

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°; $[\alpha]^{25}_D +16.6^\circ$ (*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; $[\alpha]^{25}_D +25.0^\circ$ (*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 coned 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°; $[\alpha]^{25}_D +3.5^\circ$ (*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 coned 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 coned 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 coned *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; $[\alpha]^{25}_D +23.5^\circ$ (*c* 2, H_2O). *Anal.* ($C_{11}H_{15}N_4O_3 \cdot H_2O$) 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; $[\alpha]^{25}_D +25.4^\circ$ (*c* 2, H_2O). *Anal.* ($C_{13}H_{20}N_4O_3$) 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; $[\alpha]^{25}_D +4.0^\circ$ (*c* 2, H_2O). *Anal.* ($C_{10}H_{16}N_4O_3 \cdot H_2SO_4$) C, H, N.

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

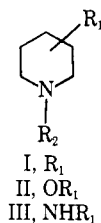
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A variety of 2-, 3-, and 4-substituted benzamidopiperidines was prepared from the corresponding benzamidopyridines by a Pd-catalyzed hydrogenation of the ring; syntheses of 1-acyl-2-, -3-, and -4-substituted benzamidopiperidines are reported. These 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.



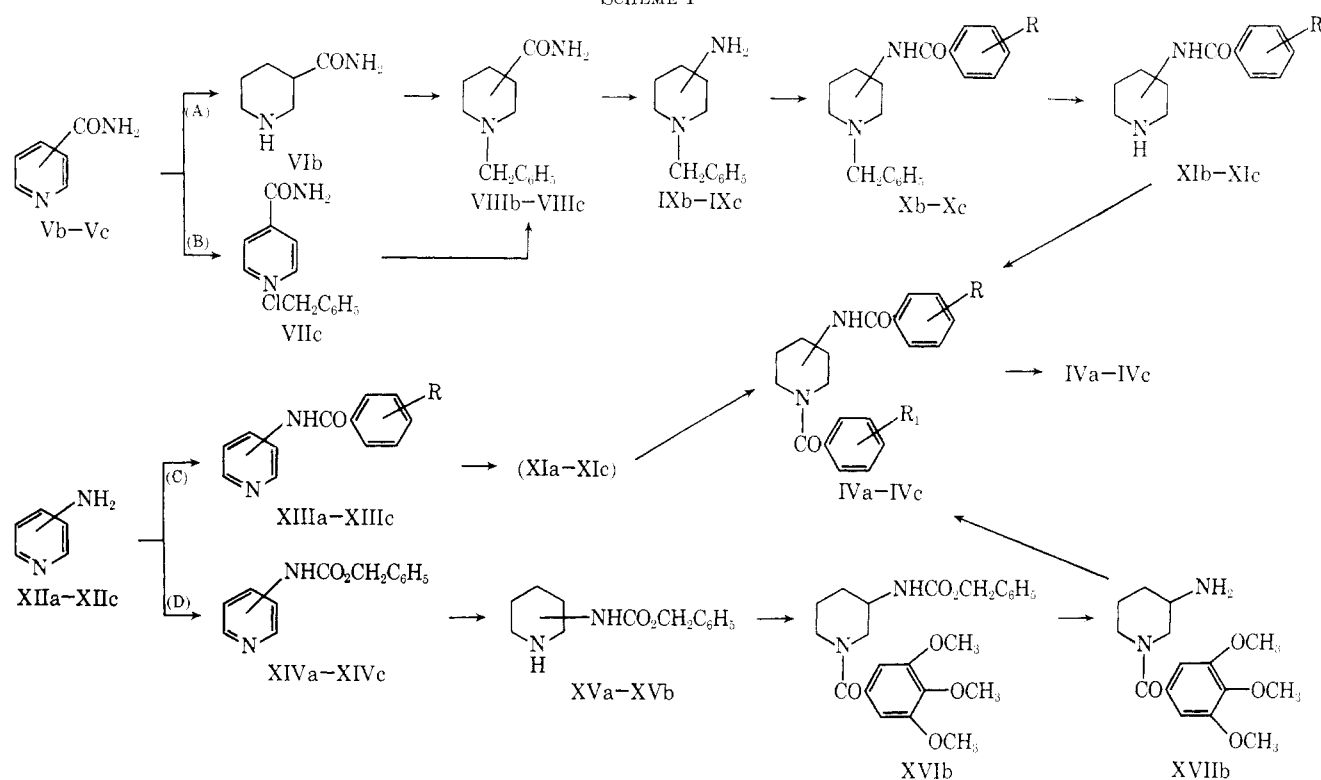
Compounds I and II, where R_1 and R_2 signify various alkyl-, arylalkyl-, or CO-containing groups, have antihistaminic and antispasmodic activities. Aminopi-

peridine 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 Nienburg¹ and Tomita² 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 Maruoka³ and Walker, *et al.*⁴ Yamada and Kikugawa⁵ 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.

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 ($\text{R}_1 = p\text{-NH}_2$) had the greatest activity, while 48 and 70 ($\text{R}_1 = o\text{-NH}_2, o\text{-Cl}$) 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 Section⁶

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

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

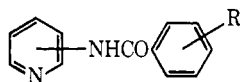
(4) G. N. Walker, M. A. Moore, and B. N. Weaver, *J. Org. Chem.*, **26**, 2740 (1961).

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

(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 $\pm 0.4\%$ 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).

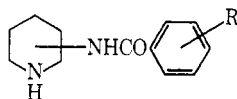
TABLE I



No.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses ^a	Position in the pyridine ring
1	3,4,5-(CH ₃ O) ₃	85	158-160	MeCN	C ₁₅ H ₁₈ N ₂ O ₄	C, H, N	3
2	3,4,5-(CH ₃ O) ₃	74	166-168.5	EtOH-H ₂ O	C ₁₅ H ₁₈ N ₂ O ₄	C, H, N	4
3	4-CH ₃ O	88	171-173	EtOAc	C ₁₃ H ₁₂ N ₂ O ₂	N	3
4	3,5-(CH ₃ O) ₂	80	77-79	MeCN	C ₁₄ H ₁₄ N ₂ O ₃ ·H ₂ O	C, H, N	3
5	4-CH ₃ O	65	144-147	MeCN	C ₁₃ H ₁₂ N ₂ O ₂	N	4
6	4-CH ₃ O	53	97-102.5	EtOAc-PE ^b	C ₁₃ H ₁₂ N ₂ O ₂	C, H; N ^c	2
7	2,3-(CH ₃ O) ₂	31	109-112	MeCN	C ₁₄ H ₁₄ N ₂ O ₃	N	3
8	2-CH ₃ O	45	134-136	MeCN	C ₁₃ H ₁₂ N ₂ O ₂ ·H ₂ O	N	3
9	4-CH ₃ O	62	110-114	MeCN	C ₁₃ H ₁₂ N ₂ O	N	3
10	2-Cl	63	141-143	MeCN	C ₁₂ H ₉ ClN ₂ O	C, H, N	3
11	4-Cl	68	145-148	MeCN	C ₁₂ H ₉ ClN ₂ O	N	3
12	3,4-CH ₂ O ₂	22	209-210	EtOH	C ₁₃ H ₁₀ N ₂ O ₃	C, H, N	4
13 ^d	3,4,5-(CH ₃ O) ₃		55-57		C ₁₅ H ₁₈ N ₂ O ₄	C, H, N	2
14 ^e		42	143-145	MeCN	C ₁₃ H ₁₂ N ₂ O ₂	C, H, N	2
15 ^e		78	166-169	EtOH	C ₁₅ H ₁₂ N ₂ O ₂	C, H, N	3
16 ^e		83	163-165	MeCN	C ₁₃ H ₁₂ N ₂ O ₂	C, H, N	4

^a Analytical results for indicated elements are within $\pm 0.4\%$ 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. Sugawara, 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 ₃ O) ₃	90	206-209	MeCN	C ₁₅ H ₂₂ N ₂ O ₄ ·HCl·0.5H ₂ O	C, H, N	3
18	3,4,5-(CH ₃ O) ₃		179-181.5	MeCN	C ₁₅ H ₂₂ N ₂ O ₄	C, H, N	3
19	4-CH ₃ O	80	234-236	MeOH	C ₁₃ H ₁₈ N ₂ O ₂	N	3
20	3,5-(CH ₃ O) ₂	88	224-226.5	MeOH	C ₁₄ H ₂₀ N ₂ O ₃ ·HCl	C, H, N	3
21	2-CH ₃ O	85	209-211	EtOH	C ₁₃ H ₁₈ N ₂ O ₂ ·HCl	N	3
22	2,3-(CH ₃ O) ₂	90	215-216.5	MeCN	C ₁₄ H ₂₀ N ₂ O ₃ ·HCl	C, H, N	3
23	3,4,5-(CH ₃ O) ₃	84	145-149	MeCN	C ₁₅ H ₂₂ N ₂ O ₄ ·HCl·H ₂ O	C, H, N	4
24	3,4,5-(CH ₃ O) ₃		185-186.5	C ₆ H ₆	C ₁₅ H ₂₂ N ₂ O ₄	C, H, N	4
25	3,4,5-(CH ₃ O) ₃	80	147-150	MeCN	C ₁₅ H ₂₂ N ₂ O ₄ ·HCl	N	2
26		74	98-100	C ₆ H ₆ -PE ^b	C ₁₃ H ₁₈ N ₂ O ₂	N	2
27		81	105-110	C ₆ H ₆ -PE ^b	C ₁₃ H ₁₈ N ₂ O 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.

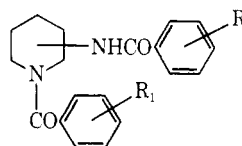
Method C. 4-(3,4,5-Trimethoxybenzamido)pyridine [2, XIIIc, R = 3,4,5-(MeO)₃].—A soln of 49.5 g (0.215 mole) of 3,4,5-trimethoxybenzoyl chloride in 130 ml of C₆H₆ was added gradually to a soln of 20 g (0.212 mole) of 4-aminopyridine in 120 ml of C₆H₆, containing 24 g (0.304 mole) of pyridine, with vigorous 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 NaHCO₃, washed (H₂O),

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 H₂O 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 H₂ 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; R₁ = p-NO₂].—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 H₂O, containing 5.4 g (0.064 mole) of NaHCO₃, 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 (H₂O), 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 piperi- dine ring
28	3,4,5-(CH ₃ O) ₃	4-NH ₂	88	125-127	<i>i</i> -PrOH-H ₂ O	C ₂₂ H ₂₇ N ₃ O ₅ ·H ₂ O	C, H, N	3
29	3,4,5-(CH ₃ O) ₃	4-NH ₂		185-187	EtOH- <i>i</i> -PrOH	C ₂₂ H ₂₇ N ₃ O ₅ ·HCl·0.5H ₂ O	C, H, N	3
30	3,4,5-(CH ₃ O) ₃	4-NO ₂	80	121-124	MeCN	C ₂₂ H ₂₅ N ₃ O ₇ ·H ₂ O	C, H, N	3
31	3,4,5-(CH ₃ O) ₃	4-NH ₂	77	214-216	DMF-MeCN	C ₂₂ H ₂₅ N ₃ O ₅ ·H ₂ O	H, N; C ^c	2
32	3,4,5-(CH ₃ O) ₃	4-NO ₂	70	205-208	MeCN	C ₂₂ H ₂₅ N ₃ O ₇	C, H, N	2
33	4-CH ₃ O	4-NH ₂	70	225-228	MeCN	C ₂₀ H ₂₃ N ₃ O ₅ ·0.5H ₂ O	C, H	3
34	4-CH ₃ O	4-NO ₂	66	186-188	MeCN	C ₂₀ H ₂₁ N ₃ O ₇	C, H, N	3
35	3,5-(CH ₃ O) ₂	4-NH ₂	74	198-200	MeCN	C ₂₁ H ₂₅ N ₃ O ₅	C, H, N	3
36	3,5-(CH ₃ O) ₂	4-NO ₂	73	214-216	MeCN	C ₂₁ H ₂₃ N ₃ O ₇	N	3
37	3,4,5-(CH ₃ O) ₃	3-NH ₂	82	219-221	DMF-H ₂ O	C ₂₂ H ₂₇ N ₃ O ₅	C, H, N	3
38	3,4,5-(CH ₃ O) ₃	3-NO ₂	98	97-100	DMF-H ₂ O	C ₂₂ H ₂₅ N ₃ O ₇ ·H ₂ O	C, H, N	3
39	3,4,5-(CH ₃ O) ₃	3,5-(NH ₂) ₂	72	164-167	<i>i</i> -PrOH	C ₂₂ H ₂₈ N ₄ O ₅ ·H ₂ O	C, H, N	3
40	3,4,5-(CH ₃ O) ₃	3,5-(NO ₂) ₂	62	128-131	MeCN	C ₂₂ H ₂₄ N ₄ O ₉	N	3
41	3,4,5-(CH ₃ O) ₃	2-NH ₂	72	172-175	<i>i</i> -PrOH-H ₂ O	C ₂₂ H ₂₇ N ₃ O ₅	C, H, N	3
42	3,4,5-(CH ₃ O) ₃	4-NH ₂	77	210-213	EtOH	C ₂₂ H ₂₇ N ₃ O ₅	C, H, N	4
43	3,4,5-(CH ₃ O) ₃	4-NH ₂		195-198	MeOH- <i>i</i> -PrOH	C ₂₂ H ₂₇ N ₃ O ₅ ·HCl	N	4
44	3,4,5-(CH ₃ O) ₃	4-NO ₂	79	252-254	MeCN	C ₂₂ H ₂₅ N ₃ O ₇	C, H, N	4
45	3,4,5-(CH ₃ O) ₃	4-NO ₂		160-162	MeCN	C ₂₂ H ₂₅ N ₃ O ₇ ·H ₂ O	C, H	4
46	3,4,5-(CH ₃ O) ₃	3-NH ₂	80	233-237	MeCN	C ₂₂ H ₂₇ N ₃ O ₅	C, H, N	4
47	3,4,5-(CH ₃ O) ₃	3-NO ₂	62	158-161	EtOH	C ₂₂ H ₂₅ N ₃ O ₇	C, H, N	4
48	3,4,5-(CH ₃ O) ₃	2-NH ₂	73	128-130	MeCN	C ₂₂ H ₂₇ N ₃ O ₅	C, H, N	4
49	3,4,5-(CH ₃ O) ₃	2-NO ₂	60	199-201	EtOH	C ₂₂ H ₂₅ N ₃ O ₇	N	4
50	4-CH ₃ O	3-NH ₂	94	230-233	MeCN	C ₂₀ H ₂₃ N ₃ O ₅	N	3
51	4-CH ₃ O	3-NO ₂	55	170-172	MeCN	C ₂₀ H ₂₁ N ₃ O ₇	C, H	3
52	3,4,5-(CH ₃ O) ₃	3-NH ₂ , 4-Cl	88	153-156	<i>i</i> -PrOH-H ₂ O	C ₂₂ H ₂₆ ClN ₃ O ₅	C, H, N	3
53	3,4,5-(CH ₃ O) ₃	3-NO ₂ , 4-Cl	56	137-139	MeCN	C ₂₂ H ₂₄ ClN ₃ O ₇	C, H, N ^d	3
54	3,4,5-(CH ₃ O) ₃	3-NH ₂ , 4-Cl	77	235-239	MeCN	C ₂₂ H ₂₆ ClN ₃ O ₅	H, N; C ^e	4
55	3,4,5-(CH ₃ O) ₃	3-NO ₂ , 4-Cl	62	224-226	MeCN	C ₂₂ H ₂₄ ClN ₃ O ₇	C, H	4
56	3,4,5-(CH ₃ O) ₃	3,4,5-(CH ₃ O) ₃	70	182-184	C ₆ H ₆	C ₂₅ H ₃₂ N ₂ O ₈	C, H, N	3
57	3,4,5-(CH ₃ O) ₃	4-CH ₃ O	46	114-117	EtOAc-PE ^b	C ₂₃ H ₂₈ N ₂ O ₆ ·H ₂ O	C, H, N	3
58	3,4,5-(CH ₃ O) ₃	4-CH ₃	73	103-105	C ₆ H ₆	C ₂₃ H ₂₈ N ₂ O ₅ ·H ₂ O	C, H, N	3
59	3,4,5-(CH ₃ O) ₃	4-Cl	69	182-184	EtOAc-PE ^b	C ₂₂ H ₂₅ ClN ₂ O ₅	C, H, N	3
60	3,5-(CH ₃ O) ₂	4-Cl	65	92-95	MeCN	C ₂₁ H ₂₃ ClN ₂ O ₄ ·H ₂ O	C, H, N	3
61	3,4,5-(CH ₃ O) ₃	2-Cl	61	203-205	MeCN	C ₂₂ H ₂₅ ClN ₂ O ₅ ·H ₂ O	C, H, N	3
62	3,4,5-(CH ₃ O) ₃	H	58	193-196	MeCN	C ₂₂ H ₂₆ N ₂ O ₅	C, H, N	3
63	4-CH ₃	4-NH ₂	83	217-218	MeCN	C ₂₀ H ₂₃ N ₃ O ₂ ·0.5H ₂ O	C, H, N	3
64	4-CH ₃	4-NO ₂	88	196-198	MeCN	C ₂₀ H ₂₁ N ₃ O ₄ ·H ₂ O	C, H, N	3
65	4-Cl	4-NH ₂	77	172-174	C ₆ H ₆ -PE ^b	C ₁₉ H ₂₀ ClN ₃ O ₂	C, H, N ^f	3
66	4-Cl	4-NO ₂	46	204-206	MeCN	C ₁₉ H ₁₈ ClN ₃ O ₄	C, H, N	3
67	3,5-(CH ₃ O) ₂	4-CH ₃	90	177-178	C ₆ H ₆ -PE ^b	C ₂₂ H ₂₆ N ₂ O ₄	N	3
68	4-CH ₃ O	4-Cl	82	208-210	MeCN	C ₂₀ H ₂₁ ClN ₂ O ₃	C, H, N	3
69	3,4,5-(CH ₃ O) ₃	2-Cl	76	197-199	EtOH	C ₂₂ H ₂₅ ClN ₂ O ₅	C, H, N	4
70	3,4,5-(CH ₃ O) ₃	4-Cl	79	232-235	EtOH	C ₂₂ H ₂₅ ClN ₂ O ₅	C, H, N	4
71	3,4,5-(CH ₃ O) ₃	4-CH ₃	73	225-228	MeCN	C ₂₃ H ₂₈ N ₂ O ₃	C, H, N	4
72	3,4,5-(CH ₃ O) ₃	3-Br	77	165-168	MeCN	C ₂₂ H ₁₉ BrN ₂ O ₃	C, H, N	4
73	4-CH ₃ O	2,4-Cl ₂	58	165-168	MeCN	C ₂₀ H ₂₆ Cl ₂ N ₂ O ₃	C, H, N	3
74	4-NH ₂	3,4,5-(CH ₃ O) ₃	72	257-259	<i>i</i> -PrOH-H ₂ O	C ₂₂ H ₂₇ N ₃ O ₅	C, H, N	3
75	4-NO ₂	3,4,5-(CH ₃ O) ₃	82	105-108	MeCN-H ₂ O	C ₂₂ H ₂₅ N ₃ O ₇ ·H ₂ O	C, N; H ^g	3
76	3,4,5-(CH ₃ O) ₃	4-AcNH	87	139-143	MeCN	C ₂₂ H ₂₉ N ₃ O ₆ ·H ₂ O	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; R₁ = *p*-NH₂].—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 H₂ was completed after 1-2 hr, and the reaction mixt was filtered

from the catalyst. The filtrate was coned *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				Dose, mg/kg, po	LD ₅₀ , mg/kg, ip
	A	B	C	TC		
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 H₂O and concd HCl (1.0 g, 0.01 mole)

and was hydrogenated in the presence of PtO₂ (1.0 g) at 40–50° and 6 atm pressure. After H₂ 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 Na₂CO₃, and the soln was extd with CHCl₃ and dried (Na₂SO₄). 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 Na₂CO₃ in 6 ml of H₂O with vigorous stirring and cooling with an ice bath. After stirring 2 hr at room temp, the soln was extd with CHCl₃. 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 H₂ 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.* (C₁₅H₂₂N₂O₄·HCl·H₂O) C, H, N.

1-(3,4,5-Trimethoxybenzoyl)-3-(p-nitrobenzamido)piperidine [75, IVb, R = p-NO₂; R₁ = 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-NH₂; R₁ = 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 Dihydrobenzofurans¹

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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 CH₂O 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 CH₂O 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 CH₂O 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 LD₅₀ (10 mg/kg). The remainder of the compounds displayed little or no activity and low toxicity (LD₅₀ 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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