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1-(3,4-Dichlorobenzamidomethyl)cyclohexyldimethylamine and Related Compounds as Potential Analgesics

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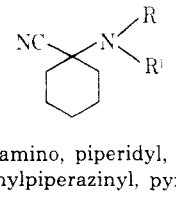
The syntheses of the title compound and 56 analogs and derivatives are reported. A number of these compounds were subjected to a primary pharmacological screen designed to detect a range of CNS effects. The results indicated that these compounds possessed analgesic activity and the title compound is being subjected to a more detailed study. This paper reports the synthetic methods, the analgesic activities, and the structure–activity relationships.

Many cyclohexyl derivatives have been synthesized and assessed for potential biological activity. In recent years several papers [1-4] and patents[5] have been published which describe the preparation and CNS activity of substituted cyclohexylamines. The synthesis of related compounds outlined in this paper represents an attempt to prepare 1,1-substituted cyclohexylamines with analgesic properties.

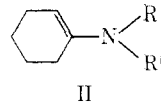
Chemistry. Cyclohexylaminonitriles of formula I were considered to be good starting materials for which several synthetic routes[1-6] were available. These routes are modi-



I, NRR^1 = dimethylamino, piperidyl, azabicyclo[3.2.2]nonyl, N^4-methylpiperazinyl, pyrrolidinyl

fications of the general procedure in which the appropriate ketone or aldehyde is allowed to react with a secondary amine and HCN under various conditions. Another variation by House, *et al.*,[7] is to treat the enamine II in $CHCl_3$ solution with acetonecyanohydrin when the aminonitrile is produced.

The method adopted in the present work was to reflux

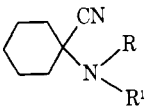


II

equimolar proportions of KCN, cyclohexanone, and the hydrochloride salt of the appropriate base in aqueous EtOH for 24 hr. The reactions proceeded smoothly and fair or good yields were obtained (Table I). Attempts to prepare the corresponding esters of these α-aminonitriles by direct alcoholysis were unsuccessful. When attempts to proceed *via* the free acids and acid chlorides failed to yield the corresponding acids, with the exception of the piperidyl compound, this route was abandoned. All the α-aminonitriles responded to treatment with H_2SO_4 for 0.25 hr on a steam bath to give good yields of the corresponding carboxamides (Table II). α-Aminonitriles have unusual properties[8,9] which are clearly demonstrated by the reaction of these compounds with Grignard reagents. In these reactions it has been found that ketone formation seldom occurs and that nitrile replacement frequently takes place. Welvart[10] has suggested that such reactions occur *via* an immonium ion. When the α-aminonitrile **3** was treated with aliphatic and aromatic Grignard reagents the expected nitrile replacement occurred, whereas with $LiAlH_4$ the normal primary amine was produced. $LiAlH_4$ in the presence of $AlCl_3$ again replaced the nitrile (Table III).

The reactions of α-aminonitriles with organolithium compounds are well documented[11-14] and Table IV shows the expected imines and ketones **17–24** and their corresponding alcohols and esters **25–29** synthesized from compounds **1–5**. Table V shows products of normal reactions between α-aminonitriles and MeLi or 2-picolyl Li. Cyclohexyldiamines and -triamines **35–38** were prepared in excellent yields by reduction of the corresponding α-aminocyclohexylnitriles with $LiAlH_4$ (Table VI). These com-

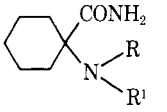
Table I. N-Substituted α-Aminonitriles



Compd	NRR[1]	Yield,[e] %	Mp, °C[f]	Formula	Analyses[h]
1	$N(CH_3)_2$	62	201–202	$C_{10}H_{19}IN_2$	C, H, I, N
2	$C_5H_{10}N$[a]	69	296–298 dec[g]	$C_{11}H_{22}ClN$	C, H, Cl, N
3	$C_8H_{14}N$[b]	41	80–81	$C_{15}H_{24}N_2$	C, H, N
4	$C_5H_{11}N_2$[c]	65	256–257	$C_{13}H_{24}IN_3$	C, H, I, N
5	C_4H_8N[d]	78	167–168	$C_{11}H_{19}ClN_2$	C, H, Cl, N

[a] Piperidyl. [b] Azabicyclo[3.2.2]nonyl. [c] N^4-Methylpiperazinyl. [d] Pyrrolidinyl. [e] Based on a double run only. [f] Uncorrected. [g] Reported mp of base[5] is 59°. [h] Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

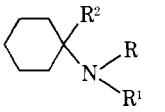
Table II. N-Substituted Cyclohexylamides



Compd	NRR[1]	Yield, %	Mp, °C[e]	Formula	Analyses
6	$N(CH_3)_2$	73	55–56	$C_9H_{18}N_2O$	C, H, N
7	$C_5H_{10}N$[a]	89	105–106[f]	$C_{12}H_{22}N_2O$	C, H, N
8	$C_8H_{14}N$[b]	44	150	$C_{15}H_{26}N_2O$	C, H, N
9	$C_5H_{11}N_2$[c]	68	107	$C_{12}H_{23}N_3O$	C, H, N
10	C_4H_8N[d]	96	106–107	$C_{11}H_{20}N_2O$	C, H, N

[a–d] See Table I. [e] Uncorrected. [f] A. Kötz and P. Merkel, *J. Prakt. Chem.*, **113**, 49 (1926), quote mp 91°.

Table III. N-Substituted Alkyl- and Arylcyclohexylamines



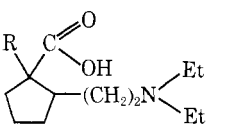
Compd	NRR[1]	R^2	Yield, %	Mp, °C[c]	Formula	Analyses
11	$C_8H_{14}N$[a]	H	75	37–38	$C_{14}H_{25}N$	C, H, N
12	$C_8H_{14}N$	CH_2NH_2	71	191–192	$C_{15}H_{20}Cl_2N_2$	C, H, Cl, N
13	$C_8H_{14}N$	CH_3		*d*	$C_{15}H_{27}N$	M^+ 221
14	$C_8H_{14}N$	C_6H_5		*d*	$C_{20}H_{29}N$	M^+ 283
15	$C_5H_{11}N_2$[b]	CH_3	34	225	$C_{13}H_{27}IN_2$	C, H, I, N
16	$C_5H_{11}N_2$	C_6H_5	74	90–91[e]	$C_{17}H_{26}N_2$	C, H, N

[a] Azabicyclo[3.2.2]nonyl. [b] N^4-Methylpiperazinyl. [c] Uncorrected. [d] Characterized by mass spectrum only, M^+ = parent molecular ion. Determined on an A.E.I. MS9 spectrometer. [e] M. Mousseron, *et al.*, *Bull. Soc. Chim. Fr.*, 3803 (1968), quote mp 68–69°.

pounds are intermediates in the synthesis of N-substituted compounds resembling the active analgesics reported by Janssen, *et al.*[2,8]

Dialkylamine groups form a fundamental part of the structure of many biologically active compounds. Examples of such compounds related to those reported in this work are the diethylamines III. Dimethylamines may be prepared by the Eschweiler-Clarke procedure.[4]

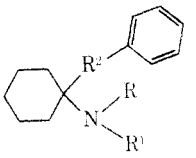
In the present work one of the aims was to investigate both formyl and methylamine derivatives for CNS effects and particularly the change in activity observed in compounds with the exocyclic nitrogen rendered nonbasic.



III, R = C_6H_5 (caramiphen)
R = 2′-MeC_6H_4

Formylation of amines with the aid of chloral hydrate was first reported by Hofmann[15] and extensively used by Blicke.[16] A mixture of formic acid and Ac_2O also acts as a formylating agent by producing formic anhydride *in situ* and acting as a mixed anhydride. Erlich[17] reported the

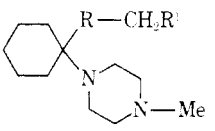
Table IV. Imino, Keto, Alcohol, and Ester Derivatives of N-Substituted Cyclohexylamines



Compd	NRR[1]	R^2	Yield, %	Mp, °C[d]	Formula	Analyses
17	$N(CH_3)_2$	C=NH	94	161–162	$C_{16}H_{25}IN_2$	C, H, I, N
18	$N(CH_3)_2$	C=O	93	206–207	$C_{15}H_{22}ClNO$	C, H, Cl, N
19	$C_8H_{14}N$[a]	C=NH	93	124–125	$C_{21}H_{30}N_2$	C, H, N
20	$C_8H_{14}N$	C=O	87	152	$C_{21}H_{29}NO$	C, H, N
21	$C_5H_{11}N_2$[b]	C=NH	84	95–96	$C_{18}H_{27}N_3$	C, H, N
22	$C_5H_{11}N_2$	C=O	81	121–122	$C_{18}H_{26}N_2O$	C, H, N
23	C_4H_8N[c]	C=NH	98	[e]	$C_{17}H_{24}N_2$	M^+ 256
24	C_4H_8N	C=O	97	50–51	$C_{17}H_{23}NO$	C, H, N
25	$N(CH_3)_2$	CHOH	72	90–91	$C_{15}H_{23}NO$	C, H, N
26	$C_8H_{14}N$	CHOH	71	135–136	$C_{21}H_{31}NO$	C, H, N
27	$C_5H_{11}N_2$	CHOH	85	227–228	$C_{18}H_{28}N_2O$	C, H, N
28	$C_5H_{11}N_2$	HCOCOMe	45	105	$C_{20}H_{30}N_2O_2$	C, H, N
29	C_4H_8N	CHOH	75	225 dec	$C_{17}H_{26}ClNO$	C, H, Cl, N

[a] Azabicyclo[3.2.2]nonyl. [b] N^4-Methylpiperazinyl. [c] Pyrrolidinyl. [d] Uncorrected. [e] Characterized by mass spectrum only and used directly to prepare the corresponding ketone.

Table V. Imino, Keto, and Picolyl Derivatives of N-Substituted Cyclohexylamines



Compd	R	R^1	Yield, %	Mp, °C[a]	Formula	Analyses
30	C=NH	H	90	[c]		
31	C=O	H	70	243–244 dec	$C_{14}H_{27}IN_2O$	C, H, I, N
32	CHOH	H	82	138–139	$C_{13}H_{26}N_2O$	C, H, N
33	C=O	2-C_6H_4N[b]	91	Oil[d]	$C_{18}H_{27}N_3O$	C, H, N
34	CHOH	2-C_6H_4N	80	104–105	$C_{18}H_{29}N_3O$	C, H, N

[a] Uncorrected. [b] 2-Pyridyl. [c] Not characterized but used directly to prepare the corresponding ketone. [d] No boiling point (faulty gauge).

reduction of formylamines using $LiAlH_4$. Thus, a four-step procedure involving two formylation and two $LiAlH_4$ reduction steps converts a primary amine to a dialkylamine and although this procedure is more laborious than the Eschweiler-Clarke process it was adopted because both formyl and methyl intermediate derivatives **39–50** can be isolated with advantage in good yield (Table VII).

In a similar manner the primary amine function in the diamino or triamino molecules **35–38** can be rendered nonbasic by the synthesis of benzamido and substituted benzamido derivatives. This also introduces an aromatic substituent which is believed to be of structural significance in analgesic molecules. Acylation of amines was reviewed by Sonntag[18] and a mechanistic study reported by Bender and Jones.[19] Good yields of the benzamides and substituted benzamides **51–58** were obtained by reacting the amine with benzoyl or substituted benzoyl chlorides in the presence of pyridine (Table VIII). **51** was reduced to the corresponding alcohol **59** which in turn was converted to the ester **60** (Table IX). Two further amine derivatives were synthesized by conventional methods. **37** was converted to the tosyl derivative **61** and **36** to the phthalimido derivative **62** where the nonbasic nitrogen is now endocyclic (Table X).

Experimental Section

The preparation of representative compounds is described and all melting points (uncorrected) were taken on an electrothermal apparatus.

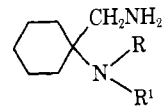
General Procedure for α-Aminonitriles. Method A as reported by Van de Westeringh, *et al.*,[6] was essentially the method used. Reflux was required for **2, 4,** and **5.**

1-(1-Azabicyclo[3.2.2]nonyl)cyclohexylamide (8). 1-(1-Cyanocyclohexyl)azabicyclo[3.2.2]nonane (4.64 g, 0.02 mol) was heated on a steam bath with H_2SO_4 (60 ml) for 0.25 hr and cooled, the mixture was poured onto crushed ice (150 g) and basified with NH_4OH, and the alkaline layer was extracted with $CHCl_3$. After drying the extract and distilling the solvent, the residual oil was triturated with petroleum ether to give prisms of the carboxamide (2.2 g, 44%): mp 150°. *Anal.* ($C_{15}H_{26}N_2O$) C, H, N.

1-Cyclohexylazabicyclo[3.2.2]nonane (11). 1-(1-Cyanocyclohexyl)azabicyclo[3.2.2]nonane (16.3 g, 0.07 mol) was dissolved in dry benzene (200 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (5.7 g, 0.14 mol) in dry Et_2O (200 ml) containing $AlCl_3$ (1.34 g, 0.01 mol). The mixture was worked up in the usual way to give plates of **11** (12.2 g, 75%): mp 37–38°. *Anal.* ($C_{14}H_{25}N$) C, H, N.

1-(1-Phenylcyclohexyl)-4-methylpiperazine (16). 1-(1-Cyano-

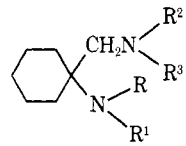
Table VI. N-Substituted Cyclohexyldiamines and -triamines



Compd	NRR[1]	Yield,[d] %	Mp, °C[e]	Formula	Analyses[f]
35	$N(CH_3)_2$	93	251–253	$C_9H_{22}Cl_2N_2$	C, H, Cl, N
36	$C_5H_{10}N$[a]	74	256–257	$C_{12}H_{26}Cl_2N_2$	C, H, Cl, N
37	$C_5H_{11}N_2$[b]	83	243–245	$C_{14}H_{31}I_2N_3$	C, H, I, N
38	C_4H_8N[c]	77	206–207	$C_{11}H_{24}Cl_2N_2$	C, H, Cl, N

[a] Piperidyl. [b] N^4-Methylpiperazinyl. [c] Pyrrolidinyl. [d] Based on a single run. [e] Uncorrected. [f] Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Table VII. Formyl and Methyl Derivatives of N-Substituted Cyclohexyldiamines and -triamines



Compd	NRR[1]	R^2	R^3	Yield,[c] %	Mp, °C[d]	Formula	Analyses
39	$N(CH_3)_2$	CHO	H	71	156–158	$C_{11}H_{23}IN_2O$	C, H, I, N
40	$N(CH_3)_2$	CH_3	H	94	232–233	$C_{10}H_{24}Cl_2N_2$	C, H, Cl, N
41	$N(CH_3)_2$	CH_3	CHO	78	59–60	$C_{11}H_{22}N_2O$	C, H, N
42	$N(CH_3)_2$	CH_3	CH_3	88	232–234	$C_{11}H_{26}Cl_2N_2$	C, H, N[e]
43	$C_5H_{10}N$[a]	CHO	H	76	Oil[f]		
44	$C_5H_{10}N$	CH_3	H	93	259–260	$C_{13}H_{28}Cl_2N_2$	C, H, Cl, N
45	$C_5H_{10}N$	CH_3	CHO	80	93–94	$C_{14}H_{26}N_2O$	G, H, N
46	$C_5H_{10}N$	CH_3	CH_3	72	224	$C_{14}H_{30}Cl_2N_2$	C, H, Cl, N
47	$C_5H_{11}N_2$[b]	CHO	H	66	97–98	$C_{13}H_{25}N_3O$	C, H, N
48	$C_5H_{11}N_2$	CH_3	H	93	Oil	$C_{13}H_{27}N_3$	C, H, N
49	$C_5H_{11}N_2$	CH_3	CHO	83	107–108	$C_{14}H_{27}N_3O$	C, H, N
50	$C_5H_{11}N_2$	CH_3	CH_3	72	171–172	$C_{16}H_{35}N_3I_2$	C, H, I, N

[a] Piperidyl. [b] N^4-Methylpiperazinyl. [c] Based on a single run. [d] Uncorrected. [e] N: calcd, 10.90; found, 10.10. Compound slightly deliquescent. [f] Not characterized other than by ir but reduced directly to the methyl derivative.

cyclohexyl)-4-methylpiperazine (2.07 g, 0.01 mol) was dissolved in dry ether (50 ml) and added dropwise to a solution of PhMgBr prepared from Mg turnings (1.1 g, 0.05 mol) and PhBr (7.85 g, 0.05 mol) in dry ether (100 ml). The mixture was worked up in the usual way and after drying the separated ether layer and distilling the solvent, the residual oil was triturated with petroleum ether to give rosettes of **16** (1.9 g, 74%): mp 90–91°. *Anal.* ($C_{17}H_{26}N_2$) C, H, N.

1-(1-Methylcyclohexyl)-4-methylpiperazine (15) was prepared using MeMgBr as in **16** and characterized as 1-(1-methylcyclohexyl)-4,4-dimethylpiperazinium iodide (1.4 g, 34%): mp 225°. *Anal.* ($C_{13}H_{27}IN_2$) C, H, I, N.

1-(1-Benzylimidoylcyclohexyl)-4-methylpiperazine (21). 1-(1-Cyanocylohexyl)-4-methylpiperazine (20.7 g, 0.1 mol) was treated with PhLi (Et_2O) and worked up in the usual way to give needles of **21** (23.9 g, 84%): mp 95–96°. *Anal.* ($C_{18}H_{27}N_3$) C, H, N.

1-(1-Benzoylcyclohexyl)-4-methylpiperazine (22). 1-(1-Benzylimidoylcyclohexyl)-4-methylpiperazine (10 g) was refluxed with HCl (100 ml) and water (100 ml) for 1 hr and worked up in the usual way to give needles of **22** (8.1 g, 81%): mp 121–122°. *Anal.* ($C_{18}H_{26}N_2O$) C, H, N.

1-(1,1′-Hydroxybenzylcyclohexyl)-4-methylpiperazine (27). **22** (7.2 g, 0.025 mol) was reduced with $LiAlH_4$ (Et_2O) and worked up in the usual way to give needles of **27** (6.1 g, 85%): mp 227–228°. *Anal.* ($C_{18}H_{28}N_2O$) C, H, N.

1-(1,1′-Acetoxybenzylcyclohexyl)-4-methylpiperazine (28). **27** (3 g) was refluxed for 3 hr with Ac_2O (12 ml) and pyridine (12 ml). Excess reagents were distilled and the residue was triturated with petroleum ether to give needles of **28** (1.5 g, 45%): mp 105°. Anal. ($C_{20}H_{30}N_2O_2$) C, H, N.

1-(1-Aminomethylcyclohexyl)-4-methylpiperazine (37). 1-(1-Cyanocyclohexyl)-4-methylpiperazine (4.1 g, 0.02 mol) was dissolved in dry Et_2O (100 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (1.52 g, 0.04 mol) in dry Et_2O (200 ml). The mixture was worked up in the usual way to give needles of **37** (3.5 g, 83%): mp 243–245°. *Anal.* ($C_{14}H_{31}I_2N_3$) C, H, I, N.

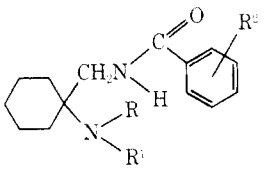
1-(1-Formylaminomethylcyclohexyl)-4-methylpiperazine (47). HCOOH (6.9 g, 0.15 mol) and Ac_2O (15.3 g, 0.15 mol) were mixed without cooling and kept at room temperature for 1 hr. **37** (8.4 g, 0.04 mol) was dissolved in HCOOH (12 ml) and the formylating mixture (16 ml) added. This produced vigorous effervescence and a rise in temperature to 70°. The mixture was left at room temperature for 2 hr and then heated on a water bath at 55° for 0.75 hr. The solvents were removed under reduced pressure yielding a viscous, brown oil which solidified to plates of **47** (6.0 g, 66.3%): mp 97–98°. *Anal.* ($C_{13}H_{25}N_3O$) C, H, N.

1-(1-Methylaminomethylcyclohexyl)-4-methylpiperazine (48). **47** (5.97 g, 0.025 mol) was reduced with $LiAlH_4$ (Et_2O) and worked up in the usual way to give **48** as a colorless oil (5.2 g, 93%). *Anal.* ($C_{13}H_{27}N_3$) C, H, N.

1-(*N*-Formyl-1-methylaminomethylcyclohexyl)-4-methylpiperazine (49). **48** (2.25 g, 0.01 mol) was formylated as in **47** to yield needles of **49** (2.13 g, 83%): mp 107–108°. *Anal.* ($C_{14}H_{27}N_3O$) C, H, N.

1-(1,1-Dimethylaminomethylcyclohexyl)-4-methylpiperazine

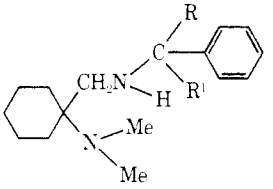
Table VIII. Substituted Benzamide Derivatives of N-Substituted Cyclohexyldiamines and -triamines



Compd	NRR^1	R^2	Yield,[b] %	Mp, °C[c]	Formula	Analyses
51	$N(CH_3)_2$	H	61	245–246	$C_{16}H_{25}ClN_2O$	C, H, N
52	$N(CH_3)_2$	4-F	59	238–239	$C_{16}H_{24}ClFN_2O$	C, H, Cl, N
53	$N(CH_3)_2$	3,4-Cl_2	63	215–216	$C_{16}H_{23}Cl_3N_2O$	C, H, Cl, N
54	$C_5H_{10}N$[a]	H	33	105–106	$C_{19}H_{28}N_2O$	C, H, N
55	$C_5H_{10}N$	4-F	87	243–245 dec	$C_{19}H_{28}ClFN_2O$	C, H, Cl, N
56	$C_5H_{10}N$	3,4-Cl_2	55	235–236 dec	$C_{19}H_{27}Cl_3N_2O$	C, H, N
57	$C_5H_{10}N$	2-Cl	79	234–236	$C_{19}H_{28}Cl_2N_2O$	C, H, Cl, N
58	$C_5H_{11}N_2$	H	68	127–128	$C_{19}H_{29}N_3O$	C, H, N

[a] Piperidyl. [b] Based on a single run. [c] Uncorrected.

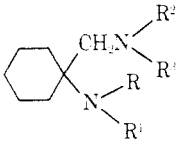
Table IX. Alcohol and Ester Derivatives of N-Substituted Cyclohexyldiamines and -triamines



Compd	R	R^1	Yield,[a] %	Mp, °C[b]	Formula	Analyses
59	H	OH	86	194–195 dec	$C_{18}H_{32}I_2N_2O$	C, H, N
60	H	$OCOCH_3$	63	177–178	$C_{18}H_{29}ClN_2O_2$	C, H, Cl, N

[a] Based on a single run. [b] Uncorrected.

Table X. Tosyl and Phthalimido Derivatives of N-Substituted Cyclohexyldiamines



Compd	NRR^1	R^2	R^3	Yield,[c] %	Mp, °C[d]	Formula	Analyses
61	$C_5H_{11}N_2$[a]	H	$C_7H_7SO_2$[e]	46	128–130	$C_{19}H_{31}N_3O_2S$	C, H, N
62	$C_5H_{10}N$[b]	NR^2R^3 =	$C_8H_4NO_2$[f]	42	143	$C_{20}H_{26}N_2O_2$	C, H, N

[a] N^4-Methylpiperazinyl. [b] Piperidyl. [c] Based on a single run. [d] Uncorrected. [e] *p*-Tosyl. [f] Phthalimido.

(50). 49 was reduced with $LiAlH_4$ (Et_2O) and worked up in the usual way to give prisms of **50** (0.47 g, 72.2%): mp 171–172°. *Anal.* ($C_{16}H_{35}N_3I_2$), C, H, I, N.

1-(3,4-Dichlorobenzamidomethyl)cyclohexyldimethylamine (53). A mixture of the base of **35** (1.0 g), 3,4-dichlorobenzoyl chloride (2 ml), and pyridine (10 ml) was allowed to stand at room temperature for 1 hr. The solid produced was filtered and recrystallized from EtOH–Et_2O to give microneedles of **53** (0.63 g, 63%): mp 215–216°. *Anal.* ($C_{16}H_{23}Cl_3N_2O$) C, H, Cl, N.

1-(1-Hydroxybenzylamino)methylcyclohexyldimethylamine (59). 1-Benzamidomethylcyclohexyldimethylamine (6.3 g, 0.025 mol) was reduced with $LiAlH_4$ (Et_2O) and worked up in the usual way to give prisms of **59** (5.43 g, 86.2%): mp 194–195° dec. *Anal.* ($C_{18}H_{32}I_2N_2O$) C, H, N.

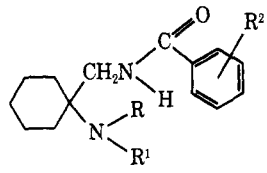
1-(1-Acetoxybenzylamino)methylcyclohexyldimethylamine (60). 59 (1.5 g) was refluxed for 3 hr with Ac_2O (5 ml) in pyridine (5 ml). The excess reagents were distilled and the residual oil was treated with EtOH–HCl to give prisms of **60** (1.1 g, 63.2%): mp 177–178°. *Anal.* ($C_{18}H_{29}ClN_2O_2$) C, H, Cl, N.

1-(1-Tosylaminomethylcyclohexyl)-4-methylpiperazine (61). **37** was shaken vigorously with TsCl in an alkaline medium and the solid filtered, washed with water, and recrystallized from EtOH to give needles of **61** (0.4 g, 46%): mp 128–130°. *Anal.* ($C_{19}H_{31}N_3O_2S$) C, H, N.

1-(1-Phthalimidomethylcyclohexyl)piperidine (62). The base of **36** (1.0 g) was refluxed with phthalic anhydride (1.0 g) and glacial AcOH (10 ml) for 1.5 hr. Excess AcOH was distilled to give needles of **62** (0.7 g, 42%): mp 143°. *Anal.* ($C_{20}H_{26}N_2O_2$) C, H, N.

Biological Studies. Thirty-five of the compounds reported were subjected to a primary pharmacological screen designed to

Table XI. Pharmacological Data of Some N-Substituted Benzamides (in the Mouse)



Compd	NRR[1]	R^2	Phenylquinone test, ED_{50}, mg/kg orally	Hot-plate test, ED_{50}, mg/kg sc
51	$N(CH_3)_2$	H	15.3 (7.6–31.0)	15.5 (5.4–42.0)
52	$N(CH_3)_2$	F	7.3 (3.3–16.1)	5.0 (1.7–15.0)
53	$N(CH_3)_2$	3,4-Cl_2	0.85 (0.4–1.7)	2.5 (1.2–6.4)
57	$C_5H_{10}N$	2-Cl	6.4 (2.03–20.8)	77.0 (32.6–170.2)
58	$C_5H_{11}N_2$	H	>1000	>100
Morphine			1.1 (0.7–1.8)	2.8 (1.1–4.8)
Codeine			5.8 (2.9–11.6)	17.0 (9.1–32.0)

detect a range of CNS effects in the mouse. At an oral dose of 100 mg/kg the following tests were performed: effects on behavior, effects on body temperature, antimaximal electroshock, antagonism of leptazol-induced convulsions, and effects on phenylquinone-induced writhing. At an oral dose of 50 mg/kg effects on the central cholinergic mechanism were examined, *e.g.*, tremor, hypothermia. At a subcutaneous dose of 100 mg/kg hot-plate effects were observed directly and on interaction with morphine.

The carboxamides **6–10** were generally inactive although **6** produced a Straub tail and raised posture in mice at an oral dose of 100 mg/kg. Ketones **18** and **22** were comparable to aspirin in their ability to inhibit writhing in mice caused by an intraperitoneal injection of phenylquinone.[20] Alcohols **25** and **29** showed a general CNS depressant activity. The anticonvulsant activity of **25** against the tonic extension of the hind limbs of the mouse induced by maximal electric shock[21] was almost 100%, as was the ability to inhibit phenylquinone-induced writhing. In the direct hot-plate test **29** gave 92% inhibition in test animals and was comparable to aspirin in the phenylquinone-induced writhing test. (See paragraph at the end of paper regarding supplementary material.)

However, the N-substituted benzamides gave the best pharmacological results and the quantitative data for these compounds are summarized in Table XI.

The dimethylamino compounds **51–53** showed well-marked and interesting activity. **51** completely abolished the reflex response of a mouse placed on the hot plate and inhibited writhing induced by phenylquinone. An improvement in activity was shown in the 4-fluoro compound **52** and in the 3,4-dichloro compound **53** while, in addition, both of these compounds produced a reduced response to pain in mice. The Straub index test was also performed on **51** at an intravenous LD_{50} of 45 mg/kg. There were no Straub tails at this dose; thus, the Straub index is $\ll 1.0$ and **51** therefore appears to possess some analgesic activity in the mouse. The compound is currently being studied in the dog using the dental pulp technique.[22,23] The results clearly show that these compounds possess analgesic activity and, in particular, **53** has been chosen for a detailed study in other species.

In an attempt to assess the importance of the nonbasic nitrogen in analgesic activity, **51** was reduced to **59** which in turn was esterified to **60**. Although activity against phenylquinone-induced writhing was completely absent in both compounds, an interesting result was shown in the hot-plate test where the ester **60** showed activity lying between that of the benzamide **51** and the alcohol **59**.

Structure–Activity Relationships. The benzamides and halogen-substituted benzamides show the most marked CNS activity. In particular, **51–53** proved worthy of extended evaluation. Within this group the importance of the nonbasic exocyclic nitrogen has been demonstrated in **51**, **59**, and **60** and the attached proton also seems to have significance. It is difficult to correlate these molecules with the structural features of morphine, but members of the group do show good, oral, analgesic properties with a minimum of addiction potential as measured by the Straub index.

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Supplementary Material Available. Primary pharmacological screening data for the 35 compounds tested and further quantitative pharmacological data for compounds **51**, **53**, and **57** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-1188.

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