Synthesis and Pharmacological Evaluation of α,α-Disubstituted Derivatives of Phenylacetonitrile and 1-Naphthylacetonitrile

SILVANO CASADIO, GIANFRANCO PALA, ELDA CRESCENZI, TIBERIO BRUZZESE, ERNESTA MARAZZI-UBERTI, AND GERMANO COPPI

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

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Fifteen α,α-disubstituted phenylacetonitriles and twenty-four α,α-disubstituted 1-naphthylacetonitriles were prepared for comparative pharmacological screening. The naphthalene derivatives appear to be more interesting than the corresponding benzene compounds, in the light of the over-all pharmacological picture. The analgesic, antiinflammatory, and antispasmodic activity was particularly pronounced for some of the naphthalene compounds. The antitussive test, performed on only a few compounds, gave promising results, which make this test worth extending to all the other substances.

During systematic investigation carried out to compare pharmacologically naphthalene compounds with analogous benzene derivatives,[1] it was found that replacement of the benzene ring by naphthalene very often enhanced the tested activities. We wish to report in the present paper the synthesis and pharmacological screening results of several α,α-disubstituted derivatives of phenylacetonitrile and 1-naphthylacetonitrile. The known benzene compounds I–V, VII, IX, and XIV have not been studied much as yet. Two of these (V and IX) have been reported to exert antispasmodic and analgesic activity,[2–4] while no pharmacological data have been found in the literature for the two known naphthalene derivatives XVI and XXIV.

The α,α-disubstituted phenylacetonitriles and 1-naphthylacetonitriles were prepared by the general procedure we recently described for α-alkylnaphthylacetonitriles.[1c] It consists of alkylating the unsubstituted nitriles, in the presence of sodamide, with an alkylaminoalkyl halide (method A) or alkyl halide (method B). A suitable solvent and reflux time were chosen for each compound. As shown in Tables I and II, this procedure gave high yields for the great majority of the new compounds and improved the yields of the known compounds.

The pharmacological screening carried out on these compounds measured the acute toxicity, behavioral effects, and analgesic, antispasmodic, antiinflammatory, diuretic, and coronary vasodilator action. In view of the interesting antitussive properties recently reported for some basic phenylacetonitriles,[5] this activity was also investigated although only for a few compounds of both series.

Experimental[6]

Chemistry. Intermediate Nitriles.—Benzyl cyanide was commercially available; 1-naphthylacetonitrile was obtained by Vogel's method,[7] using 1-chloromethylnaphthalene and potassium cyanide. The α-alkylphenylacetonitriles and α-alkyl-1-naphthylacetonitriles utilized in this study were prepared by the general method we recently reported.[1c]

α,α-Disubstituted Nitriles.—The α,α-disubstituted phenylacetonitriles and 1-naphthylacetonitriles are listed in Tables I and II, respectively. The title compounds were prepared by two different procedures which are well illustrated by the following methods A and B.

Method A. α-Isopropyl-α-(2-morpholinoethyl)phenylacetonitrile (XIII).—Sodamide (20.4 g., 0.52 mole) was added in small portions to a solution of α-isopropylphenylacetonitrile[8] (83 g., 0.52 mole) in dry benzene (1 l.). The mixture was refluxed for 2 hr., with stirring, and 2-(N-morpholino)-1-chloroethane (78 g., 0.52 mole) was added dropwise over 1 hr. The suspension was then refluxed for 6 hr. and cooled to room temperature, and water (400 ml.) was cautiously added to decompose any excess sodamide and to dissolve NaCl formed in the reaction. The benzene layer was separated and extracted with 10% HCl (1.5 l.). The acid extract was washed with ether (400 ml.) and made alkaline with 10% NaOH until just alkaline to phenolphthalein. An oil separated, which was extracted with ether (1 l.), and the ethereal solution was washed with water until neutral. Distillation of the dried (Na_2SO_4) extract yielded a solid which on crystallization from ligroin (b.p. 75–120°) gave colorless crystals, m.p. 75.5–77.5°.

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

α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetonitrile (XIX).—Sodamide (14.4 g., 0.37 mole) was added in small portions to a solution of α-(2-dimethylaminoethyl)-1-naphthylacetonitrile (XVI) (80 g., 0.34 mole) in dry ether (800 ml.). The mixture was refluxed for 2 hr. with stirring, and 2-bromopropane (45.5 g., 0.37 mole) was added dropwise over 1 hr. The suspension was refluxed for 5 hr. and then treated as described in method A to yield finally a colorless oil, b.p. 158–161° (0.5 mm.).

Pharmacology.—The approximate acute toxicity of the compounds and the behavioral effect were studied in mice, using five animals for each dose level and Irwin's method,[9] respectively. The analgesic activity was measured in mice using the hot plate technique of Adami and Marazzi[10]; the pain threshold was measured as the time necessary to cause foot licking. In all cases the compounds were administered by intraperitoneal injection.

The antispasmodic activity was investigated *in vitro* studying the inhibitory action of the compounds on isolated guinea pig ileum spasm induced by acetylcholine, histamine, nicotine, and serotonin, according to Magnus.[11]

The antiinflammatory activity was investigated in rats by the formalin-induced edema technique,[12] after intraperitoneal injec-

(1) (a) S. Casadio, G. Pala, T. Bruzzese, and E. Marazzi-Uberti, *Farmaco* (Pavia), *Ed Sci.*, **17**, 797 (1962); (b) *ibid.*, **17**, 810 (1962); (c) S. Casadio, G. Pala, and T. Bruzzese, *ibid.*, **17**, 871 (1962); (d) G. Pala, A. Mantegani, and C. Turba, *ibid.*, **18**, 521 (1963); (e) G. Pala, T. Bruzzese, and A. Mantegani, *ibid.*, **19**, 235 (1964); (f) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **19**, 731 (1964); (g) *ibid.*, **19**, 933 (1964).

(2) J. Klosa, *Arch. Pharm.*, **286**, 104 (1953).

(3) L. C. Weaver and B. E. Abreu, *J. Am. Pharm. Assoc.*, **49**, 298 (1960).

(4) H. Kasprek and K. Pfroepffer, *Arzneimittel-Forsch.*, **8**, 673 (1958).

(5) British Patent 822,695 (March 18, 1958).

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

(7) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., London, 1959, p. 763.

(8) C. G. Overberger and D. Tanner, *J. Am. Chem. Soc.*, **77**, 369 (1955).

(9) S. Irwin, Communication at the Gordon Research Conference on Medicinal Chemistry, Aug. 3–7, New London, N. H., 1959.

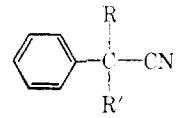
(10) E. Adami and E. Marazzi, *Arch. Intern. Pharmacodyn.*, **107**, 322 (1956).

(11) R. Magnus, *Arch. ges. Physiol.*, **102**, 123 (1904).

(12) G. Wilhelmi, *Medizinische*, **50**, 1591 (1952).

TABLE I

α,α-DISUBSTITUTED PHENYLACETONITRILES

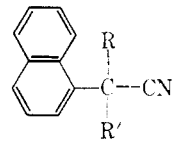


Compd.	R	R′	Method	Solvent	Reflux time, hr.	Yield, %	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
I[a]	CH_3	$(CH_3)_2N(CH_2)_2$	A	C_6H_6	2	81[b]	89–90 (0.3)	$C_{13}H_{18}N_2$	77.18	8.97	13.85	77.32	9.16	13.81
II[c]	C_2H_5	$(CH_3)_2N(CH_2)_2$	B	Et_2O	5	85[b]	102–105 (0.1)	$C_{14}H_{20}N_2$	77.73	9.32	12.95	77.95	9.42	12.78
III[d]	*i*-C_3H_7	$(CH_3)_2N(CH_2)_2$	B	Et_2O	5	90[b]	117–120 (0.4)	$C_{15}H_{22}N_2$	78.21	9.63	12.16	78.02	9.44	12.02
IV[e]	*sec*-C_4H_9	$(CH_3)_2N(CH_2)_2$	B	Et_2O	5	88[b]	107–108 (0.05)	$C_{16}H_{24}N_2$	78.63	9.90	11.46	78.71	10.01	11.53
V[f]	$(CH_3)_2N(CH_2)_2$	$(CH_3)_2N(CH_2)_2$	A	C_6H_6	8	96[b]	128–130 (0.4)	$C_{16}H_{33}N_3$	74.08	9.72	16.20	74.32	9.88	16.31
VI	CH_3	*g*	A	C_6H_6	4	72[b]	116–118 (0.14)	$C_{16}H_{22}N_2$	79.29	9.15	11.56	79.42	9.34	11.67
VII[h]	C_2H_5	*g*	B	Et_2O	5	85[b]	129–131 (0.6)	$C_{17}H_{24}N_2$	79.64	9.44	10.93	79.72	9.56	11.04
VIII	*i*-C_3H_7	*g*	B	Et_2O	5	86[b]	121–123 (0.1)	$C_{18}H_{26}N_2$	79.95	9.69	10.36	80.13	9.78	10.15
IX[i]	*sec*-C_4H_9	*g*	B	C_6H_6	5	82[b]	129–132 (0.2)	$C_{19}H_{28}N_2$	80.23	9.92	9.85	80.37	10.12	9.91
X	*g*	*g*	A	C_6H_6	8	91[b]	155–157 (0.06)	$C_{22}H_{35}N_3$	77.82	9.80	12.38	78.15	9.92	12.56
XI	CH_3	*j*	A	C_6H_6	2	69[b]	127–130 (0.07)	$C_{16}H_{20}N_2O$	73.73	8.25	11.47	73.85	8.45	11.60
XII	C_2H_5	*j*	B	C_6H_6	5	88[b]	140–142 (0.5)	$C_{18}H_{22}N_2O$	74.38	8.58	10.84	74.65	8.49	10.80
XIII	*i*-C_3H_7	*j*	A	C_6H_6	6	84[k]	75.5–77.5[l]	$C_{17}H_{24}N_2O$	74.96	8.88	10.29	75.01	9.02	10.18
XIV[m]	*sec*-C_4H_9	*j*	A	C_6H_6	6	94[k]	84.5–85.5[l]	$C_{18}H_{26}N_2O$	75.48	9.15	9.78	75.67	9.33	9.53
XV	*j*	*j*	A	$C_6H_5CH_3$	5	78[b]	163–166 (0.04)	$C_{20}H_{29}N_3O_2$	69.94	8.51	12.24	70.18	8.62	12.27

[a] J. H. Burckhalter and S. H. Johnson [*J. Am. Chem. Soc.*, **73**, 4832 (1951)] reported b.p. 132° (4 mm.), yield 50%. [b] Once distilled. [c] F. B. Tutwiler, R. G. Child, and S. N. Wrenn [*J. Org. Chem.*, **19**, 910 (1954)] reported b.p. 131–133° (4 mm.), yield 61%. [d] G. Ehrhart and H. Ott [German Patent 1,034,649 (July 24, 1958)] reported b.p. 157–158° (9 mm.). [e] Lit.[d] b.p. 153–155° (0.5 mm.). [f] F. F. Blicke, J. A. Faust, J. Krapcho, and E. Tsao [*J. Am. Chem. Soc.*, **74**, 1844 (1952)] reported b.p. 130–135° (1–2 mm.), yield 89%. [g] β-Piperidinoethyl. [h] Lit.[c] b.p. 150–154° (1.5 mm.), yield 80%. [i] Lit.[d] b.p. 154–157° (0.7 mm.). [j] β-Morpholinoethyl. [k] Crude product. [l] Recrystallized from ligroin (b.p. 75–120°). [m] Lit.[d] b.p. 198–202° (5.5 mm.).

TABLE II

α,α-DISUBSTITUTED 1-NAPHTHYLACETONITRILES



Compd.	R	R′	Method	Solvent	Reflux time, hr.	Yield, %[a]	B.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
XVI[b]	H	$(CH_3)_2N(CH_2)_2$	A	C_6H_6	5	92	165–167 (0.8)	$C_{16}H_{18}N_2$	80.63	7.61	11.76	80.77	7.65	11.92
XVII	CH_3	$(CH_3)_2N(CH_2)_2$	A	C_6H_6	2	80	170–172 (1)	$C_{17}H_{20}N_2$	80.91	7.99	11.10	81.07	8.02	11.18
XVIII	C_2H_5	$(CH_3)_2N(CH_2)_2$	B	Et_2O	5	95	151–152 (0.2)	$C_{18}H_{22}N_2$	81.16	8.33	10.52	81.34	8.40	10.45
XIX	*i*-C_3H_7	$(CH_3)_2N(CH_2)_2$	B	Et_2O	5	94	158–161 (0.5)	$C_{19}H_{24}N_2$	81.38	8.63	9.99	81.30	8.77	9.83
XX	*sec*-C_4H_9	$(CH_3)_2N(CH_2)_2$	B	Et_2O	5	92	156–159 (0.3)	$C_{20}H_{26}N_2$	81.58	8.90	9.52	81.30	8.97	9.43
XXI	$(CH_3)_2N(CH_2)_2$	$(CH_3)_2N(CH_2)_2$	A	C_6H_6	8	83	165–168 (0.6)	$C_{20}H_{27}N_3$	77.62	8.80	13.58	77.83	8.77	13.45
XXII	H	$CH_3(C_2H_5)N(CH_2)_2$	A	C_6H_6	5	88	160–162 (0.8)	$C_{17}H_{20}N_2$	80.91	7.99	11.10	80.78	8.04	10.96
XXIII	*i*-C_3H_7	$CH_3(C_2H_5)N(CH_2)_2$	B	C_6H_6	8	85	144–146 (0.1)	$C_{20}H_{26}N_2$	81.58	8.90	9.52	81.49	8.79	9.54
XXIV[c]	H	$(C_2H_5)_2H(CH_2)_2$	A	C_6H_6	5	93	132–135 (0.1)	$C_{16}H_{22}N_2$	81.16	8.33	10.52	80.94	8.29	10.35
XXV	*i*-C_3H_7	$(C_2H_5)_2N(CH_2)_2$	B	Et_2O	5	91	141–143 (0.2)	$C_{21}H_{28}N_2$	81.77	9.15	9.08	81.84	9.04	9.14
XXVI	H	$CH_3(C_6H_5CH_2)N(CH_2)_2$	A	C_6H_6	5	80	195–198 (0.2)	$C_{22}H_{22}N_2$	81.04	7.05	8.91	84.19	7.14	9.04
XXVII	*i*-C_3H_7	$CH_3(C_6H_5CH_2)N(CH_2)_2$	B	C_6H_6	8	78	198–200 (0.3)	$C_{26}H_{28}N_2$	84.22	7.93	7.86	83.97	7.94	7.82
XXVIII	H	*d*	A	Et_2O	5	97	184–186 (0.8)	$C_{19}H_{22}N_2$	81.97	7.97	10.06	82.11	8.07	10.03
XXIX	CH_3	*d*	A	C_6H_6	2	73	176–179 (0.2)	$C_{20}H_{24}N_2$	82.14	8.27	9.58	82.05	8.28	9.63
XXX	C_2H_5	*d*	B	Et_2O	5	80	173–175 (0.3)	$C_{21}H_{26}N_2$	82.31	8.55	9.14	82.19	8.53	9.22
XXXI	*i*-C_3H_7	*d*	B	Et_2O	5	86	178–180 (0.3)	$C_{22}H_{28}N_2$	82.45	8.81	8.74	82.60	8.75	8.83
XXXII	*sec*-C_4H_9	*d*	B	Et_2O	5	87	171–174 (0.1)	$C_{23}H_{30}N_2$	82.58	9.04	8.38	82.70	9.09	8.35
XXXIII	*d*	*d*	A	C_6H_6	8	95	201–204 (0.2)	$C_{26}H_{28}N_2$	80.16	9.06	10.79	80.07	8.98	10.86
XXXIV	H	*e*	A	Et_2O	5	93	191–193 (0.7)	$C_{18}H_{20}N_2O$	77.11	7.19	9.99	77.23	7.23	9.96
XXXV	CH_3	*e*	A	C_6H_6	2	68	196–198 (0.6)	$C_{19}H_{22}N_2O$	77.52	7.53	9.52	77.72	7.55	9.40
XXXVI	C_2H_5	*e*	A	C_6H_6	2	74	196–199 (0.5)	$C_{20}H_{24}N_2O$	77.88	7.84	9.08	78.02	7.76	9.08
XXXVII	*i*-C_3H_7	*e*	A	C_6H_6	6	67	184–187 (0.4)	$C_{22}H_{28}N_2O$	78.22	8.13	8.69	78.34	8.17	8.70
XXXVIII	*sec*-C_4H_9	*e*	A	C_6H_6	6	74	188–191 (0.4)	$C_{23}H_{30}N_2O$	78.53	8.39	8.33	78.51	8.42	8.37
XXXIX	*e*	*e*	A	$C_6H_5CH_3$	5	91	203–206 (0.2)	$C_{27}H_{32}N_2O_2$	73.25	7.94	10.68	73.21	7.90	10.57

[a] Once distilled. [b] N. Sperber, D. Papa, E. Schwenk, M. Sherlock, and R. Fricano [*J. Am. Chem. Soc.*, **73**, 5752 (1951)] reported b.p. 171–173° (2 mm.), yield 75%. [c] E. Tagmann, E. Sury, and K. Hoffmann [*Helv. Chim. Acta*, **35**, 1235 (1952)] reported b.p. 156–160° (0.15 mm.), yield not reported. [d] β-Piperidinoethyl. [e] β-Morpholinoethyl.

tion. The inhibiting action was measured 2 hr. after administration of the compounds.

The diuretic action was studied after oral administration in rats, according to Lipschitz, *et al.*[13] The urine was measured volumetrically and collected over 5 hr.; the activity was expressed as the ratio of the urine excreted by the test animals to that excreted by the controls.

The effect on the coronary flow was determined using perfused isolated rabbit heart, according to the classical Langendorff procedure as modified by Setnikar.[14] The compounds were tested at a concentration of 1 mg./l. of perfusion fluid.

(13) W. L. Lipschitz, Z. Hadidian, and A. Kerpesar, *J. Pharmacol. Exptl. Therap.*, **79**, 97 (1943).

(14) I. Setnikar, *Farmaco* (Pavia), *Ed. Sci.*, **11**, 750 (1956).

Table III

Pharmacological Screening Results of α,α-Disubstituted Phenylacetonitriles

Compd.	Approx. LD_{50} (mouse), mg./kg. i.p.	Effects on behavior @ (mouse)	mg./kg. i.p.	Analgesic activity (mouse) Increase of reaction time, %	@ mg./kg. i.p.	Antispasmodic activity *in vitro*,[a] % 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.	Diuretic activity (rat) Test vol. Control vol.	@ mg./kg. *p.o.*
I	300–350	Moderate irritability increase, moderate muscle hypotonia	12.5	38	12.5	30	24	5	42	21	12.5	Inactive	50
II	150–175	Nothing noticeable	12.5	35	12.5	28	31	16	24	23	12.5	Inactive	50
III	150–175	Nothing noticeable	12.5	37	12.5	38	15	38	42	25	12.5	1.30	50
IV	125–175	Moderate irritability increase, moderate muscle hypertonia	12.5	13	12.5	32	19	82	39	36	12.5	1.34	50
V	320–360	Moderate irritability increase, moderate muscle hypotonia	12.5	23	12.5	21	19	10	33	28	12.5	1.11	50
VI	140–180	Moderate behavior excitement, moderate muscle hypertonia	12.5	16	12.5	29	35	38	28	8	12.5	Inactive	50
VII	130–175	Moderate behavior excitement	12.5	31	12.5	23	47	11	21	7	12.5	Inactive	50
VIII	70–80	Moderate behavior excitement	12.5	12	12.5	42	29	42	22	10	12.5	1.44	50
IX	140–180	Moderate behavior excitement	12.5	19	12.5	37	23	23	48	32	12.5	1.39	50
X	300–350	Moderate irritability increase, moderate muscle hypertonia	25	37	25	26	24	24	25	13	25	1.43	50
XI	320–370	Nothing noticeable	12.5	11	12.5	40	8	33	41	36	12.5	1.26	50
XII	150–170	Moderate irritability increase	12.5	15	12.5	23	21	17	35	23	12.5	Inactive	50
XIII	280–330	Moderate irritability increase, moderate muscle hypotonia	25	15	25	24	28	37	37	15	25	1.09	50
XIV	190–210	Moderate irritability increase	12.5	24	12.5	19	39	20	23	13	12.5	Inactive	50
XV	770–820	Moderate behavior excitement	25	15	25	5	35	23	12	9	25	1.41	50
Morphine·HCl				67	5								
Phenylbutazone										18	100		
Hydrochlorothiazide												1.56	6.25

[a] All compounds were tested at a concentration of 1 γ/ml. The ED_{50} values for the standard compounds are atropine sulfate (anticholinergic), 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.

The antitussive activity was studied in guinea pigs by the acrolein inhalation test.[15] The compounds were administered by intraperitoneal injection 0.5 hr. before the start of the tests. The highest dosage level which did not provoke an obvious toxic symptomatology in experimental animals was used for each test. Morphine, phenylbutazone, hydrochlorothiazide, atropine, diphenydramine, hexamethonium, and chlorpromazine were used as standards for comparison of the analgesic, antiinflammatory, diuretic, and antispasmodic activity, respectively.

Results and Discussion

The pharmacological screening results of α,α-disubstituted phenylacetonitriles are reported in Table III. Most of the compounds produced effects on the behavior of mice appearing as increased irritability and an alteration of body muscle tonus. These effects, however, have only slight pharmacological significance. Some of the substances showed a certain diuretic activity on oral administration, which was particularly marked for VIII (α-isopropyl-α-2-piperidinoethyl-), IX (α-*sec*-butyl-α-2-piperidinoethyl-), X (α,α-di-2-piperidinoethyl-), and XV (α,α-di-2-morpholinoethylphenylacetonitrile). As for the antiinflammatory activity, nearly all of the compounds significantly inhibited the formalin-induced edema, particularly XI (α-methyl-α-2-morpholinoethylphenylacetonitrile), which was found to be active at a dose as high as 1/30 of the approximate LD_{50}. No significant change in the pain threshold of mice was observed after intraperitoneal administration of the substances. The *in vitro* antispasmodic activity was found to be slight for all the compounds tested, in agreement with the results of an investigation by Klosa[2] on nitriles of a similar type. None of the compounds produced any significant changes in the coronary flow. Finally, as for the antitussive activity, only III (α-isopropyl-α-2-dimethylaminoethyl-), IV, and XIII (α-isopropyl-α-2-morpholinoethylphenylacetonitrile) were tested; while III and especially XIII were found to inhibit experimental cough, IV was found to be inactive.

The results for α,α-disubstituted 1-naphthylacetonitriles are reported in Table IV. In general the compounds caused CNS depression, which appeared as motor incoordination and as a decrease in spontaneous motility, irritability, and body muscle tonus. The whole series was found to inhibit significantly formalin-induced edema: XXVI (α-2-methylbenzylaminoethyl-), XXIX (α-methyl-α-2-piperidinoethyl-), XXXVIII (α-*sec*-butyl-α-2-morpholinoethyl-), and XXXVII (α-iso-

(15) B. Silvestrini and C. Pozzati, *Arch. Intern. Pharmacodyn.*, **129**, 249 (1960).

Table IV

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

Compd.	Approx. LD_{50} (mouse), mg./kg. i.p.	Effects on behavior @ (mouse)	Analgesic activity (mouse) Increase of reaction time, @ mg./kg. i.p.	%	Antispasmodic activity *in vitro*,[a] % 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.	Anti-inflammatory activity (rat) Inhibition of edema, @ mg./kg. i.p.	%	Diuretic activity (rat) Tyst vol. Control vol.	@ mg./kg. p.o.
XVI	320–360	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia	100	58	100	Inactive	27	27	29	25	100	1.12	100
XVII	300–350	Moderate CNS depression, moderate motor incoordination	100	85	100	Inactive	Inactive	38	31	30	100	1.43	100
XVIII	320–360	Moderate CNS depression, moderate motor incoordination	100	99	100	30	33	61	9	24	100	1.69	100
XIX	150–180	Moderate CNS depression, moderate motor incoordination, moderate muscle hypotonia	100	158	100	23	65	52	28	35	100	1.77	100
XX	310–340	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia	100	79	100	Inactive	100	Inactive	58	31	100	1.77	100
XXI	600–650	Nothing noticeable	200	19	200	20	63	38	25	11	200	1.77	200
XXII	180–220	Moderate behavior excitement	25	61	25	Inactive	15	Inactive	Inactive	28	25	1.22	50
XXIII	160–190	Moderate behavior excitement, moderate motor incoordination	25	52	25	40	36	45	37	30	25	1.53	50
XXIV	150–180	Moderate behavior excitement	25	56	25	21	Inactive	12	19	38	25	1.24	50
XXV	140–170	Moderate muscle hypotonia	25	20	25	45	37	35	19	25	25	Inactive	50
XXVI	380–420	Moderate CNS depression, moderate muscle hypotonia	50	107	50	63	66	44	32	59	50	Inactive	50
XXVII	180–220	Nothing noticeable	50	105	50	85	85	61	76	38	50	1.16	50
XXVIII	130–160	Marked CNS depression, moderate motor incoordination, marked muscle hypotonia, ptosis and ipsilateral flexor reflexes alteration	100	76	100	39	91	90	88	38	100	1.53	50
XXIX	140–170	Moderate CNS depression, moderate motor incoordination, moderate ptosis reflex alteration	50	116	100	76	96	11	100	62	100	1.33	50
XXX	150–180	Moderate CNS depression, moderate motor incoordination, moderate ptosis reflex alteration	50	64	50	100	89	64	30	33	50	1.09	50
XXXI	90–110	Moderate CNS depression, moderate motor incoordination, moderate ptosis reflex alteration	50	17	50	100	99	68	41	29	50	1.20	50
XXXII	140–170	Moderate CNS depression, moderate motor incoordination	50	19	50	100	92	66	40	45	50	1.27	50
XXXIII	180–220	Moderate CNS depression, moderate motor incoordination, moderate ptosis reflex alteration	100	56	100	Inactive	20	Inactive	30	28	100	Inactive	50
XXXIV	1000–1100	Moderate CNS depression, moderate motor incoordination	200	30	200	17	Inactive	29	25	41	200	1.43	50
XXXV	770–820	Moderate CNS depression, moderate motor incoordination	200	27	200	17	Inactive	25	19	42	200	1.16	200
XXXVI	680–730	Nothing noticeable	100	46	100	Inactive	Inactive	Inactive	Inactive	21	100	Inactive	100
XXXVII	590–640	Moderate CNS depression, moderate motor incoordination, moderate muscle hypotonia	200	130	200	Inactive	Inactive	Inactive	85	71	200	1.21	100
XXXVIII	380–420	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia	100	56	100	37	46	40	80	68	200	Inactive	100

Table IV (*Continued*)

Compd.	Approx. LD_{50} (mouse), mg./kg. i.p.	Effects on behavior (mouse)	Analgesic activity (mouse) mg./kg. i.p.	Increase of reaction time, % @ mg./kg. i.p.	Antispasmodic activity *in vitro*,[a] % 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.	Anti-inflammatory activity (rat) Inhibition of edema, % @ mg./kg. i.p.	Diuretic activity (rat) Test vol. Control vol. @ mg./kg. p.o.
XXXIX	1200–1300	Marked CNS depression, moderate motor incoordination, moderate muscle hypotonia, marked pinna reflex alteration, moderate ipsilateral flexor reflex alternation	200	35 @ 200	31	42	Inactive	76	40 @ 200	1.77 @ 200
Morphine·HCl				67 @ 5						
Phenylbutazone									18 @ 100	
Hydrochlorothiazide										1.56 @ 6.25

[a] All compounds were tested at a concentration of 1 γ/ml. The ED_{50} values for the standard compounds are atropine sulfate (anticholinergic), 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.

propyl-α-2-morpholinoethyl-1-naphthylacetonitrile) were particularly active, the latter being the most interesting owing to its low toxicity. As for analgesic activity, many of the compounds greatly increased the pain threshold of mice, especially XIX (α-isopropyl-α-2-dimethylaminoethyl-1-naphthylacetonitrile) and XXXVII. XVIII (α-ethyl-α-2-dimethylaminoethyl-), XIX, XX (α-*sec*-butyl-α-2-dimethylaminoethyl-), and XXXIX (α,α-di-2-morpholinoethyl-1-naphthylacetonitrile) produced significant increases in water excretion on oral administration. Compounds XXIX, XXX (α-ethyl-α-2-dimethylaminoethyl-), XXXI (α-isopropyl-α-2-piperidinoethyl-), and XXXII (α-*sec*-butyl-α-2-piperidinoethyl-1-naphthylacetonitrile) showed a significant *in vitro* antispasmodic activity, which was most obvious against acetylcholine and histamine. None of the compounds produced any significant changes in the coronary flow. Among the substances tested for antitussive activity (XIX, XX, and XXXVII), only XIX was found to inhibit the experimental cough.

Some considerations on the pharmacological differences between benzene and naphthalene derivatives may be drawn from the above results. First, the benzene series appears to be more toxic, an obvious toxic symptomatology also being observed at relative low dosage levels. As for behavioral changes in mice, α,α-disubstituted phenylacetonitriles produce CNS excitation, whereas α,α-disubstituted 1-naphthylacetonitriles cause signs of depression. The analgesic action appears to be an interesting property of the naphthalene series and preliminary tests indicate XIX to be the most promising compound. Both benzene and naphthalene derivatives possess antiinflammatory activity as they inhibit formalin-induced edema; however, α,α-disubstituted 1-naphthylacetonitriles show the greater potency. As for the antispasmodic activity, only α-alkyl-α-2-piperidinoethyl derivatives of the naphthalene series appear to be of some interest, owing to their significant action against acetylcholine and histamine. The diuretic activity of both series on oral administration is of slight importance, because of the high dosage levels (50–200 mg./kg.) at which the reported data were obtained. In contrast to basic nitriles recently reported,[16] both the benzene and naphthalene derivatives have no vasodilator activity. The results obtained with the few antitussive test compounds indicate that this investigation is worth extending to all other members of the two series.

In the light of the above results, it is difficult to make any statements about structure–activity relationships, except that the naphthalene derivatives appear to be more interesting than the corresponding benzene compounds as regards the general pharmacological picture. Replacement of the phenyl group in the basic nitrile structure by naphthyl enhances particularly the analgesic, antiinflammatory, and antispasmodic activity. The data reported suggest that the activities can be generally enhanced by branching of the alkyl chain α in the acetonitrile structure. However, this hypothesis obviously requires more detailed study.

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(16) Knoll Akt.-Ges. Chemische Fabriken, Belgian Patent 615,861 (Oct. 1, 1962); *Chem. Abstr.*, **59**, 13892*d* (1963).