Formula	Calcd., % C	H	N	F	Neut. equiv.	Found, % C	H	N	F	Neut. equiv.
$C_9H_{14}O_5$	...	...	...	...	...	...	...	...	...	...
$C_9H_{13}FO_5 \cdot H_2O$	45.38	6.35	...	...	...	45.26	5.92	...	...	...
$C_{15}H_{17}FN_4O_8$	45.00	4.28	14.00	4.75	...	44.43	3.68	13.93	5.37	...
$C_4H_5FO_3 \cdot 0.5H_2O$	37.2	4.68	...	...	...	37.98	4.72	...	...	...
$C_4H_5FO_3 \cdot 1.5H_2O$	...	...	...	12.9	147.0	...	...	...	12.36	146.6
$C_4H_5FO_3 \cdot 3H_2O$	27.6	6.38	...	10.92	...	27.8	6.54	...	11.10	...
$C_{10}H_{16}O_5$	...	...	...	...	...	...	...	...	...	...
$C_{10}H_{13}FO_5$	51.28	6.46	...	8.11	...	50.50	6.23	...	8.31	...
$C_{16}H_{19}FN_4O_8$	46.38	4.62	13.52	4.59	...	45.91	4.49	13.15	5.36	...
$C_5H_7FO_3$	44.78	5.26	...	14.17	134.1	44.10	5.58	...	13.51	139.6
$C_5H_7FO_3 \cdot 1.5H_2O$	37.27	6.26	...	11.79	161.1	38.00	5.75	...	11.01	159.0
$C_{15}H_{18}O_5$	...	...	...	...	...	...	...	...	...	...
$C_{15}H_{17}FO_5$	60.80	5.78	...	6.41	...	61.46	5.84	...	6.03	...
$C_{21}H_{21}FN_4O_8$	52.94	4.44	...	3.99	...	53.26	4.44	...	4.38	...
$C_{10}H_9FO_3 \cdot H_2O$	56.07	5.18	...	8.87	214.2	56.13	5.14	...	8.79	218.2

21, 1949); *Chem. Abstr.*, **44**, 3025*b* (1950). [f] Nondistillable liquid. [g] Nondistillable liquid. The analytical sample was prepared by passing a solution [4 g. in a mixture of 50 ml. of ether and 50 ml. of petroleum ether (b.p. 30–60°)] through a 6 × 150 mm. column of alumina (Matheson Coleman and Bell chromatographic grade, 80–200 mesh).

TABLE III

EFFECT OF COMPOUNDS ON RABBIT MUSCLE LACTATE DEHYDROGENASE (RATES OF REDUCTION BY DPNH)[a]

Compound	Concn., *M*	Rate relative to pyruvate—Compd. alone	Compd. plus pyruvate
$CH_3COCOOH$	1×10^{-2}	1.00[b]	...
$FCH_2COCOOH$	1×10^{-3}	0.48	0.97
$CH_3CHFCOCOOH$ (III)	1×10^{-3}	0.19	1.03
$CH_3CH_2CHFCOCOOH$ (VI)	1×10^{-3}	0.02	1.05
$C_6H_5CH_2CHFCOCOOH$ (IX)	1×10^{-3}	0.00	0.97

[a] Rates were determined by following the decrease in optical density at 340 mμ with a Beckman DU spectrophotometer. Each cuvette contained 2.00 ml. of triethanolamine buffer (0.4 *M*, adjusted to pH 7.4 with HCl, prepared according to H. U. Bergmeyer, "Methods of Enzymatic Analysis," Academic Press Inc., New York, N. Y., 1963, p. 254); 0.40 ml. of DPNH, 5×10^{-4} *M*; 0.60 ml. of substrate and/or inhibitor; and 0.002 ml. of lactate dehydrogenase (0.1 mg./ml.). DPNH and lactate dehydrogenase from rabbit muscle were obtained from Sigma Chemical Co., St. Louis, Mo. The reaction was started by the addition of enzyme and the optical density change was measured against a blank containing all the components listed above except DPNH. [b] This rate (40.8 μmoles of DPN formed/min.) was arbitrarily taken as 1.00.

and VI). In the case of compounds III and VI, the anhydrous acid was converted to the sesquihydrates IIIa and VIa by allowing it to stand exposed to the air for a few hours. Upon heating (about 70°) in a beaker covered with a watch glass, IIIa melted and evaporated; the condensate on the watch glass soon solidified, giving the trihydrate IIIb.

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Preparation of Some ω-(Pyridylalkyl)benzamide and Benzoate Derivatives

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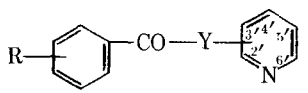
In the present communication we report on the preparation of some pyridylalkyl esters and amides of benzoic acid and its nuclear-substituted derivatives and their quaternary salts. The appropriate acid chloride was treated in benzene solution with 2-(β-aminoethyl)pyridine, 2-aminopyridine, and γ-hydroxypropylpyridine. On boiling the mixture for several hours the base of the corresponding acid amide was obtained from the benzene filtrate. Acid esters were isolated as hydrochlorides after evaporation of the filtrate, dissolving the residue in ethanol, and acidification by hydrochloric acid. The hydrochlorides and methiodides of the acid amide derivatives were also prepared. The compounds thus prepared are listed in Table I.

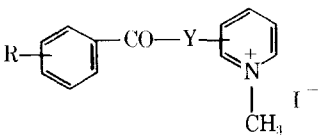
According to Dew's method the compounds showed a sedative activity against the excitant effect of deoxyephedrine (DOE).[1] For comparison, Trioxazine (3,4,5-trimethoxybenzoylmorpholine), a new Hungarian drug, was chosen.[2] Some biological properties of the most active compounds are shown in Table II.

(1) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).
(2) J. Borsy, *Arch. Intern. Pharmacodyn.*, **127**, 426 (1960).

TABLE I



Compd.	R	-Y-	Yield, %	M.p., °C.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Cl, % Calcd.	Cl, % Found	N, % Calcd.	N, % Found	Position in the pyridine
1	H	NH	76	183–184	$C_{12}H_{10}N_2O$	72.72	72.54	5.08	5.16			14.14	13.53	2′
				174–176	$C_{12}H_{10}N_2O\cdot HCl$					15.11	15.24	11.94	12.07	
2	H	$NH(CH_2)_2$	66	68–70	$C_{14}H_{14}N_2O$	74.31	74.18	6.23	6.13			12.38	12.18	2′
3	3,4,5-$(CH_3O)_3$	NH	89	55–57	$C_{15}H_{16}N_2O_4$	62.50	62.65	5.59	5.63			9.71	9.94	2′
				200–201	$C_{15}H_{16}N_2O_4\cdot HCl$					10.92	11.08	8.62	8.77	
4	3,4,5-$(CH_3O)_3$	$NH(CH_2)_2$	66	121–122	$C_{17}H_{20}N_2O_4$	64.54	64.23	6.37	6.18			8.85	8.53	2′
				180–182	$C_{17}H_{20}N_2O_4\cdot HCl$					10.05	10.25	7.94	7.76	
5	H	$O(CH_2)_3$	56	Hygr.	$C_{15}H_{13}NO_2\cdot HCl$					12.77	12.50	5.04	5.30	2′
				120–125										
6	H	$O(CH_2)_3$	65	123–127	$C_{15}H_{15}NO_2\cdot HCl$					12.77	12.63	5.04	5.08	3′
7	H	$O(CH_2)_3$	54	130–134	$C_{15}H_{15}NO_2\cdot HCl$					12.77	12.82	5.04	5.14	4′
8	3,4,5-$(CH_3O)_3$	$O(CH_2)_3$	81	158–162	$C_{18}H_{21}NO_5\cdot HCl$					9.64	9.88	3.80	4.17	2′
9	3,4,5-$(CH_3O)_3$	$O(CH_2)_3$	89	162–164	$C_{18}H_{21}NO_5\cdot HCl$					9.64	9.54	3.80	3.86	3′
10	3,4,5-$(CH_3O)_3$	$O(CH_2)_3$	86	171–177	$C_{18}H_{21}NO_5\cdot HCl$					9.64	9.68	3.80	3.65	4′
11	3,5-Cl_2	$O(CH_2)_3$	47	151–155	$C_{15}H_{13}Cl_2NO_2\cdot HCl$	51.97	52.42	4.07	4.27			4.04	4.28	2′
12	3,5-Cl_2	$O(CH_2)_3$	53	156–158	$C_{15}H_{13}Cl_2NO_2\cdot HCl$	51.97	52.18	4.07	4.23			4.04	3.91	3′
13	3,5-Cl_2	$O(CH_2)_3$	67	168–174	$C_{15}H_{13}Cl_2NO_2\cdot HCl$	51.97	52.20	4.07	4.40			4.04	4.37	4′
14	4-NO_2	$O(CH_2)_3$	42	153–156	$C_{15}H_{14}N_2O_4\cdot HCl$	55.82	55.46	4.68	5.18			8.68	8.63	2′
15	4-NO_2	$O(CH_2)_3$	60	106–110	$C_{15}H_{14}N_2O_4\cdot HCl$	55.82	55.42	4.68	4.52			8.68	8.62	3′
16	4-NO_2	$O(CH_2)_3$	71	131–133	$C_{15}H_{14}N_2O_4\cdot HCl$	55.82	55.90	4.68	4.84			8.68	8.70	4′
17	2-Cl	$O(CH_2)_3$		118–122	$C_{15}H_{14}ClNO_2\cdot HCl$	57.71	57.80	4.84	4.80			4.49	4.24	4′



18	H	NH	35	225–228	$C_{13}H_{13}IN_2O$							8.23	8.29	2′
19	H	$NH(CH_2)_2$	56	168–172	$C_{15}H_{17}IN_2O$							7.61	7.59	2′
20	3,4,5-$(CH_3O)_3$	NH	72	184–185	$C_{16}H_{19}IN_2O_4$							6.51	6.26	2′
21	3,4,5-$(CH_3O)_3$	$NH(CH_2)_2$	86	165–167	$C_{18}H_{23}IN_2O_4$[a]							6.11	5.89	2′

[a] *Anal.* Calcd.: I, 27.69. Found: I, 27.29.

TABLE II

Compd. no.[a]	LD50 mouse, mg./kg. i.p.	Sedative action: Spontaneous motility ED50, mouse, mg./kg. i.p.	Rel. activity[b]	Antagonism against DOE ED50 mouse, mg./kg. i.p.	Rel. activity[b]
8	290	100	0.6	60	3.0
9	650	100	0.6	60	3.0
10	700	100	0.6	75	2.4
11	235	80	0.8	200	0.9
12	290	70	0.9	170	1.0
13	255	43	1.5	70	2.5
14	580	77	0.8	200	0.9
15	320	88	0.7	170	1.0
16	400	78	0.8	87	2.0
17	400	35	1.9	55	3.3
Trioxazine	1300	65	1.0	180	1.0

[a] From Table I. [b] Compared with Trioxazine.

Experimental Section

N-[2-(2-Pyridyl)ethyl]-3,4,5-trimethoxybenzamide.—3,4,5-Trimethoxybenzoyl chloride (23.2 g. 0.1 mole) in 250 ml. of benzene was treated with 25 g. of K_2CO_3 and 0.1 mole (12.2 g.) of 2-(β-aminoethyl)pyridine. After being refluxed for 2 hr., the mixture was filtered. From the filtrate, 21 g. (66%) of the base (m.p. 121–122°) was obtained after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.23; H, 6.18; N, 8.53.

On acidifying an acetone solution of the base, the **hydrochloride,** m.p. 180–182°, precipitated.

Anal. Calcd. for $C_{17}H_{20}N_2O_4 \cdot HCl$: Cl, 10.05; N, 7.94. Found: Cl, 10.25; N, 7.76.

The **methiodide,** prepared in acetone (24 hr., room temperature), had m.p. 165–167°, yield 86%. Other methiodides were similarly prepared.

Anal. Calcd. for $C_{18}H_{23}IN_2O_4$: I, 27.69; N, 6.11. Found: I, 27.39; N, 5.89.

3-(2-Pyridyl)propyl 3,4,5-Trimethoxybenzoate.—3,4,5-Trimethoxybenzoyl chloride (0.1 mole, 23.1 g.) in 250 ml. of benzene and 0.1 mole (13.7 g.) of 2-(γ-hydroxypropyl)pyridine were left overnight, then refluxed 1 hr. The hydrochloride of the title compound (31 g., 81%) was obtained on filtering the cooled solution; m.p. 158–162° (from ethanol).

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot HCl$; Cl, 9.64; N, 3.80. Found: Cl, 9.88; N, 4.17.

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Synthesis of 1,4-Disubstituted Piperazines. I[1]

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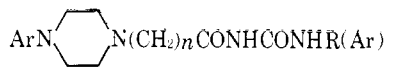
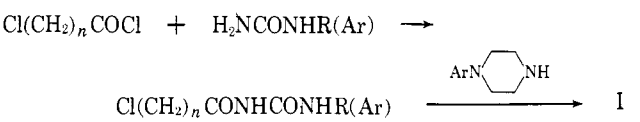
Many new 1,4-disubstituted piperazines of type I have been synthesized as potential pharmacological agents. The acylurea substituent, present in such sedative–hypnotic agents as carbromal, ectylurea, and the barbiturates, attached to the piperazine ring could



I

offer some interesting compounds, since many clinically used piperazines, meclizine, chlorcyclizine, hydroxyzine, and prochlorperazine, function as ataractic, sedative, or antihistaminic agents.

The compounds of structure I, listed in Table II, were synthesized by the reaction sequence indicated below. Data on the chloroacylurea intermediates are presented in Table I.



Biological Data.[2]—The 1,4-disubstituted piperazines were tested for various activities. Compounds **1, 3, 5, 15,** and **16** were inactive in hexobarbital potentiation experiments in mice (loss of righting reflex) at 100 mg./kg. i.p. for 90 sec. However, **2, 4,** and **11** showed minimum activity (40% effective). Among others tested, only **1** gave 40% protection against pentylenetetrazole-induced convulsions at 100 mg./kg. i.p. in mice.

As trichomonacidal agents, **1, 7, 10, 13, 14,** and **16** were ineffective. Compound **2,** however, in a culture tube testing method, arrested the growth of the trichomonads at 1:1000 concentration after incubating for 48 hr. Given *in vivo* against a *T. gallinae* infection in hamsters, **2** enabled 75% of the test animals to clear, as compared with 88% for aminitrazole at 100 mg./kg. *p.o.* Also, against a *T. gallinae* infection in hamsters at 100 mg./kg. *p.o.*, the following compounds gave the following protection: **3,** 25%; **4,** 40%; and, at 200 mg./kg. *p.o.*, **6,** 55%.

Compounds **7, 10, 11, 14,** and **15** were inactive as psychomotor stimulants at 300 mg./kg. *p.o.* in mice. In preventing reserpine ptosis in mice (antidepressant), the minimal significant dose (MSD) for **11** was 50 mg./kg., whereas the MSD for imipramine was 30 mg./kg.

Also, these compounds were tested for various other activities and found to be ineffective. Some of these were anthelmintic, schistosomacidal, antibacterial, antivitamin, antiinflammatory, and antielectroshock.

Experimental Section

The chemicals were purchased from Eastman. All microanalyses were performed at the Sterling-Winthrop Research Institute. 1-Phenylpiperazine[3] and 1-*p*-chlorophenylpiperazine[4] were prepared by a literature method. The chloroacylurea intermediates (Table I) were prepared by combining the N-alkyl- or N-arylureas with the appropriate chloroacyl chloride and warming, if necessary.

1,4-Disubstituted Piperazines (Table II). Procedure A.—The aryl piperazine (2 equiv.) and 1 equiv. of the chloroacylurea were refluxed in alcohol for 0.5–2 hr. The mixture was then

(1) The support of this work by the Sterling-Winthrop Research Institute, Rensselaer, N. Y., is gratefully acknowledged.

(2) The author is indebted to the Biological Division of the Sterling-Winthrop Research Institute for conducting these physiological studies.

(3) C. B. Pollard, *J. Org. Chem.*, **24**, 1175 (1959).

(4) C. B. Pollard and T. H. Wickers, *J. Am. Chem. Soc.*, **76**, 1853 (1954).