stirred suspension of 313 mg (1 mmol) of the *tert*-butyloxycarbonyl derivative **3** in 6 mL of dry methylene chloride was added, under an argon atmosphere, 3 mL (2.15 mmol) of triethylamine. To the resulting solution was added, at −78 °C, a solution of 0.2 g (1.4 mmol) of benzenesulfenyl chloride in 2 mL of methylene chloride during 15 min. After being allowed to reach room temperature, the solution was evaporated, and the residue was taken up in a mixture of ethyl acetate and water. The stirred mixture was acidified to pH 2 with 1 N HCl. The aqueous phase was extracted with more ethyl acetate, and the combined organic extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel plates (hexane–ethyl acetate–acetic acid, 50:50:1, v/v) to give in the upper band 215 mg of isomer A of the N-protected phenylthio lactone **8**. High-resolution MS Calcd for $C_{21}H_{27}NO_6S$ (M^+): *m/e* 421.1559. Found: *m/e* 421.1513. From the lower band, 89 mg of the isomer **8B** was obtained. High-resolution MS Calcd for $C_{21}H_{27}NO_6S$ (M^+): *m/e* 421.1559. Found: *m/e* 421.1521. Treatment of **8A** with 5 mL of 98% formic acid during 5 h, evaporation, and trituration of the residue with ether furnished 154 mg (42% from **3**) of **isomer A** of the **phenylthio lactone 9·HCO$_2$H**: mp 236–237 °C dec (colorless powder from water); $[\alpha]^{22}_D$ 13.5° (*c* 0.5, AcOH); ^{1}H NMR (CD_3CO_2D) δ 1.48 (s, CH_3), 2.59 (dd, *J* = 6 and 18 Hz, one of CH_2CO), 3.0–3.1 (m, H_4 and one of CH_2CO), 3.2–3.35 (m, H_3), 3.36 (AB q, *J* = 14.5 Hz, CH_2S), 3.35–3.5 (m, one of H_5), 3.84 (dd, *J* = 8 and 12 Hz, one of H_5), 4.29 (s, H_2), 7.2–7.3 (m, 3 Ar H), 7.4–7.5 (m, 2 Ar H). Anal. ($C_{17}H_{21}NO_6S$) C, H, N, S. A similar treatment of **8B** afforded 64 mg (17% from **3**) of **isomer B** of the **phenylthio lactone 9·HCO$_2$H**: mp 266–267 °C dec (colorless powder from water); $[\alpha]^{22}_D$ −20° (*c* 0.5, AcOH); ^{1}H NMR (CD_3CO_2D) δ 1.59 (s, CH_3), 2.64 (dd, *J* = 5.4 and 20.2 Hz, one of CH_2CO), 3.03 (ddd, *J* = 8, 8 and 12 Hz, H_4), 3.1–3.25 (m, one of CH_2CO), 3.24 (AB q, *J* = 13.7 Hz, CH_2S), 3.25–3.5 (m, H_3 and one of H_5), 3.67 (dd, *J* = 8 and 12 Hz, one of H_5), 4.34 (s, H_2), 7.2–7.4 (m, 3 Ar H), 7.4–7.5 (m, 2 Ar H). Anal. ($C_{17}H_{21}NO_6S$) C, H, N, S.

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Registry No. 1, 487-79-6; 3, 75466-86-3; 4, 78166-25-3; 5 (isomer 1), 83220-92-2; 5 (isomer 2), 83289-36-5; 5 methyl ester (isomer 1), 83220-93-3; 5 methyl ester (isomer 2), 83289-39-8; 6 (isomer 1), 83289-37-6; 6 (isomer 2), 83289-38-7; 7 (isomer 1), 83289-40-1; 7 (isomer 2), 83289-41-2; 8 (isomer 1), 83220-94-4; 8 (isomer 2), 83289-42-3; 9 (isomer 1), 83289-43-4; 9 (isomer 2), 83289-44-5; 11 (X = I), 83220-95-5; 11 (X = OH), 83220-96-6; NMDA, 6384-92-5; L-Glu, 56-86-0; Quis, 52809-07-1.

Synthesis and Pharmacological Studies of 4,4-Disubstituted Piperidines: A New Class of Compounds with Potent Analgesic Properties

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A series of 4,4-disubstituted piperidines has been synthesized and evaluated for analgesic activity. Several of these analogues show analgesic potency comparable to morphine in the mouse writhing and tail-flick tests. A number of compounds exhibit high affinity for [^{3}H]naloxone binding sites in rat brain membranes. Among the most potent derivatives are compounds **15** and **48**. Although opiate-like, attempts to modify this activity with various substituents have failed to produce antagonistic properties. A few of these analogues also show marked long-lasting serotonin antagonism in the guinea pig serotonin toxicity test and the DL-5-hydroxytryptophan induced head-twitch model in the mouse.

The search for a potent, nonaddictive analgesic with emphasis upon agonist–antagonist activity has been in progress for many years. Due to the interesting analgesic properties of 4-substituted piperidines, such as meperidine,[1-3] ketobemidone,[4,5] and fentanyl,[6-8] attempts were made to find long-acting, strong analgesics that do not cause respiratory depression or physical dependence. Although significant dissociation of analgesic and dependence liability has not been attained for this type of compound, previous work by Küehnis and co-workers[9] on 1-substituted 4-(1-acetylalkyl)-4-hydroxypiperidines stimulated our research interest. We describe here the synthesis and biological activities of a similar class of 4,4-disubstituted piperidines,[10] whose substituents are illustrated in Table I.

In order to convert potent narcotic agonists into antagonists, it has been generally considered necessary to use allyl, propyl, or cyclopropylmethyl groups[11-14] at the basic nitrogen. Although this type of substitution has failed to produce antagonistic properties in the piperidine series, e.g., when the *N*-methyl group of meperidine[15-17] was replaced with an allyl side chain, it was thought of interest to investigate whether similar effects would result following

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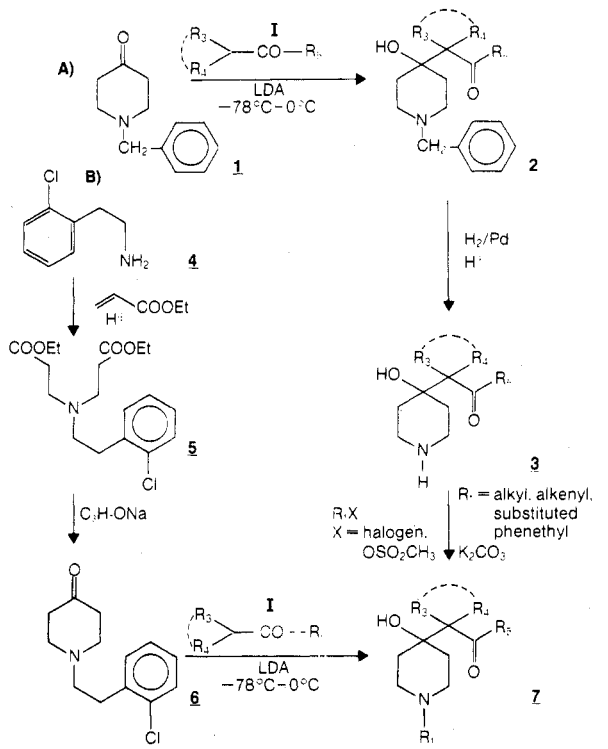
Scheme I

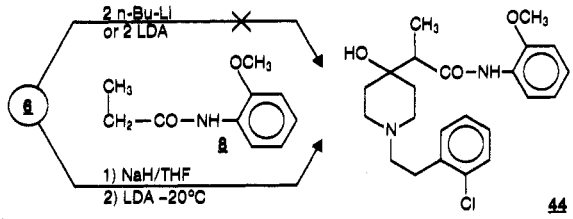


substitution of the basic and nonbasic nitrogen of structure 7. The chemistry and structure–activity relationships of these derivatives are discussed in this paper.

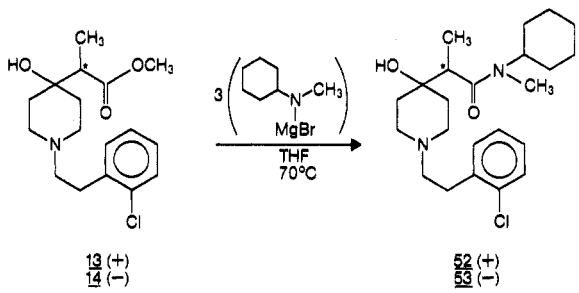
Chemistry. Two general synthetic routes were employed for the preparation of these piperidine analogues (Scheme I). (A) The primary approach involved the condensation of the commercially available 1-benzyl-4-piperidinone 1 with the appropriate alkyl-, substituted aryl-, or cycloalkylamides[18] in the presence of a strong base. Use of lithium diisopropylamide (LDA)[19] or lithium cyclohexylisopropylamide[20] prepared from the corresponding amines and *n*-butyllithium at general temperatures of −78 to 0 °C in dry tetrahydrofuran resulted in the formation of the desired 4,4-disubstituted 1-benzylpiperidines 2 in generally good yields. Catalytic debenzylation in the presence of 10% palladium on charcoal in acetic acid or methanolic hydrochloride acid at 50 psi and 50 °C furnished the nor compounds 3 in usually quantitative yields. Treatment of 3 with alkyl, alkenyl, or substituted phenethyl halides (bromides or chlorides) or their corresponding methansulfonates[21a,b] in solvents such as dimethylformamide, dimethylacetamide, or 2-butanone in the presence of potassium carbonate at 20–100 °C furnished the desired 1-alkylated piperidines 7 in reasonable yields (Table I).

The second approach (B) involved the synthesis of 1-(2-chlorophenethyl)-4-piperidinone (6)[22-24] according to

Scheme II



Scheme III



Scheme I: upon condensation with alkyl- or cycloalkylamides as described in method A compounds 7 were afforded in good overall yields.

No attempts were undertaken to optimize the yields. The compounds described under Experimental Section only represent examples of the reactions listed in Scheme I.

Several points deserve brief mention. Attention was given to the design of analogues of compound 28 bearing larger groups at the 2-position of the propionamide moiety. In an attempt to prepare cyclic analogues of 28, we condensed the rather rigid *N*-cyclohexyl-*N*-methyl-1-cyclopentanecarboxamide in the presence of LDA at −78 °C with 6, which furnished compound 31 in moderate yield.

Alternatively, no reaction was achieved with 6 when the hindered *N*-methyl-*N*-cyclohexyl-2-ethylhexanamide was used under similar conditions. However, we found that 3-[1-[2-(2-chlorophenyl)ethyl]-4-hydroxy-4-piperidinyl]-1-[2-(2-chlorophenyl)ethyl]-4-piperidinone was formed using lithium diethylamide (prepared from diethylamine and *n*-butyllithium) in tetrahydrofuran at −78 °C in 20–30% yield. This result confirms our idea that the amide anion has been formed, but instead of adding to 6 it generated the enolate anion of the latter, affording the undesired condensation product. No self-condensation of 1-(2-chlorophenethyl)-4-piperidone (6) has otherwise been observed throughout this work.

In the course of our structure–activity studies of the most interesting analogues, 15 and 48, further modification, particularly on the amide nitrogen with groups like allyl or propargyl, attracted our attention. Since a direct condensation of *N*-allyl-*N*-(2-methoxyphenyl)propionamide (*N*-allyl-*N*-cyclohexylpropionamide in the presence of LDA at −78 °C condensed in yields of 35% with 6 to give 36) failed under a number of strongly basic conditions at various temperatures, it became desirable to introduce these functional groups at the final stage of the synthesis. This synthetic problem was resolved by a procedure reported by Hauser and co-workers[25] using the generated dianion of *N*-(2-methoxyphenyl)propionamide (8).[18,26] Although *n*-BuLi or LDA failed to produce the desired

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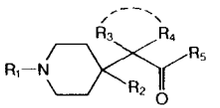
Table I. Physical Properties and Analgesic Data of 4,4-Disubstituted Piperidine Analogues



compd	R_1[n]	R_2	R_3	R_4	R_5[n]	method	mp, °C	yield, %	formula[a]	ED_{50},[e,m] mg/kg PQW, po	tail flick sc	tail flick po
9	$PhCH_2$	OH	CH_3	H	Me-N-cHx	A	182–184	93	$C_{22}H_{34}N_2O_2 \cdot HCl$			
10	H				Me-N-cHx	A[b]		91	$C_{15}H_{28}N_2O_2$			
11	2-Cl-PhEt	OH	CH_3	H	O-Ph	A	178–179	34	$C_{22}H_{26}ClNO_3 \cdot HCl$			
12	2-Cl-PhEt	OH	CH_3	H	O-Me	A	122–123	73	$C_{17}H_{24}ClNO_3 \cdot HMl$[i]			
(+)-13	2-Cl-PhEt	OH	CH_3	H	O-Me	A	149–151	73	$C_{17}H_{24}ClNO_3 \cdot C_{18}H_{14}O_8$[i]			
(−)-14	2-Cl-PhEt	OH	CH_3	H	O-Me	A	150–151	58	$C_{17}H_{24}ClNO_3 \cdot C_{18}H_{14}O_8$[i]			
15	2-Cl-PhEt	OH	CH_3	H	Me-N-cHx	A	159–161	78	$C_{23}H_{35}ClN_2O_2 \cdot HMl$[k]	10.8	3.2 (2.2–5.0)	22
16	3-MeO-PhEt	OH	CH_3	H	Me-N-cHx	B	190–191	41	$C_{24}H_{38}N_2O_3 \cdot HBr$	>18 (−25)	>18 (0)	−100 (−60)
17	PhEt	OH	CH_3	H	Me-N-cHx	B	215–217	60	$C_{23}H_{36}N_2O_2 \cdot HCl$	18 (−53)	18 (−60)	>56 (−35)
18	4-Me-PhEt	OH	CH_3	H	Me-N-cHx	B	215–217	33	$C_{24}H_{38}N_2O_2 \cdot HCl$	<56 (−69)	>3.2 (−20)	100 (−60)
19	methyl	OH	CH_3	H	Me-N-cHx	A	215–217	54	$C_{16}H_{30}N_2O_2 \cdot HCl$	>56 (−17)	>56 (−0)	>100 (−40)
20	*n*-allyl	OH	CH_3	H	Me-N-cHx	B	166–168	50	$C_{18}H_{32}N_2O_2 \cdot HFu$[k]	1 (−2)	32 (−40)	NT[l]
21	*n*-heptyl	OH	CH_3	H	Me-N-cHx	B	118–120	60	$C_{22}H_{42}N_2O_2 \cdot HBr$	>56 (−25)	>56 (−20)	>100 (0)
22	2-Cl-PhEt	OCOEt	CH_3	H	Me-N-cHx	A[d]	215–217	85	$C_{26}H_{39}ClN_2O_3 \cdot HFu$[k]	<56 (−81)	<3.2 (−0)	−18 (−0)
23	2-Cl-PhEt	OCOEt	CH_3	H	Pr-N-(2-MeO-Ph)	A[d]	152–154	59	$C_{29}H_{39}ClN_2O_4 \cdot HMl$[k]	1 (−48)	32 (−8)	100 (−80)
24	2-Cl-PhEt	H	CH_3	H	Me-N-cHx	A[e]	235–237	70	$C_{23}H_{35}ClN_2O \cdot HCl$	<18 (−35)	2.9	37
25	2-Cl-PhEt	OH	H	H	Me-N-cHx	A	207–208	57	$C_{22}H_{33}ClN_2O_2 \cdot HCl$	>18 (−16)	>3.2 (−40)	<56 (−80)
26	2-Cl-PhEt	OH	$(CH_2)_3CH_3$	H	Me-N-cHx	A	165–167	20	$C_{26}H_{41}ClN_2O_2 \cdot HFu$[k]	>56 (−24)	>56 (−24)	>100 (−20)
27	2-Cl-PhEt	OH	$CH(CH_3)_2$	H	Me-N-cHx	A	118–124	40	$C_{25}H_{39}ClN_2O_2 \cdot HBr$	<56 (−91)	>56 (−20)	>100 (−40)
28	2-Cl-PhEt	OH	CH_3	CH_3	Me-N-cHx	A	170–172	76	$C_{24}H_{37}ClN_2O_2 \cdot CH_3SO_3H$	26	21 (12.0–36.8)	>100 (−40)
29	2-Cl-PhEt	OH	CH_3	CH_3	Et-N-(2-MeO-Ph)	A	172–173	32	$C_{26}H_{35}ClN_2O_3 \cdot HFu$[k]	>18 (−40)	>56 (−0)	>100 (−0)
30	2-Cl-PhEt	OH	CH_3	CH_3	H-N-(2-MeO-Ph)	A	168–170	10	$C_{24}H_{31}ClN_2O_3 \cdot HCl$	<56 (−28)	>32 (−20)	sedation
31	2-Cl-PhEt	OH	$-(CH_2)_4-$		Me-N-cHx	A	215–217	40	$(C_{26}H_{39}ClN_2O_2)_2 \cdot Fu$[k]	>56 (−28)	>56 (−20)	100 (−60)
32	2-Cl-PhEt	OH	$-(CH_2)_2-$		Me-N-cHx	A	228–229	20	$C_{24}H_{35}ClN_2O_2 \cdot HFu$[k]	>56 (−42)	10 (−60)	−32 (−60)
33	2-Cl-PhEt	OH	CH_3	H	H-N-*n*-Bu	A[f]	132–133	40	$C_{20}H_{31}ClN_2O_2 \cdot HMl$[k]	>32 (−44)	>18 (−80)	<100 (−60)
34	2-Cl-PhEt	OH	CH_3	H	H-N-cHx	A[f]	110–111	72	$C_{22}H_{33}ClN_2O_2$	>56 (−67)	>3.2 (−80)	<56 (−60)
35	2-Cl-PhEt	OH	CH_3	H	Pr-N-cHx	A	168–170	45	$C_{25}H_{39}ClN_2O_2 \cdot HMl$[k]	<32 (−85)	>10 (−40)	56 (−60)
36	2-Cl-PhEt	OH	CH_3	H	CH_2=$CHCH_2$-N-cHx	A	135–140	35	$(C_{25}H_{37}ClN_2O_2)_2 \cdot C_{10}H_8O_6S_2$[k]	<32 (−73)	4 (3.1–3.2)	−100 (−20)
37	2-Cl-PhEt	OH	CH_3	H	cHx-N-cHx	A	155–158	60	$C_{28}H_{43}ClN_2O_2 \cdot HMl$[k]	<56 (−64)	>56 (−20)	>100 (−20)
38	2-Cl-PhEt	OH	CH_3	H	*t*-Bu-N-cHx	A	174–175	65	$C_{26}H_{41}ClN_2O_2 \cdot HCl$	<56 (−77)	>10 (−0)	>56 (20)
39	2-Cl-PhEt	OH	CH_3	H	*n*-Bu-N-*n*-Bu	A	140–142	66	$C_{24}H_{39}ClN_2O_2 \cdot HFu$[k]	<30 (−84)	<50 (−80)	<100 (−100)
40	2-Cl-PhEt	OH	CH_3	H	Me-N-(2-MeO-Ph)	A	174–175	53	$C_{24}H_{31}ClN_2O_3 \cdot HFu$[k]	18 (−47)	0.68 (0.53–0.88)	>18 (20)
41	2-Cl-PhEt	OH	CH_3	H	Me-N-(2-EtO-Ph)	A	170–172	67	$C_{25}H_{33}ClN_2O_3 \cdot HMl$[k]	1.8 (−55)	0.51	<32 (80)
42	2-Cl-PhEt	OH	CH_3	H	Me-N-(4-Cl-Ph)	A	195–196	40	$C_{23}H_{28}Cl_2N_2O_2 \cdot HFu$[k]	9.7	6.8	>56 (−0)
43	2-Cl-PhEt	OH	CH_3	H	Me-N-(3-MeO-Ph)	A	171–173	61	$C_{24}H_{31}ClN_2O_3 \cdot HFu$[k]	<56 (−84)	>10 (0)	NT[l]
44	2-Cl-PhEt	OH	CH_3	H	H-N-(2-MeO-Ph)	A	111–113	38	$C_{23}H_{29}ClN_2O_3 \cdot HFu$[k]	5.6 (−49)	>18 (−0)	NT[l]
45	2-Cl-PhEt	OH	CH_3	H	Me-N-(3-OH-Ph)	A[h]	164–165	52	$C_{23}H_{29}ClN_2O_3$	>18 (−6)	>56 (−0)	NT[l]
46	2-Cl-PhEt	OH	CH_3	H	CH_2=$CHCH_2$-N-(2-MeO-Ph)	A[g]	173–175	60	$C_{26}H_{33}ClN_2O_3 \cdot HFu$[k]	0.56 (−55)	0.09 (0.070–0.123)	7.6
47	2-Cl-PhEt	OH	CH_3	H	CH_3CH_2-N-(2-MeO-Ph)	A	86–88	53	$C_{25}H_{33}ClN_2O_3 \cdot HMl$[k]	56 (−53)	0.07 (0.058–0.084)	4.9
48	2-Cl-PhEt	OH	CH_3	H	Pr-N-(2-MeO-Ph)	A	177–179	25	$C_{26}H_{35}ClN_2O_3 \cdot HFu$[k]	1.8 (−98)	0.11 (0.080–0.160)	5.4
49	2-Cl-PhEt	OH	CH_3	H	CH≡CCH_2-N-(2-MeO-Ph)	A[g]	185–186	45	$C_{26}H_{31}ClN_2O_3 \cdot HFu$[k]	0.56 (−77)	0.13 (0.085–0.20)	5.4

50	2-Cl-PhEt	OH	CH_3	H	Et-N-(2-EtO-Ph)	A	160–162	50	$C_{26}H_{35}ClN_2O_3 \cdot HMI^k$	1.8 (−79)	0.26 (0.18–0.36)	10 (−60)
51	2-Cl-PhEt	OH	CH_3	H	Pr-N-(2-EtO-Ph)	A	230–233	32	$(C_{27}H_{37}ClN_2O_4)_2 \cdot C_{10}H_8O_6S_2^k$	0.18 (−56)	0.41 (0.34–0.49)	11
(+)-52	2-Cl-PhEt	OH	CH_3	H	Me-N-cHx	A[i]	115–117	32	$C_{23}H_{35}ClN_2O_2 \cdot HMI^k$	20	42	100 (−70)
(−)-53	2-Cl-PhEt	OH	CH_3	H	Me-N-cHx	A[i]	115–116	35	$C_{23}H_{35}ClN_2O_2 \cdot HMI^k$	10	3.8	100
morphine										1.4	3.4 (2.6–4.4)	23

[a] Analyses for C, H, N, O, S, and halogens were within ±0.4% of the theoretical values. [b] Obtained from 9 by catalytic debenzylation with Pd on charcoal in acetic acid or ethanolic hydrochloric acid. [c] The ED_{50} of each substance is estimated graphically according to the method described by Lichtfield et al.[35] and taken to be the dose of drug that reduces abdominal contractions (PQW test) or the heat-induced tail flicks (tail-flick tests) by 50%. [d] Esterification of the hydroxy analogues 15 and 48 using propionyl chloride in the presence of triethylamine.[21b,30] [e] Prepared by dehydration of 9 with concentrated H_2SO_4, followed by catalytic hydrogenation, N-alkylation, and conversion of the ester via the acid chloride[18] to 24. [f] Prepared by aminolysis of 11 with primary amines.[31] [g] Similarly prepared as described by Hauser[25] by condensation of the lithium–sodium dianion of *N*-(2-methoxyphenyl)propionamide (8)[26] with 6, followed by N-alkylation. [h] Methoxy cleavage of 43 using HBr (48%) in acetic acid.[32] [i] Resolved via the ester 12 and aminolized according to H. L. Bassett.[27] [k] Abbreviations used are: Fu, fumarate; HFu, hydrogen fumarate; HMI, hydrogen maleate. $C_{10}H_8O_6S_2$ and $C_{18}H_{14}O_8$ stand for 1,5-naphthylenedisulfonate and dibenzoyltartrate, respectively. [l] NT = not tested. [m] Where an ED_{50} is given, 95% confidence limits appear in parentheses (Litchfield et al.[35]). For the remaining compounds, no exact ED_{50} was determined, and the number in parentheses indicates the percentage of animals in the group showing analgesia. In the PQW test, analgesia is defined as the reduction of the number of abdominal contractions for a group of five animals compared with a control group. In the tail-flick test, extensions of the reaction times of more than 75% over the pretreatment value in the same mouse are regarded as denoting analgesia. [n] Abbreviations used: PhEt = phenethyl; Hx, cyclohexyl.

dianion of 8, treatment of 8 with sodium hydride in dry tetrahydrofuran, followed by addition of the resulting sodium *N*-(2-methoxyphenyl)propionamide solution to 3 equiv of freshly prepared LDA in dry THF at −20 °C, furnished, after quenching with 6, compound 44 in moderate yield (Scheme II). N-Alkylation was performed in the usual manner with sodium hydride in dry THF and allyl or propargyl bromide to give compounds 46 and 49.

It also became desirable to investigate the optical antipodes of compound 15. Initial attempts to separate the racemic mixture with optically active acids failed, but resolution of the ester 12 was achieved with dibenzoyltartaric acid. Treatment of the free base of the pure antipodes 13 and 14 with 3 equiv of bromomagnesium *N*-cyclohexylmethylamide in dry THF at reflux for 3 h resulted in the desired aminolysis[27] to give the pure isomers 52 and 53 in reasonable yield (Scheme III). Interestingly, similar conditions using lithium *N*-cyclohexyl-*N*-methylamide[28] resulted primarily in a retroaldol condensation to give 6.

Structure–Activity Relationships. The method of assay for the analgesic activities is outlined under Experimental Section. Morphine was used as standard. Almost from the onset of this study, compound 15 proved to be a potent analgesic, although opiate-like in its properties. In order to improve the potency or to find pure or mixed antagonist activities, 15 was systematically derivatized at numerous positions with the following results (Table I).

The analgesic tests indicate that the optimum activity is associated with a 2-chlorophenethyl moiety (R_1) at the basic nitrogen. Other substituted phenethyl, as well as aliphatic, groups (16–21) exhibit decreasing potencies or are devoid of such activities. Neither agonistic nor antagonistic potencies were observed with groups like allyl or heptyl.

With regard to R_2, the analgesic activity seems to be associated with a free hydroxy group capable of hydrogen bonding to the amide C=O, thereby orienting the group on the amide nitrogen to favorably interact with the opiate receptor. However, when the hydroxy group (R_2) is replaced with a hydrogen, only a slight decrease of the analgesic activity was observed (24). This finding, although only confirmed on one compound, might suggest that a non-hydrogen-bonded amide group at the 4-position of the piperidine moiety also interacts favorably with the analgesic receptor. The potency of the esters 22 and 23 has completely vanished compared to the respective hydroxy analogues.

With respect to R_3, a methyl group at the 2-position exhibits the highest potency. Hydrogen or bulky aliphatic groups (25–27) are devoid of analgesic properties. If R_3 is a methyl group, the most potent analogues are found to be associated with R_4 hydrogen. Although weak in analgesia, replacement of the hydrogen (R_4) with a methyl group provides the biologically interesting analogue 28. Anilides of this type, e.g., 29 and 30, do not possess analgesic properties. Furthermore, R_3 and R_4, together as cyclopentane and cyclopropane analogues (31 and 32), respectively, are devoid of analgesia.

With regard to R_5, the most potent analgesic aliphatic amides are those with a cyclohexyl group associated with a methyl substituent. Secondary amides, e.g, compounds 33 and 34, do not exhibit analgesic activity at doses below about 18 mg/kg. No antagonistic activities are observed

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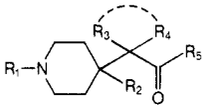
Table II. Analgesic Activity in the Mouse and Inhibition of [^{3}H]Naloxone Binding to Rat Brain Membranes



compd[e]	R_2	R_3	R_4	R_5[f]	IC_{50}, nM, of sp naloxone binding[a] no NaCl	100 mM NaCl	+NaCl/ −NaCl	analgesia ED_{50}, mg/kg,[b,c] tail flick, sc
15	OH	CH_3	H	Me-N-cHx	45	450	10.0	3.2 (2.2-5.0)
36	OH	CH_3	H	CH_2=$CHCH_2$-N-cHx	2.4	20	8.3	4.0 (3.1-5.2)
40	OH	CH_3	H	Me-N-(2-MeO-Ph)	3.3	51	15.4	0.68 (0.53-0.88)
47	OH	CH_3	H	Et-N-(2-MeO-Ph)	0.94	6.3	6.7	0.07 (0.0058-0.084)
48	OH	CH_3	H	Pr-N-(2-MeO-Ph)	0.51	0.66	1.3	0.11 (0.080-0.160)
46	OH	CH_3	H	CH_2=$CHCH_2$-N-(2-MeO-Ph)	0.41	2.9	7.1	0.09 (0.070-0.123)
49	OH	CH_3	H	CH≡CCH_2-N-(2-MeO-Ph)	0.41	4.2	10.2	0.13 (0.085-0.20)
41	OH	CH_3	H	Me-N-(2-EtO-Ph)	0.98	10	10.2	0.51 (0.37-0.70)
50	OH	CH_3	H	Et-N-(2-EtO-Ph)	0.55	1.8	3.3	0.26 (0.18-0.36)
51	OH	CH_3	H	Pr-N-(2-EtO-Ph)	0.8	0.95	1.2	0.41 (0.34-0.49)
28	OH	CH_3	CH_3	Me-N-cHx	550	825	1.5	21 (12.0-36.8)
29	OH	CH_3	CH_3	Et-N-(2-MeO-Ph)	7.5	35	4.7	>56 (0), NT[d]
morphine					4.5	73	16.2	3.4 (2.6-4.4)
pentazocine					12.5	87	7.1	13 (6.2-27.3)
buprenorphine					0.41	0.44	1.1	
naloxone					1.4	12	8.6	

[a] IC_{50} is the nanomolar concentration of substance required to inhibit by 50% the specific binding of [^{3}H]naloxone (1 nM)[29] to preincubated (30 min at 37 °C) membranes of rat brain without cerebellum. The incubation was performed in triplicate at 25 °C for 40 min in the presence or absence of 100 mM NaCl. The "NaCl ratio" is defined as the ratio of the IC_{50} values in the presence and absence of 100 mM NaCl.[34b] Values are the means of at least two independent determinations with SEM of less than 25%.[34c] [b] ED_{50} is estimated graphically according to the method of Litchfield et al.[35] [c] 95% confidence limits appear in parentheses. [d] NT = not tested. [e] R_1 = 2-chlorophenethyl. [f] Abbreviations used are: cHx, cyclohexyl.

with the propyl and allyl analogues **35** and **36**, respectively. Furthermore, bulky aliphatic or cycloaliphatic groups (e.g., **37–39**) lead to a loss of activity. Replacement of the cyclohexane ring, on the other hand, with 2-methoxy (**40**) or 2-ethoxyphenyl substituents (**41**), respectively, results in compounds having marked analgesic activity. Other aromatic substituents (**42–45**) at different positions, as well as secondary anilides, are less potent or do not show analgesia. While having similar potencies to **40**, allyl, ethyl, propyl, and propargyl analogues **46–49** have no antagonistic properties. The most interesting compound is the *N*-propyl analogue **48** with a potency approximately 30 to 200 times that of morphine, depending on the test used. This compound also produced mydriasis, accompanied by a Straub tail response and CNS-depressant effects at higher doses. A total inhibition of these effects by naloxone indicates the existence of opiate-like properties.

The effect of the antipodes of compound **15** has been investigated. The levorotatory isomer (−)-**53** is somewhat more potent than its counterpart (+)-**52**, but both are less potent than their respective racemates **15**. As of this time we cannot offer an explanation why neither optical isomer is as active as the racemate. That these compounds were acting at opiate receptors was illustrated by their in vitro activity in the [^{3}H]naloxone binding assay.[29] From our new series, compound **48** is the most potent inhibitor in this assay, the affinity being comparable to buprenorphine (see Table II).

Slightly less potent in the [^{3}H]naloxone binding assay are compounds **46** and **49**, as well as the respective ethoxy analogues **50** and **51**. A number of other analogues, including compound **15** and **28**, exhibit affinities similar to those of pentazocine and morphine. It has been proposed that the "NaCl ratio" is an indicator for the relative agonistic vs. antagonistic potency of analgesic drugs.[34b] In the present study, however, no evidence was found to suggest that compounds with a low "NaCl ratio", i.e., compounds **48**, **51** and **28**, have antagonistic or dualistic properties. Some of these compounds also show marked, long-lasting serotonin antagonistic properties in the guinea pig serotonin toxicity test[37] and the DL-5-HTP-induced head-twitch model in the mouse (Table III).[38]

Of striking interest is compound **15**, which displays, after oral and subcutaneous administration in the guinea pig, serotonin antagonistic activities comparable to cyproheptadine and lasting up to 24 h. Similar results are observed with compound **28**. Other analogues, e.g., **25**, **34**, and **37**, are generally less potent or completely devoid of such properties. Marked serotonin antagonism, comparable to that of the serotonin antagonist pizotifen,[39] is also found with some of the most potent analgesics, such as compounds **47**, **48**, and **51**, in the 5-HTP-induced head-twitch test in the mouse.

In conclusion, the described 4,4-disubstituted piperidines

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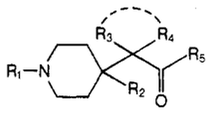
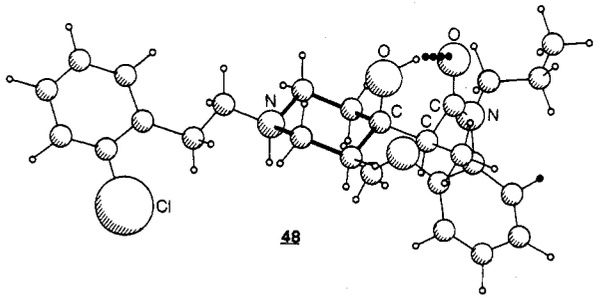
Table III. Effects on Serotonin Antagonism[a] in Guinea Pig and the DL-5-HTP[c] Induced Head Twitches in the Mouse[b]



compd[g]	R_2	R_3	R_4	R_5[h]	ED_{50},[d] mg/kg, after specified hour	5 HTP antagonism in the mouse: dose range mg/kg sc	5 HTP antagonism in the mouse: ED_{50}, mg/kg sc
15	OH	CH_3	H	Me-N-cHx	0.5 h: 0.015 sc (0.012-0.018); 0.01 po (0.008-0.015)	0.01-0.3	0.07
					3 h: 0.002 sc (0.001-0.005); 0.007 po (0.006-0.008)		
					6 h: 0.007 sc (0.005-0.01); 0.009 po (0.005-0.015)		
					24 h: 0.028 sc (0.019-0.04); 0.045 po (0.031-0.085)		
28	OH	CH_3	CH_3	Me-N-cHx	0.5 h: 0.055 sc (0.033-0.094); 0.103 po (0.037-0.284)	0.03-10	0.1
					3 h: 0.01 sc (0.003-0.031); 0.07 po (0.026-0.190)		
					6 h: 0.05 sc (0.039-0.065); 0.14 po (0.09-0.21)		
					24 h: >0.1 sc; 0.135 po (0.07-0.243)		
25	OH	H	H	Me-N-cHx	3 h: 0.05-0.1 sc[f]		
34	OH	CH_3	H	H-N-cHx	3 h: 0.05-0.1 sc[f]		
37	OH	CH_3	H	cHx-N-cHx	no antagonism		
47	OH	CH_3	H	Et-N-(2-MeO-Ph)		0.03-1	0.07
48	OH	CH_3	H	Pr-N-(2-MeO-Ph)		0.003-0.1	0.015
51	OH	CH_3	H	Pr-N-(2-EtO-Ph)		0.003-0.1	0.015
cyproheptadine					3 h: 0.027 sc[f] (0.015-0.05); 0.09 po	0.003-0.1	0.015
pizotifen						0.003-0.1	0.015

[a] D. Roemer and H. Weidmann, *Med. Welt*, 17, 2791 (1966). [b] S. J. Corne, R. W. Pickering, and B. T. Warner, *Br. J. Pharmacol.*, 20, 106 (1963). [c] 5-HTP = 5-hydroxytryptophan. [d] The ED_{50} is estimated graphically according to the method of Litchfield et al.[35] [e] The ED_{50} was the dose that reduced the mean number of head twitches by 50% compared to the saline-treated control group (N = 5-10). [f] Only tested at 3 h. [g] R_1 = 2-chlorophenethyl. [h] Abbreviations used are: cHx, cyclohexyl.

represent a novel class of compounds, some with significant analgesic and serotonin antagonistic properties: Our results provide support for the idea that the optimal activities with regard to analgesia and relative affinity to the opiate receptor labeled with [^{3}H]naloxone are associated with a piperidine ring bearing at the 4-position an *N*-(2-alkoxyphenyl)-2-propionamide group and a 2-chlorophenethyl moiety at the piperidine nitrogen. The isobutyramide analogues, on the other hand, exhibit extremely low binding and no analgesic properties. This specificity is apparently strongly influenced by the steric bulk at the amide 2-position. X-ray analysis of compound **48** has revealed that the molecular conformation is stabilized by a strong intramolecular hydrogen bond. The low affinity to the naloxone receptor and the loss of analgesic activity of the dimethyl analogue **29** might suggest that the methyl groups are forcing the molecule out of its hydrogen-bonded conformation and thereby diminishing the interaction with the analgesic receptor.



48

Experimental Section

The structures of all compounds are supported by NMR spectroscopy (Varian 90 or 100 MHz). Melting points were obtained on a Büchi capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results were within ±0.4% of the theoretical values (abbreviations used: Fu, fumarate; HFu, hydrogen fumarate; HMl, hydrogen maleate). Dry THF, DIPA, LDA, $MgSO_4$, and K_2CO_3 (20%) stands for dry tetrahydrofuran, diisopropylamine, lithium diisopropylamide, magnesium sulfate, and potassium carbonate solution (20%), respectively.

Methods of Biological Evaluation. The method employed was based on those described by E. A. Siegmund et al.[33] and J. F. Emele et al.,[34] by measuring the inhibition of phenylbenzoquinone-induced writhing (PQW) and the delay in response to a noxious heat stimulus (D'Amour and Smith[36] tail-flick method). The method for protection against a lethal dose of serotonin in the guinea pig was that described by Roemer and Weidmann.[37] The method for assessing the inhibition of 5-HTP-induced head twitches in the mouse was based on that described by Corne et al.[38] The assay employed for the [^{3}H]naloxone binding was based on that described by Pless et al.[34c]

2-(1-Benzyl-4-hydroxy-4-piperidinyl)-*N*-cyclohexyl-*N*-methylpropionamide (9). To a stirring solution of 30.36 g (0.3 mol) of DIPA in 500 mL of dry THF, which was cooled to −75 °C and blanketed under a dry nitrogen atmosphere, was added dropwise 183 mL (0.3 mol) of *n*-BuLi (1.5 M) in hexane. The mixture was stirred for 15 min at −75 °C and a solution of 25.0 g (0.15 mol) of *N*-cyclohexyl-*N*-methylpropionamide in 50 mL of dry THF was slowly added during a period of 0.5 h. Stirring was continued for 20 min, and a solution of 28.4 g (0.15 mol) 1-benzyl-4-piperidinone in 50 mL of dry THF was added dropwise within 1 h. The reaction was stirred for 30 min at −75 °C, and the temperature was raised to −30 °C. The mixture was dropwise

decomposed with a solution of 20 mL of K_2CO_3 (20%), and the organic layer was decanted. The residue was triturated with two portions of ether, the combined organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure. The product crystallized from acetone/ether; addition of ethanol/hydrochloric acid (5.2 N), gave the hydrochloride of **9**: yield 49.8 g (93%); mp 182–184 °C. Anal. ($C_{22}H_{34}N_2O$·HCl) C, H, Cl, N, O.

Similarly prepared was **phenyl 2-[1-(2-chlorophenethyl)-4-hydroxy-4-piperidinyl]propionate (11).** Compound 11 was prepared by the method described for **9** from 24 g (0.16 mol) of phenyl propionate and 19 g (0.08 mol) of 1-(2-chlorophenethyl)-4-piperidinone in the presence of LDA (0.2 mol) at −75 °C in dry THF; crystallization from 2-propanol furnished 11.6 g (34%) of **11** as the crystalline hydrochloride, mp 178–179 °C. Anal. ($C_{22}H_{26}ClNO_3$·HCl) C, H, Cl, N, O.

Also prepared according to this procedure was **methyl 2-[1-(2-chlorophenethyl)-4-hydroxy-4-piperidinyl]propionate (12)** from 26.4 g (0.3 mol) of methyl propionate and 47.7 g (0.2 mol) of 1-(2-chlorophenethyl)-4-piperidinone in the presence of LDA (0.6 mol) at −75 °C in dry THF; after the usual workup, 53.4 g (73%) of **12** was obtained as a crystalline maleate from acetone, mp 122–123 °C. Anal. ($C_{17}H_{24}ClNO_3$·HMl) C, H, Cl, N, O.

General Examples for the Synthesis of Various Amides. *N*-Ethyl-*N*-(2-methoxyphenyl)propionamide (I). To a stirring solution of 34.0 g (0.224 mol) of *N*-ethyl-2-methoxyaniline[18,26] and 53 mL of triethylamine (0.381 mol) in 350 mL of chloroform was added dropwise a solution of 31.0 g (0.335 mol) of propionyl chloride in 100 mL of chloroform so as to maintain the exothermic reaction below 40 °C. The mixture was stirred for 1 h at 20 °C and transferred to a separatory funnel. The organic layer was washed with two portions (100 mL) of 2 N hydrochloric acid, 100 mL of K_2CO_3 (20%), and water. The organic solution was dried over $MgSO_4$ and evaporated under reduced pressure to give 51.3 g of crude red-brown oil, which was distilled under high vacuum: yield 40.5 g (87%); bp 124–128 °C (0.05 mm). Anal. ($C_{12}H_{17}NO_2$) C, H, N, O.

***N*-Cyclohexyl-2-(4-hydroxy-4-piperidinyl)-*N*-methylpropionamide (10).** A solution of 49 g (0.26 mol) of **9** in 500 mL of acetic acid was hydrogenated in the presence of 5 g of 10% palladium on charcoal at 45 psi and 50 °C over a period of 15 h at which time 1 equiv of hydrogen uptake was completed. The catalyst was filtered, and the filtrate was evaporated under reduced pressure. The oily residue was dissolved in 200 mL of chloroform, and the organic layer was washed with 100 mL of 2 N NaCl and twice with 100 mL of water. The organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure to give 33.9 g (91%) of nearly pure **10**, which was used without further purification in the next step.

***N*-Cyclohexyl-2-[1-(3-methoxyphenethyl)-4-hydroxy-4-piperidinyl]-*N*-methylpropionamide (16).** To a stirring mixture of 12.0 g (0.045 mol) of **10** in 120 mL of dimethylformamide and 12.4 g (0.09 mol) of potassium carbonate was added at 100 °C dropwise a solution of 12.6 g (0.055 mol) of 3-methoxyphenethyl methanesulfonate in 50 mL of dimethylformamide during a period of 1 h. The reaction was stirred for 30 min at 100 °C, cooled to 20 °C, and filtered. The K_2CO_3 was washed with two 50-mL portions of chloroform, and the filtrate was thoroughly evaporated under reduced pressure at 70–80 °C. The residue was taken up in chloroform, the organic layer was washed with two portions of 2 N hydrochloric acid, and the aqueous phase was made alkaline with 2 N NaOH and extracted twice with chloroform. The organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated thoroughly under reduced pressure to give 14.4 g of crude **16**, which was converted to its crystalline hydrobromide from acetone. Recrystallization from acetone/ether resulted in 9.6 g (41.2%) of pure **16**, mp 190–191 °C. Anal. ($C_{24}H_{38}N_2O_3$·HBr) C, H, Br, N, O.

General Examples for the Synthesis of Various Methanesulfonates. 2-Methoxyphenethyl Methanesulfonate.[21a] To a cold (0–5 °C), stirring solution of 18.0 g (0.118 mol) of 2-methoxyphenethyl alcohol[21b] and 19.6 g (0.19 mol) of triethylamine in 180 mL of chloroform was added dropwise a solution of 17.2 g (0.15 mol) of methansulfonyl chloride in 50 mL of chloroform. The mixture was stirred for 15 min at 0–5 °C, transferred to a separatory funnel, and washed with 100 mL of 2 N hydrochloric acid and water. The organic phase was dried over $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure to furnish 26.5 g (97%) of pure ester, which was used in the next step without further purification. A sample was distilled in the Kugelrohr for microanalysis. Anal. ($C_{10}H_{14}O_4S$) C, H, O, S.

***N*,*N*-Bis(2-carbethoxyethyl)-2-chlorophenethylamine (5).** 2-Chlorophenethylamine (311 g 2 mol)[22,23] was added dropwise to a solution of ethyl acrylate (500 g, 5 mol) and acetic acid (15 mL) with stirring over a period of 15–20 min. (The temperature rose to 40 °C, and a white crystalline solid precipitated.) The temperature was then elevated to 60 °C (oil bath, 70 °C), at which time a clear solution was formed again. Stirring was continued for 6 h, and excess ethyl acrylate and acetic acid were thoroughly removed under reduced pressure at 85–95 °C to provide 702 g (98.7%) of almost pure **5**, which was used without further purification in the next step.

1-(2-Chlorophenethyl)-4-piperidinone (6).[24] Sodium (60 g 2.6 mol) was added portionwise, under a dry nitrogen atmosphere and stirring, to 1200 mL of preheated (oil bath, 100 °C) 2-propanol, and the mixture was stirred for 1 h to dissolve all the sodium. Compound **5** (702 g 1.87 mol) was then slowly added under reflux and stirring, and the mixture was refluxed for an additional hour thereafter. The reaction was cooled to 20 °C, and a mixture of 430 mL of water and 860 mL of concentrated hydrochloric acid was carefully added during a period of 1 h (the reaction was slightly exothermic, increasing the temperature to 50 °C). The oil bath temperature was raised to 130 °C, and the 2-propanol–water mixture was partially removed over a mounted distillation head until the carbon dioxide evolution had completely stopped. Water (2 × 250 mL) was added at 1-h intervals, and the distillation was continued until a total of 2 L of solvent (2-propanol–water) within 6 h had been distilled over. The mixture was chilled (ice–water), and 1-L of sodium hydroxide (15%) was added. The solution was transferred to a separatory funnel, and extracted twice with 1 L of chloroform. The organic layer was washed with water several times and dried over $MgSO_4$. Filtration and removal of the solvent in vacuo gave 427 g of oily residue, which was recrystallized from diisopropyl ether to afford 320 g (67%) of **6**, mp 43–44 °C. Anal. ($C_{13}H_{16}ClNO$) C, H, Cl, N, O.

2-[1-(2-Chlorophenethyl)-4-hydroxy-4-piperidinyl]-*N*-cyclohexyl-*N*-methylpropionamide (15). To a stirred solution of 28.5 g (0.28 mol) of DIPA in 400 mL of dry THF cooled to −75 °C and blanketed under a dry nitrogen atmosphere was added dropwise 112 mL (0.28 mol) of *n*-BuLi (2.5 M) in hexane. The mixture was stirred for 15 min at −75 °C, and a solution of 25.0 g (0.15 mol) of *N*-cyclohexyl-*N*-methylpropionamide in 100 mL of dry THF was slowly added over a period of 0.5 h. Stirring was continued for 1 h, and a solution of 32.0 g (0.14 mol) of **6** in 150 mL of dry THF was slowly introduced. The reaction was stirred for 1 h at −75 °C, and the temperature was raised to −20 °C. The mixture was decomposed with a solution of 25 mL of K_2CO_3 (20%), and the organic layer decanted. The residue was triturated with some ether, and the combined organic layer was dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure furnished 60 g of crude **15**, which was crystallized from 300 mL of ethanol containing 15.7 g (1 equiv) of maleic acid. Recrystallization from ethanol gave 42.7 g (78%), mp 159–161 °C, of pure **15**. Anal. ($C_{23}H_{35}ClN_2O_2$·HMl) C, H, Cl, N, O.

2-[4-(Propionyloxy)-1-(2-chlorophenethyl)-4-piperidinyl]-*N*-(2-methoxyphenyl)-*N*-propylpropionamide (23). To a stirring solution of 6.4 g (0.0139 mol) of **48** and 4.0 g (0.039 mol) of triethylamine in 100 mL of dichloromethane was dropwise added a solution of 2.6 g (0.028 mol) of propionyl chloride in 10 mL of dichloromethane at 20 °C. The reaction was refluxed for 2 h, cooled, and transferred to a separatory funnel. The organic solution was washed with a solution of K_2CO_3 (20%) and water, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was taken up in acetone/ether, and the product was crystallized by the addition of 1 equiv of maleic acid. Recrystallization from acetone–ether furnished 5.2 g (59%) of **23**, mp 152–154 °C. Anal. ($C_{29}H_{39}ClN_2O_4$·HMl) C, H, Cl, N, O.

2-[1-(2-Chlorophenethyl)-4-hydroxy-4-piperidinyl]-*N*-cyclohexylpropionamide (34). Compound **11** (11.0 g, 0.028 mol) was heated for 3 h, while stirring at 90–100 °C, in 25 mL (0.218 mol) of cyclohexylamine. The excess cyclohexylamine was re-

moved under reduced pressure, and the dark residue was taken up in 150 mL of chloroform and washed with 20 mL of 2 N sodium hydroxide (to remove phenol) and water. The organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated in vacuo to furnish 12.8 g of crude **34**, which crystallized from ether–pentane to give 8.0 g (72%) of pure **34**, mp 110–111 °C. Anal. ($C_{22}H_{33}ClN_2O_2$) C, H, Cl, N, O.

2-[1-(2-Chlorophenethyl)-4-hydroxy-4-piperidinyl]-*N*-(2-methoxyphenyl)propionamide (44). To a stirred solution of 30.3 g (0.3 mol) of DIPA in 450 mL of dry THF, which was cooled to −20 °C and blanketed with a dry nitrogen atmosphere, was added dropwise 190 mL (0.3 mol) of *n*-BuLi (1.6 M) in hexane. The reaction was stirred for 15 min, and a solution of sodium *N*-(2-methoxyphenyl)propionamide (0.15 mol), freshly prepared from 27 g (0.15 mol) of *N*-(2-methoxyphenyl)propionamide and 8.0 g of sodium hydride (0.16 mol), in 250 mL of dry THF was dropwise added within 10–15 min at −20 °C. The reaction was stirred for 30 min, and a solution of 23.8 g (0.1 mol) of **6** in 250 mL of dry THF was slowly introduced over a period of 3 h. The reaction was allowed to stir for 30 min at −20 °C, and a solution of 100 mL of K_2CO_3 (20%) was then added. The solvent was decanted, the residue was dried over $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure. The product was dissolved in 400 mL of dichloromethane, and the organic phase was extracted with 100 mL of 2 N hydrochloric acid (**44** remains in the organic layer) and washed with a solution of K_2CO_3 (20%) and water. The organic solution was dried over $MgSO_4$ and filtered, the filtrate was evaporated under reduced pressure, and the residue was purified by passing it through a column of silica gel (Merck 60, 70–230 mesh ASTM). Elution with CH_2Cl_2 and CH_2Cl_2 + 2% MeOH furnished 22.8 g (54.8 g) of almost pure **44**, which crystallized as the fumarate from acetone. Recrystallization from acetone gave 20.4 g (38%) of **44**, mp 111–113 °C. Anal. ($C_{23}H_{29}ClN_2O_3$·HFu) C, H, Cl, N, O.

***N*-Allyl-2-[1-(2-chlorophenethyl)-4-hydroxy-4-piperidinyl]-*N*-(2-methoxyphenyl)propionamide (46).** To a stirring solution of 6.2 g (0.015 mol) of **44** in 80 mL of dry THF, blanketed with dry nitrogen, was added at once 0.8 g of sodium hydride (50% oil suspension) (0.015 mol). The reaction was stirred for 1 h at 20 °C, cooled in an ice bath, and treated dropwise with 1.4 mL (0.0165 mol) of allyl bromide in 20 mL of dry THF. The mixture was stirred for 24 h at 20 °C, and slowly decomposed with a solution of 5 mL of K_2CO_3 (20%). The solvent was decanted, the residue was triturated with some THF, the combined organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on Merck silica gel 60 (70–230 mesh, ASTM). Elution with CH_2Cl_2 and CH_2Cl_2 + 5% MeOH furnished 5.2 g of almost-pure **46**, which crystallized as the hydrogen fumarate from ethanol–ether. Recrystallization from ethanol–ether gave 5.1 g (60%) of **46**, mp 173–174.5 °C. Anal. ($C_{26}H_{33}ClN_2O_3$·HFu) C, H, Cl, N, O.

Resolution of Methyl 2-[1-(2-Chlorophenethyl)-4-hydroxy-4-piperidinyl]propionate (12). Compound **12** (222.1 g, 0.68 mol) and (−)-dibenzoyltartaric acid (256 g, 0.68 mol) were dissolved under heating on the steam bath, the resulting solution was filtered, and the filtrate was allowed to stand at 20 °C for 60 h. **13** (−)-dibenzoyltartrate (224.7 g, 96%), mp 142–144 °C, $[\alpha]^{20}_D$ +59.7°, was collected and recrystallized three times from ethanol: yield 170 g (73%); mp 149–151 °C; $[\alpha]^{20}_D$ +71.4° (*c* 1, MeOH). Anal. ($C_{17}H_{24}ClNO_3$·$C_{18}H_{14}O_8$) C, H, Cl, N, O. The product was dissolved in chloroform, and the organic layer was washed with a solution of K_2CO_3 (20%) and water. The organic solution was dried over $MgSO_4$ and filtered, and the filtrate was thoroughly evaporated under reduced pressure to furnish 60 g (74%) of **13** free base as a colorless oil: $[\alpha]^{20}_D$ +11.9° (*c* 1, $CHCH_3$).

In a similar fashion, the resolution of 110.8 (0.34 mol) of crude **14** with 128 g (0.34 mol) of (+)-dibenzoyltartaric acid in 850 mL of ethanol gave 177.1 g (76.3%) of **14** (+)-dibenzoyltartrate, mp 147–148.5 °C; $[\alpha]^{20}_d$ −61° (*c* 1, MeOH). Four recrystallizations from ethanol resulted in a yield of 135 g (58%): mp 150–151 °C; $[\alpha]^{20}_D$ −71.8° (*c* 1, MeOH). Anal. ($C_{17}H_{24}ClNO_3$·$C_{18}H_{14}O_8$) C, H, Cl, N, O. The product was dissolved in chloroform and washed with a solution of K_2CO_3 (20%) and water. The organic phase was dried over $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure to furnish 53 g (47.8%) of **14** free base as a yellowish oil: $[\alpha]^{20}_d$ −12.1° (*c* 1, $CHCl_3$).

(+)-2-[1-(2-Chlorophenethyl)-4-hydroxy-4-piperidinyl]-*N*-cyclohexyl-*N*-methylpropionamide (52). To 6.45 g (0.265 mol) of magnesium turnings blanketed with a dry nitrogen atmosphere was added dropwise a solution of 35.7 g (0.327 mol) of ethyl bromide in 100 mL of dry THF so as to maintain the temperature between 50 and 60 °C. The mixture was refluxed for 0.5 h and then cooled to 30 °C. A solution of 29.9 g (0.256 mol) of *N*-cyclohexyl-*N*-methylamine in 100 mL of dry THF was then slowly added to the stirred Grignard solution, and the resulting amide was stirred for 1 h at 20–25 °C. Compound **13** (28.8 g 0.089 mol) in 120 mL of dry THF was then added dropwise within a period of 15–20 min, and the reaction was stirred for 3 h at 65 °C (oil bath, 75 °C). The mixture was chilled to 10 °C and decomposed by adding dropwise 20 mL of a 10% solution of ammonium chloride. The organic phase was diluted with some ether and filtered over a small amount of hyflo super cel (Fluka) (to remove inorganic material), and the filtrate was evaporated under reduced pressure to give 33 g of crude **52**, which was converted to a crystalline maleate from ethanol–ether. Recrystallization from 2-propanol several times gave 14.5 g (31.6%) of pure **52**, mp 115–117 °C; $[\alpha]^{20}_D$ +26.4° (c 1, $CHCl_3$). Free base: $[\alpha]^{20}_D$ +8.6° (*c* 1, MeOH). Anal. ($C_{23}H_{35}ClN_2O_2$·HMl) C, H, Cl, N, O.

Similarly prepared was **(−)-2-[1-(2-chlorophenethyl)-4-hydroxy-4-piperidinyl]-*N*-cyclohexyl-*N*-methylpropionamide (53)** from 25.2 g (0.078 mol) of **14** and bromomagnesium *N*-cyclohexylmethylamide (0.234 mol) in dry THF for 3 h at 65 °C, which after the usual workup gave 14.8 g (35%) of pure **53** as the maleate, mp 115–116 °C; $[\alpha]^{20}_D$ −26.5° (*c* 1, $CHCl_3$). Free base: $[\alpha]^{20}_D$ −8.0° (*c* 1, MeOH). Anal. ($C_{23}H_{35}ClN_2O_2$·HMl) C, H, Cl, N, O.

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Registry No. 1, 3612-20-2; I (R_3 = Me; R_4 = H; R_5 = Me-N-cHx), 78021-83-7; I (R_3 = Me; R_4 = H; R_5 = N(Et)C_6H_4-*o*-OMe), 83604-65-3; I (R_3, R_4 = H; R_5 = Me-N-cHx), 41273-78-3; I (R_3 = Bu; R_4 = H; R_5 = Me-N-cHx), 78021-87-1; I (R_3, R_4 = Me; R_5 = Me-N-cHx), 78021-85-9; I (R_3, R_4 = $(CH_2)_4$; R_5 = Me-N-cHx), 78021-88-2; I (R_3, R_4 = $(CH_2)_2$; R_5 = Me-N-cHx), 83605-18-9; I (R_3 = Me; R_4 = H; R_5 = NHBu), 2955-67-1; I (R_3 = Me; R_4 = H; R_5 = NH-cHx), 1126-56-3; I (R_3 = Me; R_4 = H; R_5 = Pr-N-cHx), 83605-19-0; I (R_3 = Me; R_4 = H; R_5 = allyl-N-cHx), 83605-20-3; I (R_3 = Me; R_4 = H; R_5 = N,N-cHx_2), 20857-77-6; I (R_3 = Me; R_4 = H; R_5 = *t*-Bu-N-cHx), 78021-84-8; I (R_3 = Me; R_4 = H; R_5 = N,N-Bu_2), 1187-33-3; I (R_3 = Me; R_4 = H; R_5 = Me-N-C_6H_4-*o*-OMe), 38824-34-9; I (R = Me; R_4 = H; R_5 = Me-N-C_6H_4-*o*-OEt), 83605-21-4; I (R = Me; R_4 = H; R_5 = Me-N-C_6H_4-*p*-Cl), 83605-22-5; I (R = Me; R_4 = H; R_5 = Me-N-C_6H_4-*m*-OMe), 83605-23-6; I (R = Me; R_4 = H; R_5 = NH-C_6H_4-*o*-OMe), 7157-34-8; I (R_3 = Me; R_4 = H; R_5 = Me-N-C_6H_4-*m*-OH), 83605-24-7; I (R_3 = Me; R_4 = H; R_5 = allyl-N-C_6H_4-*o*-OMe), 83605-25-8; I (R_3 = Me; R_4 = H; R_5 = Pr-N-C_6H_4-*o*-OMe), 83605-26-9; I (R_3 = Me; R_4 = H; R_5 = CH_2CCH-N-C_6H_4-*o*-OMe), 83605-27-0; I (R_3 = Me; R_4 = H; R_5 = Et-N-C_6H_4-*o*-OEt), 83605-28-1; I (R_3 = Me; R_4 = H; R_5 = Pr-N-C_6H_4-*o*-OEt), 83605-29-2; I (R_3 = *i*-Pr; R_4 = H; R_5 = Me-N-cHx), 78021-86-0; I (R_3, R_4 = Me; R_5 = NH-C_6H_4-*o*-OMe), 71182-38-2; **5**, 83605-17-8; **6**, 39742-61-5; **8**, 19343-15-8; **9**, 83604-64-2; **9**·HCl, 83604-66-4; **10**, 78021-68-8; **11**·HCl, 55313-35-4; **12**·HMl, 83604-68-6; (+)-**13** (−)-dibenzoyltartrate, 83604-70-0; (+)-**13**, 83604-69-7; (−)-**14**, 83604-71-1; (−)-**14** (+)-dibenzoyltartrate, 83604-72-2; **15**, 55313-67-2; **15**·HMl, 55313-68-3; **16**, 83615-43-4; **16**·HBr, 83604-73-3; **17**·HCl, 63208-06-0; **18**·HCl, 63208-11-7; **19**·HCl, 83604-74-4; **20**·HFu, 83604-76-6; **21**·HBr, 83604-77-7; **22**·HFu, 83604-79-9; **23**, 83604-80-2; **23**·HMl, 83604-81-3; **24**·HCl, 83604-82-4; **25**·HCl, 83604-83-5; **26**·HFu, 63208-18-4; **27**·HBr, 63208-16-2; **28**·CH_3SO_3H, 83604-84-6; **29**·HFu, 83604-86-8; **30**·HCl, 83604-87-9; **31**·0.5Fu, 63208-20-8; **32**·HFu, 63208-13-9; **33**·HMl, 55313-62-7; **34**, 63208-02-6; **35**·HMl, 83604-89-1; **36**·0.5-naphthalenedisulfonic acid, 83604-63-1; **37**·HMl, 63208-05-9; **38**·HCl, 63208-08-2; **39**·HFu, 83604-90-4; **40**·HFu, 83604-92-6; **41**·HMl, 83604-94-8; **42**·HFu, 83604-96-0; **43**·HFu, 83604-98-2; **44**, 83604-99-3; **44**·HFu, 83605-00-9; **45**, 83605-01-0; **46**, 83605-02-1; **46**·HFu, 83605-03-2; **47**·HMl,

83605-05-4; **48**·HFu, 83605-07-6; **49**·HFu, 83605-09-8; **50**·HMl, 83605-11-2; **51**·0.5-napthalenedisulfonic acid, 83615-42-3; (+)-**52**, 83605-12-3; (−)-**52**, 83605-14-5; (+)-**52**·HMl, 83605-13-4; (−)-**53**·HMl, 83605-15-6; phenyl propionate, 637-27-4; methyl propionate, 554-12-1; *N*-ethyl-2-methoxyaniline, 15258-43-2; propionyl chloride, 79-03-8; 3-methoxyphenethyl methanesulfonate, 40759-46-4; 2-methoxyphenethyl methanesulfonate, 83605-16-7; 2-methoxyphenethyl alcohol, 7417-18-7; ethyl acrylate, 140-88-5; 2-chlorophenethylamine, 13078-80-3; cyclohexylamine, 108-91-8; allyl bromide, 106-95-6.

Analogues of Aminoglutethimide: Selective Inhibition of Cholesterol Side-Chain Cleavage

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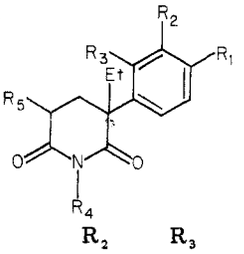
In our probing of the structural features responsible for the inhibitory activity of aminoglutethimide [**1**, 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione] toward the cholesterol side-chain cleavage enzyme system desmolase and the estrogen-forming system aromatase, targets in the action of **1** against hormone-dependent mammary tumors, analogues in several categories have been synthesized and evaluated. Of the known monoamino derivatives, the meta derivative [**2**, 3-(3-aminophenyl)-3-ethylpiperidine-2,6-dione] was as inhibitory toward desmolase as **1**, and the *N*-amino analogue [**4**, 1-amino-3-ethyl-3-phenylpiperidine-2,6-dione] was three times as inhibitory (respective K_i values of **1**, **2**, and **4** are 14, 13, and 4.6 μM), but **2** was a weak inhibitor and **4** was a noninhibitor of aromatase. Another amino analogue [**5**, 5-amino-3-ethyl-3-phenylpiperidine-2,6-dione] inhibited neither enzyme system. Reaction of glutethimide (**11**) with hydrazine and thermal cyclization of the resulting amide hydrazide (**15**) afforded an improved synthesis of **4**. Analogues having a second amino substituent, either at C-5 (**10**) or at N-1 (**14**) of the piperidine-2,6-dione residue, were less inhibitory than was **1** toward desmolase and aromatase. Among analogues having little or no inhibitory activity were hydroxy derivatives of **1** and **2**, namely, 3-(4-amino-3-hydroxyphenyl)-3-ethylpiperidine-2,6-dione (**20**) and the 3-amino-4-hydroxy analogue (**21**).

Aminoglutethimide [**1**, 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione] was patented in 1958[2] as an anticonvulsant drug but was withdrawn in 1966, mainly because it caused adrenal insufficiency.[3] Because it inhibited adrenal steroidogenesis, **1** has found use as an alternative



	R_1	R_2	R_3	R_4	R_5
1	NH_2	H	H	H	H
2	H	NH_2	H	H	H
3	H	H	NH_2	H	H
4	H	H	H	NH_2	H
5	H	H	H	H	NH_2
6	NO_2	H	H	H	H
11	H	H	H	H	H
12	H	NO_2	H	H	H
13	H	H	NO_2	H	H
16	$NHCOCH_3$	H	H	H	H
17	NHCHO	H	H	H	H
18	OH	H	H	H	H
19	OH	NO_2	H	H	H
20	NH_2	OH	H	H	H
21	OH	NH_2	H	H	H

to adrenalectomy in the treatment of metastatic breast carcinoma.[4,5] The drug inhibits several steps in the pathways of steroidogenesis, of which the principal ones appear to be conversion of cholesterol into pregnenolone[3] (mediated by desmolase) and of androstenedione and testosterone into estrone and estradiol[6] (mediated by aromatase). It is not clear which of these two major inhibitory activities of **1** is most important in determining clinical response. Blockade of the desmolase step in humans appears to be incomplete, since levels of Δ^4-steroids (progesterone, 17α-hydroxyprogesterone, and androstenedione) are actually enhanced during the first 2 weeks of therapy and are only latterly depressed below basal levels.[7] The fall in estrogens (estrone and estradiol) is immediate, and it may be that this effect on the aromatase system is the clinically relevant action, since estrogens may well be of greater relevance to tumor growth in vivo than other steroids. However, it has been suggested[7] that the initial increase in Δ^4-steroids results from a stimulation of the action of the 3β-ol dehydrogenase Δ^5–Δ^4-isomerase complex by the drug, resulting in preferential conversion of Δ^5-steroid precursors into progesterone, and further,[8] that the resulting combined effects of estrogen suppression and androgen preservation both contribute to tumor regression, since, in postmenopausal women, androgen administration may ameliorate growth of breast carcinomas.[9] Comparison of **1** and its analogues with 4-hydroxyandrostenedione[10] and its congeners having activity against aromatase but

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