TABLE I[a]

ARYLSULFONYL-1-METHYL-S-ISOTHIOSEMICARBAZIDES

XSONHNHC(=NH)SCH$_3$

I

X	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
C_6H_5	124–125 dec	95	$C_8H_{11}N_3O_2S_2$	39.18	4.49	39.49	4.63
p-$CH_3OC_6H_4$	141–142 dec	91	$C_9H_{13}N_3O_3S_2$	39.31	4.72	39.36	4.70
p-$C_2H_5OC_6H_4$	157–158 dec	99	$C_{10}H_{15}N_3O_3S_2$	41.52	5.19	41.48	5.40
p-n-$C_3H_7OC_6H_4$	151–152 dec	93	$C_{11}H_{17}N_3O_3S_2$	43.59	5.61	43.50	5.32
p-n-$C_4H_9OC_6H_4$	132–133 dec	70	$C_{12}H_{19}N_3O_3S_2$	45.42	5.99	45.72	6.01
$C_6H_5CH_2$	142	62	$C_9H_{13}N_3O_2S_2$	41.69	5.01	41.79	4.8

[a] Melting points were taken in open capillary tubes. The yields reported are those after one recrystallization. Elemental analyses were made by Dr. J. Calderón, of Instituto "Alonso Barba" of Madrid, Spain.

mental conditions of Lora-Tamayo, *et al.*, were also tried, those of Hoggarth gave much better results. The formulas and experimental data for the compounds prepared are presented in Table I.

Experimental Section

The arysulfonylthiosemicarbazide (5 mmoles) was suspended in 5 ml of 1 *N* NaOH. Several minutes of vigorous stirring produced a clear yellow solution. To this was added 0.78 g (5.6 mmoles) of methyl iodide in 1 ml of 95% ethanol. Precipitation of the white, crystalline product was complete in 15–20 min. Samples for analysis were recrystallized from ethanol–water.

A New Naphthylacetamide Derivative

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Our interest in antiinflammatory drugs derived from naphthalene, of which thus far α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (I)[1] has been the best representative, has led us to synthesize the 4-isobutyl derivative in analogy with 4-isobutylphenylacetic acid (ibufenac), a product known to exert a marked analgesic and antiinflammatory action.[2] The new compound, α-isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetamide, possesses an analgesic action distinctly superior to that of I.

Experimental Section[3]

The 1-isobutylnaphthalene required was obtained by a new general method for preparing 1-alkylnaphthalenes, which will be described in a later paper.

1-Chloromethyl-4-isobutylnaphthalene.—A mixture of trioxymethylene (8.5 g, 0.283 mole), glacial acetic acid (110 g), and anhydrous HCl (11.7 g, 0.321 mole) was gently heated until the trioxymethylene dissolved, and then 1-isobutylnaphthalene (40 g, 0.217 mole) was added and the flask carefully was closed and heated for 20 hr at 65–70°. After cooling, the mixture was poured into water, the separated oil was extracted with benzene, and the resulting solution was washed with water and Na_2CO_3 and then dried (Na_2SO_4). The benzene was removed *in vacuo* and the product was distilled, bp 135–137° (0.3 mm), giving a colorless oil (35.2 g, 69.8% yield).

Anal. Calcd for $C_{15}H_{17}Cl$: C, 77.40; H, 7.36; Cl, 15.23. Found: C, 77.24; H, 7.28; Cl, 14.95.

4-Isobutyl-1-naphthylacetonitrile.—A mixture of 1-chloromethyl-4-isobutylnaphthalene (46.5 g, 0.2 mole), KCN (17.8 g, 0.274 mole), ethanol (77 ml), and water (30 ml) was refluxed for 1 hr. The alcohol was distilled, the residue was extracted with ether, and the solution was washed with water and then dried (Na_2SO_4). After distilling the solvent, the residue was purified by distilling at 145–147° (0.4 mm), and the oily product then was treated with petroleum ether (bp 40–70°) to give colorless crystals (18.3 g, 41% yield). On recrystallization from petroleum ether, the compound melted at 78–79° (cor).

Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.48; H, 7.73; N, 6.18.

α-(2-Dimethylaminoethyl)-4-isobutyl-1-naphthylacetonitrile.—This procedure follows the method previously described.[4] 4-Isobutyl-1-naphthylacetonitrile (26.8 g, 0.12 mole) was alkylated with 2-(*N*,*N*-dimethylamino)-1-chloroethane (13.55 g, 0.126 mole), refluxing for 5 hr in benzene (400 ml) in the presence of sodamide (4.9 g, 0.126 mole). The product obtained was distilled at 170–173° (0.4 mm) to give a colorless oil (22.9 g, 65% yield).

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.04; H, 9.01; N, 9.30.

α-Isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetonitrile.—Alkylation of the above nitrile (22.9 g, 0.078 mole) with 2-bromopropane (12.4 g, 0.101 mole) was performed by refluxing for 18 hr in benzene (500 ml) and in the presence of sodamide (3.94 g, 0.101 mole). The distilled product, bp 174–176° (0.6 mm), was a colorless oil (17.6 g, 67.1% yield).

Anal. Calcd for $C_{23}H_{32}N_2$: C, 82.09; H, 9.59; N, 8.33. Found: C, 81.16; H, 9.40; N, 8.17.

α-Isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetamide.—The hydrolysis was performed according to the general method recently reported.[1b] α-Isopropyl-α-(2-dimethylaminoethyl)-4-isobutyl-1-naphthylacetonitrile (33.6 g, 0.1 mole) was refluxed for 120 hr with a 1:1:1 mixture (131 ml) of concentrated H_2SO_4, glacial acetic acid, and water. The crude product was distilled at 188–191° (0.25 mm) to give a viscous oil (12.05 g, 34% yield).

Anal. Calcd for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90. Found: C, 78.52; H, 9.59; N, 7.73.

(1) α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide, naphthypramide. (a) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964); (b) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 594 (1965); (c) G. Pala, S. Casadio, T. Bruzzese, E. Crescenzi, and E. Marazzi-Uberti, *ibid.*, **8**, 698 (1965).

(2) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, *Nature*, **200**, 271 (1963).

(3) The boiling points are uncorrected.

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

Derivatives of 2-Azabicyclo[2.2.2]octane. II[1,2]

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Amides of formula I, related to the respiratory stimulant, diethylnicotinamide, were prepared. Reduction of these compounds gave a series of compounds represented by formulas II–V.

(1) Part I of this series: F. J. Villani and C. A. Ellis, *J. Med. Chem.*, **9**, 185 (1966).

(2) Isoquinuclidine, the common name of this ring system, is used throughout this manuscript.

TABLE I

No.	R	X	Method	Yield, %	Mp, °C	Bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Hydrochloride Mp, °C	Hydrochloride Formula	Hydrochloride Calcd, % C	Hydrochloride Calcd, % H	Hydrochloride Found, % C	Hydrochloride Found, % H
1	2-Pyridyl	O	A	63	123–124[a]		$C_{13}H_{16}N_2O$	72.11	7.46	72.18	7.41	180–181	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	61.42	7.07
2	3-Pyridyl	O	A	78	103–104[a]		$C_{13}H_{16}N_2O$	72.11	7.46	72.09	7.43	201–203	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	61.61	6.42
3	4-Pyridyl	O	A	72	101–102.5[a]		$C_{13}H_{16}N_2O$	72.11	7.46	72.21	7.16	234–235	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	62.14	6.70
4	2-Piperidyl	O	B	81	94–96[b]	150–155 (1)	$C_{13}H_{22}N_2O$	70.22	9.93	70.09	9.67	286–287	$C_{13}H_{22}N_2O \cdot HCl$	60.33	8.96	59.99	8.79
5	3-Piperidyl	O	B	69	102–103[b]	170–178 (2)	$C_{13}H_{22}N_2O$	70.22	9.93	70.69	9.81	263–264	$C_{13}H_{22}N_2O \cdot HCl$	60.33	8.96	60.56	9.30
6	4-Piperidyl	O	B	70	113–115[a]	173–178 (3)	$C_{13}H_{22}N_2O$	70.22	9.93	69.96	9.89	326–327	$C_{13}H_{22}N_2O \cdot HCl$	60.33	8.96	60.39	9.15
7	N-Me-2-piperidyl	O	C	74	62–63[c]	164–168 (3)[d]	$C_{14}H_{24}N_2O$	71.14	10.24	71.21	10.16	279–281	$C_{14}H_{24}N_2O \cdot HCl$	61.63	9.24	61.96	9.19
8	N-Me-3-piperidyl	O	C	76	63–65[e,f]	155–157 (0.5)	$C_{14}H_{24}N_2O$	71.14	10.24	71.48	10.40	240–242	$C_{14}H_{24}N_2O \cdot HCl \cdot H_2O$	57.82	9.36	57.92	9.32
9	N-Me-4-piperidyl	O	C	72	66–68[g]	150–157 (2)	$C_{14}H_{24}N_2O$	71.14	10.24	71.16	10.35	275–278	$C_{14}H_{24}N_2O \cdot HCl$	61.63	9.24	61.40	9.38
10	2-Pyridyl	H_2	D	40		140–143 (5)[h]	$C_{13}H_{18}N_2$	77.18	8.97	77.28	9.01	263–264	$C_{13}H_{18}N_2 \cdot 2HCl$	56.73	7.33	57.13	7.19
11	3-Pyridyl	H_2	D	38		114–119 (2)[i]	$C_{13}H_{18}N_2$	77.18	8.97	76.86	9.40	231–233	$C_{13}H_{18}N_2 \cdot 2HCl$	56.73	7.33	56.38	7.14
12	4-Pyridyl	H_2	D	59		125–127 (3)[j]	$C_{13}H_{18}N_2$	77.18	8.97	77.25	8.91	233–234	$C_{13}H_{18}N_2 \cdot 2HCl$	56.73	7.33	56.70	7.66
13	2-Piperidyl	H_2	B	51		140–150 (10)[k]	$C_{13}H_{24}N_2$	74.94	11.61	74.52	10.92	202–204	$C_{13}H_{24}N_2 \cdot 2HCl$	55.49	9.32	55.35	9.25
14	N-Me-2-piperidyl	H_2	D	73		132–135 (6)[l]	$C_{14}H_{26}N_2$	75.61	11.79	75.58	11.71						
15	3-Piperidyl	H_2	B[m]	46								277–278	$C_{13}H_{24}N_2 \cdot 2HCl$	55.49	9.32	55.81	9.55
16	4-Piperidyl	H_2	B[m]	43								263–265	$C_{13}H_{24}N_2 \cdot 2HCl \cdot H_2O$	52.17	9.43	52.52	9.68

[a] From isopropyl acetate. [b] From benzene–petroleum ether (bp 30–60°). [c] From ether. [d] $n^{25}D$ 1.5216. [e] $n^{29}D$ 1.5205. [f] From petroleum ether. [g] From hexane. [h] $n^{27}D$ 1.5422. [i] $n^{31}D$ 1.5370. [j] $n^{31}D$ 1.5340. [k] $n^{25}D$ 1.5072. [l] $n^{25}D$ 1.5008. [m] Isolated as the hydrochloride salt.

I, X = O
IV, X = H_2

II, R = H; X = O
III, R = CH_3; X = O
V, R = H; X = H_2

Experimental Section[3]

N-Nicotinoylisoquinuclidine. Method A.—A solution of 100 g (0.66 mole) of ethyl nicotinate, 73 g (0.66 mole) of isoquinuclidine, and 700 ml of hexane was dried by azeotropic distillation using a Dean–Stark trap. After 2 hr, 4 g of commercial anhydrous sodium methoxide was added and heating was continued for 20 hr. The solvent was removed by vacuum distillation on the steam bath. Water was added and the product was extracted with chloroform. After removal of the solvent the residue was recrystallized.

N-Nipecotoylisoquinuclidine. Method B.—A solution of 30 g (0.14 mole) of N-nicotinoylisoquinuclidine, 2 g of PtO_2, 11.7 ml of concentrated HCl, and 200 ml of absolute ethanol was reduced in a Parr hydrogenator at 4.2 kg/cm². The reduction was complete in about 3 hr. The catalyst was filtered and the filtrate was concentrated *in vacuo* to a residue, which was dissolved in water, made basic with NH_4OH, and extracted with chloroform. The product was purified by the method given in Table I.

N-(1-Methylnipecotoyl)isoquinuclidine. Method C.—A mixture of 18 g (0.08 mole) of N-nipecotoylisoquinuclidine, 30 g of formic acid (98%), and 24 ml of 37% formaldehyde was heated on the steam bath for 48 hr. The colorless solution was concentrated to dryness *in vacuo*, the residue was suspended in water, made basic with NH_4OH, and extracted with chloroform.

N-(3-Picolyl)isoquinuclidine. Method D.—A suspension of N-nicotinoylisoquinuclidine (40 g, 0.185 mole) in 300 ml of ether was added to a refluxing suspension of 15 g (0.4 mole) of $LiAlH_4$ in 1 l. of anhydrous ether, and the reaction mixture was heated under reflux with stirring for 15–20 hr. After the usual decomposition, the product was distilled.

(3) All melting points are corrected. Microanalysis was performed by Mr. Edwin Connor of these laboratories.

Substitution in the Hydantoin Ring. IV. N-3-*p*-Bromoanilinomethyl Derivatives

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The condensation of primary and secondary aliphatic or aromatic amines with formaldehyde and phthalimide or succinimide has been shown in previous studies in this laboratory to produce phthalimidomethyl and succinimidomethyl derivatives of amines which are particularly useful for identification purposes.[1] More recently a series of N-3-aryl- (and alkyl-) aminomethylhydantoins prepared by condensing various hydantoins with formaldehyde and amines has been reported.[2] In the present study this condensation is extended to include the preparation of a number of N-3-*p*-bromoanilinomethylhydantoins. The hydantoins used in this investigation were prepared from the corresponding ketone, ammonium carbonate, and potassium cyanide according to

(1) (a) H. W. Heine, M. B. Winstead, and R. P. Blair, *J. Am. Chem. Soc.*, **78**, 672 (1956); (b) M. B. Winstead, and H. W. Heine, *ibid.*, **77**, 1913 (1955); (c) M. B. Winstead, K. V. Anthony, L. L. Thomas, R. G. Strachan, and H. J. Richwine, *J. Chem. Eng. Data*, **7**, 414 (1962).

(2) M. B. Winstead, D. E. Barr, C. R. Hamel, D. J. Renn, H. I. Parker, and R. M. Neumann, *J. Med. Chem.*, **8**, 117 (1965).