3,3-Diphenyl-3-(2-alkyl-1,3,4-oxadiazol-5-yl)propylcycloalkylamines, a Novel Series of Antidiarrheal Agents

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A series of 4-amino-2,2-diarylbutyronitriles (3) prepared for testing as inhibitors of gastrointestinal propulsive activity did not show any enhancement over such existing agents as diphenoxylate and loperamide. However, conversion of the nitrile group to a 2-methyl-1,3,4-oxadiazol-5-yl function led to compounds **5g** and **5j**, statistically equipotent to diphenoxylate and loperamide in the mouse and showing a very low order of analgesic activity. Structural modifications determined that the best separation of antipropulsive and analgesic effects was obtained when the amino group was bicyclic and the oxadiazole ring had a 2-methyl substituent. The most potent compounds were the analogues of diphenoxylate and loperamide where the oxadiazole ring was present, but these compounds had marked analgesic activity.

The treatment of diarrhea with opium extracts dates back several centuries to the Chinese. In recent years, opium extracts have given way to opiate derivatives, e.g., codeine, and synthetic agents, e.g., meperidine. However, the use of these agents as antidiarrheal drugs is severely limited by the concomitant analgesic and addictive properties. Recently Janssen and co-workers found that useful antidiarrheal drugs devoid of many narcotic properties could be obtained. Diphenoxylate[1] (1) and loperamide[2] (2) are clinically effective antidiarrheal agents; however, both compounds can be considered as derivatives of synthetic analgesic agents.

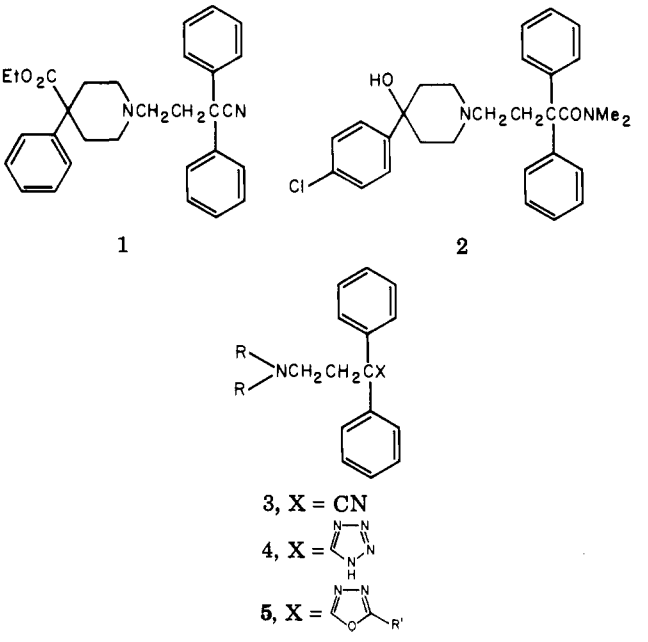
Efforts in our laboratories were directed toward synthetic agents that were not derivatives of 4-phenylpiperidine analgesic agents and had no overt CNS effects in test animals and were at least as effective as 1 and 2 for inhibition of gastrointestinal propulsion (Chart I).

Initial studies were directed toward the synthesis of 4-dialkylamino-2,2-diarylbutyronitriles 3, where R_2N– comprises an unsubstituted cyclic amine; however, these compounds had a very low order of activity. Previous work from this laboratory demonstrated that 3 can be converted to tetrazoles 4 and subsequently to 5-substituted 2-methyl-1,3,4-oxadiazoles 5.[3] This led us to synthesize a series of oxadiazoles 5 and evaluate their constipating and CNS properties.

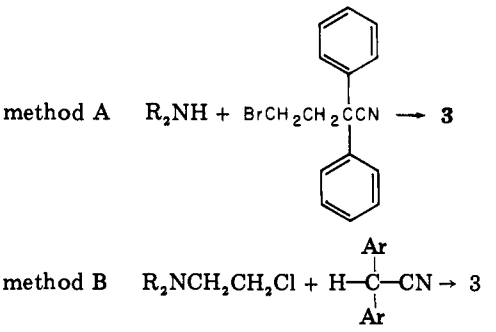
Chemistry. The synthesis of nitriles 3 was readily achieved either by alkylation of secondary amines (secondary amines were either obtained from commercial sources or prepared by known procedures; see Experimental Section) with 4-bromo-2,2-diphenylacetonitrile (method A) or by alkylation of diarylacetonitrile with the appropriate chloroalkylamine (method B) (see Scheme I). Thus, method A allows for the synthesis of a variety of cyclic amines, while method B is useful for constructing analogues with substituted phenyl or other aromatic rings. In addition, alkylation of diphenylacetonitrile with 2-(2-chloropropyl)-2-azabicyclo[2.2.2]octane gave a mixture of side-chain methylated compounds (**3j,k**) which were readily separated by chromatography (see Table I).

The tetrazoles 4 were prepared from nitriles 3 by the previously reported procedures.[3,4] The oxadiazoles 5 (Table II) were prepared by refluxing a mixture of 4 and the appropriate acyl anhydride or acyl chloride in C_5H_5N until the evolution of N_2 was no longer apparent.[5] In some cases, the oxadiazoles were oils or gums and it was necessary to prepare the amine salts to obtain crystalline compounds. The unsubstituted oxadiazole (6) was obtained by mild basic hydrolysis of 12 and subsequent decarboxylation.[5] More vigorous hydrolysis (refluxing 5% HCl) of 12 led to rupture of the oxadiazole and afforded the hydrazide 17 in good yield (Table III).

Chart I



Scheme I

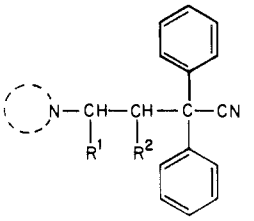


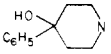
Discussion

No significant antipropulsive or analgesic activity was seen for the unsubstituted monocyclic amines (**3a–d, 5a–d**) whether or not the oxadiazole ring was present (Table IV). The most potent compounds were the 4-disubstituted piperidines (**5e,f**); however, the analgesic activity of these compounds was also enhanced with respect to 1 and 2. The bicyclic amines (**5g,j**), however, show good separation of analgesic and antipropulsive activities and are equipotent to loperamide and diphenoxylate in the mouse cecal test.

The fact that **5g** and **5j** showed marginal analgesic activity at the maximum screening dose (100 mg/kg) led us to explore the effects of structural modifications of **5g**.

Table I. 2,2-Diphenyl-4-cycloalkylaminobutyronitriles



Compd		R_1	R_2	Method	Crystn solvent[a]	Yield, %	Mp, °C	Formula
3a	$N(CH_2)_4$	H	H	B[b]	SKB	34.5	73-74.5	$C_{20}H_{22}N_2$
3b	$N(CH_2)_5$			B[c]	MeOH	28	73-75	$C_{21}H_{24}N_2$
3c				B	SKB	11.5	79.5-80.5	$C_{21}H_{22}N_2$
3d	Morpholino			B[c]	SKB	82	80.5-82	$C_{20}H_{22}N_2O$
3e				B[d]	*e*	52	221-223	$C_{27}H_{28}N_2O \cdot HCl \cdot 2H_2O$
3f				B[f]	Et_2O	63.5	96-99	$C_{23}H_{26}N$
3g				B[f]	P	66	82-84	$C_{22}H_{24}N_2$
3h				A[f]	Et_2O	74	215-220	$C_{24}H_{28}N_2 \cdot HCl$
3i				B[f]		40	87-88	$C_{23}H_{26}N_2$
3j		CH_3	H	A	P	40	80-18.5	$C_{24}H_{28}N_2$[g]
3k		H	CH_3	A	Et_2O-P	25	133-134	$C_{24}H_{28}N_2$

[a] SKB = Skellysolve B, P = pentane, An = acetone. [b] Reference 13. [c] D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 500 (1949). [d] C. L. C. Carron, A. F. Jullien, and P. M. Manoury, French Demande 2158108 (1973); *Chem. Abstr.*, 79, 115450v (1973). [e] Precipitated from dilute HCl. [f] J. W. Cusic and P. Yonan, U.S. Patent 3 318 869 (1967); *Chem. Abstr.*, 68, 68903f (1968). [g] C: calcd, 83.67; found, 84.25.

This resulted in changes of the size of the bicyclic amine, variations in the substituent on the oxadiazole ring (R_3, Table II), substitution of other groups for the oxadiazole ring, methylation of the side chain (R_1 and R_2), and substitutions on the aromatic rings. Removal of a methylene group from or insertion of an additional methylene group into the bicyclic amine led to compounds (**5h,i**) of considerably lower activity, whereas potent activity was retained in **5j**, isomeric to **5g**. This observation suggests that the bicyclic amine requires only one carbon atom in addition to the nitrogen atom in the bridge.

The contribution of the oxadiazole ring to the activity of these compounds is not clear. Activity is maximal for the 2-methyloxadiazole (**5g**). The fact that alkyl groups larger than methyl on the oxadiazole cause a marked reduction in activity suggests that the steric requirement is rather stringent. The slightly reduced activity for the unsubstituted oxadiazole (**6**) may reflect its increased lability to hydrolytic cleavage.[6] Such a hydrolysis product would lead to relatively inactive compounds (**17**, **18**). Electron-withdrawing substituents (**11**–**13**) on the oxadiazole also greatly suppress activity. Methylation of the two-carbon chain is known to enhance the analgesic potency of methadone-type compounds;[7] however, the antipropulsive activity of **5k** and **5m** shows no enhancement. The analgesic activity of **5m** does show about a threefold increase with respect to **5k**, which is consistent with the observed increased potency of methadone vs. isomethadone.[8]

Removal of the oxadiazole (**14**), substitution by carboxamide (**15**) or dimethylcarboxamide (**16**), or substitution on one of the phenyl groups (**21**, **22**) was not beneficial to activity. Substituting a phenyl by 2-pyridyl (**19**) caused a slight decrease in potency, while the 3-pyridyl analogue **20** caused a significant decrease. Presumably, the 3-pyridyl nitrogen affords more of an additional binding site to the receptor than does the nitrogen of the 2-pyridyl group.

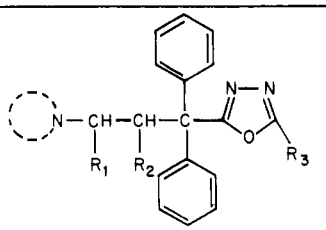
No biology is reported for the tetrazoles **4** because of a uniform lack of activity. This may be a consequence of their extreme lipid insolubility. In fact, the acidity of the tetrazole ring lends a zwitterionic character to these compounds, such that they are soluble in acidic or basic solution but precipitate from solution when the pH approaches neutrality.

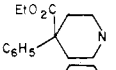
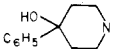
We have assumed that diphenoxylate, loperamide, and **5g** exert their antidiarrheal effect through an opiate-type mechanism. This has been demonstrated to be the case, since the antidiarrheal effects of these agents are effectively antagonized by naloxone.[9] The fact that **5g** is opiate-like in its action on the gut but has marginal effects on the CNS suggests that a separation of antidiarrheal and analgesic properties is possible. Thus **5g** represents a novel series of compounds with potential antidiarrheal activity. Unlike diphenoxylate and loperamide, **5g** is not a derivative of a synthetic narcotic analgesic agent. Further biological and clinical studies are currently underway.

Experimental Section

Chemistry. NMR (Varian A-60D, $CDCl_3$ or Me_2SO-d_6, Me_4Si standard) and ir (Beckman IR-12, $CHCl_3$ or Nujol mull) spectra were consistent with all structures and were determined by Mr. A. Damascus, Searle Spectroscopy Laboratory. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within 0.4% of the theoretical

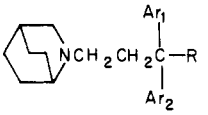
Table II. 1-[3,3-Diphenyl-3-(2-alkyl-1,3,4-oxadiazol-5-yl)propyl]cycloalkylamines



Compd		R_1	R_2	R_3	Crystn solvent[a]	Yield, %	Mp, °C	Formula
5a	$N(CH_2)_4$	H	H	CH_3	Et_2O-SKB	77	87-88.5	$C_{22}H_{25}N_3O$
5b	$N(CH_2)_5$				Et_2O-SKB	78	93-95	$C_{23}H_{27}N_3O$
5c					Et_2O-P	67	100.5-102	$C_{23}H_{25}N_3O$
5d	Morpholino				SKB	54	153-155	$C_{22}H_{25}N_3O_2$
5e					Et_2O	68	120-121	$C_{32}H_{35}N_3O_3$[b]
5f					Et_2O	56[c]	160-162	$C_{29}H_{31}N_3O_2$
5g					Et_2O-SKB	84	121-123	$C_{25}H_{29}N_3O$
5h					Et_2O-P	85	130-132	$C_{24}H_{27}N_3O$
5i					Et_2O	69	140-142	$C_{26}H_{31}N_3O$
5j					SKB	32	98-101	$C_{25}H_{29}N_3O$
5k		CH_3	H		Et_2O-P	64	131.5-133.5	$C_{26}H_{31}N_3O$[d]
5m		H	CH_3		MeOH-P	54	190-191	$C_{26}H_{31}N_3O \cdot C_2H_2O_4$
6		H	H	H	An-Et_2O	29[e]	233-234.5	$C_{24}H_{27}N_3O \cdot HCl \cdot 0.5C_3H_6O$
7				Et	MeOH-Et_2O	40	175-178	$C_{26}H_{31}N_3O \cdot H_3PO_4 \cdot 0.5H_2O$
8				*t*-Bu	SKB	38	121-121.5	$C_{28}H_{38}N_3O$[f]
9					SKB	10	127-129.5	$C_{34}H_{41}N_3O$
10				C_6H_5	SKB	58	140-141	$C_{30}H_{31}N_3O$
11				CF_3	An-Et_2O	38	174-175	$C_{25}H_{26}F_3N_3O \cdot HCl$
12				CO_2Et	EtOH-Et_2O	57	198-200	$C_{27}H_{31}N_3O_3 \cdot HCl$
13				$CONH_2$	Et_2O	47[e]	98-101	$C_{25}H_{31}N_4O_2 \cdot H_2O$

[a] See footnote *a*, Table I. [b] C: calcd, 75.41; found, 74.95. [c] After hydrolysis of acetate. [d] C: calcd, 77.77; found, 78.48. [e] See Experimental Section. [f] C: calcd, 78.28; found, 78.80.

Table III. 2-(3-Substituted 3,3-diarylpropyl)-2-azabicyclo[2.2.2]octanes



Compd	Ar_1	Ar_2	R	Crystn solvent[a]	Yield, %	Mp, °C	Formula
14	C_6H_5	C_6H_5	H	An	46[b]	251-254	$C_{22}H_{27}N \cdot HCl$
15			$CONH_2$	PhH-Et_2O	69[b]	196-199	$C_{23}H_{28}N_2O$
16			$CONMe_2$	An-MeOH	38[b]	265-266	$C_{25}H_{32}N_2O \cdot HCl$
17			$CONHNH_2$	Et_2O-SKB	65[b]	117-119	$C_{23}H_{29}N_3O$
18			CONHNHAc	An	53[b]	248-249.5	$C_{25}H_{31}N_3O_2 \cdot HCl$
19		2-C_5H_4N	OXA[c]	Et_2O	50	109-110	$C_{24}H_{28}N_4O$
20		3-C_5H_4N	OXA	MeOH-Et_2O	22	171-172	$C_{24}H_{28}N_4O \cdot C_2H_2O_4$
21		4-ClC_6H_4	OXA	Et_2O	64	97-102	$C_{25}H_{28}ClN_3O$
22	4-$MeOC_6H_4$	2-C_5H_4N	OXA	MeOH-Et_2O	46	155.5-158.5	$C_{25}H_{30}N_4O_2 \cdot C_2H_2O_4 \cdot H_2O$

[a] See footnote *a*, Table I. [b] See Experimental Section. [c] OXA = 2-methyl-1,3,4-oxadiazol-5-yl.

values and were determined by Mr. E. Zielinski, Searle Microanalytical Laboratory. Melting points were determined in open capillary tubes in a Thomas-Hoover capillary melting point apparatus and are uncorrected.

2-Azabicyclo[2.2.2]octane,[10] **7-azabicyclo[2.2.1]heptane,**[11] **and 6-azabicyclo[3.2.1]octane**[12] were prepared according to published procedures.

4-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,2-diphenylbutyronitrile Hydrochloride (3h). Method A. A mixture of 4-bromo-2,2-diphenylbutyronitrile (51.3 g, 0.171 mol) and 3-azabicyclo[3.2.2.]nonane (45.0 g, 0.36 mol) in Me_2SO (125 ml) was heated on a steam bath overnight. The mixture was cooled, diluted with H_2O, and made strongly basic with NaOH. The aqueous mixture was extracted with Et_2O, and the Et_2O solution

Table IV. Inhibition of Gastrointestinal Propulsion in Mice

Compd	ED_{50},[a] cecal test	ED_{50},[b] tail clip	Therapeutic ratio[c]
Morphine SO_4	41.3 (±6.7)	43	1.0 (0.9-1.2)
1	3.1 (±1.3)	8.8	2.8 (2-4.9)
2	1.1 (±0.3)	101	91.8 (72-126)
3a	24.2 (±7.8)	100	4.1 (3.1-6.1)
3b	30[d]	100	3.3
3c	>100[e]	>100[e]	1
3d	>100[e]	>100[e]	1
3e	54.8 (±16.0)	50	0.9 (0.7-1.3)
3f	54.7 (±16.0)	50	0.9 (0.7-1.3)
3g	13.3 (±4.0)	100	7.5 (5.8-10.8)
3h	>100[e]	>100[e]	1
3i	24.2 (±7.8)	>100[e]	4.1 (3.1-6.0)
3j	30[d]	>100[e]	>3
3k	>100[e]	>100[e]	1
5a	30 (±6.4)	50	1.7 (1.4-2.1)
5b	100[d]	100	1
5c	75[d]	100	1.3
5d	>100[e]	100	1
5e	0.22 (±0.12)	1	4.5 (2.9-10)
5f	0.82 (±0.19)	1	1.2 (1.0-1.6)
5g	2.3 (±0.8)	112	48.7 (36.1-74.7)
5h	13.9 (±4)	50	3.6 (2.8-5.0)
5i	38.4 (±16.3)	30	0.8 (0.5-1.7)
5j	1.6 (±1.4)	100	62.5 (33.3-500)
5k	30[d]	30	1
5m	26.7 (±7.7)	100	3.7 (2.9-5.3)
6	6.8 (±1.8)	100	14.7 (13.1-20)
7	16.6 (±9.5)	100	6.0 (3.8-14.1)
8	50[d]	50	1
9	>100[e]	>100[e]	1
10	20.4 (±5.0)	100	4.9 (3.9-6.5)
11	34.5 (±17.0)	30	0.9 (0.6-1.7)
12	>100[e]	>100[e]	1
13	93.0 (±10)	100	1 (0.9-1.2)
14	36[d]	100	2.8
15	30[d]	100	3.3
16	30[d]	100	3.3
17	>100[e]	>100[e]	1
18	>100[e]	30	0.3
19	4.0 (±1.3)	50	12.5 (9.4-18.5)
20	45.4 (±21.8)	50	1.1 (0.7-2.1)
21	77.4 (±46.5)	100	1.3 (0.8-3.2)
22	>100[e]	>100[e]	1

[a] mg/kg ig administered 0.5 h before charcoal meal (± standard error). [b] mg/kg ig graphically estimated. [c] ED_{50} tail clip/ED_{50} cecal test. [d] Graphically estimated. [e] Inactive at maximal dose (100 mg/kg).

was washed with H_2O and then with dilute HOAc to remove any unreacted secondary amine. The Et_2O solution was extracted with dilute HCl, the acid solution made basic and extracted with Et_2O, and the resulting Et_2O solution was dried, evaporated, and distilled at 218–230° (0.1 mm) to give a colorless oil, 34 g (58%). An ether solution of the oil was treated with HCl to afford **3h**, mp 215–220°. Anal. ($C_{24}H_{28}N_2$·HCl) C, H, N.

4-Pyrrolidino-2,2-diphenylbutyronitrile (3a). Method B. A mixture of *N*-2-chloroethylpyrrolidine hydrochloride (54 g, 0.31 mol), diphenylacetonitrile (61.3 g, 0.31 mol), and granular KOH (42 g, 0.75 mol) in methyl ethyl ketone (MEK, 1.25 l.) was refluxed and stirred for 17 h. After cooling, the mixture was filtered and the filter cake washed with MEK. The combined filtrates were evaporated, and the residue was taken up in Et_2O and washed several times with H_2O. The Et_2O solution was extracted with 10% HCl; the acid solution was made basic and reextracted with Et_2O. The Et_2O solution was dried (anhydrous K_2CO_3) and evaporated leaving an oil which crystallized on standing. Recrystallization of this solid from Skellysolve B gave **3a**: 31.9 g (35%); mp 73–74.5° (lit.[13] 72–73°). Anal. ($C_{20}H_{22}N_2$) C, H, N.

5-(1,1-Diphenyl-3-pyrrolidinopropyl)-1*H*-tetrazole (4a). A mixture of **3a** (6.0 g, 0.021 mol), NaN_3 (13.6 g, 0.21 mol), NH_4Cl (11.2 g, 0.21 mol), and LiCl (8.9 g, 0.21 mol) in DMF (30 ml) was heated under an atmosphere of N_2 at 125° for 66 h or until no starting material could be detected by TLC (10% MeOH–CH_2Cl_2 on silica). The reaction mixture was diluted with H_2O (100 ml), made alkaline (15% KOH), and extracted with Et_2O (2 × 25 ml). The aqueous solution was adjusted to pH 7 (10% HCl) and the resulting mixture shaken with CH_2Cl_2 (80 ml). At this point, a solid formed and was filtered off, washed successively with H_2O and Et_2O, and air-dried (60°) overnight, affording **4a**: 4.4 g (59.5%); mp 235–237°. Anal. ($C_{20}H_{23}N_5$·H_2O) C, H, N.

1-[3,3-Diphenyl-3-(2-methyl-1,3,4-oxadiazol-5-yl)propyl]pyrrolidine (5a). A mixture of **4a** (3.0 g, 9 mmol) and Ac_2O (6.0 ml, 64 mmol) in dry C_5H_5N (40 ml) was refluxed for 1 h. The dark solution was cooled and evaporated in vacuo. The residue was partitioned between Et_2O and dilute NaOH. The Et_2O layer was washed with H_2O, dried (anhydrous Na_2SO_4), and treated with Darco, and the solvent was evaporated. The crude solid was recrystallized from Et_2O–Skellysolve B to afford **5a**: 2.27 g (77%); mp 87–88.5°; ir ($CHCl_3$) 1550 cm^{-1} (-C=N-); NMR ($CDCl_3$) δ 2.4 (3 H, singlet, CH_3). Anal. ($C_{22}H_{25}N_3O$) C, H, N.

2-[3,3-Diphenyl-3-(1,3,4-oxadiazol-2-yl)propyl]-2-azabicyclo[2.2.2]octane Hydrochloride Hemiacetonate (6). A mixture of **12** (8.0 g, 16.6 mmol) in 5% NaOH (200 ml) was stirred and refluxed for 5 min. The solution was cooled, diluted with H_2O (100 ml), and extracted with Et_2O. The aqueous phase was adjusted to pH 6.5, and the gummy solid that formed was extracted into CH_2Cl_2. The CH_2Cl_2 solution was dried (anhydrous Na_2SO_4) and worked up to give the crude carboxylic acid, 4.9 g. Recrystallization of the acid from CH_2Cl_2–MeOH gave the pure acid: 3.1 g (44%); mp 128–129° (gas evolution). Anal. ($C_{25}H_{27}N_3O_3$·0.5H_2O) C, N, N.

The purified acid (3.1 g, 7.2 mmol) was placed in a flask and heated in an oil bath (145–150°) for 15 min, during which time a gas was evolved. The cooled melt was dissolved in Et_2O, filtered, and evaporated, and the residue was taken up in Me_2CO and acidified with HCl. The solid that formed was removed by filtration, washed with Me_2CO, and dried to afford **6**: 2.1 g (66%); mp 233–234.5°. Anal. ($C_{24}H_{27}N_3O$·HCl·0.5C_3H_6O) C, H, N, Cl.

2-[3,3-Diphenyl-3-(2-carboxamido-1,3,4-oxadiazol-5-yl)propyl]-2-azabicyclo[2.2.2]octane Hydrate (13). A solution of **12** (0.5 g) in EtOH (10 ml), H_2O (5 ml), and concentrated NH_4OH (3 ml) was allowed to stand at room temperature overnight. The crystals that formed were removed by filtration, washed with fresh EtOH, and dried to afford **13** (237 mg, 47%), mp 98–101°. Anal. ($C_{25}H_{31}N_4O_2$·H_2O) C, H, N.

3,3-Diphenylpropyl-2-(2-azabicyclo[2.2.2]octane) Hydrochloride (14). A mixture of 3,3-diphenylpropionyl chloride (4.5 g, 0.02 mol), 2-azabicyclo[2.2.2]octane (2.9 g, 0.02 mol), and Et_3N (2.0 g, 0.02 mol) in PhH (100 ml) was refluxed for 1.5 h. The mixture was cooled and washed successively with dilute NaOH, H_2O, dilute HCl, H_2O, and dilute $NaHCO_3$. The PhH solution was dried (anhydrous Na_2SO_4) and the solvent evaporated affording 5.2 g of crude solid, which was recrystallized from Et_2O to give 2.3 g (36%) of amide, mp 132–136°. Anal. ($C_{22}H_{25}NO$) C, H, N.

Reduction of the amide (2.2 g, 6.9 mmol) with $LiAlH_4$ (0.26 g, 6.9 mmol) in Et_2O (80 ml) gave, after workup, 1.01 g of crude amine. Treatment of an Et_2O solution of the amine with HCl gave 1.1 g of crude **14**, which was recrystallized from Me_2CO to give 0.46 g (46%) of colorless solid, mp 251–254°. Anal. ($C_{22}H_{27}N$·HCl) C, H, N, Cl.

4-(2-Azabicyclo[2.2.2]octan-2-yl)-2,2-diphenylbutyramide (15). A solution of **3f** (14.3 g, 43 mmol) in concentrated H_2SO_4 (46 ml) was heated on a steam bath for 2.5 h. After cooling, the solution was poured into an ice-water mixture and made basic (NaOH). The solid that formed was extracted into CH_2Cl_2, the extract was dried (Na_2SO_4), and the solvent evaporated at reduced pressure. Recrystallization of the residue from PhH gave pure **15**: 10.4 g (69%); mp 196–199°. Anal. ($C_{23}H_{28}N_2O$) C, H, N.

4-(2-Azabicyclo[2.2.2]octan-2-yl)-2,2-diphenyl-*N*,*N*-dimethylbutyramide (16). Alkylation of *N*,*N*-dimethyl-2,2-diphenylacetamide (4.8 g, 24 mmol) with 2-(2-chloroethyl)-2-azabicyclo[2.2.2]octane (3.8 g, 24 mmol) with $NaNH_2$ (0.86 g, 24 mmol) as a base in $PhCH_3$ (150 ml) gave, after workup and acidification, 3.6 g (38%) of **16**, mp 265–266°. Anal. ($C_{25}H_{32}N_2O$·HCl) C, H, N, Cl.

4-(2-Azabicyclo[2.2.2]octan-2-yl)-2,2-diphenylbutyrylhydrazine (17). A suspension of **12** (0.5 g) in 5% HCl (10 ml) was refluxed 1 h. After cooling, the solution was made basic (NaOH) and extracted with Et_2O. The Et_2O solution was dried (anhydrous Na_2SO_4), the solvent evaporated, and the crude product recrystallized (Et_2O–SKB) to give **17**: 0.26 g (65%); mp 117–119°. Anal. ($C_{23}H_{29}N_3O$) C, H, N.

***N*-4-(2-Azabicyclo[2.2.2]octan-2-yl)-2,2-diphenylbutyryl-*N'*-acetylhydrazine Hydrochloride (18).** A solution of **5g** (3 g) and concentrated HCl (6 ml) was stirred overnight at room temperature. The solvents were evaporated at reduced pressure and the gummy residue was stirred in a mixture of Et_2O and Me_2CO until crystallization was completed. The solid was filtered, washed with Me_2CO, and dried to afford pure **18**: 1.9 g (53%); mp 248–249.5°; NMR ($CDCl_3$) δ 2.0 (3 H, singlet, CH_3). Anal. ($C_{25}H_{31}N_3O_2$·HCl) C, H, N, Cl.

Biology. The inhibition of gastrointestinal (gi) propulsion was studied in the charcoal meal cecal test as adapted from techniques previously described.[14-16] In these experiments, the extent of gi propulsion was measured with the aid of nonabsorbable and visually identifiable markers such as charcoal. Six male Charles River mice, 20–25 g, were fasted in screen-bottom cages with water supplied ad libitum for 24 h prior to the test. The animals were intragastrically (ig) pretreated with the test compounds employing a 0.5% methylcellulose suspension. The total volume of the suspension administered to these animals was kept constant at 10.0 ml/kg. The control group received the same volume of 0.5% methylcellulose solution. Thirty minutes after compound administration, the animals were given a single 0.2-ml dose of 10% suspension of charcoal powder in 1.0% methylcellulose solution. The animals were sacrificed 3.5 h later, and the cecum was examined on an all-or-none basis. In 95% of all control animals, charcoal was present in the cecum. Antidiarrheal drugs, such as diphenoxylate hydrochloride, interfere with the gi propulsive activity, so the presence or absence of charcoal in the cecum provides a measure for the pharmacological responses to these compounds. Consequently, the median effective dose (ED_{50}) can thus be calculated using the logistic method of Berkson.[17]

The analgesic activities were assayed by a modification of the mouse tail clip method of Bianchi and Franceschini.[18] The group of mice ($N = 6$) used in the charcoal meal cecal test was subjected to a pressure-standardized artery clip approximately 1 in. from the base of the tail. Those mice that did not respond by turning and biting at the clip within 15 s were scored positive for analgesic effects, and a provisional ED_{50} was graphically estimated. The separation of CNS and inhibition of gi propulsion effects can thus be expressed as a therapeutic index (ED_{50} analgesia/ED_{50} cecal test).

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Cinnoline-3-propionic Acids, a New Series of Orally Active Antiallergic Substances

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The synthesis of a series of 4-oxo-1,4-dihydrocinnolin-3-ylpropionic acids and their derivatives by a novel intramolecular Borsche-type cyclization from the corresponding substituted 4,5-dihydro-1*H*,3*H*-1-benzazocine-2,6-diones is described. These compounds show high activity in antiallergic bioassays and are of possible value in the treatment of asthma.

Disodium cromoglycate has been shown to be an effective and important drug for the treatment of certain types of asthma.[1] This drug is usually administered directly into the respiratory tract and, consequently, the search for an orally active replacement continues. Marked oral activity in humans has recently been reported for a number of series, namely, the 2-xanthonecarboxylic acids,[2] the 3-(5-tetrazolyl)thioxanthone 10,10-dioxides,[3] and the azapurin-6-ones,[4] and in animals for the nitroindan-1,3-diones[5] and the 3-(4-oxo-4*H*-1-benzopyran-3)acrylic acids.[6] During a chemical investigation of the oximation of 4,5-dihydro-1*H*,3*H*-1-benzazocine-2,6-dione (**1a**), an unexpected ring contraction was observed and the product was identified as 4-oxo-1,4-dihydrocinnolin-3-ylpropionic acid (**2**). On account of the structural resemblance of these rearrangement products to certain phenanthrolinecarboxylic acids[2] and their homologous relationship to 4-cinnolone-3-carboxylic acids,[8] the antiallergic potential of these compounds has been assessed from their relative activities in passive cutaneous anaphylaxis reaction (PCA)[9] in the rat using the heat-labile homocytotropic antibody. The methods of preparation and the biological activities in passive cutaneous anaphylaxis of the 4-oxo-1,4-dihydrocinnolin-3-ylpropionic acids, esters, and N-1 alkyl-