Synthesis and Pharmacological Evaluation of α,α-Disubstituted Derivatives of Phenylacetamide and 1-Naphthylacetamide

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Fifteen α,α-disubstituted phenylacetamides and eighteen α,α-disubstituted 1-naphthylacetamides were prepared for comparative pharmacological screening. As previously found for the corresponding nitriles, the naphthalene derivatives appeared to be more interesting than the benzene derivatives. The antiinflammatory, local anesthetic, and diuretic activity of some of the substances of both series was particularly pronounced.

This work, which deals with the synthesis and pharmacological screening of many α,α-disubstituted phenylacetamide and 1-naphthylacetamide derivatives is a continuation of our study on the comparative pharmacological properties of corresponding naphthalene and benzene compounds.[1] Only compound I had been studied up to the present (for antispasmodic activity),[2] but some other phenylacetamides of similar structure have been more extensively investigated.[3]

The α,α-disubstituted phenylacetamides were obtained by the classical technique which involves hydrolysis of the corresponding nitriles with 90% sulfuric acid,[4-6] the reaction time depending on the steric hindrance of the nitrile used. As shown in Table I, the yields were high for the majority of the compounds.

Sulfuric acid (90%) was found to be a poor hydrolyzing agent for α,α-disubstituted 1-naphthylacetonitriles, which were advantageously hydrolyzed by a 1:1:1 mixture of concentrated sulfuric acid, glacial acetic acid, and water. The reaction time varied markedly from compound to compound, ranging from 24 hr. for XVI to 144 hr. for XVIII. Because of the great steric hindrance of these nitriles, the yields of α,α-disubstituted 1-naphthylacetamides were slightly lower than those obtained for α,α-disubstituted phenylacetamides, as shown in Table II.

Pharmacological screening included studies of acute toxicity, behavioral effects, and antiinflammatory, diuretic, local anesthetic, antispasmodic, and analgesic action.

Experimental[7]

Chemistry. Intermediate Nitriles.—The α,α-disubstituted phenylacetonitriles and 1-naphthylacetonitriles were prepared as previously reported.[1]

α,α-Disubstituted Amides.—The α,α-disubstituted phenylacetamides and 1-naphthylacetamides are listed in Tables I and II, respectively. The preparation of the compounds is illustrated by the following two examples.

α-Ethyl-α-(2-piperidinoethyl)phenylacetamide (VII). α-Ethyl-α-(2-piperidinoethyl)phenylacetonitrile (12.4 g., 0.05 mole) was dissolved in 90% H_2SO_4 (25 ml.). The solution was heated at 90–95° for 3 hr., cooled to room temperature, and poured with stirring onto crushed ice (35 g.). The resulting solution was washed with ether, filtered with charcoal, and made alkaline with 30% NaOH. The separated oil was extracted with $CHCl_3$, the extract was dried ($MgSO_4$), and the chloroform was removed under reduced pressure. The residue was fractionated, the product distilling at 152–155° (0.09 mm.) as a very viscous colorless oil.

α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (XVIII).—α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetonitrile (10 g., 0.05 mole) was dissolved in a 1:1:1 mixture of concentrated H_2SO_4, glacial acetic acid, and water (39 ml.). The solution was refluxed for 144 hr., cooled to room temperature, diluted with water, and made alkaline with 30% NaOH. The separated pasty product was extracted with ether, the extract was washed with water and then dried ($MgSO_4$). Distillation of the solvent yielded a solid which, on crystallization from ligroin (b.p. 75–120°), gave colorless crystals, m.p. 134–135°.

Pharmacology.—The acute toxicity, behavioral effects, and analgesic, antispasmodic, antiinflammatory, and diuretic activities were investigated by the techniques previously described.[1] Topical local anesthetic action was tested in guinea pigs by the corneal method of Chance and Lobstein.[8] The highest dosage level which did not provoke an obvious toxic symptomatology in experimental animals was used for each test. Cocaine, morphine, phenylbutazone, hydrochlorothiazide, atropine, diphenhydramine, hexamethonium, and chlorpromazine were used as standards for comparison of the local anesthetic, analgesic, antiinflammatory, diuretic, and antispasmodic activities.

Results and Discussion

The pharmacological screening results of α,α-disubstituted phenylacetamides are reported in Table III. Most of the compounds caused signs of CNS depression in mice, such as decreased spontaneous motility, irritability, body muscle tonus, and pinna, ipsilateral flexor, and corneal reflexes. A number of the substances showed some diuretic activity on oral administration, which was particularly evident for IX (α-*sec*-butyl-α-2-piperidinoethyl-) and X (α,α-di-2-piperidinoethylphenylacetamide). Nearly all of the compounds were found to exert antiinflammatory activity against formalin-induced edema, especially II (α-ethyl-α-2-dimethylaminoethylphenylacetamide). As for the hot plate analgesic method, many of the substances increased the pain threshold of mice after intraperitoneal administration, and this effect was more pronounced for IV (α-*sec*-butyl-α-2-dimethylaminoethyl-), VIII (α-isopropyl-α-2-piperidinoethyl-), and XIV (α-*sec*-

(1) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 589 (1965).

(2) W. B. Wheatley, W. F. Minor, W. M. Byrd, W. E. Fitzgibbon, Jr., M. E. Speeter, L. C. Cheney, and S. B. Binkley, *J. Org. Chem.*, **19**, 794 (1954).

(3) D. K. de Jongh, E. G. Van Proosdij-Hartzema, and P. Janssen, *Arch. Intern. Pharmacodyn.*, **103**, 100 (1955).

(4) P. Janssen, D. Zivkovic, P. Demoen, D. K. de Jongh, and E. G. Van Proosdij-Hartzema, *ibid.*, **103**, 82 (1955).

(5) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor, and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

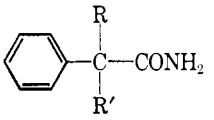
(6) L. C. Cheney, R. R. Smith, and S. B. Binkley, *J. Am. Chem. Soc.*, **71**, 53 (1949).

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

(8) M. R. A. Chance and H. Lobstein, *J. Pharmacol. Exptl. Therap.*, **82**, 203 (1944).

Table I

α,α-Disubstituted Phenylacetamides

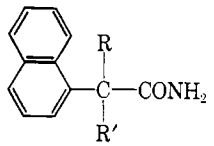


Compd.	R	R′	Reaction time, hr.	Yield, %	B.p. (mm.) or m.p., °C.	Crystn. solvent[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
I[b]	CH_3	$(CH_3)_2N(CH_2)_2$	3	79[c]	95–97	H	$C_{13}H_{20}N_2O$	70.87	9.15	12.72	71.26	8.96	12.52
II	C_2H_5	$(CH_3)_2N(CH_2)_2$	3	92[c]	87–88	H	$C_{14}H_{22}N_2O$	71.75	9.46	11.96	71.83	9.52	12.14
III	*i*-C_3H_7	$(CH_3)_2N(CH_2)_2$	6	84[c]	110.5–112	L	$C_{15}H_{24}N_2O$	72.54	9.74	11.28	72.83	9.92	11.37
IV	*sec*-C_4H_9	$(CH_3)_2N(CH_2)_2$	8	77[d]	146–150 (0.2), 101–102	E	$C_{16}H_{26}N_2O$	73.24	9.99	10.68	73.56	9.73	10.98
V[e]	$(CH_3)_2N(CH_2)_2$	$(CH_3)_2N(CH_2)_2$	3	78[c]	102.5–103	L–C	$C_{16}H_{27}N_3O$	69.27	9.81	15.15	69.42	10.06	15.18
VI	CH_3	*f*	3	80.5[d]	164–168 (0.2)		$C_{16}H_{24}N_2O$	73.80	9.29	10.76	74.14	9.18	10.90
VII	C_2H_5	*f*	3	68.5[d]	152–155 (0.09)		$C_{17}H_{26}N_2O$	74.41	9.55	10.21	74.53	9.52	10.32
VIII	*i*-C_3H_7	*f*	7	90[c]	114–114.5	H–A	$C_{18}H_{28}N_2O$	74.95	9.79	9.78	75.14	9.88	9.71
IX	*sec*-C_4H_9	*f*	10	88[c]	120–122	L–A	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	75.41	9.84	9.48
X[g]	*f*	*f*	3	86[c]	116.5–117.5	A	$C_{22}H_{35}N_3O$	73.90	9.87	11.75	74.10	9.91	11.53
XI	CH_3	*h*	3.5	99[c]	137–138.5	B–C	$C_{15}H_{21}N_3O_2$	68.67	8.45	10.68	68.83	8.43	10.86
XII	C_2H_5	*h*	3	82.5[c]	126–127.5	C–B–A	$C_{16}H_{24}N_2O_2$	69.53	8.75	10.14	69.65	8.92	10.01
XIII	*i*-C_3H_7	*h*	9	87.5[c]	148.5–149.5	A	$C_{17}H_{26}N_2O_2$	70.31	9.02	9.65	70.65	8.95	9.46
XIV	*sec*-C_4H_9	*h*	8	84[c]	138.5–139.5	A	$C_{18}H_{28}N_2O_2$	71.01	9.27	9.20	71.20	9.13	9.10
XV	*h*	*h*	3	73.5[c]	144.5–146	B–L	$C_{20}H_{31}N_3O_3$	66.45	8.64	11.63	66.81	8.80	11.55

[a] A = ethyl acetate, B = benzene, C = cyclohexane, E = petroleum ether (b.p. 40–70°), H = hexane, L = ligroin (b.p. 75–120°). [b] W. B. Wheatley, W. F. Minor, W. M. Byrd, W. E. Fitzgibbon, Jr., M. E. Speeter, L. C. Cheney, and S. B. Binkley [*J. Org. Chem.*, **19**, 794 (1954)] reported m.p. 95–96.5°, yield 73%. [c] Crude product. [d] Once distilled. [e] Prepared as the dipicrate by M. Borovička and M. Protiva, *Chem. Listy*, **51**, 2118 (1957). [f] β-Piperidinoethyl. [g] P. A. J. Janssen, D. Zizkovic, and P. Demoen [*J. Am. Chem. Soc.*, **77**, 4423 (1955)] reported m.p. 117°, yield 69%. [h] β-Morpholinoethyl.

Table II

α,α-Disubstituted 1-Naphthylacetamides



Compd.	R	R′	Reaction time, hr.	Yield, %	B.p. (mm.) or m.p., °C.	Crystn. solvent[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % H
XVI	CH_3	$(CH_3)_2N(CH_2)_2$	24	76[b]	72–73	L	$C_{17}H_{22}N_2O$	75.52	8.20	10.36	75.21	8.37	10.35
XVII	C_2H_5	$(CH_3)_2N(CH_2)_2$	24	74[c]	181–182 (0.4), 61–63		$C_{18}H_{24}N_2O$	76.02	8.51	9.85	75.78	8.69	9.65
XVIII	*i*-C_3H_7	$(CH_3)_2N(CH_2)_2$	144	77[b]	134–135	L	$C_{19}H_{26}N_2O$	76.47	8.78	9.39	76.86	8.99	9.59
XIX	*sec*-C_4H_9	$(CH_3)_2N(CH_2)_2$	144	72[b]	92.5–93.5	P	$C_{20}H_{28}N_2O$	76.88	9.03	8.97	77.02	8.89	9.13
XX	$(CH_3)_2N(CH_2)_2$	$(CH_3)_2N(CH_2)_2$	24	70[b]	114.5–115.5	B–L	$C_{20}H_{29}N_3O$	73.35	8.93	12.83	73.72	9.06	12.95
XXI	*i*-C_3H_7	$CH_3(C_2H_5)N(CH_2)_2$	120	73[c]	188–190 (0.1)		$C_{20}H_{28}N_2O$	76.88	9.03	8.97	77.02	8.99	8.79
XXII	*i*-C_3H_7	$(C_2H_5)_2N(CH_2)_2$	120	68[c]	180–182 (0.1), 55–57		$C_{21}H_{30}N_2O$	77.25	9.26	8.58	77.54	9.44	8.74
XXIII	*i*-C_3H_7	$CH_3(C_6H_5CH_2)N(CH_2)_2$	72	66[c]	203–205 (0.1)		$C_{25}H_{30}N_2O$	80.17	8.07	7.48	80.34	7.97	7.34
XXIV	CH_3	*d*	24	70[b]	137–138	L	$C_{20}H_{26}N_2O$	77.38	8.44	9.03	77.02	8.55	9.22
XXV	C_2H_5	*d*	24	72[b]	106.5–107.5	D	$C_{21}H_{28}N_2O$	77.73	8.70	8.63	77.43	8.45	8.65
XXVI	*i*-C_3H_7	*d*	96	70[b]	117.5–118.5	E	$C_{22}H_{30}N_2O$	78.06	8.93	8.28	78.19	8.81	8.49
XXVII	*sec*-C_4H_9	*d*	96	67[b]	164.5–165.5	E	$C_{23}H_{32}N_2O$	78.36	9.15	7.95	78.12	9.04	8.07
XXVIII	*d*	*d*	24	76[b]	159.5–160.5	L	$C_{26}H_{37}N_3O$	76.61	9.15	10.31	76.47	9.19	10.42
XXIX	CH_3	*e*	24	71[b]	178–179	A–L	$C_{19}H_{24}N_2O_2$	73.04	7.74	8.97	73.27	7.86	9.04
XXX	C_2H_5	*e*	24	63[b]	153–154	A–L	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58	73.89	8.14	8.63
XXXI	*i*-C_3H_7	*e*	96	62[b]	186–187	A–L	$C_{21}H_{28}N_2O_2$	74.08	8.29	8.23	74.25	8.12	8.30
XXXII	*sec*-C_4H_9	*e*	96	67[b]	163.5–164.5	A–L	$C_{22}H_{30}N_2O_2$	74.54	8.53	7.90	74.82	8.38	7.83
XXXIII	*e*	*e*	24	78[b]	177–178	D	$C_{24}H_{33}N_3O_3$	70.04	8.08	10.21	70.31	7.98	10.32

[a] A = ethanol, B = benzene, D = diluted ethanol, E = ether, L = ligroin (b.p. 75–120°), P = petroleum ether (b.p. 40–70°). [b] Crude product. [c] Once distilled. [d] β-Piperidinoethyl. [e] β-Morpholinoethyl.

butyl-α-2-morpholinoethylphenylacetamide). Compounds IV, VI (α-methyl-α-2-piperidinoethylphenylacetamide) and IX showed significant antispasmodic activity *in vitro*. As for the local anesthetic action, III (α-isopropyl-α-2-dimethylaminoethyl-), IX, and XII (α-ethyl-α-2-morpholinoethylphenylacetamide) were found to be of some interest.

The results for α,α-disubstituted 1-naphthylacetamides are reported in Table IV. Most of the compounds showed CNS depression which appeared as a slight increase in passivity, decrease of the spontaneous motility, irritability, body muscle tonus, and of the pinna, ipsilateral flexor, and corneal reflexes, and slight motor incoordination. The whole series was found to greatly inhibit formalin-induced edema, in particular, XVIII (α-isopropyl-α-2-dimethylaminoethyl-), XIX (α-*sec*-butyl-α-2-dimethylaminoethyl-), XXI (α-isopropyl-α-2-methylethylaminoethyl-), XXII (α-isopropyl-α-2-diethylaminoethyl-), and XXIII (α-isopropyl-α-2-methylbenzylamino-ethyl-1-naphthylacetamide) were found to be very active. All the compounds were active as diuretics and particularly striking increases in water

TABLE III

PHARMACOLOGICAL SCREENING RESULTS OF α,α-DISUBSTITUTED PHENYLACETAMIDES

Compd.	Approx. LD_{50} (mouse), mg./kg. i.p.	Effects on behavior @ (mouse)	Surface local anesthetic activity (guinea pig), mg./kg. i.p.	Surface local anesthetic activity (guinea pig), %[a]	Analgesic activity (mouse) Increase of reaction time, @ mg./kg. i.p.	Analgesic activity (mouse) Increase of reaction time, %	Antispasmodic activity *in vitro*[b], % inhibition of spasms produced by Acetylcholine 1 × 10^{-7} g./ml.	Histamine 1 × 10^{-6} g./ml.	Nicotine 2 × 10^{-6} g./ml.	Serotonin 1 × 10^{-6} g./ml.	Antiinflammatory activity (rat) Inhibition of edema, @ mg./kg. i.p.	Antiinflammatory activity (rat) Inhibition of edema, %	Diuretic activity (rat) Test vol. Control vol.	Diuretic activity (rat) @ mg./kg. *p.o.*
I	780–820	Nothing noticeable	200	26	200	26	52	27	24	39	200	15	1.25	100
II	320–350	Nothing noticeable	200	16	200	25	44	24	23	8	200	36	1.52	100
III	270–320	Moderate spontaneous motility decrease, moderate motor incoordination	100	66	100	46	61	27	50	20	100	22	Inactive	100
IV	250–290	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia, moderate pinna, ipsilateral flexor, and corneal reflex alterations	200	9	200	77	100	100	90	87	200	20	1.22	100
V	280–330	Moderate CNS depression, moderate pinna reflex alteration	100	9	100	42	34	22	55	84	100	11	Inactive	100
VI	300–340	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia	100	11	100	24	100	95	86	92	100	18	Inactive	100
VII	270–320	Moderate behavior excitement	100	4	100	49	100	82	54	25	100	29	Inactive	100
VIII	260–310	Moderate CNS depression, moderate motor incoordination, moderate muscle hypotonia	200	18	200	110	100	15	42	73	200	25	Inactive	100
IX	150–170	Moderate CNS excitement, moderate pinna and corneal reflex alterations, reduction of the response to pain	100	65	100	52	100	100	87	76	100	20	1.80	100
X	120–150	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia, moderate pinna, ipsilateral flexor, and corneal reflex alterations	50	13	50	37	92	36	49	72	50	8	1.60	100
XI	650–690	Moderate CNS depression, moderate motor incoordination, moderate ipsilateral flexor reflex alteration	400	6	400	92	78	Inactive	37	32	400	30	1.30	100
XII	680–730	Moderate spontaneous motility decrease, moderate pinna reflex alteration	100	50	100	Inactive	23	27	40	15	100	26	1.53	100
XIII	620–660	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia, moderate pinna and ipsilateral flexor reflex alterations	100	Inactive	100	34	88	Inactive	34	33	100	23	1.35	100
XIV	380–420	Moderate CNS depression, moderate motor incoordination	100	40	100	88	92	58	87	86	100	22	1.50	100
XV	1560–1640	Moderate CNS depression, moderate motor incoordination, moderate muscle hypotonia	400	12	400	64	85	100	44	100	400	22	Inactive	100
Morphine·HCl					5	67								
Phenylbutazone											100	18		
Hydrochlorthiazide													1.56	6.25

[a] All compounds were tested at a concentration of 1 mg./ml. The ED_{50} value for the standard cocaine hydrochloride is 0.70 mg./ml.
[b] All compounds were tested at a concentration of 10 γ/ml. The ED_{50} values for the standard compounds are atropine sulfate (antiacetylcholinic), 0.0035 γ/ml.; diphenhydramine hydrochloride (antihistaminic), 0.0074 γ/ml.; hexamethonium bitartrate (antinicotinic), 0.88 γ/ml.; and chlorpromazine hydrochloride (antiserotoninic), 0.055 γ/ml.

excretion were obtained with XVIII, XX (α,α-di-2-dimethylaminoethyl-), XXVI (α-isopropyl-α-2-piperidinoethyl-), XXVII (α-*sec*-butyl-α-2-piperidinoethyl-), XXXI (α-isopropyl-α-2-morpholinoethyl-), and XXXII (α-*sec*-butyl-α-2-morpholinoethyl-1-naphthylacetamide). A number of the substances showed a marked local anesthetic action which was most interesting in the case of XXIV (α-methyl-α-2-piperidinoethyl-), XXV (α-ethyl-α-2-piperidinoethyl-), XXVI, XXVII, XXX (α-ethyl-α-2-morpholinoethyl-1-naphthylacetamide), XXXI, and XXXII. Compounds XXIII, XXVI, and XXVII were found to have a signifi-

Table IV

Pharmacological Screening Results of α,α-Disubstituted 1-Naphthylacetamides

Compd.	Approx. LD_{50} (mouse), mg./kg. i.p.	Effects on behavior @ (mouse)	Surface local anesthetic activity, guinea pig, %[a] mg./kg. i.p.	Analgesic activity (mouse) Increase of reaction time, @ mg./kg. i.p.	Antispasmodic activity *in vitro*,[b] % inhibition of spasms produced by Acetylcholine 1 × 10^{-7} g./ml.	Histamine 1 × 10^{-6} g./ml.	Nicotine 1 × 10^{-6} g./ml.	Serotonin 1 × 10^{-6} g./ml.	Antiinflammatory activity (rat) Inhibition of edema, @ mg./kg. i.p.	Diuretic activity (rat) Test vol./Control vol. @ mg./kg. *p.o.*
XVI	150–180	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia, marked pinna reflex alteration	100	60	7	100	36	6	91	24	30	100	1.54	100
XVII	130–160	Nothing noticeable	100	68	Inactive	100	Inactive	29	13	21	28	100	1.25	100
XVIII	250–270	Moderate CNS depression, moderate motor incoordination, moderate muscle hypotonia, marked pinna reflex alteration	200	45	71	200	Inactive	Inactive	29	Inactive	86	200	2.37	200
XIX	270–320	Moderate spontaneous motility decrease, moderate irritability increase, moderate muscle hypotonia	100	75	48	100	71	73	100	93	72	100	1.64	100
XX	140–170	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia, moderate pinna and ipsilateral flexor reflex alterations	100	28	26	100	Inactive	9	12	Inactive	18	100	1.99	100
XXI	200–220	Moderate behavior excitement, moderate muscle hypotonia	100	Inactive	81	100	22	43	34	35	56	100	1.74	50
XXII	155–170	Moderate behavior excitement, moderate CNS excitement	50	Inactive	22	50	26	27	31	14	45	50	1.64	50
XXIII	120–150	Nothing noticeable	25	18	16	25	100	89	92	79	43	25	1.16	50
XXIV	180–220	Marked CNS depression, moderate motor incoordination, marked muscle hypotonia, moderate pinna reflex alteration	100	86	21	100	92	50	84	12	35	100	1.23	100
XXV	180–220	Marked CNS depression, moderate motor incoordination, marked muscle hypotonia	100	88	22	100	81	42	Inactive	66	30	100	1.35	100
XXVI	130–160	Moderate muscle hypotonia	100	82	52	100	100	100	100	100	28	100	2.18	100
XXVII	140–170	Nothing noticeable	100	89	11	100	100	100	100	100	37	100	1.92	100
XXVIII	90–110	Marked CNS depression, moderate motor incoordination, marked muscle hypotonia, marked pinna, ipsilateral flexor, and corneal reflex alterations	50	44	47	25	19	Inactive	31	18	22	50	1.32	50
XXIX	280–330	Marked CNS depression, moderate motor incoordination, moderate ipsilateral flexor reflex alteration	100	39	39	100	17	16	44	55	15	100	1.49	100
XXX	90–110	Nothing noticeable	50	92	56	50	25	22	88	75	14	50	Inactive	50
XXXI	290–330	Nothing noticeable	100	83	49	100	Inactive	52	49	22	20	100	2.06	100
XXXII	130–170	Moderate motor incoordination	100	85	78	100	Inactive	19	9	37	35	100	2.19	100
XXXIII	600–660	Moderate CNS depression, moderate motor incoordination, moderate muscle hypotonia, moderate pinna and corneal reflex alterations	200	41	41	200	Inactive	Inactive	Inactive	Inactive	15	200	1.15	200
Morphine·HCl					67	5								
Phenylbutazone											18	100		
Hydrochlorthiazide													1.56	6.25

[a] All compounds were tested at a concentration of 1 mg./ml. The ED_{50} value for the standard cocaine hydrochloride is 0.70 mg./ml.
[b] All compounds were tested ata concentration of 10 γ/ml. The ED_{50} values for the standard compounds are atropine sulfate (antiacetylcholinic), 0.0035 γ/ml.; diphenhydramine hydrochloride (antihistaminic), 0.0074 γ/ml.; hexamethonium bitartrate (antinicotinic), 0.88 γ/ml.; and chlorpromazine hydrochloride (antiserotoninic), 0.055 γ/ml.

cant antispasmodic action *in vitro*. With the exception of XVIII, XXI, and XXXII, all the compounds possessed only a slight analgesic action.

The most interesting feature revealed during this investigation is the marked antiinflammatory activity shown by both series. The α,α-disubstituted 1-naphthylacetamides in particular seem to be very active and worthy of more detailed study. Another point of interest is the diuretic action, as it is concurrent with the antiinflammatory activity. Here also, the naphthalene derivatives appear to be more potent than the corresponding benzene compounds. Both series cause CNS depression in mice and the symptomatology of these effects is rather similar. All the tested compounds show only slight analgesic action, although this is more pronounced for the α,α-disubstituted phenylacetamides. The naphthalene derivatives appear to be more active as local anesthetics, the most interesting of these being some amides with a piperidinoethyl or morpholinoethyl group in the α-position. A number of compounds of both series possess antispasmodic activity, but this requires further experimental study for a more accurate evaluation. Finally, the benzene derivatives generally appear to be less toxic than the corresponding naphthalene compounds.

Of all the tested substances, α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide was submitted, in the light of its interesting pharmacological pattern, to a more detailed pharmacological and toxicological investigation.[9] This substance is now undergoing clinical trials as an antiinflammatory agent.

From the point of view of the general pharmacological picture, the naphthalene derivatives seem to be more interesting than the corresponding benzene compounds.

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Nonsteroidal Antiinflammatory Agents. Some Arylacetic Acids

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A series of arylacetic acids which exhibit antiinflammatory activity are described. The principal members of the series are derivatives of 1-naphthaleneacetic acid, and structure–activity relationships are discussed, particularly with regard to antiultraviolet erythema activity. Substituents on the α-carbon atom of 1-naphthaleneacetic acid exert a pronounced influence on antiinflammatory activity. Alkyl group substitution normally results in a loss of antiinflammatory activity, while unsaturated groups as exemplified by furfuryl and benzyl retain or enhance the antiinflammatory activity of 1-naphthaleneacetic acid. The biological results are discussed with reference to the established antirheumatic agent, phenylbutazone, and compared with the new antiinflammatory arylacetic acid derivatives ibufenac and indomethacin.

During the last few years several reports have appeared concerning new drugs of potential value for the symptomatic treatment of rheumatoid arthritis and similar inflammatory conditions of connective tissue. Notable among these newer drugs are the N-arylanthranilic acid derivatives, mefenamic acid[1] and flufenamic acid,[2] and the arylacetic acids, indomethacin [1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid][3] and ibufenac (4-isobutylphenylacetic acid).[4]

In this report a novel series of arylacetic acids are described which also have demonstrated antiinflammatory activity.

While the mode of action of nonsteroidal antiinflammatory agents is unknown, numerous laboratory procedures are available for demonstrating antiinflammatory activity in animal tests. The primary test procedure used to assay antiinflammatory activity in this study was the antiultraviolet erythema test in guinea pigs.[5] Phenylbutazone and most other clinically effective nonsteroidal antiinflammatory drugs are active in this test which was made quantitative by using phenylbutazone as a standard in each experiment. Addition assays of antiinflammatory activity were employed for certain compounds. These included the rat paw edema test using kaolin as irritant,[6] the cotton pellet test[7] in which the per cent inhibition of granuloma was estimated, and the Randall and Selitto test[8] which

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