride, m.p., 202–203° and $[\alpha]_D^{25}$ −18.9 (2% in water). If the ethanolic solution of phenampromid was treated instead with *d*-tartaric acid, *d*-*N*-(1-methyl-2-piperidinoethyl)propionanilide-*d*-tartrate, m.p. 204.5–205.5° and $[\alpha]_D^{52}$ + 23.7 (2% in water), separated and was in turn converted to *d*-*N*-(1-methyl-2-piperidinoethyl)propionanilide hydrochloride, m.p. 202–203° and $[\alpha]_D^{25}$ + 18.9 (2% in water).

EXPERIMENTAL

Preparation of salts. The salts were prepared by treating an ethanolic solution of the base with ethanolic hydrogen chloride or aqueous nitric acid. If the salt did not precipitate upon cooling or dilution with ether, the mixture was concentrated to remove the solvent and then treated with ether. Trituration and cooling caused crystallization. Unless otherwise noted, the salts were recrystallized from ethanol or ethanol by addition of ether.

2-Bromopropionamides. The 2-bromopropionamides[12] were prepared by the following general procedure, which combines features of several literature procedures. A solution of 1 mole of the appropriate amine in 150 ml. of ether was added dropwise to a stirred solution of 0.5 mole of 2-bromopropionyl bromide in 500 ml. of ether. Cooling was applied during this addition to hold the temperature below 15°. The reaction mixture was stirred for 1–2 hr. longer and then filtered to remove the amine hydrobromide. The precipitate was washed with ether, the ether filtrates were evaporated, and the residues were distilled. Alternatively, the ether solution of crude 2-bromopropionamide was not distilled but was washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and treated directly with an amine as described below. These compounds are skin irritants and should be handled with care.

2-Aminopropionamides (Table II). A mixture of 1 mole of the 2-bromopropionamide (distilled or prepared *in situ* in ether) and 2 moles of the appropriate amine was refluxed in benzene for 6–20 hr. and then filtered to remove the precipitated amine hydrobromide. The filtrate was concentrated and then treated with an excess of aqueous potassium hydroxide. The desired product usually precipitated, and was filtered and recrystallized from ethanol. When precipitation did not occur, the oil was extracted with ether and distilled.

Alkylenediamines (Tables III and VII). *Method A.* A mixture of 1 mole of the dialkylaminoalkyl chloride hydrochloride, 1.5 moles of the appropriate aniline, 2.0 moles of sodium carbonate, and about 500 ml. of toluene was refluxed with stirring for about 18 hr. and then cooled. One mole of 5*N* potassium hydroxide was added and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layers were dried over magnesium sulfate and distilled. Many of these compounds gave poor analyses even after redistillation. In spite of this they generally gave satisfactory reaction products.

Method B. A solution of 0.1 mole of the 2-aminopropionamide in 100 ml. of tetrahydrofuran was added dropwise to a solution of 0.2 mole of lithium aluminum hydride in 200 ml. of tetrahydrofuran. The mixture was refluxed for 5–8 hr., and then cooled and treated with 7.6 ml. of water, 23 ml. of 15% sodium hydroxide, and finally with 23 ml. of water. The reaction mixture was filtered and the precipitate was washed with tetrahydrofuran or ether. The organic layers were dried and distilled.

Method C. A mixture of 37.2 g. of 1-[2-(*m*-anisidino)propyl]piperidine (prepared by Method B) and 150 ml. of 48% hydrobromic acid was refluxed for 42 hr. and then concentrated. The gummy residue was treated with dilute alkali until about *p*H 9 was reached. The precipitate was filtered, washed with water, and recrystallized from ethanol. The yield of *m*-(1-methyl-2-piperidinoethylamino)phenol, m.p. 150–152°, was 16.7 g. (48%).

m-(2-Piperidinopropyl)phenol was prepared by essentially the same procedure except that the product was a viscous oil which was purified by distillation and used without analysis.

Acylated alkylenediamines (Tables IV–VII). *Method D.* A solution of 0.05 mole of the alkylenediamine in about 25 ml. of the appropriate anhydride was heated on the steam bath for 2–4 hr. and then distilled. The products usually analyzed correctly without redistillation.

Method E. m-Hydroxy-N-(2-piperidinopropyl)propionanilide. A mixture of 6.2 g. of *m*-(2-piperidinopropyl)phenol, 2.7 g. of propionyl chloride, and 25 ml. of benzene was heated on the steam bath for 3 hr., cooled, and then treated with 5.8 ml. of 5*N* sodium hydroxide. The benzene layer was separated, and the residue was extracted with ether in which the product appeared to be more soluble. The organic layers were combined, dried over magnesium sulfate and distilled. The yield of *m*-hydroxy-*N*-(2-piperidinopropyl)-propionanilide, b.p. 210–215° (0.1 mm.), was 43%. The infrared absorption curve showed a strong band at 6.08 μ and a very weak band at 5.67 μ, evidence that amidation rather than esterification had occurred.

N-(tert-Aminoalkyl)carbanilates (Table VIII). A solution of 0.05 mole of the ethylenediamine in about 50 ml. of ethanol or benzene was cooled and 0.05–0.07 mole of the alkyl chloroformate was added. The reaction mixture was refluxed for 1–3 hr. and then concentrated to remove the solvent. An excess of aqueous potassium hydroxide was added (with cooling) and the product was extracted into ether. The ether extracts were dried over magnesium sulfate and then distilled under reduced pressure.

Resolution studies. l-N-(1-Methyl-2-piperidinoethyl)propionanilide hydrochloride. A solution of 22.5 g. (0.168 mole) of *l*-malic acid and 46.0 g. (0.168 mole) of *N*-(1-methyl-2-piperidinoethyl)propionanilide in 400 ml. of ethanol was cooled, and the precipitate which separated was filtered and washed with ethanol and then ether. The yield of crude *l*-*N*-(1-methyl-2-piperidinoethyl)propionanilide-*l*-malate, m.p. 168–173°, was 34.2 g. Three recrystallizations from ethanol resulted in 24.3 g. (71%) of pure product, m.p. 178.5–179.5° and $[\alpha]_D^{25}$ −16.3 (2% in water).

Anal. Calcd. for $C_{21}H_{32}N_2O_6$: C, 61.7; H, 7.9; N, 6.9. Found: C, 61.7; H, 7.8; N, 7.1.

A mixture of 20.4 g. (0.05 mole) of *l*-*N*-(1-methyl-2-piperidinoethyl)propionanilide-*l*-malate and 120 ml. (0.12 mole) of 1*N* sodium hydroxide was extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate, and treated with 30 ml. of 2.1*N* ethanolic hydrogen chloride. The precipitate was filtered and recrystallized from ethanol by addition of ether. The yield of *l*-*N*-(1-methyl-2-piperidinoethyl)propionanilide hydrochloride, m.p. 202–203° and $[\alpha]_D^{25}$ −18.9 (2% in water), was 8.2 g. (36% over-all).

Anal. Calcd. for $C_{17}H_{27}ClN_2O$: C, 65.7; H, 8.8; Cl, 11.4; N, 9.0. Found: C, 65.5; H, 8.6; Cl, 11.7; N, 9.0.

d-N-(1-Methyl-2-piperidinoethyl)propionanilide hydrochloride. A solution of 12.6 g. (0.084 mole) of *d*-tartaric acid and 46 g. (0.168 mole) of *N*-(1-methyl-2-piperidinoethyl)-propionanilide in 350 ml. of ethanol was cooled, and the precipitate which separated was washed with ethanol and then ether. The yield of crude *d*-*N*-(1-methyl-2-piperidino-

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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.

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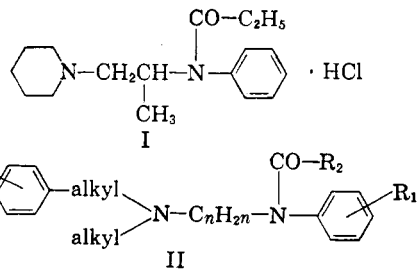
A series of *N*-(*tert*-aminoalkyl)anilides and -carbanilates containing the phenalkyl moiety has been prepared. Some of these compounds show analgesic potency in the codeine to morphine range. *N*-[2-(Methylphenethylamino)propyl]propionanilide sulfate, diampromid, has been chosen for clinical trial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

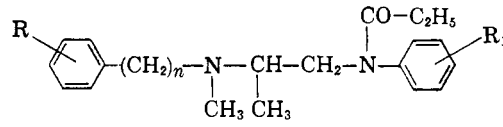
II

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.

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