1,4-Bisamides of 1,2,3,4-Tetrahydroquinoxaline.—To a solution of 0.05 mole of tetrahydroquinoxaline in 100 ml of anhydrous chloroform at 0° was added dropwise with constant stirring a solution of 0.11 mole of the acyl chloride in 50 ml of anhydrous $CHCl_3$. When the addition was complete, the mixture was refluxed until evolution of HCl had ceased. Filtration, followed by concentration *in vacuo*, and when necessary trituration with ether, gave solids that were purified by recrystallization from ethanol. The compounds prepared by this method are listed in Tables I and II (method A).

1-Ethyl-4-(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxaline (IV).—Reaction of 0.031 mole of 1-ethyl-1,2,3,4-tetrahydroquinoxaline[14] in 75 ml of chloroform with 0.031 mole of 3-chloropropionyl chloride in 25 ml of $CHCl_3$ by the general procedure described above gave an 84% yield of a thick oil. Treatment of this oil in ether with HCl gave the hydrochloride, mp 140–142° (from tetrahydrofuran).

Anal. Calcd for $C_{13}H_{17}ClN_2O \cdot HCl$: C, 54.05; H, 6.27; N, 9.69; Cl, 24.52. Found: C, 54.16; H, 6.51; N, 9.91; Cl, 24.25.

Amides of Tetrahydroquinoline and Tetrahydroisoquinoline.—Using the same general procedure as described above for the bisamides, 0.05 mole of amine and 0.06 mole of acyl chloride were allowed to react to give after recrystallization from ethanol the materials listed in Table III.

1,4-(Diacrylyl)-1,2,3,4-tetrahydroquinoxalines.—The 1,4-bis-(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxalines in benzene were chromatographed over Merck reagent grade aluminum oxide and eluted with benzene–ethanol (9:1) to give, as previously reported,[5] the compounds listed in Table II (method B).

(14) R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.*, **24**, 205 (1959).

1,4-Diformyl-1,2,3,4-Tetrahydroquinoxaline (V, R = H).—A solution of 0.036 mole of quinoxaline in 30 ml of formic acid and 100 ml of dimethylformamide was refluxed for 16 hr. The resulting solution was poured onto ice and the aqueous solution was extracted continuously with ether for 48 hr. The ethereal solution was dried and concentrated *in vacuo* to give an oil which crystallized on trituration with ethanol. Recrystallization from ethanol gave 3.0 g (44%), mp 125–126°, lit.[7] mp 119–122°.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.29; N, 14.72. Found: C, 63.12; H, 5.14; N, 14.69.

1,4-Bis(chlorocarbonyl)-1,2,3,4-tetrahydroquinoxaline (V, R = Cl).—A solution of 0.03 mole of 1,2,3,4-tetrahydroquinoxaline in 30 ml of benzene was added dropwise with stirring and cooling to a solution of 0.06 mole of phosgene in 50 ml of benzene. After addition the mixture was refluxed for several hours and concentrated *in vacuo* to give 5.9 g (76%) of a solid, mp 92–93° (from isopropyl ether).

Anal. Calcd for $C_{10}H_8Cl_2N_2O_2$: C, 46.35; H, 3.11; N, 10.81; Cl, 27.37. Found: C, 46.50; H, 3.22; N, 10.66; Cl, 27.16.

1,4-Bis(2-chloroethyl)-1,2,3,4-tetrahydroquinoxaline (VI).—A solution of 0.015 mole of 1,4-bis(chloroacetyl)-1,2,3,4-tetrahydroquinoxaline in 200 ml of tetrahydrofuran (THF) was added dropwise with stirring to 50 ml of a 1 *N* solution of borane under nitrogen at −10°. After the resulting mixture was refluxed for 1 hr, 8 ml of 6 *N* HCl was added followed by 75 ml of water. The THF was distilled and excess solid NaOH was added. The resulting mixture was extracted with ether, and the dried ether extract was concentrated to give 3.55 g (80%) of a yellow oil. The hydrochloride was prepared and recrystallized from THF, mp 149–152°.

Anal. Calcd for $C_{12}H_{16}Cl_2N_2 \cdot HCl$: C, 48.76; H, 5.80; N, 9.48; Cl, 35.98. Found: C, 49.00; H, 5.71; N, 9.47; Cl, 35.92.

Hypoglycemic Activity and Pharmacological Picture of 4-(1-Naphthyl)butylamine Derivatives

SILVANO CASADIO, TIBERIO BRUZZESE, GIANFRANCO PALA, GERMANO COPPI, AND CARLA TURBA

Research Laboratories of Istituto De Angeli S.p.A., Milan, Italy

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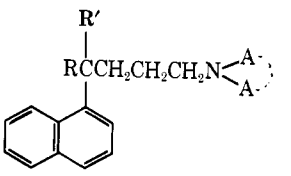
Forty-nine 4-(1-naphthyl)butylamine derivatives were prepared for hypoglycemic tests. They were also submitted to comprehensive screening, in order to obtain as complete as possible a pharmacological picture. The majority of the compounds examined revealed marked hypoglycemic activity, and of these the α-isopropyl-α-(3-dimethylaminopropyl)- (XXIII) and α,α-di(3-dimethylaminopropyl)-1-naphthylacetic acids (XXIV) were found to be the most active and comparable with chlorpropamide. None of the other actions investigated revealed anything of particular interest.

Our finding[1] that some α-aminoethyl-1-naphthylacetic acids possess hypoglycemic activity has led us to extend this investigation to compounds with related structures. Preliminary studies showed that substitution with an aminopropyl chain in the α position of 1-naphthylacetic acid was the most promising for reaching the highest activity, and an extensive series of 4-(1-naphthyl)butylamines of the following general structure was prepared. The methods used in obtaining the new compounds were quite similar to those reported in previous papers[1,2] and, in any case, are well illustrated in the Experimental Section.



R = H, alkyl, or aminopropyl
R′ = CN, $CONH_2$, CO_2H, CO_2R'', CONHR″, $CONPr_2$, CONHCONHPr, CNHR″, or COEt (R″ = alkyl, cyclohexyl, allyl, or phenyl)
NAA = tertiary amino group

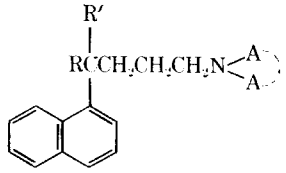
The title compounds were submitted to a pharmacological investigation which included not only examination of the hypoglycemic action, but also studies of acute toxicity, behavioral effects, and antiinflammatory, analgesic, local anesthetic, antitussive, diuretic, antispasmodic, antipyretic, choleretic, and hypoten-

(1) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **9**, 603 (1966).

(2) (a) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 589 (1965); (b) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 594 (1965); (c) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 731 (1964); (d) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **19**, 933 (1964).

Table I

4-(1-Naphthyl)butylamine Derivatives



Compd	R	R′	$N<^{A^-}_{A^-}$	Method	Yield, %	Bp (mm) or mp, °C	Formula	Calcd, %			Found, %		
								C	H	N	C	H	N
I	H	CN	$N(CH_3)_2$	A	82[a]	163–165 (0.6)	$C_{17}H_{20}N_2$	80.91	7.99	11.10	81.27	8.14	10.93
II	C_2H_5	CN	$N(CH_3)_2$	B	83[a]	154–156 (0.3)	$C_{18}H_{24}N_2$	81.38	8.63	9.99	81.85	8.65	10.19
III	*i*-C_3H_7	CN	$N(CH_3)_2$	B	90[a]	144–146 (0.2), 84–85[b]	$C_{20}H_{26}N_2$	81.58	8.90	9.52	82.25	8.85	9.63
IV	$(CH_3)_2N(CH_2)_3$	CN	$N(CH_3)_2$	B	86[a]	172–173 (0.3)	$C_{22}H_{31}N_3$	78.29	9.26	12.45	77.81	9.30	12.38
V	H	CN	$N(C_2H_5)_2$	A	74[a]	156–158 (0.2)	$C_{19}H_{24}N_2$	81.38	8.63	9.99	81.05	8.49	9.87
VI	*i*-C_3H_7	CN	$N(C_2H_5)_2$	B	86[a]	167–168 (0.3)	$C_{22}H_{30}N_2$	81.93	9.38	8.69	81.57	9.27	8.63
VII	$(C_2H_5)_2N(CH_2)_3$	CN	$N(C_2H_5)_2$	B	85[a]	178–180 (0.2)	$C_{26}H_{39}N_3$	79.54	9.99	10.68	78.74	9.91	10.55
VIII	H	CN	Pyrrolidino	A	61[c]	85–86[d]	$C_{19}H_{22}N_2$	81.97	7.97	10.06	81.52	7.86	10.19
IX	*i*-C_3H_7	CN	Pyrrolidino	B	74[a]	165–168 (0.1)	$C_{22}H_{28}N_2$	82.45	8.81	8.74	82.25	8.68	8.83
X	H	CN	Piperidino	A	89[c]	100–101[d]	$C_{20}H_{24}N_2$	82.14	8.27	9.58	81.89	8.17	9.73
XI	*i*-C_3H_7	CN	Piperidino	B	73[a]	175–178 (0.1)	$C_{23}H_{30}N_2$	82.58	9.04	8.38	82.51	9.04	8.47
XII	H	CN	Morpholino	A	92[c]	105–106[d]	$C_{18}H_{22}N_2O$	77.52	7.53	9.52	77.67	7.58	9.60
XIII	*i*-C_3H_7	CN	Morpholino	A	58[a]	188–191 (0.3)	$C_{22}H_{28}N_2O$	78.53	8.39	8.33	77.85	8.32	8.28
XIV	C_2H_5	$CONH_2$	$N(CH_3)_2$	C	85[a]	210–212 (0.6)	$C_{19}H_{26}N_2O$	76.47	8.78	9.39	75.63	8.68	9.49
XV	*i*-C_3H_7	$CONH_2$	$N(CH_3)_2$	D	77[a]	194–196 (0.2)	$C_{20}H_{28}N_2O$	76.88	9.03	8.97	77.23	9.10	9.00
XVI	$(CH_3)_2N(CH_2)_3$	$CONH_2$	$N(CH_3)_2$	C	92[c]	133–134[d]	$C_{22}H_{33}N_3O$	74.32	9.36	11.82	74.46	9.33	11.65
XVII	*i*-C_3H_7	$CONH_2$	$N(C_2H_5)_2$	D	73[a]	201–203 (0.4)	$C_{22}H_{32}N_2O$	77.60	9.47	8.23	76.99	9.40	8.28
XVIII	$(C_2H_5)_2N(CH_2)_3$	$CONH_2$	$N(C_2H_5)_2$	C	70[c]	98–99[b]	$C_{26}H_{40}N_3O$	75.86	10.04	10.21	76.31	10.09	10.24
XIX	*i*-C_3H_7	$CONH_2$	Pyrrolidino	D	72[c]	134–135[d]	$C_{22}H_{30}N_2O$	78.06	8.93	8.28	78.08	8.97	8.32
XX	*i*-C_3H_7	$CONH_2$	Piperidino	D	79[c]	112–113[d]	$C_{23}H_{32}N_2O$	78.36	9.15	7.95	78.68	9.07	8.03
XXI	*i*-C_3H_7	$CONH_2$	Morpholino	D	70[a]	222–225 (0.2)	$C_{22}H_{30}N_2O_2$	74.54	8.53	7.90	74.53	8.60	8.02
XXII	C_2H_5	COOH	$N(CH_3)_2$	E	94[c]	251–252[e,i]	$C_{19}H_{22}NO_2 \cdot HCl$	67.93	7.80	4.17	67.67	7.81	4.15
XXIII	*i*-C_3H_7	COOH	$N(CH_3)_2$	F	92[c]	228–229[e,g]	$C_{20}H_{27}NO_2 \cdot HCl$	68.65	8.07	4.00	67.98	7.99	4.06
XXIV	$(CH_3)_2N(CH_2)_3$	COOH	$N(CH_3)_2$	E	94[c]	241–242[e,j] dec	$C_{22}H_{32}N_2O_2 \cdot 2HCl$	61.53	7.98	6.53	61.04	7.94	6.47
XXV	*i*-C_3H_7	COOH	$N(C_2H_5)_2$	E	86[c]	205–206[e,h]	$C_{22}H_{31}NO_2 \cdot HCl$	69.91	8.54	3.71	69.12	8.40	3.61
XXVI	$(C_2H_5)_2N(CH_2)_3$	COOH	$N(C_2H_5)_2$	F	95[c]	231–232[e,i]	$C_{26}H_{40}N_2O_2 \cdot 2HCl$	64.31	8.72	5.77	63.09	8.83	5.63
XXVII	*i*-C_3H_7	COOH	Pyrrolidino	F	86[c]	172–173[e,i]	$C_{22}H_{29}NO_2 \cdot HCl$	70.29	8.05	3.72	70.54	8.11	3.70
XXVIII	*i*-C_3H_7	COOH	Piperidino	F	88[c]	227–228[e,i]	$C_{23}H_{31}NO_2 \cdot HCl$	70.84	8.27	3.59	70.91	8.31	3.61
XXIX	*i*-C_3H_7	COOH	Morpholino	F	93[c]	226–227[e,i] dec	$C_{22}H_{29}NO_3 \cdot HCl$	67.41	7.72	3.57	67.08	7.80	3.52
XXX	*i*-C_3H_7	$COOCH_3$	$N(CH_3)_2$	G	66[a]	158–160 (0.1)	$C_{21}H_{29}NO_2$	77.02	8.93	4.28	76.53	8.83	4.32
XXXI	*i*-C_3H_7	$COOC_2H_5$	$N(CH_3)_2$	G	63[a]	172–174 (0.9)	$C_{22}H_{31}NO_2$	77.37	9.15	4.10	78.14	9.17	4.17
XXXII	*i*-C_3H_7	$COOC_3H_7$	$N(CH_3)_2$	G	85[a]	167–170 (0.3)	$C_{23}H_{33}NO_2$	77.70	9.36	3.94	77.29	9.36	4.00
XXXIII	*i*-C_3H_7	$COOCH(CH_3)_2$	$N(CH_3)_2$	G	68[a]	177–179 (0.4)	$C_{23}H_{33}NO_2$	77.70	9.36	3.94	77.25	9.20	4.01
XXXIV	*i*-C_3H_7	$COOC_6H_{11}$	$N(CH_3)_2$	G	43[a]	201–203 (0.5)	$C_{26}H_{37}NO_2$	78.94	9.43	3.54	78.16	9.35	3.56
XXXV	*i*-C_3H_7	$COOCH_2CH{=}CH_2$	$N(CH_3)_2$	G	68[a]	175–177 (0.4)	$C_{23}H_{31}NO_2$	78.14	8.84	3.96	78.18	8.74	4.11

Compd	R	R′	NAA	Method	Yield, %	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
XXXVI	*i*-C_3H_7	$COOC_6H_5$	$N(CH_3)_2$	H	81[e]	111–112[d]	$C_{26}H_{31}NO_2$	80.17	8.02	3.60	80.78	8.09	3.62
XXXVII	$(CH_3)_2N(CH_2)_3$	$COOC_2H_5$	$N(CH_3)_2$	G	62[a]	179–180 (0.2)	$C_{24}H_{36}N_2O_2$	74.96	9.44	7.29	75.69	9.53	7.36
XXXVIII	*i*-C_3H_7	$COOC_2H_5$	$N(C_2H_5)_2$	G	42[a]	172–174 (0.2)	$C_{24}H_{35}NO_2$	78.00	9.55	3.79	77.45	9.57	3.89
XXXIX	*i*-C_3H_7	$CONHCH_3$	$N(CH_3)_2$	I	84[a]	180–181 (0.2)	$C_{21}H_{30}N_2O$	77.25	9.26	8.58	77.82	9.44	8.42
XL	*i*-C_3H_7	$CONHC_2H_5$	$N(CH_3)_2$	I	57[a]	183–185 (0.3)	$C_{22}H_{32}N_2O$	77.60	9.47	8.23	77.59	9.36	8.08
XLI	*i*-C_3H_7	$CONHC_3H_7$	$N(CH_3)_2$	J	70[a]	182–183 (0.3)	$C_{23}H_{34}N_2O$	77.92	9.67	7.90	77.01	9.57	7.79
XLII	*i*-C_3H_7	$CONHC_6H_{11}$	$N(CH_3)_2$	J	46[a]	202–205 (0.2)	$C_{26}H_{38}N_2O$	79.14	9.71	7.10	79.11	9.60	7.09
XLIII	*i*-C_3H_7	$CONHCH_2CH{=}CH_2$	$N(CH_3)_2$	J	59[a]	185–187 (0.4)	$C_{23}H_{32}N_2O$	78.36	9.15	7.95	77.78	9.04	7.84
XLIV	$(CH_3)_2N(CH_2)_3$	$CONHC_3H_7$	$N(CH_3)_2$	I	53[a]	200–202 (0.5)	$C_{25}H_{39}N_3O$	75.52	9.89	10.57	74.91	9.96	10.64
XLV	*i*-C_3H_7	$CON(C_3H_7)_2$	$N(CH_3)_2$	K	28[a]	167–169 (0.3)	$C_{25}H_{40}N_2O$	78.73	10.17	7.06	78.10	9.94	6.92
XLVI	*i*-C_3H_7	$CONHCONHC_3H_7$	$N(CH_3)_2$	L	94[c]	*k*	$C_{24}H_{35}N_3O_2$	72.51	8.87	10.57	72.20	8.99	10.58
XLVII	C_2H_5	$C(NH)C_2H_5$	$N(CH_3)_2$	M	83[a]	173–175 (0.3)	$C_{21}H_{30}N_2$	81.23	9.74	9.02	80.81	9.67	8.89
XLVIII	*i*-C_3H_7	$C(NH)C_3H_7$	$N(CH_3)_2$	N	70[a]	169–171 (0.3)	$C_{23}H_{34}N_2$	81.60	10.12	8.28	81.48	9.99	8.39
IL	C_2H_5	COC_2H_5	$N(CH_3)_2$	O	67[a]	160–162 (0.5)	$C_{21}H_{29}NO$	80.98	9.39	4.50	81.97	9.36	4.63

[a] Once distilled. [b] Crystallized from petroleum ether (bp 40–70°). [c] Crude product. [d] Crystallized from ligroin (bp 75–120°). [e] Hydrochloride. [f] Crystallized from ethanol. [g] Crystallized from ethanol–ligroin (bp 75–120°). [h] Crystallized from acetone–isopropyl alcohol. [i] Crystallized from isopropyl alcohol. [j] Crystallized from acetone. [k] Attempts at distillation resulted in some decomposition.

sive action, as well as their *in vitro* antibacterial, antifungal, trichomonicidal, and antiamebal effects.

Experimental Section[3]

Chemistry.—The new compounds are listed in Table I, along with yields, physical constants, and analytical data.

Nitriles (I–XIII) were prepared according to the general procedure we recently described,[2a] and which consists in alkylating nonsubstituted nitriles with an aminoalkyl or alkyl halide in the presence of sodamide.

Method A. α-(3-Dimethylaminopropyl)-1-naphthylacetonitrile (I).—Sodamide (8.2 g, 0.21 mole) was cautiously added to a solution of 1-naphthylacetonitrile (33.4 g, 0.2 mole) in anhydrous benzene (200 ml), refluxing the mixture with stirring for 2 hr. After cooling to 40°, a solution of 3-(N,N-dimethylamino)-1-chloropropane (25.5 g, 0.21 mole) in anhydrous benzene (150 ml) was added dropwise over 1 hr. The suspension was then refluxed for 6 hr and cooled to room temperature, and water was cautiously added. The benzene layer was separated and extracted with dilute HCl and the acid extract was washed with ether and made alkaline with 10% NaOH. The oil which separated was extracted with ether and the solution was washed with water and dried (Na_2SO_4). After removal of the solvent the residue was distilled at 163–165° (0.6 mm) to give a colorless oil.

Method B differed from method A in that an aminoalkyl or an alkyl halide was treated with an α-aminoalkylnitrile.

α-Isopropyl-α-(3-diethylaminopropyl)-1-naphthylacetonitrile (VI).—Sodamide (10.1 g, 0.26 mole) was cautiously added to a solution of V (56.1 g, 0.2 mole) in anhydrous benzene (300 ml) and the mixture was refluxed with stirring for 2 hr. After cooling to 40°, 2-bromopropane (32 g, 0.26 mole) was added dropwise over 1 hr. The mixture was refluxed for 6 hr and then treated as described in method A, yielding a viscous oil, bp 167–168° (0.3 mm).

Primary Amides (XIV–XXI).—The procedure consisted of hydrolyzing the nitriles with sulfuric and acetic acid, according to the general method previously described.[2b]

Method C. α-Ethyl-α-(3-dimethylaminopropyl)-1-naphthylacetamide (XIV).—II (28 g, 0.1 mole) was dissolved in a 1:1:1 mixture of concentrated H_2SO_4, glacial acetic acid, and water (109 ml). The solution was refluxed for 24 hr, cooled to room temperature, diluted with water, and made alkaline with 30% NaOH. The oil was separated and extracted with ether and the ethereal solution was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was distilled at 210–212° (0.6 mm), giving a glassy product.

Method D. α-Isopropyl-α-(3-piperidinopropyl)-1-naphthylacetamide (XX) was obtained by hydrolyzing XI for 216 hr as described in method C. After distillation at 214–217° (0.2 mm), the product was treated with ligroin (bp 75–120°) yielding colorless crystals, mp 112–113°.

Acids (XXII–XXIX).—Following the general procedure previously described,[1] the required acids were prepared by reaction of the amides with isoamyl nitrite in glacial acetic acid, and in the presence of HCl.

Method E. α-Ethyl-α-(3-dimethylaminopropyl)-1-naphthylacetic Acid Hydrochloride (XXII).—Hydrogen chloride was slowly bubbled, for 1.5 hr, at room temperature, through a cooled solution of XIV (29.8 g, 0.1 mole) in glacial acetic acid (200 ml). Freshly distilled isoamyl nitrite (37.2 ml) was added over 2 hr, with stirring, and the bright red solution was then maintained at room temperature for additional 2 hr and afterwards heated at 100° overnight. The solvent was removed at 50° under reduced pressure, and the residue was triturated with ether. On crystallization from ethanol a colorless product, mp 251–252°, was obtained.

Method F. α-Isopropyl-α-(3-morpholinopropyl)-1-naphthylacetic Acid Hydrochloride (XXIX).—XXI was treated as described in method E, but the above procedure was repeated several times until a sample of the reaction mixture, evaporated to dryness, gave a residue completely soluble in dilute NaOH. After crystallization from ethanol, the product gave colorless crystals, mp 226–227° dec.

Acid Chlorides. General Procedure.—The appropriate acid hydrochloride (30 g) was dissolved in $SOCl_2$ (150 ml) and the

(3) Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

TABLE II: PHARMACOLOGICAL SCREENING RESULTS

Compd	Approx LD_{50} (mouse), mg/kg ip	Behavior results: Effects on mouse	mg/kg ip	Hypoglycemic activity (rat) Blood sugar decrease, %	mg/kg orally	Anti-inflammatory activity (rat) Inhib of edema, %[a]	Analgesic activity (mouse) Increase of reaction time, %	mg/kg ip	Surface local anesthetic activity (guinea pig), %[b]	Anti-tussive activity (guinea pig) Inhib of coughing, %[c]	Diuretic activity (rat), vol. T/C[d]	Antispasmodic activity *in vitro*,[e] % inhibition of spasms produced by — Acetylcholine 1×10^{-5} g/ml	Histamine 1×10^{-6} g/ml	Nicotine 2×10^{-6} g/ml	Serotonin 1×10^{-6} g/ml
I	195–215	Mod spontaneous motility decrease	50	15	50	16	44	50			1.24	Inactive	Inactive	Inactive	Inactive
II	150–170	Mod behavior excitement, mod motor incoordination	50	Inactive	50	Inactive	65	50		33		89	96	88	29
III	140–160	Mod CNS depression, mod muscle hypotonia	25	21	50	18	47	25			1.35	38	24	22	36
IV	140–170	Mod behavior excitement, marked motor incoordination	100	40 20	50 10	Inactive	54	100		18	1.19	27	46	27	28
V	130–150	Marked behavior excitement	50	Inactive	50	52	48	50		20		64	31	Inactive	39
VI	140–160	Mod spontaneous motility decrease	25	21 20	50 10	28	30	25		13		100	100	100	100
VII	160–190	Mod behavior excitement, mod muscle hypotonia	50	21 21	50 10	15	32	50		Inactive		28	71	59	16
VIII	50–60	Mod behavior excitement	25	Inactive	50	25	40	25		Inactive		24	81	68	Inactive
IX	60–80	Marked CNS depression, marked motor incoordination, muscle hypotonia	50	26 18	50 10	Inactive	134	50		Inactive		81	100	93	100
X	130–150	Marked CNS depression, motor incoordination, marked muscle hypotonia	50	Inactive	50	Inactive	53	50		16		73	75	95	20
XI	310–350	Mod passivity increase, mod motor incoordination	25	32 25	50 10	16	43	25		20	2.00	57	85	53	100
XII	340–370	Behavior excitement, mod muscle hypotonia	50	Inactive	50	Inactive	53	50		28		18	Inactive	91	38
XIII	150–180	Mod CNS depression, marked motor incoordination	100	11	50	Inactive	87	100		Inactive		30	61	61	37
XIV	90–110	Behavior excitement, motor incoordination	50	23 19	50 10	Inactive	57	50	59	21	3.20	Inactive	27	Inactive	31
XV	185–195	Mod behavior excitement, mod muscle hypotonia	100	20	50	18	13	100	33		1.66	96	100	94	98
XVI	140–170	Mod spontaneous motility decrease, mod	25	36 32	50 10	Inactive	47	25	40	Inactive		28	12	Inactive	10

		motor incoordination, marked muscle hypotonia													
XVII	90–120	Mod behavior excitement	50	19 13	50 10	44	37	50	52	16	1.41	Inactive	84	84	64
XVIII	60–80	Mod spontaneous motility decrease, mod muscle hypotonia	25	28 24	50 10	Inactive	60	25	49	45	Inactive	22	10	17	24
XIX	150–170	Mod spontaneous motility decrease, mod muscle hypotonia	100	30 20	50 10	Inactive	30	100	83	Inactive	1.74	28	20	Inactive	10
XX	70–90	Mod behavior excitement, mod motor incoordination	25	17	50	Inactive	49	25	61	17		37	22	15	55
XXI	180–210	Mod spontaneous motility decrease, mod motor incoordination, mod ipsilateral flexor reflex decrease	50	13	50	28	50	50	62	Inactive	1.31	18	63	13	28
XXII	1150–1230	Mod behavior excitement	200	27 16	50 10	Inactive	34	200			Inactive				
XXIII	600–650	Mod motor incoordination	100	34 25	50 10	Inactive	30	100			1.27				
XXIV	1180–1250	Mod spontaneous activity decrease	200	35 30	50 10	Inactive	58	200			Inactive				
XXV	580–650	Mod CNS depression	200	25 13	50 10	Inactive	58	200			Inactive				
XXVI	380–420	Mod CNS depression	200	27 25	50 10	Inactive	43	200			Inactive				
XXVII	290–330	Mod spontaneous motility and irritability decrease	100	27 18	50 10	Inactive	47	100			Inactive				
XXVIII	190–220	Mod behavior excitement	100	27 16	50 10	Inactive	66	100			Inactive				
XXIX	270–320	Mod behavior excitement	50	19 Inactive	50 10	Inactive	55	50			Inactive				
XXX	130–160	Mod spontaneous motility decrease, mod muscle hypotonia, moderate ipsilateral flexor reflex decrease	25	30 28	50 10	16	38	25	15	42		47	52	79	75
XXXI	60–75	Marked behavior excitement, mod motor incoordination	50	49 31	50 10	16	46	25	39	Inactive	2.86	57	73	84	67
XXXII	65–80	Mod CNS depression, mod muscle hypotonia	50	Inactive	50	Inactive	66	50	42	Inactive	1.70	79	96	42	62
XXXIII	60–80	Irritability increase, mod pinna reflex increase, mod muscle hypotonia	50	Inactive	50	25	61	50	42	Inactive	1.71	40	89	68	38

Table II (*Continued*)

Compd	Approx LD_{50} (mouse), mg/kg ip	Behavior results: Effects on mouse	mg/kg ip	Hypoglycemic activity (rat): Blood sugar decrease %	mg/kg orally	Anti-inflammatory activity (rat): Inhib of edema, %[a]	Analgesic activity (mouse): Increase of reaction time, %	mg/kg ip	Surface local anesthetic activity (guinea pig): Inhib of cough, %[b]	Anti-tussive activity (guinea pig): Inhib of cough, %[c]	Diuretic activity (rat), vol. T/C[d]	Antispasmodic activity *in vitro*[e]: % inhibition of spasms produced by: Acetylcholine 1×10^{-7} g/ml	Histamine 1×10^{-6} g/ml	Nicotine 2×10^{-8} g/ml	Serotonin 1×10^{-6} g/ml
XXXIV	95–110	Marked CNS depression, motor incoordination, mod muscle hypotonia	50	Inactive	50	Inactive	73	50	38	30	Inactive	70	43	49	49
XXXV	280–310	Mod spontaneous motility decrease, moderate motor incoordination	50	Inactive	50	31	52	50	28	Inactive		82	83	64	55
XXXVI	285–320	Mod behavior excitement, muscle hypotonia, mod pinna reflex increase	50	Inactive	50	Inactive	31	50	32	47		46	83	58	49
XXXVII	145–165	Marked CNS depression, marked motor incoordination, mod muscle hypotonia	100	25 15	50 10	13	82	100	35	Inactive	Inactive	22	24	Inactive	41
XXXVIII	70–85	Mod CNS depression, motor incoordination, marked pinna reflex decrease	50	17 13	50 10	42	57	50	28	38		82	89	38	50
XXXIX	185–210	Mod behavior excitement, mod motor incoordination	50	29 20	50 10	28	20	50	20	Inactive		26	37	74	67
XL	140–160	Mod behavior excitement	50	26 15	50 10	21	19	50	22	Inactive		Inactive	32	35	56
XLI	275–310	Mod spontaneous motility decrease	50	35 31	50 10	Inactive	37	50	15	Inactive	2.43	41	34	25	33
XLII	135–160	Mod behavior excitement	50	30 20	50 10	48	31	50	29	14	3.56	46	45	37	48
XLIII	120–140	Mod behavior excitement, motor incoordination, mod muscle hypotonia	50	28 19	50 10	21	25	50	17	Inactive		18	75	14	Inactive
XLIV	70–85	Mod CNS depression, marked motor incoordination, mod muscle hypotonia	50	24 Inactive	50 10	Inactive	77	50	35	35	Inactive	32	26	Inactive	80
XLV	130–150	Mod behavior excitement	50	33 27	50 10	34	49	50	19	Inactive	1.43	Inactive	94	78	81
XLVI	195–210	Mod spontaneous motility decrease, mod motor incoordination, mod muscle hypotonia	50	31 Inactive	50 10	28	39	50	61	Inactive	1.31	24	24	50	30

XLVII	75–85	Mod motor incoordination, mod pinna reflex decrease	50	31 23	50 10	25	43	50	55	13		45	35	35	Inactive
XLVIII	140–160	Mod spontaneous motility decrease, motor incoordination, mod muscle hypotonia	50	38 18	50 10	19	20	50	71	Inactive	2.01	93	82	88	100
II	90–105	Mod spontaneous motility decrease, mod motor incoordination, mod muscle hypotonia	25	27 21	50 10	45	30	25	85	Inactive	1.68	87	100	97	100
Chlorpropamide				37 32	50 10										
Phenylbutazone							61 67	100 5							
Morphine·HCl						37			50						
Cocaine·HCl										37					
Oxolamine															
Hydrochlorothiazide											1.56				

[a] Tested orally at 100 mg/kg. [b] The compounds were tested at a concentration of 1 mg/ml. The ED_{50} value for the standard is 0.7 mg/ml. [c] Tested intraperitoneally at 5 mg/kg. [d] Tested orally at 50 mg/kg; the standard was tested at 6.25 mg/kg. [e] The compounds were tested at a concentration of 1 μg/ml. The ED_{50} values for the standards are atropine sulfate (antiacetylcholinic), 0.0035 μg/ml; diphenhydramine hydrochloride (antihistaminic), 0.0074 μg/ml; hexamethonium bitartrate (antinicotinic), 0.88 μg/ml; and chlorpromazine hydrochloride (antiserotoninic), 0.055 μg/ml.

solution was allowed to stand for 3 hr. Anhydrous ether was added and the solid precipitate was collected by filtration and triturated with ether, giving 90–95% yields of fairly pure product.

Esters (XXX–XXXVIII).—The method adopted involved the reaction of acid chlorides with sodium alkoxides.

Method G. Isopropyl α-Isopropyl-α-(3-dimethylaminopropyl)-1-naphthylacetate (XXXIII).—Sodium (4.6 g, 0.2 g-atom) was dissolved in isopropyl alcohol (300 ml) with heating to 50°, and α-isopropyl-α-(3-dimethylaminopropyl)-1-naphthylacetyl chloride hydrochloride (36.8 g, 0.1 mole) was then added to the cooled solution. The mixture was stirred for 3 hr, the solvent was distilled under reduced pressure, and ether was added to the residue and filtered. After removal of the solvent, the product distilled as a colorless oil, bp 177–179° (0.4 mm).

Method H. Phenyl α-isopropyl-α-(3-dimethylaminopropyl)-1-naphthylacetate (XXXVI) was prepared from the acid chloride and phenol as described in method G, but ethanol was added as the solvent. After crystallization from ligroin (bp 75–120°), it melted at 111–112°.

Secondary amides (XXXIX–XLIV) were prepared by reaction of the acid chlorides with excess amines, in benzene solution.

Method I. N-Propyl-α,α-di(3-dimethylaminopropyl)-1-naphthylacetamide (XLIV).—α,α-Di(3-dimethylaminopropyl)-1-naphthylacetyl chloride hydrochloride (44.8 g, 0.1 mole) was added in portions to a solution of propylamine (29.5 g, 0.5 mole) in anhydrous benzene (400 ml), cooling moderately. The mixture was stirred for 3 hr and then allowed to stand overnight, afterwards filtering, and distilling the benzene under reduced pressure. Ether was added to the residue, the solution was filtered, and the solvent was removed. Distillation of the residue at 200–202° (0.5 mm) gave a colorless oil.

Method J. N-Allyl-α-isopropyl-α-(3-dimethylaminopropyl)-1-naphthylacetamide (XLIII).—Reaction of the acid chloride with allylamine, as described in method I, gave a mixture which was allowed to stand for 3 hr at room temperature and then refluxed for 2 hr. The crude product isolated was then refluxed with 15% NaOH for 1 hr to destroy any unreacted chloride, the oil in suspension was extracted with ether, and the solution was washed with water and dried (Na_2SO_4). After removal of the solvent the residue was distilled at 185–187° (0.4 mm) to give an oily product.

Miscellaneous Derivatives. N,N-Dipropyl-α-isopropyl-1-naphthylacetamide.—α-Isopropyl-1-naphthylacetyl chloride[4] (49.3 g, 0.2 mole) was added dropwise to a solution of dipropylamine (48.6 g, 0.48 mole) in anhydrous benzene (300 ml), with stirring. The mixture was refluxed for 2 hr, allowed to stand overnight, and then filtered. The solution was then washed with water and dried (Na_2SO_4), and the benzene was removed under reduced pressure. Distillation of the residue at 154–156° (0.1 mm) gave a colorless oil (54.1 g, 87% yield).

Anal. Calcd for $C_{21}H_{29}NO$: C, 80.98; H, 9.39; N, 4.50. Found: C, 80.64; H, 9.35; N, 4.58.

Method K. N,N-Dipropyl-α-isopropyl-α-(3-dimethylaminopropyl)-1-naphthylacetamide (XLV).—N,N-Dipropyl-α-isopropyl-1-naphthylacetamide was alkylated with 3-(N,N-dimethylamino)-1-chloropropane in the presence of sodamide, as described in method B. Anhydrous toluene was used as the solvent, as in the preparation of the analogous tertiary amides.[2c] The crude product was fractionated, bp 167–169° (0.3 mm), giving a very viscous oil.

Method L. N-[α-Isopropyl-α-(3-dimethylaminopropyl)-1-naphthylacetyl]-N′-propylurea (XLVI).—A solution of XV (31.2 g, 0.1 mole) and propyl isocyanate (21.3 g, 0.25 mole) in toluene (500 ml) was refluxed for 48 hr, cooled, and extracted with dilute HCl. The solution was made alkaline with 5% Na_2CO_3, the oil was separated and extracted with ether, and the ethereal solution was washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a viscous oil which, on attempts at distillation, showed some decomposition.

Method M. 1-Dimethylamino-4-ethyl-4-(1-naphthyl)-5-iminoheptane (XLVII).—This method follows the general procedure previously described.[2d] A solution of II (28 g, 0.1 mole) in anhydrous toluene (100 ml) was added to Grignard reagent prepared from magnesium (4.86 g, 0.2 g-atom) and ethyl iodide (31.2 g, 0.2 mole) in anhydrous ether (100 ml). The ether was

(4) G. Pala, T. Bruzzese, and A. Mantegani, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 235 (1964).

distilled and the residue was maintained at 95° for 16 hr. The mixture was then cooled and 10% HCl was cautiously added (400 ml). The acid layer was separated and made alkaline with 30% NaOH, the oily product was extracted with ether, and the resulting ethereal solution was dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was distilled at 173–175° (0.3 mm), giving a colorless oil.

Method N. 1-Dimethylamino-4-isopropyl-4-(1-naphthyl)-5-iminooctane (XLVIII).—A solution of III (29.4 g, 0.1 mole) in anhydrous toluene (100 ml) was added to Grignard reagent prepared by magnesium (9.7 g, 0.4 g-atom) and propyl bromide (49.2 g, 0.4 mole) in anhydrous ether (200 ml). The ether was distilled and the residue was maintained at 95° for 120 hr. The mixture was then cooled and treated as described in method M. The product obtained was a colorless oil, bp 169–171° (0.3 mm).

Method O. 1-Dimethylamino-4-ethyl-4-(1-naphthyl)-5-heptanone (IL).—XLVII (31 g, 0.1 mole) was refluxed for 288 hr with concentrated HCl (500 ml), and the cooled mixture was diluted with water, washed with ether, and made alkaline with 30% NaOH. The oil was separated and extracted with ether, the solution was dried (Na_2SO_4), and the ether was distilled yielding an oily product, bp 160–162° (0.5 mm).

Pharmacology.—The acute toxicity, behavioral effects, and hypoglycemic, analgesic, local anesthetic, antitussive, diuretic, antispasmodic, antipyretic, and choleretic activities were investigated by the techniques previously described.[1,2a,b] The antiinflammatory activity was tested orally in rats, using the carrageenin-induced edema technique.[5] The action on the arterial pressure was studied in rats under urethan anesthesia (1 g/kg ip), recording the pressure at the carotid by means of a physiological pressure transducer connected to a Sanborn polygraph. The antibacterial, antifungal, and trichomonicidal activities were studied *in vitro*, as described by Coppi, *et al.*[6] the antiamebal action was examined *in vitro*, according to de Carneri.[7] Chlorpropamide, phenylbutazone, morphine, cocaine, oxolamine, hydrochlorothiazide, and atropine, diphenhydramine, hexamethonium, and chlorpromazine were used as standards for comparison, respectively, of the hypoglycemic, antiinflammatory, analgesic, local anesthetic, antitussive, diuretic, and antispasmodic activities.

Results and Discussion

Table II gives the most interesting results of the pharmacological screening. As expected, the majority of the compounds examined displayed a marked hypoglycemic action on oral administration. Considered as a whole, the acids showed the greatest activity, whereas the amides, substituted or not, esters, and nitriles showed a decreasing order of activity. Nothing definite can as yet be stated about the ureides, ketimines, and ketones, because of the scarcity of available data. Moreover, when considering the toxicity, even if merely approximately, the series of acids is seen to be by far the most promising. Another point of interest was the increased potency imparted to the compounds by substitution of the α-methylene group with an isopropyl or aminopropyl radical, compared with the other substituents tested. The hypoglycemic action was particularly evident in the case of XXIII (α-isopropyl-α-3-dimethylaminopropyl-) and XXIV (α,α-di-3-dimethylaminopropyl-1-naphthylacetic acid), the potency of which, at a dose of either 50 or 10 mg/kg was of the same order as that of the reference standard, chlorpropamide.

As for the other activities investigated, many of the compounds showed CNS depression which appeared as a slight motor incoordination, decrease of the spontaneous motility, body muscle tonus, and of the pinna and ipsilateral flexor reflexes. A number of the substances were found to exert antiinflammatory activity against carrageenin-induced edema, this effect being particularly marked for V (α-3-diethylaminopropyl-1-naphthylacetonitrile), XVII (α-isopropyl-α-3-diethylaminopropyl-1-naphthylacetamide), XXXVIII (ethyl α-isopropyl-α-3-diethylaminopropyl-1-naphthylacetate), XLII (N-cyclohexyl-α-isopropyl-α-3-dimethylaminopropyl-1-naphthylacetamide), and IL (1-dimethylamino-4-ethyl-4-naphthyl-5-heptanone). As for the hot plate analgesic method, the activity found was modest in every case when compared with that of morphine, but was more interesting, especially for IX (α-isopropyl-α-3-pyrrolidinylpropyl-1-naphthylacetonitrile), when phenylbutazone was taken as the reference standard. Many of the compounds showed a marked local anesthetic action which was most interesting in the case of XIX (α-isopropyl-α-3-pyrrolidinylpropyl-1-naphthylacetamide), XLVIII (1-dimethylamino-4-isopropyl-4-naphthyl-5-iminooctane), and IL. Among the substances tested for antitussive activity, XVIII (α,α-di-3-diethylaminopropyl-1-naphthylacetamide), XXX (methyl α-isopropyl-α-3-dimethylaminopropyl-1-naphthylacetate), XXXVI (phenyl α-isopropyl-α-3-dimethylaminopropyl-1-naphthylacetate), and XXXVIII were found to inhibit significantly the experimental cough. A number of the compounds showed some diuretic activity, which was more pronounced for XIV (α-ethyl-α-3-dimethylaminopropyl-1-naphthylacetamide), XXXI (ethyl α-isopropyl-α-3-dimethylaminopropyl-1-naphthylacetate), and XLII. As for the antispasmodic activity *in vitro*, only compounds VI (α-isopropyl-α-3-diethylaminopropyl-1-naphthylacetonitrile), IX, XV (α-isopropyl-α-3-dimethylaminopropyl-1-naphthylacetamide), XLVIII, and IL were found to be of some interest. Nothing of particular interest was found in investigating the antipyretic, choleretic, and hypotensive actions, as well as the *in vitro* antibacterial, antifungal, trichomonicidal, and antiamebal effects.

Due to the promising results shown in the preliminary hypoglycemic testing of XXIII and XXIV, these two compounds are now undergoing a more detailed pharmacological and toxicological study and this will be reported in the near future. An investigation of other substances chemically related to the title compounds is also in progress, in order to shed more light on the structure–hypoglycemic activity relationships.

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