Neither compound nor the standards, administered intradermally or intraperitoneally, had an effect on the development of hemorrhage in the Arthus reaction. Both compounds produced comparable inhibition of local and systemic lesions in adjuvant-induced arthritis in the rat and of paralysis in experimental allergic encephalomylitis. These inhibitions were observed at or near toxic levels, but the toxicity was considered adjuvant-related. Morton and Chatfield[11] had indicated that the adjuvant-induced arthritic rat probably does not detoxify compounds as efficiently as do normal rats because of impaired liver function. When II was tested in normal or adjuvant-treated rats at daily oral doses of 60 mg/kg a marked increase in lethality was observable by the eleventh day in the drug-adjuvant treated group (13/15 deaths), as compared with the drug, nonadjuvant treated group (2/15 deaths). II was more effective than I in decreasing cell induration in the delayed hypersensitivity skin reaction (tuberculin) in the guinea pig, in suppressing hemagglutinin production in the mouse, and in inhibiting TdR uptake by mouse thymus cells in culture. Neither compound was active as a membrane stabilizer. Both compounds demonstrated analgesic activity in the writhing and Randall-Sellito assays, and neither compound produced gastric erosions in the fasted rat. Because of the low acute oral toxicity of I and II in the rat and in the mouse and because they lack ulcerogenic potential, both compounds possess favorable therapeutic indices. These data indicate that both I and II possess antiinflammatory activity of considerable interest; they compare favorably with indomethacin, phenylbutazone, and niflumic acid. Compound I has been selected for further toxicological studies.

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Synthetic Antidiarrheal Agents. 2,2-Diphenyl-4-(4′-aryl-4′-hydroxypiperidino)butyramides

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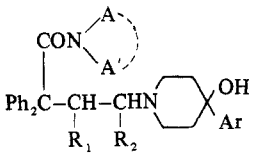
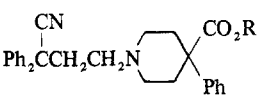
The synthesis of a series of 2,2-diphenyl-4-(4′-aryl-4′-hydroxypiperidino)butyramides and the preliminary evaluation of their antidiarrheal activities are described. Intermediates are (tetrahydro-3,3-diphenyl-2-furylidene)ammonium salts prepared from 4-bromo-2,2-diphenylbutyric acid (**2**). 4-(*p*-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutyramide HCl (**30**, loperamide) and 4-(4-chloro-α,α,α-trifluro-*m*-tolyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutyramide HCl (**33**, fluperamide) were approximately two times more potent than diphenoxylate and had a considerably better relative constipating specificity.

As part of a continuing effort to develop novel antidiarrheal agents, a series of 2,2-diphenyl-4-(4′-aryl-4′-hydroxypiperidino)butyramides of formula I were prepared. Diphenoxylate (IIa), a well-known antidiarrheal[1] and potent inhibitor of the peristaltic relfex activity of guinea pig ileum *in vitro*,[2] belongs to a series of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotic acid esters. With IIa the aim to synthesize analgesic type compounds devoid of analgesic action, but behaving as highly active inhibitors of gastrointestinal propulsion and defaecation, was achieved. The active metabolite of IIa, difenoxine (IIb),[3] was found to be five times more potent than IIa and to possess a better safety margin.[4-8]

The original objective of this study was to replace the cyano group of II by an amide function, but the approach led invariably to less active or inactive compounds. However, when the carboxyl substituent on the piperidine ring was replaced by a hydroxyl group as well, improvement in activity was found. This modification was surprising, since 4-aryl-4-piperidinols are typical moieties of neuroleptics,



I

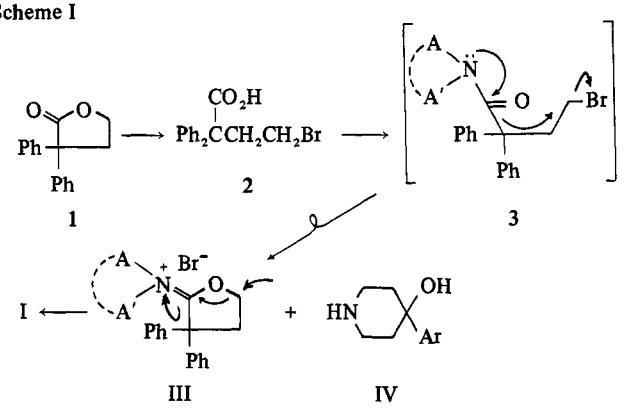


IIa, R = Et
b, R = H

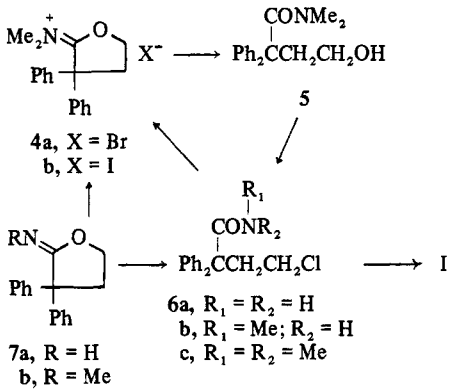
such as haloperidol, trifluperidol, moperone, and clofluperol.[9]

Chemistry. The synthesis of the teritary butyramides I is outlined in Schemes I and II. Ring opening of 2,2-diphenyl-4-hydroxybutyric acid γ-lactone (**1**) with HBr in AcOH afforded 4-bromo-2,2-diphenylbutyric acid (**2**).[10] Subsequent treatment of **2** with $SOCl_2$ and reaction of the intermediate acid chloride with an appropriate secondary amine yielded the corresponding (tetrahydro-3,3-diphenyl-2-furylidene)-ammonium salts III (Table I). Compounds **3** rearranged spontaneously under the reaction conditions. The structure of ammonium salts III was evident from spectral data (Experimental Section) and from their reactivity. Compounds III

Scheme I



Scheme II

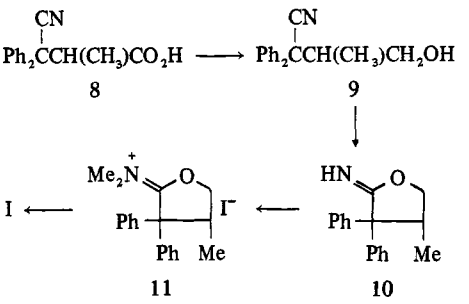


reacted extremely fast with 4-aryl-4-piperidinols IV to give the desired end products I. Treatment of dimethyl(tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide (**4a**) with aqueous base afforded 4-hydroxy-*N*,*N*-dimethyl-2,2-diphenylbutyramide (**5**), which was converted with $SOCl_2$ to the corresponding 4-chloro compound **6c**. Compound **6c** rearranged slowly to the corresponding ammonium salt of type III upon warming in an inert solvent. Reaction of **6c** with IV afforded end products I (Table II).

Primary and secondary butyramides I were prepared by substitution reaction of **6a** and **6b** with the appropriate 4-aryl-4-piperidinols IV. Compounds **6a** and **6b** were synthesized by ring opening of the corresponding 3,3-diphenyl-2-iminotetrahydrofurans **7a** and **7b** with HCl.[11] Quaternization of **7b** with MeI afforded ammonium iodide **4b**. Alkylation of **7a** with $LiNH_2$ and MeI yielded monomethylated compound **7b**.

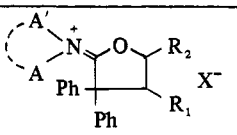
The β- and γ-methyl-substituted butyramides I were prepared by condensation of the appropriately substituted (tetrahydro-3,3-diphenyl-2-furylidene)ammonium salts **11** and **14** with 4-aryl-4-piperidinols IV. The synthesis of **11** and **14** is outlined in Schemes III and IV. Treatment of 3-

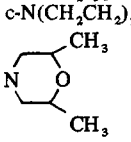
Scheme III



cyano-3,3-diphenylisobutyric acid[12] with $SOCl_2$ followed by reduction of the intermediate acid chloride with $NaBH_4$ in DMF afforded the corresponding alcohol **9**. Acid cyclization of **9** gave tetrahydro-4-methyl-3,3-diphenyl-2-furanimine (**10**). Alkylation of **10** followed by quaternization yielded ammonium iodide **11**. Allylation of the appropriately N,N-disubstituted 2,2-diphenylacetamide **12** with $NaNH_2$ in xylene afforded the corresponding 2,2-diphenyl-4-pentenamide **13**. Cyclization of **13** with HBr in AcOH

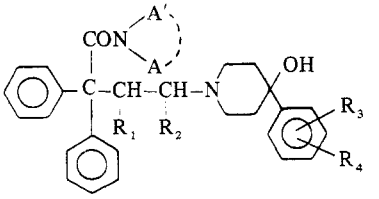
Table I. (Tetrahydro-3,3-diphenyl-2-furylidene)ammonium Salts



Compd	N(A')(A)	R_1	R_2	X	Crystn solvent	Yield purified, %	Mp, °C	Formula[a]
4a	NMe_2	H	H	Br	*i*-BuCOMe	50	181–182	$C_{18}H_{20}BrNO$
4b	NMe_2	H	H	I	*i*-BuCOMe	63	217–218	$C_{18}H_{20}INO$
11	NMe_2	Me	H	I	*i*-BuCOMe	35	180–181	$C_{19}H_{22}INO$
14a	NMe_2	H	Me	Br	*i*-BuCOMe	74	207–208	$C_{19}H_{22}BrNO$
14b	c-$N(CH_2)_4$	H	Me	Br	*i*-BuCOMe	88	226–227	$C_{21}H_{24}BrNO$
15	NEt_2	H	H	Br	*i*-BuCOMe	58	172–174	$C_{20}H_{24}BrNO$
16	$N(CH_2CH{=}CH_2)_2$	H	H	Br	*i*-Pr_2O	53	98–100	$C_{22}H_{24}BrNO$
17	NEtMe	H	H	Br	Me_2CO	50	172–173	$C_{19}H_{22}BrNO$[c]
18	N-*i*-PrMe	H	H	Br				$C_{20}H_{24}BrNO$[b,c]
19	NMe-*n*-Pr	H	H	Br	*i*-BuCOMe	49	170–172	$C_{20}H_{24}BrNO$[c]
20	$NMeCH_2C_6H_5$	H	H	Br	*i*-BuCOMe	31	112–113	$C_{24}H_{24}BrNO$[c]
21	c-$N(CH_2)_4$	H	H	Br	*i*-BuCOMe	45	186–188	$C_{20}H_{22}BrNO$[c]
22	c-$N(CH_2)_5$	H	H	Br	*i*-BuCOMe	52	166–167	$C_{21}H_{24}BrNO$
23	c-$N(CH_2)_5$-*m*-CH_3	H	H	Br	*i*-BuCOMe	70	198–199	$C_{22}H_{26}BrNO$[c]
24	c-$N(CH_2)_5$-*p*-CH_3	H	H	Br	*i*-BuCOMe	40	193–194	$C_{22}H_{26}BrNO$
25	c-$N(CH_2CH_2)_2O$	H	H	Br	*i*-BuCOMe	30	175–177	$C_{20}H_{22}BrNO_2$
26		H	H	Br	*i*-Pr_2O	30	143–144	$C_{22}H_{26}BrNO_2$

[a] Analyzed for C, H, and N. [b] Crude oil (not analyzed for C, H, and N). [c] The possibility of geometric isomerism due to restricted rotation of the C=N⁺ bond was not further investigated.

Table II. 2,2-Diphenyl-4-(4′-aryl-4′-hydroxypiperidino)butyramides



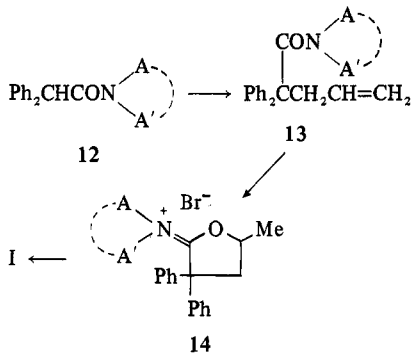
Compd	N(A′)(A′)	R_1	R_2	R_3	R_4	Crystn solvent	Yield purified, %	Mp, °C	Formula[a]
27	NH_2	H	H	4-Cl	H	*i*-BuCOMe	10	236-237	$C_{27}H_{29}ClN_2O_2 \cdot HCl$
28	NHMe	H	H	H	H	*i*-PrOH	40	218-219	$C_{28}H_{32}N_2O_2 \cdot HCl$
29	NHMe	H	H	4-Cl	H	*i*-BuCOMe	40	237-238	$C_{28}H_{31}ClN_2O_2 \cdot HCl$
30	NMe_2	H	H	4-Cl	H	*i*-PrOH	58	222-223	$C_{29}H_{33}ClN_2O_2 \cdot HCl$
31	NMe_2	H	H	4-Me	H	Me_2CO	41	206-207	$C_{30}H_{36}N_2O_2 \cdot HCl$
32	NMe_2	H	H	3-Cl	4-Cl	*i*-BuCOMe	80	239-240	$C_{29}H_{32}Cl_2N_2O_2 \cdot HCl$
33	NMe_2	H	H	4-Cl	3-CF_3	*i*-PrOH	64	215-216	$C_{30}H_{32}ClF_3N_2O_2 \cdot HCl$
34	NMe_2	H	H	H	H	PhMe	60	130-131	$C_{29}H_{34}N_2O_2$
35	NMe_2	H	H	4-Br	H	*i*-BuCOMe	64	123-124	$C_{29}H_{33}BrN_2O_2 \cdot H_2O$
36	NMe_2	H	H	3-CF_3	H	*i*-BuCOMe	34	185-186	$C_{30}H_{33}F_3N_2O_2 \cdot HCl$
37	NMe_2	H	H	4-F	H	*i*-PrOH	82	233-234	$C_{29}H_{33}FN_2O_2 \cdot HCl \cdot 0.5i\text{-PrOH}$[b]
38	NMe_2	H	H	2-Me	4-Me	*i*-BuCOMe	43	126-127	$C_{31}H_{38}N_2O_2 \cdot HCl \cdot H_2O$
39	NMe_2	H	H	2-MeO	5-MeO	THF	40	180-181	$C_{31}H_{38}N_2O_4 \cdot HNO_3$
40	NEt_2	H	H	4-Cl	3-CF_3	*i*-BuCOMe	69	220-221	$C_{32}H_{36}ClF_3N_2O_2 \cdot HCl$
41	NEt_2	H	H	4-F	H	*i*-BuCOMe	45	135-136	$C_{31}H_{37}FN_2O_2$
42	NEt_2	H	H	3-Cl	4-Cl	*i*-PrOH	60	245-246	$C_{31}H_{36}Cl_2N_2O_2 \cdot HCl$
43	NEt_2	H	H	H	H	*i*-PrOH	71	248-249	$C_{31}H_{38}N_2O_2 \cdot HCl \cdot 0.5i\text{-PrOH}$
44	NEt_2	H	H	3-CF_3	H	*i*-BuCOMe	75	222-223	$C_{32}H_{37}F_3N_2O_2 \cdot HCl$
45	NEt_2	H	H	4-Br	H	*i*-BuCOMe	36	145-146	$C_{31}H_{37}BrN_2O_2 \cdot 0.5H_2O$
46	NEt_2	H	H	4-Cl	H	*i*-PrOH	44	236-237	$C_{31}H_{37}ClN_2O_2 \cdot HCl \cdot 0.5i\text{-PrOH}$[c]
47	c-N$(CH_2)_4$	H	H	H	H	*i*-BuCOMe	56	187-188	$C_{31}H_{36}N_2O_2$
48	c-N$(CH_2)_4$	H	H	4-F	H	*i*-BuCOME	62	192-193	$C_{31}H_{35}FN_2O_2$
49	c-N$(CH_2)_4$	H	H	4-Cl	3-CF_3	*i*-BuCOMe	30	188-189	$C_{32}H_{34}ClF_3N_2O_2 \cdot HCl$
50	c-N$(CH_2)_4$	H	H	3-Cl	4-Cl	EtOH	49	200-201	$C_{31}H_{34}Cl_2N_2O_2 \cdot HCl$
51	c-N$(CH_2)_4$	H	H	3-CF_3	H	*i*-BuCOMe	40	117-118	$C_{32}H_{35}F_3N_2O_2 \cdot HCl \cdot 2H_2O$
52	c-N$(CH_2)_4$	H	H	4-Cl	H	*i*-BuCOMe	53	168-169	$C_{31}H_{35}ClN_2O_2$
53	c-N$(CH_2)_5$	H	H	4-Cl	3-CF_3	*i*-BuCOMe	64	204-205	$C_{33}H_{36}ClF_3N_2O_3 \cdot HCl$
54	c-N$(CH_2)_5$	H	H	3-Cl	4-Cl	Me_2CO	37	202-203	$C_{32}H_{36}Cl_2N_2O_2 \cdot HCl$
55	c-N$(CH_2)_5$	H	H	3-CF_3	H	*i*-BuCOMe	62	200-201	$C_{33}H_{37}F_3N_2O_2 \cdot HCl$
56	c-N$(CH_2)_5$	H	H	H	H	*i*-BuCOMe	51	240-241	$C_{32}H_{38}N_2O_2 \cdot HCl$
57	c-N$(CH_2)_5$	H	H	4-Cl	H	EtOH	66	251-253	$C_{32}H_{37}ClN_2O_2 \cdot HCl$[d]
58	c-N$(CH_2CH_2)_2O$	H	H	3-CF_3	H	*i*-BuCOMe	62	213-214	$C_{32}H_{35}F_3N_2O_3 \cdot HCl$
59	c-N$(CH_2CH_2)_2O$	H	H	4-Cl	3-CF_3	*i*-BuCOMe	65	243-244	$C_{32}H_{34}ClF_3N_2O_3 \cdot HCl$
60	c-N$(CH_2CH_2)_2O$	H	H	3-Cl	4-Cl	*i*-BuCOMe	78	242-243	$C_{31}H_{34}Cl_2N_2O_3 \cdot HCl$
61	c-N$(CH_2CH_2)_2O$	H	H	H	H	*i*-PrOH	49	182-183	$C_{31}H_{36}N_2O_3 \cdot HCl \cdot 0.5i\text{-PrOH}$
62	c-N$(CH_2CH_2)_2O$	H	H	4-Cl	H	Me_2CO	72	257-258	$C_{31}H_{35}ClN_2O_3 \cdot HCl$
63	N(CH$_3$)O(CH$_3$)	H	H	4-Cl	H	*i*-BuCOMe	36	241-242	$C_{33}H_{39}ClN_2O_3 \cdot HCl$
64	c-N$(CH_2)_5$-*m*-CH_3	H	H	4-Cl	H	*i*-BuCOMe	71	215-216	$C_{33}H_{39}ClN_2O_2 \cdot HCl$
65	c-N$(CH_2)_5$-*p*-CH_3	H	H	4-Cl	H	*i*-BuCOMe	85	235-236	$C_{33}H_{39}ClN_2O_2 \cdot HCl$
66	NMeEt	H	H	4-Cl	H	PhMe	30	215-216	$C_{30}H_{35}ClN_2O_2 \cdot HCl$
67	NMe-*n*-Pr	H	H	4-Cl	H	*i*-BuCOMe	78	190-191	$C_{31}H_{37}ClN_2O_2 \cdot HCl$
68	NMe-*i*-Pr	H	H	4-Cl	H	*i*-BuCOMe	73	225-226	$C_{31}H_{37}ClN_2O_2 \cdot HCl$
69	$NMeCH_2Ph$	H	H	4-Cl	H	*i*-BuCOMe	60	225-226	$C_{35}H_{37}ClN_2O_2 \cdot HCl$
70	$N(CH_2CH{=}CH_2)_2$	H	H	4-Cl	H	EtOH	60	258-259	$C_{33}H_{37}ClN_2O_2 \cdot HCl$
71	NMe_2	Me	H	4-Cl	H	*i*-PrOH	54	196-197	$C_{30}H_{35}ClN_2O_2 \cdot HCl \cdot 0.5i\text{-PrOH}$
72	NMe_2	Me	H	4-Cl	3-CF_3	*i*-PrOH	45	200-201	$C_{31}H_{34}ClF_3N_2O_2$
73	NMe_2	Me	H	3-CF_3	H	*i*-PrOH	40	252-253	$C_{31}H_{35}F_3N_2O_2 \cdot HCl$
74	NMe_2	H	Me	4-Cl	H	EtOH	40	200-201	$C_{30}H_{35}ClN_2O_2$
75	NMe_2	H	Me	4-F	H	*i*-BuCOMe	20	165-166	$C_{30}H_{35}FN_2O_2$
76	NMe_2	H	Me	H	H	*i*-BuCOMe	43	193-194	$C_{30}H_{36}N_2O_2$
77	NMe_2	H	Me	3-CF_3	H	*i*-BuCOMe	48	169-170	$C_{31}H_{35}F_3N_2O_2$
78	NMe_2	H	Me	4-Cl	3-CF_3	*i*-BuCOMe	45	207-208	$C_{31}H_{34}ClF_3N_2O_2 \cdot HCl$
79	c-N$(CH_2)_4$	H	Me	H	H	*i*-BuCOMe	57	168-169	$C_{32}H_{38}N_2O_2$
80	c-N$(CH_2)_4$	H	Me	4-Cl	H	*i*-BuCOMe	71	206-207	$C_{32}H_{37}ClN_2O_2$
81	c-N$(CH_2)_4$	H	Me	4-F	H	*i*-BuCOMe	27	186-187	$C_{32}H_{37}FN_2O_2$
82	c-N$(CH_2)_4$	H	Me	3-CF_3	H	*i*-BuCOMe	30	133-134	$C_{33}H_{37}F_3N_2O_2 \cdot HCl \cdot 2H_2O$

[a] Analyzed for C, H, and N. [b] C: calcd, 69.49; found, 69.01. [c] C: calcd, 68.28; found, 67.83. [d] C: calcd, 69.43; found, 68.91.

gave the desired 5-methyl-substituted ammonium bromides **14**.

Pharmacology. For screening female Wistar rats were used. ED_{50} values with 95% confidence limits were computed by Finney's iterative method.[13] The oral antidiarrheal activity was assessed by measuring the protection from diarrhea caused by castor oil.[4] The analgesic activity was assessed by measuring the warm water induced tail withdrawal reflex.[14] The ratio of the ED_{50} value in the tail withdrawal test over the ED_{50} value which gives protection for

Scheme IV



1 hr in the castor oil test was used as a criterion for the relative constipating specificity (RCS).

Results and Discussion

The results are summarized in Table III. All compounds tested showed antidiarrheal activity. The combination of antidiarrheal potency and high relative constipating specificity was optimal when the amide group was tertiary, bearing two small alkyl groups, such as dimethylamino **(30-39)** or ethylmethylamino **(66)**. Introduction of a secondary amide **(28, 29)** resulted in a tenfold decrease of antidiarrheal potency and primary amide **27** had a very low potency. When $N < \begin{matrix}A\\A'\end{matrix}$ was diethylamino **(40-46)** the compounds were equipotent, but a twofold increase in analgesic potency worsened the RCS. The corresponding pyrrolidino compounds **(47-52, 79-82)** were two or three times less active but retained high RCS. The piperidino **(53-57, 64, 65)** and morpholino **(58-63)** derivatives showed a large decrease in antidiarrheal potency with the exception of compound **56** which had a high antidiarrheal potency and a high RCS. β-Methyl branching (R_1 = Me, **71-73**) resulted in increased antidiarrheal potency but also in a sharp increase of analgesic potency, with consequent loss of RCS. γ-Methyl branching (R_2 = Me, **74-82**) had similar influence although less pronounced.

Substitution on the 4-phenyl ring of the 4-piperidinol moiety was optimal for *p*-Cl **(30)**, *m*-CF_3, *p*-Cl **(33)**, and *p*-Br **(35)**. The unsubstituted compound **34** was a very potent antidiarrheal but also a strong analgesic. *m*-CF_3 **(36)** and *p*-F **(37)** substitution gave an increase in antidiarrheal potency but afforded too strongly analgesic compounds. *p*-Me substitution **(31)** resulted in a tenfold loss of potency, while *m,p*-diCl **(32)** and *o,p*-diMe **(38)** substitution retained antidiarrheal potency but gave a lower RCS.

Loperamide **(30)** and fluperamide **(33)** were selected for further investigation. They were approximately two times more potent than diphenoxylate (IIa) and 50 times more potent than codeine. Compared with IIa and codeine, **30** and **33** had a far superior relative constipating specificity (Table IV).

Experimental Section

Melting points were taken on a Tottoli melting point apparatus and are corrected. All compounds were routinely checked for their structure by uv and ir spectrometry (uv, Beckman DK-2A and ir, Perkin-Elmer 421). Nmr spectra were recorded by means of a Bruker HX-60 spectrometer. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

4-Bromo-2,2-diphenylbutyric Acid (2). A mixture of **1** (600 g, 2.5 mol) and 48% HBr in AcOH (1200 ml) was stirred for 48 hr. The precipitate was collected by filtration, washed with H_2O and PhMe, and crystallized from *i*-Pr_2O to give pure **2** (670 g, 84%), mp 135-137°. *Anal.* ($C_{16}H_{15}BrO_2$) C, H.

Dimethyl(tetrahydro-3,3-diphenyl-2-furylidene)ammonium Bromide (4a). To a suspension of **2** (227 g, 0.71 mol) in $CHCl_3$ (1500 ml) was added $SOCl_2$ (160 ml) dropwise. The mixture was refluxed for 4 hr and allowed to cool, and the solvent was removed *in vacuo*. The crude acid chloride (227 g, 93%) was used without purification. To a solution of dimethylamine (5.4 g, 0.12 mol) and Na_2CO_3 (25.4 g, 0.24 mol) in H_2O (100 ml) was added dropwise a solution of 4-bromo-2,2-diphenylbutyroyl chloride (33.8 g, 0.1 mol) in PhMe (100 ml), while the temperature was kept between 0 and 5°. The mixture was stirred for an additional 2 hr and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was crystallized from *i*-BuCOMe to give pure **4a** (17.3 g, 50%): mp 181-182°; uv max (95% EtOH) 255 nm (ϵ

Table III. Antidiarrheal Activity in Rats

Compd	ED_{50},[a] castor oil	ED_{50},[b] tail withdrawal	Rel constipating specificity[c]
27	5.00[d]	>40	>8
28	0.16[d]	5	31
29	1.00[d]	40	40
30	0.15 (0.11-0.20)	80	533
31	1.26 (0.53-2.99)	⩾160	⩾127
32	0.26 (0.18-0.40)	100	385
33	0.15 (0.11-0.21)	70	467
34	0.012 (0.006-0.021)	3.0	250
35	0.10 (0.06-0.17)	80	800
36	0.020 (0.010-0.042)	4.0	200
37	0.040 (0.019-0.085)	20	500
38	0.16 (0.10-0.27)	20	125
39	0.57 (0.37-0.86)	⩾160	⩾281
40	0.080 (0.042-0.153)	20	250
41	0.044 (0.024-0.079)	10	227
42	0.31 (0.20-0.48)	80	258
43	0.025 (0.014-0.045)	3.0	120
44	0.017 (0.007-0.037)	2.0	118
45	0.33 (0.21-0.52)	32	97
46	0.17 (0.11-0.25)	40	235
47	0.016 (0.009-0.030)	7.0	437
48	0.16 (0.10-0.58)	40	250
49	0.45 (0.31-0.66)	160	355
50	0.50 (0.25-0.98)	>320	>640
51	0.11 (0.07-0.17)	10	91
52	0.27 (0.18-0.40)	160	593
53	5.00[d]	>160	>32
54	2.50[d]	>160	>64
55	0.53 (0.29-0.94)	160	302
56	0.25 (0.17-0.38)	>320	>1280
57	1.76 (1.13-2.73)	>160	>91
58	0.63 (0.29-1.39)	>160	>251
59	1.26 (0.55-2.89)	>160	>127
60	8.00[d]	>160	>20
61	0.50[d]	130	260
62	10[d]	160	16
63	10[d]	⩾160	⩾16
64	10[d]	>160	>16
65	10[d]	>160	>16
66	0.13 (0.07-0.29)	⩾160	⩾1231
67	0.54[d]	>160	>296
68	0.54[d]	>160	>296
69	1.24 (0.56-2.72)	>160	>129
70	10[d]	>160	>16
71	0.025 (0.013-0.045)	1.0	40
72	0.028 (0.015-0.055)	1.25	45
73	0.006 (0.004-0.009)	1.25	208
74	0.070 (0.048-0.102)	20	286
75	0.032 (0.014-0.071)	20	622
76	0.057 (0.035-0.094)	20	351
77	0.022 (0.012-0.039)	2.5	114
78	0.060 (0.029-0.124)	2.5	42
79	1.26 (0.64-2.48)	>40	>32
80	0.42 (0.19-0.91)	40	95
81	1.26 (0.66-2.84)	>40	>32
82	2.07 (0.89-4.81)	>80	>39

[a] mg/kg po at 1 hr after castor oil (confidence limits). [b] mg/kg po (graphically estimated). [c] ED_{50} tail withdrawal/ED_{50} castor oil (1 hr). [d] Graphically estimated.

Table IV. Antidiarrheal Activity of Loperamide, Fluperamide, Diphenoxylate, and Codeine in Rats

Compd	ED_{50}, castor oil[a] 1 hr	2 hr	4 hr	8 hr	ED_{50},[b] tail withdrawal	RCS[c]	LD_{50}[d]
Loperamide	0.15 (0.11-0.20)	0.29 (0.23-0.38)	0.61 (0.45-0.83)	1.81 (1.25-2.63)	80	533	185 (135-254)
Fluperamide	0.15 (0.11-0.21)	0.20 (0.15-0.28)	0.31 (0.23-0.43)	0.77 (0.51-1.16)	70	467	86 (48-156)
Diphenoxylate	0.16 (0.11-0.23)	0.54 (0.40-0.72)	1.41 (1.07-1.87)	4.77 (3.44-6.61)	6	37	221 (133-367)
Codeine	2.85 (1.87-4.35)	10.8 (8.7-13.5)	28.8 (21.5-38.6)	69.9 (50.1-97.7)	36	13	427 (302-603)

[a] mg/kg po at stated hour after caster oil (confidence limits). [b] mg/kg po (graphically estimated). [c] ED_{50} tail withdrawal/ED_{50} castor oil at 1 hr. [d] Mortality after 7 days in mg/kg po (confidence limits).

540) and 261 (425); ir (KBr) 1675-1680 cm^{-1} (C=N); nmr ($CDCl_3$) δ 3.03 (s, 3), 3.50 (t, 2), 3.8 (s, 3), 4.89 (t, 2), and 7.51 ppm (s, 10). *Anal.* ($C_{18}H_{20}BrNO$) C, H, N. Other compounds prepared by this method were **15-26.**

***N,N*-Dimethyl-2,2-diphenyl-4-hydroxybutyramide (5).** A solution of **4a** (7.5 g, 0.021 mol) in H_2O (50 ml) was alkalized with aqueous NaOH and the mixture extracted with Et_2O. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was crystallized from *i*-Pr_2O to afford pure **5** (5.6 g, 94%), mp 131-132°. *Anal.* ($C_{18}H_{21}NO_2$) C, H, N.

4-Chloro-*N,N*-dimethyl-2,2-diphenylbutyramide (6c). A mixture of **5** (12 g, 0.042 mol) and $SOCl_2$ (6.4 g, 0.054 mol) in $CHCl_3$ (100 ml) was refluxed for 2 hr. The solvent was removed *in vacuo* and the residue crystallized from *i*-Pr_2O to give pure **6c** (7 g, 53%), mp 136-137°. *Anal.* ($C_{18}H_{20}ClNO$) C, H, N.

***N*-(Tetrahydro-3,3-diphenyl-2-furylidene)methylamine Hydrobromide (7b).** To a mixture of 35% aqueous methylamine (100 g, 1.13 mol) and Na_2CO_3 (106 g, 1 mol) in H_2O (1000 ml) and PhMe (800 ml) was added dropwise 4-bromo-2,2-diphenylbutyroyl chloride (337.5 g, 1 mol) in PhMe (200 ml), while the temperature was kept between 0 and 5°. The mixture was allowed to come to room temperature and the precipitate collected by filtration. The solid was taken up into $CHCl_3$, the solution dried ($MgSO_4$), and the solvent removed *in vacuo.* The residue was crystallized from *i*-BuCOMe to afford pure **7b** (223 g, 67%), mp 159-161°. *Anal.* ($C_{17}H_{17}NO \cdot HBr$) C, H, N.

4-Chloro-*N*-methyl-2,2-diphenylbutyramide (6b). **7b** (33.2 g, 0.1 mol) was converted to base in the usual way and dissolved in *i*-BuCOMe. The mixture was refluxed while dry HCl gas was bubbled through for 30 min. The solvent was removed *in vacuo* and the residue crystallized from *i*-Pr_2O to give pure **6b** (20.2 g, 70%), mp 150-152°. *Anal.* ($C_{17}H_{18}ClNO$) C, H, N. Compound **6a** was prepared similarly.

Dimethyl(tetrahydro-3,3-diphenyl-2-furylidene)ammonium Iodide (4b). A solution of **7b** (12.6 g, 0.05 mol) and MeI (14.2 g, 0.1 mol) in *i*-BuCOMe was refluxed overnight. The solvent was removed *in vacuo* and work-up as for **4a** afforded pure **4b** (12.4 g, 63%): mp 217-218°; nmr ($CDCl_3$) δ 2.99 (s, 3), 3.47 (t, 2), 3.82 (s, 3), 4.87 (t, 2), and 7.48 ppm (s, 10). *Anal.* ($C_{18}H_{20}INO$) C, H, N.

Tetrahydro-4-methyl-3,3-diphenyl-2-furanimine Hydrochloride (10). 3-Cyano-3,3-diphenylisobutyric acid **8** (45 g, 0.17 mol) was refluxed with $SOCl_2$ (30 ml) in $CHCl_3$. The solvent was removed *in vacuo;* the crude acid chloride was dissolved into DMF and added dropwise to a mixture of $NaBH_4$ (7.5 g) in DMF (150 ml). The mixture was stirred at room temperature overnight. AcOH (15 ml) was added and the mixture poured onto ice-H_2O. The mixture was extracted with *i*-Pr_2O, the organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo.* The crude oil **9** (45 g) was dissolved into dry Et_2O (250 ml) saturated with dry HCl gas. The mixture was left overnight at 0°. The solvent was removed *in vacuo* and the residue crystallized from *i*-BuCOMe to give pure **10** (20 g, 40%), mp 186-189°. *Anal.* ($C_{17}H_{17}NO$) C, H, N.

Dimethyl(tetrahydro-4-methyl-3,3-diphenyl-2-furylidene)-ammonium Iodide (11). To a suspension of **10** (5.75 g, 0.02 mol) in THF (50 ml) was added in small portions $LiNH_2$ (0.92 g, 0.04 mol) and the mixture refluxed for 2 hr. MeI (14.2 g, 0.1 mol) was added dropwise and reflux continued for an additional 12 hr. The mixture was poured into H_2O and extracted with *i*-BuCOMe. Further quaternization and work-up as described for **4b** afforded pure **11** (2.8 g, 35%), mp 180-181°. *Anal.* ($C_{19}H_{22}INO$) C, H, N.

***N,N*-Dimethyl-2,2-diphenyl-4-pentenamide (13a).** To a mixture of 50% $NaNH_2$ suspended in xylene (120 g, 1.5 mol) and PhMe (500 ml) was added dropwise *N,N*-dimethyl-2,2-diphenylacetamide (310 g, 1.3 mol) in PhMe (1000 ml). The mixture was refluxed for 1 hr, allyl bromide (212 g, 1.75 mol) was added dropwise, and reflux continued for 2 hr. H_2O (500 ml) was added, and the organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was crystallized from *i*-Pr_2O to give pure **13a** (249 g, 69%), mp 110-112°. *Anal.* ($C_{19}H_{21}NO$) C, H, N.

Dimethyl(tetrahydro-5-methyl-3,3-diphenyl-2-furylidene)ammonium Bromide (14a). A solution of **13a** (88 g, 0.31 mol) in AcOH (300 ml) was treated with HBr gas until saturation. The solvent was removed *in vacuo* and the residue crystallized from *i*-BuCOMe to afford pure **14a** (83 g, 74%), mp 207-208°. *Anal.* ($C_{19}H_{22}BrNO$) C, H, N. Compound **14b** was prepared similarly.

4-(*p*-Chlorophenyl)-4-hydroxy-*N,N*-dimethyl-α,α-diphenyl-1-piperidinebutyramide Hydrochloride (30). From a suspension of 4-*p*-chlorophenyl-4-piperidinol (4.2 g, 0.02 mol) and Na_2CO_3 (8 g, 0.075 mol) in *i*-BuCOMe (250 ml), the H_2O was removed with the aid of a Dean-Stark trap. Then **4a** (7.6 g, 0.022 mol) was added, the mixture refluxed for 2 hr and filtered, and the solvent removed *in vacuo.* The residue was dissolved into *i*-PrOH and neutralized with HCl gas. Crystallization from *i*-PrOH afforded pure **30** (6 g, 58%), mp 222-223°. *Anal.* ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) C, H, N. Other compounds prepared by this method were **31-82.**

4-(*p*-Chlorophenyl)-4-hydroxy-α,α-diphenyl-1-piperidinebutyramide Hydrochloride (27). A suspension of **6a** (6.85 g, 0.025 mol), 4-*p*-chlorophenyl-4-piperidinol (10.5 g, 0.05 mol), and a trace KI in *i*-BuCOMe (250 ml) was refluxed for 12 hr. Work-up as above afforded pure **27** (1.2 g, 10%), mp 236-237°. *Anal.* ($C_{27}H_{29}ClN_2O_2 \cdot HCl$) C, H, N. Other compounds prepared by this method were **28** and **29.**

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