Synthetic Analgesics. Synthesis and Pharmacology of the Diastereoisomers of *N*-[3-Methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide and *N*-[3-Methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide

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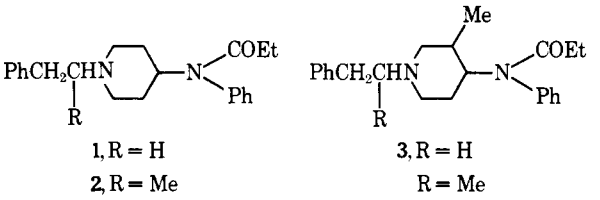
The synthesis of the respective diastereoisomers and enantiomers of *N*-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide and *N*-[3-methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide is reported. Analgesic activity is evaluated in the tail withdrawal test in rats. *cis*-(+)-*N*-[3-Methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (**23**) is found to be an extremely potent analgesic, up to 6684 times morphine. Compound **23** has a fast onset of action, a shorter duration of action than morphine, and an unusually high safety margin.

As part of a continuing effort to develop novel analgesic agents a series of methyl-substituted derivatives of fentanyl (**1**) was prepared. Fentanyl, a well-known analgesic characterized by high potency, a rapid onset, and short duration of action,[1,2] belongs to a series *N*-[1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamides.[3] At the time of the peak effect (Table IV) **1** is about 300 times more potent than morphine in the tail withdrawal test in rats.[4] It is known that methyl substitution in the side chain α to the basic nitrogen of **1** (compound **2**) enhances the analgesic activity.[3] On the other hand, the activity-enhancing effects of 3-methyl substitution in the piperidine ring of 4-phenylpiperidine analgesics are well documented.[5-8]

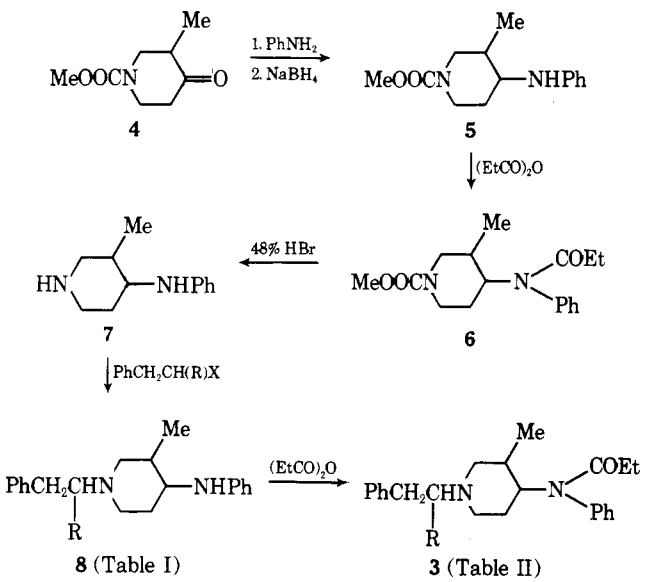
These considerations have led to synthesis of the different diastereoisomers and enantiomers of *N*-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (**3**, R = H) and *N*-[3-methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (**3**, R = Me). The recent publication of Riley, *et al.*,[9] has prompted us to report our results.



1, R = H; **2**, R = Me; **3**, R = H; R = Me

Chemistry. The synthesis is outlined in Scheme I. Formation of the Schiff base of methyl 3-methyl-4-oxopiperidinecarboxylate[10] with aniline followed by reduction with $NaBH_4$ afforded an approximately 7:3 mixture of *cis*- and *trans*-methyl 3-methyl-4-(phenylamino)-1-piperidinecarboxylate (**5**). Propionylation of **5**, with propionic anhydride in PhMe under reflux, yielded crystalline methyl 3-methyl-4-[*N*-(1-propionoxy)-*N*-phenylamino]-1-piperidinecarboxylate (**6**), which was separated in its respective cis and trans diastereoisomers **6a** and **6b** by fractional crystallization from *i*-Pr_2O–*i*-PrOH.

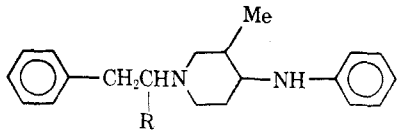
Scheme I



Attempts to remove the *N*-carbomethoxy group of **6** selectively under either acidic or basic conditions were unsuccessful. Brief treatment of **6a** and **6b** with 48% HBr under reflux afforded the corresponding *cis*- and *trans*-3-methyl-*N*-phenylpiperidineamines **7a** and **7d**. Fractional crystallization of the *d*-tartaric acid salt of *cis*-(±)-**7a** from Me_2CO–MeOH and subsequent conversion to free base gave optically pure *cis*-(−)-**7b**. Similarly, fractional crystallization of the *l*-tartaric acid salt of *cis*-(±)-**7a** from Me_2CO–MeOH and subsequent conversion to free base afforded corresponding *cis*-(+) derivative **7c**. Since *trans*-(±)-**21**, prepared from *trans*-(±)-**7d**, is at least five times less active than corresponding *cis*-(±)-**20**, prepared from *cis*-(±)-**7a**, resolution of trans-(±)-**7d** was not further investigated at this stage of the study.

Substitution of the respective 3-methylpiperidineamines (**7a–d**) with 2-phenylethyl chloride or preferably 2-phenylethyl bromide yielded corresponding 3-methyl-1-(2-phenylethyl)-*N*-phenyl-4-piperidineamines **8** respectively *cis*-(±)-**9**, *cis*-(−)-**11**, *cis*-(+)-**12**, and *trans*-(±)-**10** (Table I). Treatment of compounds **9–12** with propionic anhydride in PhMe under reflux afforded respectively end products *cis*-(±)-**20**, *trans*-(±)-**21**, *cis*-(−)-**22**, and *cis*-(+)-**23** (Table II). Oxalates of **22** and **23a** were difficult to crystallize; therefore, the most active enantiomer *cis*-(+)-**23** was crystallized as nitrate salt **23b**, which cocrystallized with 1 mol of *i*-PrOH. Structure assignment for **20** and **21** was made on the basis of the 100-MHz nmr spectrum. Assuming a chair conformation for the piperidine ring, one would expect that the most predominant conformer would have an equatorial 4-N(COEt)Ph group with an equatorial 3-Me group for the trans compound and an axial 3-Me group for the cis compound. This was confirmed by the splitting pattern of the 4-proton on the piperidine ring. Cis compound **20** showed a multiplet, centered at δ 4.40, consisting of a doublet (J = 12.5 Hz) of triplets (J = 5 Hz). On the other hand, trans compound **21** showed a multiplet, centered at δ 4.53, consisting of a triplet (J = 12.5 Hz) of doublets (J = 4.5 Hz). *cis*-*N*-[3-Methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamides were prepared by substitution of **7a** with 1-methyl-2-phenylethanol methanesulfonate in boiling *i*-BuCOMe in the presence of Na_2CO_3, affording a diastereoisomeric

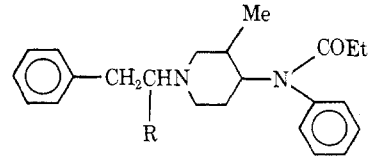
Table I. 3-Methyl-1-(1-R-2-phenylethyl)-*N*-phenyl-4-piperidineamines



Compd	R	$[\alpha]^{25}D$,[a] deg	Crystn solvent[b]	Yield purified, %	Mp, °C	Formula
cis-(±)-**9**	H		A	61	254–255	$C_{20}H_{26}N_2 \cdot 2HCl$[c]
trans-(±)-**10**	H		B	80	168–169	$C_{20}H_{26}N_2 \cdot C_2H_2O_4$[c]
cis-(−)-**11**	H	−46.7		77		$C_{20}H_{26}N_2$[d,e]
cis-(+)-**12**	H	+46.2		59		$C_{20}H_{26}N_2$[d,f]
cis-(±)-**13**	Me		A	92	169–171	$C_{21}H_{28}N_2 \cdot 2HCl$[c]
K_1-*cis*-(±)-**14**	Me		C	66[h]	256–257	$C_{21}H_{28}N_2 \cdot 2HCl$[g]
K_1-*cis*-(±)-**15**	Me		C	72[h]	274–275	$C_{21}H_{28}N_2 \cdot 2HCl$[g]
K_1-*cis*-(−)-**16**	Me	−57.0	A	64[h]	258–259	$C_{21}H_{28}N_2 \cdot 2HCl$[g]
K_2-*cis*-(−)-**17**	Me	−33.2	A	72[h]	276–277	$C_{21}H_{28}N_2 \cdot 2HCl$[g]
K_1-*cis*-(+)-**18**	Me	+58.1	C	66[h]	253–255	$C_{21}H_{28}N_2 \cdot 2HCl$[g]
K_2-*cis*-(+)-**19**	Me	+32.5	A	70[h]	273–276	$C_{21}H_{28}N_2 \cdot 2HCl$[g]

[a] l = 10 cm, c 4% in MeOH. [b] A = *i*-Pr_2O–*i*-PrOH; B = *i*-PrOH–Me_2CO; C = *i*-PrOH. [c] *Anal.* C, H, N. [d] Oil. [e] Glc 99.1%. [f] Glc 98.5%. [g] *Anal.* Cl. [h] Assuming that **13** contains a 1:1 ratio of K_1 and K_2.

Table II. *N*-[3-Methyl-1-(1-R-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamides



Compd	R	$[\alpha]^{25}D$,[a] deg	Crystn solvent[b]	Yield purified, %	Mp, °C	Formula[c]
cis-(±)-**20**	H		A	64	163–164	$C_{23}H_{30}N_2O \cdot C_2H_2O_4$
trans-(±)-**21**	H		A	41	159–160	$C_{23}H_{30}N_2O \cdot C_2H_2O_4$[d]
cis-(−)-**22**	H	−6.1	A	46	111–112	$C_{23}H_{30}N_2O \cdot C_2H_2O_4$
cis-(+)-**23a**	H	+7.04	A	59	105–106	$C_{23}H_{30}N_2O \cdot C_2H_2O_4$
cis-(+)-**23b**	H	+1.0	B	67	95–96	$C_{23}H_{30}N_2O \cdot C_3H_7OH \cdot HNO_3$
cis-(±)-**24**	Me		C	34	237–238	$C_{24}H_{32}N_2O \cdot HCl$
K_1-*cis*-(±)-**25**	Me		C	86	260–261	$C_{24}H_{32}N_2O \cdot HCl$[e]
K_2-*cis*-(±)-**26**	Me		C	38	269–270	$C_{24}H_{32}N_2O \cdot HCl$
K_1-*cis*-(+)-**27**	Me	+18.1	C	42	214–215	$C_{24}H_{32}N_2O \cdot HCl$
K_2-*cis*-(−)-**28**	Me	−12.1	C	29	118–119	$C_{24}H_{32}N_2O \cdot HCl$[f]
K_1-*cis*-(−)-**29**	Me	−17.3	C	48	213–214	$C_{24}H_{32}N_2O \cdot HCl$
K_2-*cis*-(+)-**30**	Me	+10.62	C	56	132–133	$C_{24}H_{32}N_2O \cdot HCl$[g]

[a] l = 10 cm, c 4% in MeOH. [b] A = *i*-PrOH–Me_2CO; B = *i*-PrOH; C = *i*-Pr_2O–*i*-PrOH. [c] *Anal.* C, H, N. [d] C: calcd, 68.16; found, 67.72. [e] C: calcd, 71.88; found, 71.35. [f] C: calcd, 71.88; found, 71.28. [g] C: calcd, 71.88; found, 71.19.

mixture (± 1:1) of *cis*-3-methyl-1-(1-methyl-2-phenylethyl)-*N*-phenylpiperidineamine (**13**). Attempts to separate the mixture by fractional crystallization or with the aid of column chromatography failed, partly owing to instability of dihydrochloride salt **13**. However, separation was effected by countercurrent distribution between aqueous buffer at pH 2.6 (upper phase) and $CHCl_3$ (lower phase). After 5000 transfers a distribution r max$_1$ 3140 (K_1 = 1.702) and r max$_2$ 3360 (K_2 = 2.055), β = 1.21, was obtained.† Compounds **14** and **15** and their respective derivatives were termed K_1 and K_2 according to the distribution constants. Spectral data did not show enough characteristic differences to allow unequivocal structure assignment. Propionylation of **14** and **15** afforded respectively end products K_1-*cis*-(±)-**25** and K_2-*cis*-(±)-**26** (Table II).

The enantiomers of **25** and **26** were prepared starting from *cis*-(−)- and *cis*-(+)-3-methyl-*N*-phenyl-4-piperidineamine (**7b** and **7c**). Substitution with 1-methyl-2-phenylethanol methanesulfonate, followed by separation *via* countercurrent distribution, afforded respectively K_1-*cis*-(−)-**16** and K_2-*cis*-(−)-**17** (from **7b**), and K_1-*cis*-(+)-**18** and K_2-*cis*-(+)-**19** (from **7c**, Table I). Propionylation of **16**–**19** yielded respectively end products K_1-*cis*-(+)-**27**, K_2-*cis*-(−)-**28**, K_1-*cis*-(−)-**29**, and K_2-*cis*-(+)-**30** (Table II).

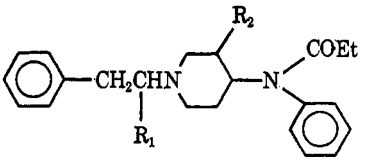
Pharmacology. Female Wistar rats of 200 ± 5 g of body weight were used. The analgesic activity was assessed by measuring the warm water induced tail withdrawal reflex,[3,11] after iv administration of the compounds to be tested. ED_{50} values and 95% fiducial limits for pronounced analgesia (reaction time >10 sec) were calculated by the method of Litchfield and Wilcoxon.[12] LD_{50} values were determined after iv injection (0.2 ml/100 g of body weight over a period of 5 sec).

Results and Discussion

All compounds tested showed a typical morphine-like profile. ED_{50} values for the all or none effect of pronounced analgesia are given in Table III. Introduction of a methyl group in the 3 position of the piperidine ring of fentanyl (**1**) enhances analgesic activity. Trans compound **21** is somewhat more potent than fentanyl (**1**). However, the corresponding cis diastereoisomer **20** is approximately eight times more active than **1**. Analgesic activity of **20**

†Countercurrent distributions were performed at the University of Gent.

Table III. Analgesic Activity. Tail Withdrawal Rats



Compd	R_1	R_2	Config[a]	n[b]	ED_{50}[c] (confidence limits)
1	H	H		303	0.011 (0.0095–0.0140)
2	Me	H	(±)	30	0.0085 (0.0067–0.0108)
20	H	Me	(±)-*cis*	30	0.0018 (0.0013–0.0024)
21	H	Me	(±)-*trans*	30	0.0094 (0.0070–0.0127)
22	H	Me	(−)-*cis*	30	0.068 (0.051–0.091)
23b	H	Me	(+)-*cis*	217	0.00058 (0.00049–0.00068)
24	Me	Me	(±)-*cis*	30	0.0018 (0.0013–0.0024)
25	Me	Me	(±)-K_1-*cis*	30	0.0027 (0.0019–0.0038)
26	Me	Me	(±)-K_2-*cis*	30	0.0021 (0.0015–0.0029)
27	Me	Me	(+)-K_1-*cis*	30	0.048 (0.037–0.061)
28	Me	Me	(−)-K_2-*cis*	30	0.056 (0.041–0.076)
29	Me	Me	(−)-K_1-*cis*	30	0.00075 (0.00054–0.00101)
30	Me	Me	(+)-K_2-*cis*	30	0.0011 (0.00077–0.0014)

[a]See Experimental Section. [b]Number of animals. [c]mg/kg iv, reaction time >10 sec.

Table IV. ED_{50} Values at Different Time Intervals after Iv Injection in the Tail Withdrawal Test in Rats

Compd		Hr after iv injection									
		1/32	1/16	1/8	1/4	1/2	1	2	4	6	8
23b	ED_{50}[a]	0.00095	0.00076	0.00066	0.00067	*0.00065*	0.00113	0.00322	0.0090	0.0268	0.0600
	L.L.[b]	0.00077	0.00061	0.00046	0.00052	0.00048	0.00086	0.00269	0.0070	0.0191	0.0461
	U.L.[c]	0.00115	0.00094	0.00091	0.00085	0.00087	0.00146	0.00385	0.0116	0.0376	0.0781
Fentanyl	ED_{50}[a]	0.0135	0.0119	*0.0114*	0.0138	0.0232	0.0458	0.168	0.920	1.670	3.070
	L.L.	0.0117	0.0101	0.0098	0.0121	0.0194	0.0391	0.130	0.708	1.289	1.988
	U.L.	0.0156	0.0141	0.0133	0.0157	0.0278	0.0536	0.217	1.195	2.164	4.741
Morphine	ED_{50}[a]	6.35	4.60	3.80	3.63	*3.15*	4.61	7.60	30.0	80.0	103
	L.L.	5.28	3.54	3.25	3.05	2.82	3.51	6.17	22.2	36.1	49.4
	U.L.	7.63	5.97	4.45	4.32	3.52	6.06	9.36	40.5	177	215
Pethidine	ED_{50}[a]	7.00	*6.17*	6.20	7.00	10.8	27.9	>40	>40	>40	>40
	L.L.	5.71	4.06	4.13	5.58	8.57	21.4				
	U.L.	8.58	9.39	9.31	8.78	13.6	36.4				
		Potency Ratio									
Morphine		1	1	1	1	1	1	1	1	1	1
Pethidine		0.907	0.746	0.613	0.519	0.292	0.165	<0.190	<0.750	<2.00	<2.58
Fentanyl		470	387	333	263	136	101	45.2	32.6	47.9	33.6
23b		6684	6053	5758	5418	4846	4080	2360	3333	2985	1717

[a]Italized data represent lowest ED_{50} in mg/kg. [b]L.L. = lower limit in mg/kg. [c]U.L. = upper limit in mg/kg.

resides as expected mainly in one enantiomer, namely cis-(+) compound **23b**, which is approximately 16 times more potent than fentanyl, while its cis-(−) counterpart **22** is some 120 times less potent than **23**. It is of interest to know the absolute configuration of **23b**. Preliminary observations, based upon the method of Cervincka[13] applied on one of the precursors, seem to indicate a 3-*S*,4-*R* configuration.‡ *cis*-(±)-*N*-[3-Methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (**24**), with an additional methyl group in the side chain α to the basic nitrogen, does not show the same enhancement of activity as for **2** in comparison with **1**; **24** has the same activity as **20**. Moreover, the respective diastereoisomers **25** and **26** do not show any appreciable difference in analgesic potency. The analgesic activity of **25** and **26** resides also mainly in one enantiomer, **29** and **30**. The only difference between K_1 and K_2 compounds seems to be duration of action. K_2 compounds **26** and **30** are somewhat longer acting than their respective counterparts **25** and **29**. On the basis of these data **23b** was selected for further investigation. ED_{50} values at different time intervals after iv injection were determined for **23b**, in comparison with fentanyl (**1**), morphine, and pethidine (Table IV). Compound **23b** reaches a peak effect (lowest ED_{50} value) after 7.5 min; the peak effect lasts until 30 min after administration. Fentanyl, morphine, and pethidine reach a peak effect after 7.5, 30, and 3.75 min, respectively. Relative potency ratios (morphine = 1) are given for each time interval (Table IV). LD_{50} values, after iv injection, and safety margins in acute experiments in rats (expressed by the ratios LD_{50}/lowest ED_{50} in the tail withdrawal test) are summarized in Table V. Compound **23b** has a six times higher safety margin than fentanyl and a 22 times higher safety margin than morphine.

It can be concluded that *cis*-(+)-*N*-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (**23**) is an extremely potent analgesic agent, up to 6684 times morphine. Compound **23** has a fast onset of action, a shorter duration of action than morphine, and an unusually high safety margin.

‡Unpublished results.

Experimental Section

Melting points were taken on a Tottoli melting point apparatus and are uncorrected. All compounds were routinely checked for their structure by uv and ir spectrometry (uv, Beckman DK-2A; ir, Perkin-Elmer 421). Nmr spectra were recorded by means of a Bruker HX-60 spectrometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Where analyses are indicat-

Table V. LD_{50} Values after IV Injection in Rats[a]

Compd	LD_{50}	L.L.	U.L.	Safety margin[b]
23b	1.08	0.80	1.47	1:1662
Fentanyl	2.91	2.31	3.67	1:255
Morphine	238	108	523	1:75.6
Pethidine	30.2	26.0	35.0	1:4.89

[a] 0.2 ml/100 g of body weight over a period of 5 sec. [b] LD_{50}/lowest ED_{50}.

ed by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Methyl 3-Methyl-4-(phenylamino)-1-piperidinecarboxylate (5). A mixture of methyl 3-methyl-4-oxo-1-piperidinecarboxylate (4) (32 g, 0.187 mol), $PhNH_2$ (22 g, 0.21 mol), and a few crystals of TsOH in PhMe (160 ml) was refluxed for 3 hr and the H_2O collected with the aid of a Dean-Stark trap. The mixture was allowed to cool and the solvent removed *in vacuo*. The residue was distilled *in vacuo* to afford methyl 3-methyl-4-phenylimino-1-piperidinecarboxylate **4a** (38 g, 82.5%): bp 149–158° (0.1–0.4 mm). *Anal.* ($C_{14}H_{18}N_2O_2$) N. To a solution of **4a** (38 g, 0.154 mol) in MeOH (130 ml) was added in small portions $NaBH_4$ (5.3 g, 0.141 mol) and the mixture was warmed at 50° for an additional 60 min. H_2O (70 ml) was added dropwise; the mixture was concentrated to a volume of about 100 ml and extracted with PhMe. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was distilled *in vacuo* to give **5** (35 g, 91.52%): bp 171–172° (0.1–0.15 mm). *Anal.* ($C_{14}H_{20}N_2O_2$) N. Compound **5** consisted of an approximately 7:3 mixture of cis and trans diastereoisomers, based upon the crude yield of *cis*-**6a** and *trans*-**6b** obtained by propionylation of **5**.

***cis*- and *trans*-Methyl 3-Methyl-4-[*N*-(1-propionoxy)-*N*-phenylamino]-1-piperidinecarboxylate (6a,b).** A solution of **5** (248.3 g, 1 mol) and propionic anhydride (198 g, 1.39 mol) was stirred and refluxed overnight. The reaction mixture was allowed to cool, alkalized with dilute NaOH solution, and washed with H_2O. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. Fractional crystallization from *i*-PrOH–*i*-Pr_2O (1:1) afforded **6a** (214 g, 70.3%) and **6b** (29 g, 9.5%). Recrystallization afforded pure **6a**: mp 153–154°. *Anal.* ($C_{17}H_{24}N_2O_3$) C, H, N. Pure **6b** was obtained similarly: mp 133–134°. *Anal.* ($C_{17}H_{24}N_2O_3$) C, H, N.

***cis*-(±)-3-Methyl-*N*-phenyl-4-piperidineamine Hydrochloride (7a).** A mixture of **6a** (130 g, 0.427 mol) and 48% aqueous HBr (750 ml) was refluxed for 3 hr, allowed to cool, alkalized with NaOH, and extracted with PhMe. The organic phase was dried ($MgSO_4$), the solvent removed *in vacuo*, and the residue distilled *in vacuo* to give **7a** (74 g, 91%): bp 140–145° (0.4 mm). Conversion to the HCl salt and crystallization from *i*-PrOH gave pure **7a**: mp 222–224°. *Anal.* ($C_{12}H_{18}N_2$·HCl) C, H, N. Similarly, starting from **6b**, *trans*-**7d** was obtained as crude oil: base titration calculated for $C_{12}H_{18}N_2$: 190.28; found, 194.44.

Optical Resolution of 7a. To a boiling solution of **7a** (99 g, 0.52 mol) and (+)-tartaric acid (78.15 g, 0.52 mol) in a minimal amount of MeOH was added boiling Me_2CO until slight turbidity. The mixture was allowed to crystallize overnight. The precipitate (70 g) was collected by filtration and the filtrate set aside. Recrystallization from Me_2CO–MeOH afforded 54.5 g of the *d*-tartrate: $[\alpha]^{25}D$ −19.7° (MeOH). Conversion to free base gave 31 g of *cis*-(−)-**7b**: mp 91–92°; $[\alpha]^{25}D$ −5.9° (MeOH). *Anal.* ($C_{12}H_{18}N_2$) C, H, N.

The filtrate was concentrated *in vacuo*; the residue was dissolved in H_2O, alkalized with dilute NaOH, and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue (57 g, 0.3 mol) and (−)-tartaric acid (45.26 g, 0.3 mol) were dissolved in a minimal amount of boiling MeOH, Me_2CO was added until slightly turbid, and the mixture was allowed to stand overnight. The precipitate (74 g) was collected by filtration and recrystallized from Me_2CO–MeOH affording 60.5 g of the *l*-tartrate: $[\alpha]^{24}D$ +20.3° (MeOH). Conversion to free base gave 33 g of *cis*-(+)-**7c**: mp 93.5–94.5°; $[\alpha]^{25}D$ +6.1° (MeOH). *Anal.* ($C_{12}H_{18}N_2$) C, H, N.

***cis*-(±)-3-Methyl-1-(2-phenylethyl)-*N*-phenyl-4-piperidineamine Dihydrochloride (9).** A suspension of **7a** (5.8 g, 0.026 mol), 2-phenylethyl chloride (3.8 g, 0.027 mol), Na_2CO_3 (10.6 g, 0.1 mol), and a few crystals of KI in *i*-BuCOMe (200 ml) was stirred and refluxed overnight. The precipitate was removed by filtration and the solvent removed *in vacuo*. The oily residue was dissolved in *i*-Pr_2O and neutralized with HCl in *i*-PrOH. The precipitate was collected by filtration and recrystallized from *i*-Pr_2O to give pure **9** (5.8 g, 61%): mp 254–255°. *Anal.* ($C_{20}H_{26}N_2$·2HCl) C, H, N. Corresponding *trans*-(±)-**10** was prepared similarly starting from **7d**.

***cis*-(−)-3-Methyl-1-(2-phenylethyl)-*N*-phenyl-4-piperidineamine (11).** A suspension of **7b** (5.25 g, 0.03 mol), 2-phenylethyl bromide (6.25 g, 0.033 mol), Na_2CO_3 (6.5 g, 0.06 mol), and a few crystals of KI in *i*-BuCOMe (200 ml) was stirred and refluxed overnight. Work-up as described for **9** afforded the dihydrochloride salt (7.8 g) which was converted to free base **11** (6.8 g, 77%) as a yellow oil: glc 99.1% (2 m, 3% SE30, Chromosorb 80–100 AW HMDS); $[\alpha]^{25}D$ −46.7° (MeOH). Corresponding cis-(+) compound **12** (glc 98.5%, $[\alpha]^{25}D$ +46.2°) was obtained similarly, starting from **7c**.

***cis*-(±)-3-Methyl-1-(1-methyl-2-phenylethyl)-*N*-phenyl-4-piperidineamine Dihydrochloride (13).** A mixture of **7a** (5.7 g, 0.03 mol), 1-methyl-2-phenylethanol methanesulfonate (7 g, 0.033 mol), and Na_2CO_3 (8 g, 0.075 mol) in *i*-BuCOMe (300 ml) was stirred and refluxed for 48 hr. The mixture was allowed to cool and extracted with H_2O, the organic phase dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was crystallized as the HCl salt from *i*-Pr_2O–*i*-PrOH to give **13** (10.5 g, 92%): mp 169–171°. *Anal.* ($C_{21}H_{28}N_2$·2HCl) C, H, N.

Separation of Diastereoisomeric *cis*-3-Methyl-1-(1-methyl-2-phenylethyl)-*N*-phenyl-4-piperidineamine by Means of Countercurrent Distribution. Buffer at pH 2.6 (2.18 ml of 0.2 *M* Na_2HPO_4 and 17.82 ml of 0.1 *N* citric acid) was used as upper phase and $CHCl_3$ as lower phase. The cell train, consisting out of 500 cells with a volume of 23 ml, was fed with 10.5 g of base of **13**, spread over 22 cells. After 5000 transfer steps the following separation was obtained: *r* max_1 3140, K_1 = 1.702 and *r* max_2 3360, K_2 = 2.055. This allowed the recuperation of 3.5 g of **14** (33%) spread over 25 cells (K_1 = 1.60), 1.1 g of a mixture of **14** and **15** spread over 35 cells, and 3.77 g of **15** (36%) spread over 45 cells (K_2 = 2.07).

Compounds **16–19** were obtained similarly by countercurrent distribution of the substitution products prepared from 1-methyl-2-phenylethanol methanesulfonate and **7b** or **7c**, respectively.

***cis*-(±)-*N*-[3-Methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide Oxalate (20).** A solution of **9** (15 g, 0.05 mol) and propionic anhydride (13 g, 0.1 mol) in $PhMe_2$ (400 ml) was refluxed overnight. The mixture was allowed to cool and alkalized with NH_4OH. The organic phase was washed several times with H_2O and dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was crystallized as the oxalate salt from Me_2CO–*i*-PrOH affording pure **20** (14 g, 64%): mp 163–164°; 100-MHz nmr ($CDCl_3$) δ 1.0 (t, 3, $-COCH_2CH_3$), 1.12 (d, 3, 3-CH_3), 1.92 (m, 2, $-COCH_2CH_3$), 4.40 (d, of t, 1, J = 12.5, 5 Hz, H_4), 7.15 and 7.29 (2 br s, 10). *Anal.* ($C_{23}H_{30}N_2O$·$C_2H_2O_4$) C, H, N.

Compounds **21–30** (Table II) were prepared similarly, starting respectively from **10–19** (Table I).

***trans*-(±)-*N*-[3-Methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide oxalate (21):** mp 159–160°; 100-MHz nmr ($CDCl_3$) δ 1.0 (t, 3, $-COCH_2CH_3$), 1.02 (d, 3, 3-CH_3), 1.90 (m, 2, $-COCH_2CH_3$), 4.53 (t of d, 1, J = 12.5, 4.5 Hz, H_4), 7.13 and 7.30 (2 br s, 10). *Anal.* ($C_{23}H_{30}N_2O$·$C_2H_2O_4$) H, N; C: calcd, 68.16; found, 67.72.

***cis*-(±)-*N*-[3-Methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide hydrochloride 24:** mp 237–238°; 60-MHz nmr ($CDCl_3$) δ 0.99 (t, 3, $-COCH_2CH_3$), 1.19 (d, 3, 3-CH_3), 1.45 (d, 3, $-CH_2CH(CH_3)N<$), 1.95 (m, 2, $-COCH_2CH_3$), 4.48 (m, 1, H_4), 7.14 and 7.28 (2 br s, 10). *Anal.* ($C_{24}H_{32}N_2O$·HCl) C, H, N.

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Potential Nonequilibrium Analgetic Receptor Inactivators. Further Pharmacologic Studies of *N*-Acylanileridines

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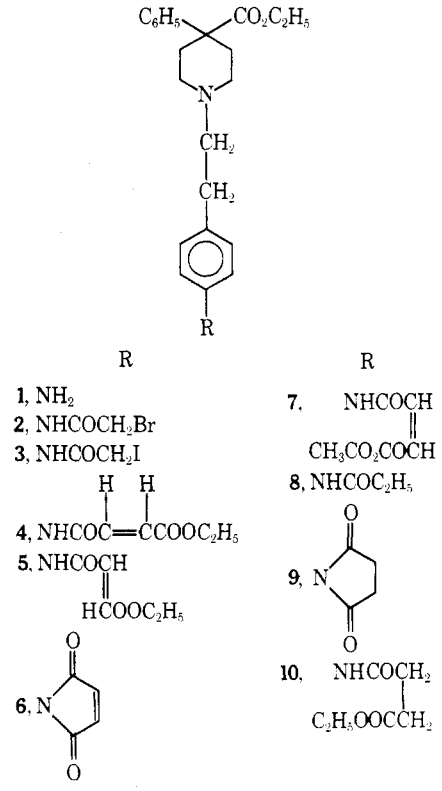
The antagonistic property of ethyl *p*-(4-ethoxycarbonyl-4-phenyl-1-piperidinoethyl)fumaranilate (**5**) was investigated. Compound **5** was found to antagonize morphine analgesia in a complex manner which could not be described as a simple competitive or noncompetitive type. The antagonism, however, lasted for over 6 hr suggesting that **5** has a high affinity for the analgesic receptors. Compound **5** appeared to possess dependence liability in the single-dose suppression test. In the electrically stimulated isolated guinea pig ileum, **5** acted like an agonist. No antagonistic activity of **5** was apparent in the latter two tests.

In a previous communication, we reported the synthesis and analgesic potencies of six *N*-acylanileridines having various alkylating moieties.[1] One compound, namely, ethyl *p*-(4-ethoxycarbonyl-4-phenyl-1-piperidinoethyl)fumaranilate (**5**), appeared to significantly inhibit morphine analgesia. Since the specific narcotic antagonist, naloxone, prevented this inhibition by the anileridine derivative, it was suggested that this compound might have the capacity to alkylate analgesic receptors selectively. A further quantitation of the inhibition of morphine analgesia by **5** is recorded in the present paper.

Since it was of interest to see whether or not the alkylating *N*-acylanileridines could affect narcotic receptors other than those for analgesia, two other pharmacologic parameters were utilized. It is generally known that if animals become physically dependent on one narcotic, they exhibit cross dependence to the other narcotic agents. Taking advantage of this fact, the capacity of the various alkylating *N*-acylanileridines to supress morphine abstinence was assessed. The other parameter employed was the effect of *N*-acylanileridines on the electrically stimulated isolated guinea pig ileum. Studies on the ileum were of interest since it has been demonstrated that the agonistic activity of a series of analgesics in this preparation correlated remarkably well with the analgesic potency in man.[2-4]



Experimental Section

Compounds. All the compounds used in this study were those synthesized and described previously.[1] They were anileridine derivatives containing either various alkylating functions (**2-7**) or nonalkylating groups (**8-10**) that are structurally similar to the alkylating moieties.

Estimation of ED_{50}. Male Sasco mice (Omaha, Neb.) weighing between 20 and 30 g were used in these determinations. The analgesic assay used was a modification of the hot-plate method described by Eddy and Leimbach.[5] The animal responses were made quantal by establishing an end point at the mean peak effect in each group which represented an increase in the reaction time of an individual animal of greater than three standard deviations of the control mean reaction time for all animals used in the group. For example, if an animal initially had a reaction time of 8 sec and the standard deviation for this particular group of animals was 3 sec, a reaction time after drug treatment of >17 sec would be considered a significant increase in the reaction time. An animal having a 10-sec reaction time in this group would be considered a positive responder if the reaction time exceeded 19 sec. The usual control time in these animals was about