The acid hydrolysis (6 *N* HCl, 110°, 24 hr) of **9** produced **4** and histidine.

Phthalyl-ε-aminocaproic Acid.—The mixture of 14.8 g of phthalic anhydride and 13.1 g of **5** was allowed to react by the same procedure described for the synthesis of Pht-δ-aminovaleric acid: yield, 96.9%; mp 105-106°. *Anal.* ($C_{14}H_{15}NO_4$) C, H, N.

Phthalyl-ε-aminocaproyl chloride was prepd as described before: yield, 93.0%; mp 66–67°.

Phthalyl-ε-aminocaproyl-L-histidine was prepd as described before: yield, 46.0%; mp 225-226°; $[\alpha]^{25}D$ +16.6° (*c* 1, H_2O). *Anal.* ($C_{20}H_{22}N_4O_5$) H, N; C: calcd, 60.29; found, 57.37.

ε-Aminocaproyl-L-histidine (10) was prepd and purified as described before: yield, 86.0%; mp 236-237° dec; $[\alpha]^{25}D$ +25.0° (*c* 2, H_2O). *Anal.* ($C_{12}H_{20}N_4O_3$) C, H, N. The acid hydrolysis as described gave **5** and histidine.

B. Carbobenzoxy Method. Carbobenzoxy-δ-aminovaleric Acid.—To a soln of 20.6 g of **4** in 100 ml of 2 *N* NaOH in a flask cooled in an ice bath, 34 g of benzyl chloroformate and 50 ml of 4 *N* NaOH were added simultaneously to the vigorously stirred soln over a period of 20–25 min. The mixt was stirred for an additional 10 min. The soln was cooled in an ice bath and acidified to congo red with concd HCl. The ppt was filtered, washed with a small portion of cold H_2O, and dried in the desiccator *in vacuo*; yield, 60.4%; mp 102-103°. *Anal.* ($C_{13}H_{17}NO_4$) C, H, N.

L-Histidine Methyl Ester·2HCl.—A soln of 22.4 g of dry powdered L-histidine·2HCl and 320 ml of anhyd MeOH was heated on a water bath and dry HCl gas was introduced. The heating was continued for 3 hr. The resulting soln was cooled and allowed to stand in the ice bath and treated with Et_2O to furnish fine, colorless crystals which were recrystd from MeOH-Et_2O: yield, 96.0%; mp 198-199°; $[\alpha]^{25}D$ +3.5° (*c* 2, H_2O).

δ-Aminovaleryl-L-histidine (9).—To a soln of 12.5 g of Z-δ-aminovaleric acid in 250 ml of CH_2Cl_2 was added 7.0 ml of Et_3N. After the resulting soln had been chilled to −5°, 4.8 ml of ethylene chloroformate was added and the mixt was kept at the same temp for 10 min. To this soln was added rapidly a soln of L-histidine Me ester prepared by the addition of 21 ml of Et_3N to a soln of 12.2 g of L-histidine Me ester·2HCl in 250 ml of CH_2Cl_2 which had been chilled to 0°. The resulting mixt was stored at 25° for 2 days. It was then washed with 200 ml of H_2O and 200 ml of 1 *N* aq $NaHCO_3$, dried (Na_2SO_4), and concd to a syrup. It was dissolved in 100 ml of MeOH and 50 ml of 1 *N* aq NaOH was added. After storage for 3 hr at room temp, the soln was adjusted to pH 5 with 2 *N* H_2SO_4 and concd to dryness *in vacuo*. The syrupy residue was extd with two 50-ml portions of hot EtOH, and 50 ml of H_2O was added to the ext. After addition of 1.0 g of 10% Pd/C, the mixt was hydrogenated. The formation of CO_2 gas was checked occasionally until it ceased after 6 hr. The soln was filtered and concd *in vacuo*. The residual syrup was dissolved in 20 ml of H_2O and 2 *N* HCl added to give a pH below 5.0. The purification process by means of ion-exchange chromatography was the same as described before: yield, 71.8% (based on histidine Me ester·2HCl; mp 239-240° dec; $[\alpha]^{25}D$ +23.5° (*c* 2, H_2O). *Anal.* ($C_{11}H_{18}N_4O_3 \cdot H_2O$) C, H, N.

ε-Aminocaproyl-L-histidine (10).—Z-ε-Aminocaproic acid (13 g) was treated in the same way: yield, 76.0%; mp 238-239° dec; $[\alpha]^{25}D$ +25.4° (*c* 2, H_2O). *Anal.* ($C_{12}H_{20}N_4O_3$) C, H, N.

γ-Aminobutyryl-L-histidine (8).—Z-γ-Aminobutyric acid (12 g) was treated in the same way: yield, 83.6%; mp 242-244° dec; $[\alpha]^{25}D$ +4.0° (*c* 2, H_2O). *Anal.* ($C_{10}H_{16}N_4O_3 \cdot H_2SO_4$) C, H, N.

Acknowledgments.—We thank Dr. Leo G. Nutini, Professor of Biology and Experimental Medicine at the St. Thomas Institute, who established the anti-staphylococcal assay procedure, Dr. Floyd Green, of Matheson Coleman and Bell, for ir spectra, and Dr. Utako Okamoto, of the School of Medicine, Keio University, Tokyo, Japan, for valuable suggestions regarding the antifibrinolytic assay procedure. We are also indebted to the Ono Pharmaceutical Company, Ltd., Osaka, Japan, for a gift of γ-aminobutyryl-L-histidine monohydrate and the Daiichi Seiyaku Company, Ltd., Tokyo, Japan, for a gift of *trans*-4-aminomethylcyclohexane-1-carboxylic acid.

New Antiulcer Agents. 1. Syntheses and Biological Activities of 1-Acyl-2-, -3-, and -4-substituted Benzamidopiperidines

TSUTOMU IRIKURA* AND KAZUNORI KASUGA

Kyorin Chemical Laboratory, Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan

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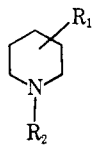
A variety of 2-, 3-, and 4-substituted benzamidopiperidines was prepared from the corresponding benzamidopyridines by a Pd-catalyzed hydrogenation of the ring; syntheses of 1-acyl-2-, -3-, and -4-substituted benzamidopiperidines are reported. These compounds were tested for curative activity on the chronic gastric ulcer in rats using the clamping-cortisone method. Some of these compounds, particularly 1-(*p*-aminobenzoyl)-4-(3,4,5-trimethoxybenzamido)piperidine, showed some antiulcer activity. Structure–activity relationships are discussed.

Pharmacologically active piperidines having one substituent at the 2, 3, or 4 position of the ring are mainly of the following 3 types.

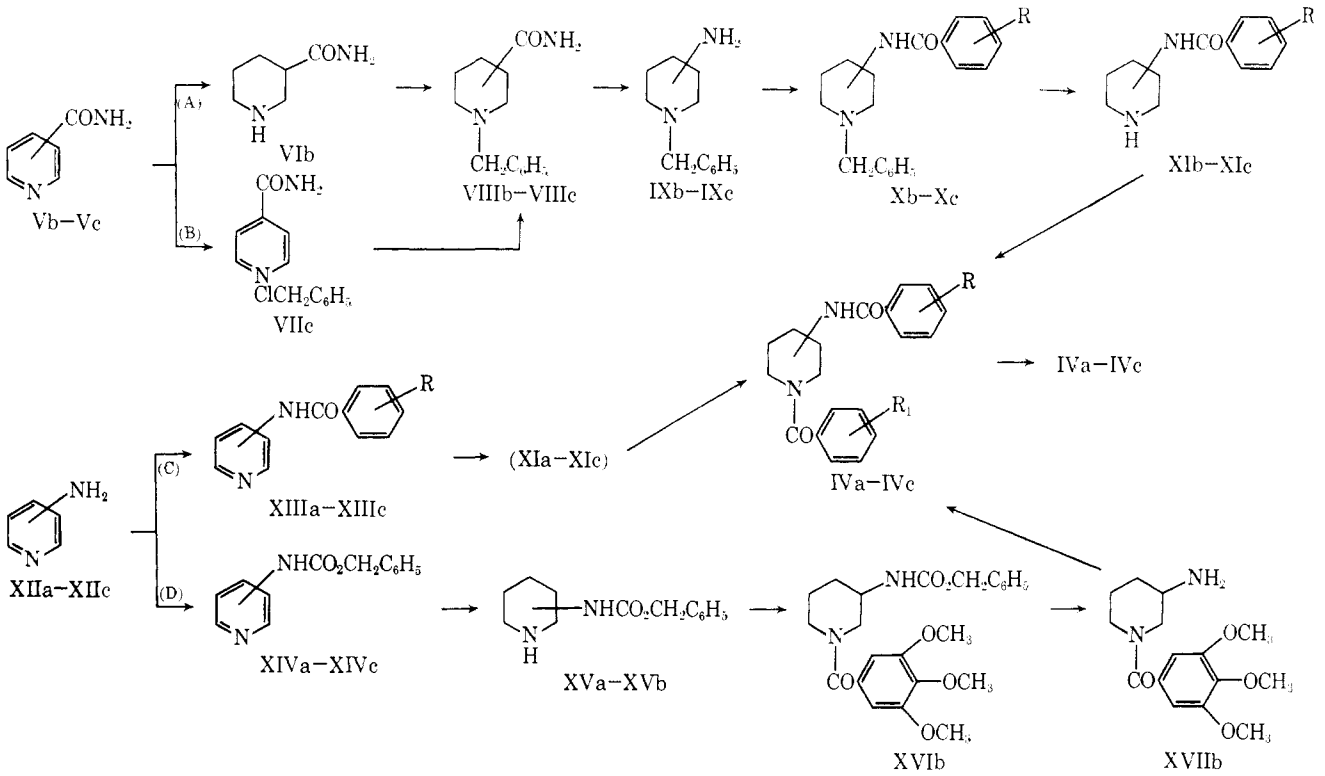


I, R_1
II, OR_1
III, NHR_1

Compounds I and II, where R_1 and R_2 signify various alkyl-, arylalkyl-, or CO-containing groups, have antihistaminic and antispasmodic activities. Aminopiperidine derivatives III, where R_1 and R_2 are various alkyl or arylalkyl groups, have been described as having antihistaminic and spasmolytic activities. However, diacyl compounds of type III do not appear to have been studied, although 1-benzoyl-3-benzamidopiperidine, 1-acetyl-4-acetamidopiperidine, and 1-benzoyl-4-benzamidopiperidine were obtained by Nienburg[1] and Tomita[2] in the course of the confirmation of the structure of aminopiperidine derivatives. We synthesized a series of 1-substituted benzoyl-2-, -3-, and -4-substituted benzamidopiperidines (IVa–IVc) and tested them for antiulcer activity by the clamping-cortisone method.

(1) H. Nienburg, *Chem. Ber.*, **70**, 635 (1937).
(2) K. Tomita, *Yakugaku Zasshi*, **71**, 1053 (1951).

SCHEME I



Methods which have been used heretofore in the syntheses of piperidines and aminopiperidines have been briefly summarized by Maruoka[3] and Walker, *et al.*[4] Yamada and Kikugawa[5] reported that 3-nitropiperidine could be obtained from 3-nitropyridine by the $NaBH_4$-catalyzed hydrogenation of the ring. Therefore, as shown in Scheme I, nicotinamide, isonicotinamide, and 2-, 3-, or 4-aminopyridine were used as the starting materials, and four procedures to synthesize *N,N'*-diacylaminopiperidines were studied. Among these, methods A and B were unsatisfactory, because acylamidopiperidines were obtained by a long process and in poor yield.

In method C, XIa–XIc were obtained by reducing XIIIa–XIIIc in HCl with 5 or 10% Pd/C at an initial pressure of 35–45 atm of H_2 at 60–80°. We found that the acylamidopyridine ring was easily reduced with 5% Pd/C. 1-Acyl-2-, -3-, and -4-acylamidopiperidines were obtained by treating XIa–XIc with an acyl chloride in the presence of aq $NaHCO_3$. When R or R_1 of IV was NO_2, the compound could be reduced with 10% Pd/C or Ra Ni in EtOH.

In method D, 2- and 3-piperidinecarbamic acid benzyl esters (XVa–XVb) were obtained by reducing 2- and 3-pyridinecarbamic acid benzyl ester (XIVa–XIVb) with PtO_2. 4-Pyridinecarbamic acid benzyl ester (XIVc), however, could not be reduced. An attempt to form 2- and 3-substituted derivatives (IVa–IVb) resulted in only obtaining 1-(3,4,5-trimethoxybenzoyl)-3-(*p*-aminobenzamido)piperidine (**74**). As a whole, method C was the most appropriate for the syntheses of *N,N'*-diacylaminopiperidines as a shorter processes with good yields; only **74** was obtained by method D. *N,N*-Diacylaminopiperidines and the intermediates synthesized are listed in Tables I–III.

(3) S. Maruoka, *Nippon Kagaku Zasshi*, **82**, 1257 (1961).

(4) G. N. Walker, M. A. Moore, and B. N. Weaver, *J. Org. Chem.*, **26**, 2740 (1961).

(5) S. Yamada and Y. Kikugawa, *Chem. Ind. (London)*, 2169 (1966).

Structure–Activity Relationships.—The results of tests by the clamping-cortisone method are recorded in Table IV. We did not record the compounds whose total curative ratio (*D*) was lower than 1.0 in this table, and we did not test nitro compounds. R had to be 3,4,5-$(CH_3O)_3$ since only **24** and **18** had healing activity. With regard to R_1 of 1-acyl-3-benzamidopiperidines, the total curative ratio (*D*) was 1.4 in **62**, but substitution on the para or ortho position of **62** with NH_2 or Cl enhanced the activity (**41**,**61**). Acetylation of NH_2 in **28** markedly reduced the curative activity (**76**). In the case of 1-acyl-4-benzamidopiperidines, **42** (R_1 = *p*-NH_2) had the greatest activity, while **48** and **70** (R_1 = *o*-NH_2, *o*-Cl) had less curative activity. Through the investigation of side effects, it was evident that 1-acyl-3-benzamidopiperidines (**28**, **35**, **41**, **58**, **63**, etc.) caused hypertrophy of the adrenals and atrophy of the testis at 1 g/kg orally for 4 consecutive days in rats. However, 1-acyl-4-benzamidopiperidines (**24**, **42**, **48**, **70**) had no side effects on the adrenals and sex organs. Consequently, we think that **42** is of potential interest as a therapeutic drug for gastric ulcer, because of its effectiveness in (A) ulcer repair, (B) mucus regeneration, and (C) collagen fiber proliferation, and its apparent lack of side effects.

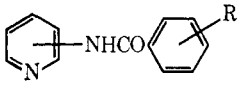
Experimental Section[6]

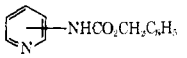
Biological Methods.[7]—Male Wistar strain rats (200–250 g) were used in this experiment. The animals were deprived of food for 24 hr prior to and for 48 hr after the operation, but were allowed free access to H_2O. Under Et_2O anesthesia, laparotomy

(6) The melting points were obtained on a micro hot stage and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(7) (a) S. Umehara, T. Tabayashi, E. Shibuya, H. Ito, M. Shimizu, and Y. Okiishi, *Chiryo*, **47**, 397 (1965); (b) T. Tabayashi and S. Umehara, *Nippon Shokakibyo Gakkai Zasshi*, **62**, 2037 (1965).

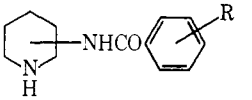
TABLE I

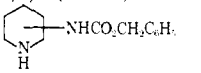


No.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]	Position in the pyridine ring
1	3,4,5-$(CH_3O)_3$	85	158–160	MeCN	$C_{15}H_{16}N_2O_4$	C, H, N	3
2	3,4,5-$(CH_3O)_3$	74	166–168.5	EtOH–H_2O	$C_{15}H_{16}N_2O_4$	C, H, N	4
3	4-CH_3O	88	171–173	EtOAc	$C_{13}H_{12}N_2O_2$	N	3
4	3,5-$(CH_3O)_2$	80	77–79	MeCN	$C_{14}H_{14}N_2O_3 \cdot H_2O$	C, H, N	3
5	4-CH_3O	65	144–147	MeCN	$C_{13}H_{12}N_2O_2$	N	4
6	4-CH_3O	53	97–102.5	EtOAc–PE[b]	$C_{13}H_{12}N_2O_2$	C, H; N[c]	2
7	2,3-$(CH_3O)_2$	31	109–112	MeCN	$C_{14}H_{14}N_2O_3$	N	3
8	2-CH_3O	45	134–136	MeCN	$C_{13}H_{12}N_2O_2 \cdot H_2O$	N	3
9	4-CH_3O	62	110–114	MeCN	$C_{13}H_{12}N_2O$	N	3
10	2-Cl	63	141–143	MeCN	$C_{12}H_9ClN_2O$	C, H, N	3
11	4-Cl	68	145–148	MeCN	$C_{12}H_9ClN_2O$	N	3
12	3,4-CH_2O_2	22	209–210	EtOH	$C_{13}H_{10}N_2O_3$	C, H, N	4
13[d]	3,4,5-$(CH_3O)_3$		55–57		$C_{15}H_{16}N_2O_4$	C, H, N	2
14[e]		42	143–145	MeCN	$C_{13}H_{12}N_2O_2$	C, H, N	2
15[e]		78	166–169	EtOH	$C_{13}H_{12}N_2O_2$	C, H, N	3
16[e]		83	163–165	MeCN	$C_{13}H_{12}N_2O_2$	C, H, N	4

[a] Analytical results for indicated elements are within ±0.4% of the theoretical values unless otherwise noted. [b] PE = petroleum ether. [c] N; calcd, 12.27; found, 11.85. [d] O. H. Hankovszky and K. Hideg, *J. Med. Chem.*, **9**, 151 (1966). [e] S. Sugasawa, S. Akaboshi, S. Toda, and H. Tomisawa, *Yakugaku Zasshi*, **72**, 192 (1952).

TABLE II



No.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]	Position in the piperidine ring
17	3,4,5-$(CH_3O)_3$	90	206–209	MeCN	$C_{15}H_{22}N_2O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N	3
18	3,4,5-$(CH_3O)_3$		179–181.5	MeCN	$C_{15}H_{22}N_2O_4$	C, H, N	3
19	4-CH_3O	80	234–236	MeOH	$C_{13}H_{18}N_2O_2$	N	3
20	3,5-$(CH_3O)_2$	88	224–226.5	MeOH	$C_{14}H_{20}N_2O_3 \cdot HCl$	C, H, N	3
21	2-CH_3O	85	209–211	EtOH	$C_{13}H_{18}N_2O_2 \cdot HCl$	N	3
22	2,3-$(CH_3O)_2$	90	215–216.5	MeCN	$C_{14}H_{20}N_2O_3 \cdot HCl$	C, H, N	3
23	3,4,5-$(CH_3O)_3$	84	145–149	MeCN	$C_{15}H_{22}N_2O_4 \cdot HCl \cdot H_2O$	C, H, N	4
24	3,4,5-$(CH_3O)_3$		185–186.5	C_6H_6	$C_{15}H_{22}N_2O_4$	C, H, N	4
25	3,4,5-$(CH_3O)_3$	80	147–150	MeCN	$C_{15}H_{22}N_2O_4 \cdot HCl$	N	2
26		74	98–100	C_6H_6–PE[b]	$C_{13}H_{18}N_2O_2$	N	2
27		81	105–110	C_6H_6–PE[b]	$C_{13}H_{18}N_2O_2$	C, H, N	3

[a,b] See corresponding footnotes in Table I.

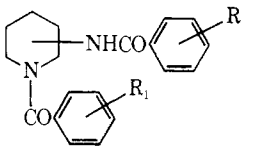
was performed through a midline epigastric incision. In the first laparotomy clamping was done with a gauze and an aluminum plate (12 × 4 mm) on the rat's stomach, which was placed on the greater curvature of the fundus, below the limiting ridge. After 24 hr, the second laparotomy was done to remove the aluminum plate and gauze. Cortisone acetate (0.07 mg/g) was administered intramuscularly for 7 days beginning on the day of the first operation. Chlortetracycline was administered to the animals to prevent infection by the oral route for a few days after the laparotomy.

Method C. 4-(3,4,5-Trimethoxybenzamido)pyridine [2, XIIIc, R = 3,4,5-(MeO)$_3$].—A soln of 49.5 g (0.215 mole) of 3,4,5-trimethoxybenzoyl chloride in 130 ml of C_6H_6 was added gradually to a soln of 20 g (0.212 mole) of 4-aminopyridine in 120 ml of C_6H_6, containing 24 g (0.304 mole) of pyridine, with vigorous stirring and cooling with an ice bath. The reaction mixt was heated for 3 hr with stirring under reflux. After cooling, the solid was filtered, neutralized by aq $NaHCO_3$, washed (H_2O), and recrystd from the solvent indicated in Table I to give **2** as colorless needles.

4-(3,4,5-Trimethoxybenzamido)piperidine [23, XIc, R = 3,4,5-(MeO)$_3$].—Compd **2** (3.0 g, 0.0104 mole) in 20 ml of EtOH containing 9 ml of H_2O and concd HCl (1.1 g, 0.0108 mole) was hydrogenated in the presence of 5% Pd/C (1.0 g) at an initial pressure of 40–45 atm at 70–80°. Uptake of H_2 was completed after 3 hr. The mixt was filtered from the catalyst. After removal of the solvent, the crude product was recrystd to give **23** as colorless prisms.

1-(*p*-Nitrobenzoyl)-4-(3,4,5-trimethoxybenzamido)piperidine [44, IVc, R = 3,4,5-(MeO)$_3$; R$_1$ = *p*-NO$_2$].—A soln of 4.3 g (0.024 mole) of *p*-nitrobenzoyl chloride in MeCN (12 ml) was gradually added to a soln of 7.7 g (0.024 mole) of **23** in 60 ml of H_2O, containing 5.4 g (0.064 mole) of $NaHCO_3$, with vigorous stirring and cooling. During the addition, the crude product sepd out. After stirring 1 hr at room temp, the product was filtered, washed (H_2O), and recrystd to give **44** as colorless needles.

TABLE III



No.	R	R_1	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]	Position in the piperidine ring
28	3,4,5-$(CH_3O)_3$	4-NH_2	88	125–127	*i*-PrOH–H_2O	$C_{22}H_{27}N_3O_5 \cdot H_2O$	C, H, N	3
29	3,4,5-$(CH_3O)_3$	4-NH_2		185–187	EtOH–*i*-PrOH	$C_{22}H_{27}N_3O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N	3
30	3,4,5-$(CH_3O)_3$	4-NO_2	80	121–124	MeCN	$C_{22}H_{25}N_3O_7 \cdot H_2O$	C, H, N	3
31	3,4,5-$(CH_3O)_3$	4-NH_2	77	214–216	DMF–MeCN	$C_{22}H_{25}N_3O_5 \cdot H_2O$	H, N; C[c]	2
32	3,4,5-$(CH_3O)_3$	4-NO_2	70	205–208	MeCN	$C_{22}H_{25}N_3O_5$	C, H, N	2
33	4-CH_3O	4-NH_2	70	225–228	MeCN	$C_{20}H_{23}N_3O_3 \cdot 0.5H_2O$	C, H	3
34	4-CH_3O	4-NO_2	66	186–188	MeCN	$C_{20}H_{21}N_3O_5$	C, H, N	3
35	3,5-$(CH_3O)_2$	4-NH_2	74	198–200	MeCN	$C_{21}H_{25}N_3O_4$	C, H, N	3
36	3,5-$(CH_3O)_2$	4-NO_2	73	214–216	MeCN	$C_{21}H_{23}N_3O_6$	N	3
37	3,4,5-$(CH_3O)_3$	3-NH_2	82	219–221	DMF–H_2O	$C_{22}H_{27}N_3O_5$	C, H, N	3
38	3,4,5-$(CH_3O)_3$	3-NO_2	98	97–100	DMF–H_2O	$C_{22}H_{25}N_3O_7 \cdot H_2O$	C, H, N	3
39	3,4,5-$(CH_3O)_3$	3,5-$(NH_2)_2$	72	164–167	*i*-PrOH	$C_{22}H_{28}N_4O_5 \cdot H_2O$	C, H, N	3
40	3,4,5-$(CH_3O)_3$	3,5-$(NO_2)_2$	62	128–131	MeCN	$C_{22}H_{24}N_4O_9$	N	3
41	3,4,5-$(CH_3O)_3$	2-NH_2	72	172–175	*i*-PrOH–H_2O	$C_{22}H_{27}N_3O_5$	C, H, N	3
42	3,4,5-$(CH_3O)_3$	4-NH_2	77	210–213	EtOH	$C_{22}H_{27}N_3O_5$	C, H, N	4
43	3,4,5-$(CH_3O)_3$	4-NH_2		195–198	MeOH–*i*-PrOH	$C_{22}H_{27}N_3O_5 \cdot HCl$	N	4
44	3,4,5-$(CH_3O)_3$	4-NO_2	79	252–254	MeCN	$C_{22}H_{25}N_3O_7$	C, H, N	4
45	3,4,5-$(CH_3O)_3$	4-NO_2		160–162	MeCN	$C_{22}H_{25}N_3O_7 \cdot H_2O$	C, H	4
46	3,4,5-$(CH_3O)_3$	3-NH_2	80	233–237	MeCN	$C_{22}H_{27}N_3O_5$	C, H, N	4
47	3,4,5-$(CH_3O)_3$	3-NO_2	62	158–161	EtOH	$C_{22}H_{25}N_3O_7$	C, H, N	4
48	3,4,5-$(CH_3O)_3$	2-NH_2	73	128–130	MeCN	$C_{22}H_{27}N_3O_5$	C, H, N	4
49	3,4,5-$(CH_3O)_3$	2-NO_2	60	199–201	EtOH	$C_{22}H_{25}N_3O_7$	N	4
50	4-CH_3O	3-NH_2	94	230–233	MeCN	$C_{20}H_{23}N_3O_3$	N	3
51	4-CH_3O	3-NO_2	55	170–172	MeCN	$C_{20}H_{21}N_3O_5$	C, H	3
52	3,4,5-$(CH_3O)_3$	3-NH_2, 4-Cl	88	153–156	*i*-PrOH–H_2O	$C_{22}H_{26}ClN_3O_5$	C, H, N	3
53	3,4,5-$(CH_3O)_3$	3-NO_2, 4-Cl	56	137–139	MeCN	$C_{22}H_{24}ClN_3O_7$	C, H; N[d]	3
54	3,4,5-$(CH_3O)_3$	3-NH_2, 4-Cl	77	235–239	MeCN	$C_{22}H_{26}ClN_3O_5$	H, N; C[e]	4
55	3,4,5-$(CH_3O)_3$	3-NO_2, 4-Cl	62	224–226	MeCN	$C_{22}H_{24}ClN_3O_7$	C, H	4
56	3,4,5-$(CH_3O)_3$	3,4,5-$(CH_3O)_3$	70	182–184	C_6H_6	$C_{25}H_{32}N_2O_8$	C, H, N	3
57	3,4,5-$(CH_3O)_3$	4-CH_3O	46	114–117	EtOAc–PE[b]	$C_{23}H_{28}N_2O_6 \cdot H_2O$	C, H, N	3
58	3,4,5-$(CH_3O)_3$	4-CH_3	73	103–105	C_6H_6	$C_{23}H_{28}N_2O_5 \cdot H_2O$	C, H, N	3
59	3,4,5-$(CH_3O)_3$	4-Cl	69	182–184	EtOAc–PE[b]	$C_{22}H_{25}ClN_2O_5$	C, H, N	3
60	3,5-$(CH_3O)_2$	4-Cl	65	92–95	MeCN	$C_{21}H_{23}ClN_2O_4 \cdot H_2O$	C, H, N	3
61	3,4,5-$(CH_3O)_3$	2-Cl	61	203–205	MeCN	$C_{22}H_{25}ClN_2O_5 \cdot H_2O$	C, H, N	3
62	3,4,5-$(CH_3O)_3$	H	58	193–196	MeCN	$C_{22}H_{26}N_2O_5$	C, H, N	3
63	4-CH_3	4-NH_2	83	217–218	MeCN	$C_{20}H_{23}N_3O_2 \cdot 0.5H_2O$	C, H, N	3
64	4-CH_3	4-NO_2	88	196–198	MeCN	$C_{20}H_{21}N_3O_4 \cdot H_2O$	C, H, N	3
65	4-Cl	4-NH_2	77	172–174	C_6H_6–PE[b]	$C_{19}H_{20}ClN_3O_2$	C, H; N[f]	3
66	4-Cl	4-NO_2	46	204–206	MeCN	$C_{19}H_{18}ClN_3O_4$	C, H, N	3
67	3,5-$(CH_3O)_2$	4-CH_3	90	177–178	C_6H_6–PE[b]	$C_{22}H_{26}N_2O_4$	N	3
68	4-CH_3O	4-Cl	82	208–210	MeCN	$C_{20}H_{21}ClN_2O_3$	C, H, N	3
69	3,4,5-$(CH_3O)_3$	2-Cl	76	197–199	EtOH	$C_{22}H_{25}ClN_2O_5$	C, H, N	4
70	3,4,5-$(CH_3O)_3$	4-Cl	79	232–235	EtOH	$C_{22}H_{25}ClN_2O_5$	C, H, N	4
71	3,4,5-$(CH_3O)_3$	4-CH_3	73	225–228	MeCN	$C_{23}H_{28}N_2O_5$	C, H, N	4
72	3,4,5-$(CH_3O)_3$	3-Br	77	165–168	MeCN	$C_{22}H_{19}BrN_2O_5$	C, H, N	4
73	4-CH_3O	2,4-Cl_2	58	165–168	MeCN	$C_{20}H_{26}Cl_2N_2O_3$	C, H, N	3
74	4-NH_2	3,4,5-$(CH_3O)_3$	72	257–259	*i*-PrOH–H_2O	$C_{22}H_{27}N_3O_5$	C, H, N	3
75	4-NO_2	3,4,5-$(CH_3O)_3$	82	105–108	MeCN–H_2O	$C_{22}H_{25}N_3O_7 \cdot H_2O$	C, N; H[g]	3
76	3,4,5-$(CH_3O)_3$	4-AcNH	87	139–143	MeCN	$C_{22}H_{29}N_3O_6 \cdot H_2O$	C, H, N	3

[a,b] See corresponding footnotes in Table I. [c] C; calcd, 63.90; found, 63.49. [d] N; calcd, 8.79; found, 9.20. [e] C; calcd, 58.99; found, 58.54. [f] N; calcd, 11.74; found, 11.27. [g] H; calcd, 5.90; found, 6.47.

1-(*p*-Aminobenzoyl)-4-(3,4,5-trimethoxybenzamido)piperidine [42, IVc, R = 3,4,5-(MeO)$_3$; R_1 = *p*-NH_2].—Compd **44** (3.5 g, 0.0079 mole) in 100 ml of EtOH was hydrogenated with 10% Pd/C (0.5 g) at ordinary temp and pressure. Uptake of H_2 was completed after 1–2 hr, and the reaction mixt was filtered from the catalyst. The filtrate was concd *in vacuo* to give colorless crystals which were recrystd to give **42** as colorless needles.

Method D. 3-Piperidinecarbamic Acid Benzyl Ester (27, XVb).—3-Pyridinecarbamic acid benzyl ester (2.3 g, 0.01 mole) (**15**, XIVb), obtained from XIIb and carbobenzoxy chloride in

TABLE IV

PHARMACOLOGICAL ACTIVITIES

No.	Ulcer index[a] A	B	C	TC	Dose, mg/kg, po	LD_{50}, mg/kg, ip
41	1.7	3.0	1.0	2.0	20	>1000
61	1.6	1.7	2.5	2.0	20	
42	2.1	1.4	2.5	1.9	20	>2000
35	2.2	1.6	2.1	1.9	20	>1000
31	1.4	2.5	1.2	1.8	15	>1000
58	1.7	1.5	2.0	1.7	20	>1000
68	1.6	1.5	2.0	1.7	20	
69	2.7	1.3	1.3	1.7	20	>1000
24	2.2	1.6	1.6	1.7	20	
28	2.2	1.2	2.2	1.7	20	>1000
63	1.6	1.5	2.0	1.7	20	
48	1.8	1.6	1.4	1.6	20	>1000
59	1.3	3.4	1.1	1.5	20	
39	0.9	4.0	1.5	1.5	20	
37	1.4	1.0	2.5	1.5	20	
18	1.2	1.2	2.3	1.5	20	
70	1.9	1.5	1.1	1.5	20	
33	1.6	1.1	2.0	1.4	20	
62	1.0	1.1	2.2	1.4	20	
76	1.1	1.0	2.2	1.3	20	
71	1.2	0.9	1.5	1.2	20	
57	0.0	1.0	2.6	1.1	20	
56	0.3	1.8	1.6	1.0	20	
Oxymethalone	2.2	1.2	1.5	1.7	50	

[a] Values indicate the ratio to the value of the control animals without receiving drugs for ulcer remedy.

the same manner as XIII from XII, was dissolved in 22 ml of EtOH containing 7 ml of H_2O and concd HCl (1.0 g, 0.01 mole) and was hydrogenated in the presence of PtO_2 (1.0 g) at 40–50° and 6 atm pressure. After H_2 uptake was completed, the mixt was cooled and filtered from the catalyst. EtOH was removed under reduced pressure, and the solid which sepd from the soln was filtered off. To the filtrate was added 10 ml of 10% aq Na_2CO_3, and the soln was extd with $CHCl_3$ and dried (Na_2SO_4). After the removal of the solvent, the resulting solid was recrystd to give **27**.

1-(3,4,5-Trimethoxybenzoyl)-3-aminopiperidine (XVIIb).—A soln of 2.2 g (0.0095 mole) of 3,4,5-trimethoxybenzoyl chloride in 5 ml of MeCN was added gradually to a soln of 2.2 g (0.0095 mole) of **27** and 0.6 g (0.0113 mole) of Na_2CO_3 in 6 ml of H_2O with vigorous stirring and cooling with an ice bath. After stirring 2 hr at room temp, the soln was extd with $CHCl_3$. The solvent was removed under reduced pressure, and the residue was hydrogenated with 10% Pd/C (0.2 g) in 100 ml of EtOH and concd HCl (0.7 ml) at ordinary temp and pressure. After H_2 uptake was completed, the mixt was filtered from the catalyst, the solvent was removed under reduced pressure, and the resulting solid was recrystd from EtOH–MeCN to give 1.6 g (65.2%) of an amorphous powder, mp 239–242°. *Anal.* ($C_{15}H_{22}N_2O_4 \cdot HCl \cdot H_2O$) C, H, N.

1-(3,4,5-Trimethoxybenzoyl)-3-(*p*-nitrobenzamido)piperidine [75, IVb, R = *p*-NO_2; R_1 = 3,4,5-(MeO)$_3$] was obtained from XVIIb by treating with *p*-nitrobenzoyl chloride as in method C.

1-(3,4,5-Trimethoxybenzoyl)-3-(*p*-aminobenzamido)piperidine [74, IVb, R = *p*-NH_2; R_1 = 3,4,5-(MeO)$_3$] was obtained from **75** in the same manner as **42** from **44**.

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Synthesis and Pharmacological Activity of Dihydrobenzofurans[1]

MATHIAS P. MERTES,* LARRY J. POWERS,

Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044

AND MILOS M. HAVA

Department of Pharmacology, University of Kansas Medical Center, Kansas City, Kansas 66103

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The synthesis of the cis and trans isomers of 5- and 7-dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran methiodide (**11a–d**) started with nitration of 3-acetoxy-2-methyl-2,3-dihydrobenzofuran and subsequent separation of the isomers *cis*-5-, *trans*-5-, *cis*-7-, and *trans*-7-nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofurans (**8a–d**). Catalytic reduction of the respective nitro compounds in the presence of CH_2O gave the corresponding dimethylamino compounds **9a–d**. Deacetylation to the alcohols **10a–d** and treatment with MeI yielded **11a–d**. Nitration of 2-methylcoumaran-3-one gave the 5- and 7-nitro ketones (**5a** and **5b**). Reduction and concurrent methylation with CH_2O followed by treatment of the separated isomers with MeI afforded 5-dimethylamino-2-methylcoumaran-3-one methiodide (**6a**) and the 7 isomer (**6b**). Using an excess of CH_2O in the same sequence with **5a** yielded the alcohol addition product, 5-dimethylamino-2-hydroxymethyl-2-methylcoumaran-3-one methiodide (**7**). Biological examination revealed muscarinic action (**6a**, 1/100 ACh) and nicotinic activity (**6a**, 1/20 nicotine, **11a**, 1/100 nicotine, **11b**, 1/200 nicotine). Both butyryl- and acetylcholinesterase were inhibited by **6a** and **6b**; the potency of **6a** ($K_i = 2.5 \times 10^{-8}$) was reflected in the LD_{50} (10 mg/kg). The remainder of the compounds displayed little or no activity and low toxicity (LD_{50} 50 to 200 mg/kg) with the exception of **11a** which was a weak muscarinic antagonist.

Acetylcholine (ACh) can assume an infinite number of conformations; based on this a great deal of research has been described that has restricted this freedom by the synthesis of rigid analogs of ACh.[2,3] Agents with a limited number of allowable conformations having both potent muscarinic and nicotinic effects are muscarine

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