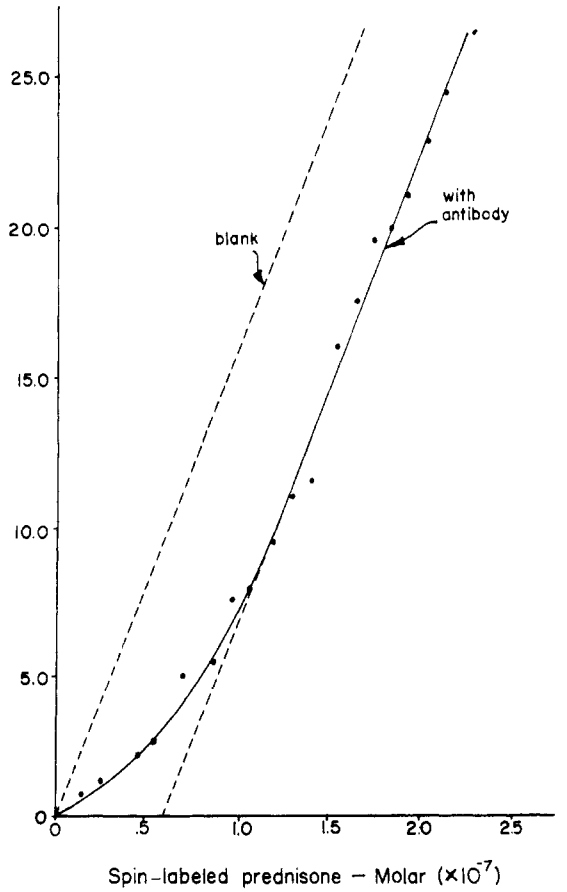

Figure 3. Calculation of the number of binding sites on prednisone antibodies.

a 4:1 ratio of pH 7.2 buffer solution and γ-globulin fraction, making a final volume of 1 mL. All calculations were made so that the spin-labeled concentration was equivalent to the original volume of blood. Low-field ESR signal intensity of uncomplexed spin-labeled steroids was measured as a function of total spin-labeled steroid concentration (Figure 3). Serum antibody binding site concentration is obtained from the horizontal displacement from the curve (Figure 3) when antibodies are present. This displacement corresponds to 6.0×10^{-7} M for 1.

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Quinazolines and 1,4-Benzodiazepines. 82.[1] 5-Pyrimidyl- and 5-Pyrazinylbenzodiazepines

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Analogues of bromazepam [7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one, A], which is a clinically useful minor tranquilizer, have been prepared by replacing the 2-pyridyl group at position 5 with 4-pyrimidyl (**5**), 2-pyrazinyl (**8**), 2,5-dimethylpyrazin-3-yl (**10**), and 2-pyrimidyl (**12**) groups. Low to moderate CNS activities in both mice and cats were found for all the new compounds. For the screening procedures used, the 2-pyrimidyl-substituted derivatives were found to be the most active new analogues although none of the activities exceeded those observed for bromazepam.

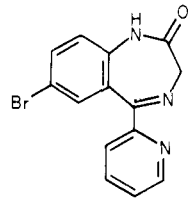
With few exceptions, all of the 1,4-benzodiazepines in clinical use have either a phenyl or a 2-halophenyl substituent at position 5.[2] It has been recognized for some time that a 5-(2-pyridyl) substituent also imparts a high level of biological activity.[3] This observation has led to intensive pharmacological and clinical investigations of bromazepam (A)[4] and its marketing as a minor tranquilizer.

Despite the interest in the 5-(2-pyridyl) compounds, few benzodiazepines carrying other heterocycles at the 5 position have been described.[3,5-7] We now wish to report the syntheses and biological activities of some 5-(2- and 4-pyrimidyl)- and 5-(2-pyrazinyl)-1,4-benzodiazepines.

Table I. Synthetic Sequences

(A) 4-Pyrimidyl:	**6**, **7**, **7-2**, **14**, **15**, **31**, and **35**
(B) 2-Pyrazinyl:	**9-2**, **16**, **17**, **32**, and **36**
(C) 2,5-Dimethylpyrazin-3-yl:	**11-3**, **18**, **19**, **20**, **21**, **33**, and **37**
(D) 2-Pyrimidyl:	(a) **13-4**, **22**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **34**, and **38**
	(b) **24**, **40**, **41**, **42**, and **39**

Chemistry. Four series of compounds have been prepared by the synthetic sequences outlined in Table I.



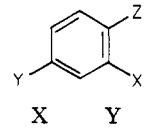
(A) 4-Pyrimidyl. 4-Pyrimidinecarboxylic acid[8] (**6**) was prepared by the oxidation of 4-methylpyrimidine with selenium dioxide[9] in 80% yield and converted to the methyl ester **7**.[10] Reaction of 2-bromo-4-chloronitrobenzene[11] (**2**) with phenyllithium at −90 °C gave the lithio reagent which was condensed with **7** to give the nitro ketone **14** in 31% yield. Hydrogenation of **14** to the amino ketone **15**, followed by bromoacetylation (to **31**) and amination, afforded 7-chloro-1,3-dihydro-5-(4-pyrimidyl)-2*H*-1,4-benzodiazepin-2-one (**35**).

(B) 2-Pyrazinyl. In the same manner as described for the preparation of **14**, methyl 2-pyrazinecarboxylate[12] (**9**) was converted to 5-chloro-2-nitrophenyl 2-pyrazinyl ketone (**16**, 47%). The nitro group was reduced with palladium on carbon in refluxing cyclohexene to give **17** in 72% yield. Bromoacetylation (to **32**) followed by amination afforded 7-chloro-1,3-dihydro-5-(2-pyrazinyl-2*H*-1,4-benzodiazepin-2-one (**36**).

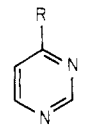
(C) 2,5-Dimethylpyrazin-3-yl. The crucial reaction in this series was the formation of the *o*-nitrobenzhydrol **18** from 2-nitrobenzaldehyde and the lithio reagent derived from 2-iodo-3,6-dimethylpyrazine[13,14] (**11**). Oxidation of **18** to the nitro ketone **19**, followed by catalytic hydrogenation (to **20**), bromination (to **21**), bromoacetylation (to **33**), and amination led to 7-bromo-1,3-dihydro-5-(2,5-dimethylpyrazin-3-yl)-2*H*-1,4-benzodiazepin-2-one (**37**).

(D) 2-Pyrimidyl. Carbon–carbon bond formation in this series involved the reaction of the carbanion generated from *o*-chlorophenylacetonitrile (**4**) and sodium hydride with 2-chloropyrimidine (**13**). The benzyl cyanide **22** thus obtained (28%) underwent air oxidation in the presence of sodium hydride to give the ketone **23** in 60% yield. Nitration of **23** gave **24** in which the chlorine is activated toward nucleophilic displacement by amines. Thus in series (A), treatment with ammonia afforded the amino nitro ketone **25**. Replacement of the nitro group with a chlorine atom through reduction and a Sandmeyer reaction necessitated acetylation of the amino group (to **26**), catalytic hydrogenation (to **27**), diazotization of the amino group followed by cuprous chloride treatment (to **28**) and chromic acid oxidation (to **29**), and deacetylation to give 2-(2-amino-5-chlorobenzoyl)pyrimidine (**30**). Bromoacetylation of **30** (to **34**) followed by amination gave 7-chloro-5-(2-pyrimidyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**38**). Alternately in series (B), the chloronitro ketone **24** was treated with ethylenediamine to give 2,3-dihydro-7-nitro-5-(2-pyrimidinyl)-1*H*-1,4-benzodiazepine (**40**), which was methylated on the 1-nitrogen with dimethyl sulfate in the presence of sodium methoxide to give **41** (61%). A reduction and Sandmeyer sequence on **41** without isolating the intermediates afforded the 7-chloro analogue **42** (34%). Compound **42** was oxidized to the lactam **39** with either chromic acid or ruthenium tetraoxide,[15] but in only 6.6 and 6.7% yield, respectively.

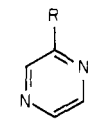
Biological Activity. The CNS activities of the new benzodiazepines as evaluated in mice and cats are summarized in Table II. The methods used, as described elsewhere,[3,16] permit a comparison with a large number of analogues tested earlier.[2,3] Although low to moderate activities are found for all of these compounds, none would appear to be more active than bromazepam. It is interesting to note that the 5-(2-pyrimidyl) compound **39** is equipotent with bromazepam and diazepam in the unanesthesized cat test and in the antipentylenetetrazole test in mice but is considerably less active in both the inclined screen and electroshock tests.



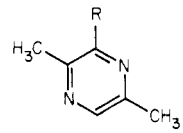
	X	Y	Z
1	NH_2	Cl	NO_2
2	Br	Cl	NO_2
3	CHO	H	NO_2
4	CH_2CN	H	Cl



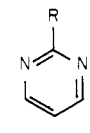
5, R = –
6, R = CO_2H
7, R = CO_2CH_3



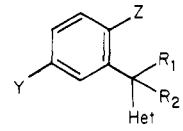
8, R = –
9, R = CO_2CH_3



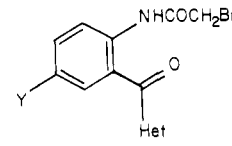
10, R = –
11, R = I



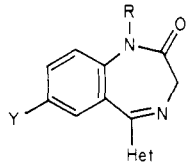
12, R = –
13, R = Cl



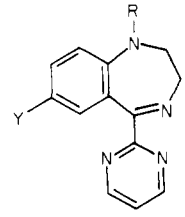
	Het	Y	Z	R_1,R_2
14	5	Cl	NO_2	=O
15	5	Cl	NH_2	=O
16	8	Cl	NO_2	=O
17	8	Cl	NH_2	=O
18	10	H	NO_2	H,OH
19	10	H	NO_2	=O
20	10	H	NH_2	=O
21	10	Br	NH_2	=O
22	12	H	Cl	H,CN
23	12	H	Cl	=O
24	12	NO_2	Cl	=O
25	12	NO_2	NH_2	=O
26	12	NO_2	$NHCOCH_3$	=O
27	12	NH_2	$NHCOCH_3$	H,OH
28	12	Cl	$NHCOCH_3$	H,OH
29	12	Cl	$NHCOCH_3$	=O
30	12	Cl	NH_2	=O



	Het	Y
31	5	Cl
32	8	Cl
33	10	Br
34	12	Cl



	Het	Y	R
35	5	Cl	H
36	8	Cl	H
37	10	Br	H
38	12	Cl	H
39	12	Cl	CH_3



40, Y = NO_2; R = H
41, Y = NO_2; R = CH_3
42, Y = Cl; R = CH_3

Experimental Section

Melting points were taken in capillaries heated in oil baths (Thomas-Hoover, calibrated). Reagent grade solvents were used. DMF stands for dimethylformamide and THF for tetrahydrofuran. All solvents were evaporated in vacuo under water aspirator pressure using water baths set at 30–80 °C (Büchi Rotavapor evaporators). Grace activated silica gel, 100–200 mesh, was used in column chromatography. Infrared (IR) spectra were determined on a Beckmann IR-9 or a Perkin-Elmer 621 grating spectrometer, mass spectra (MS) on a Jeolco-O1SG or a CEC-21-110 spectrometer, and nuclear magnetic resonance (NMR) spectra on a Varian A-60 or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard.

Table II. Pharmacological Data

Compd	Mouse (ED_{50}, mg/kg po)				Cat, muscle relaxant (MED, mg/kg po)
	Inclined screen	Antifighting	Antipentylene-tetrazole	Antimaximal electroshock	
35	>400	>100	340	>800	
36	300	50	7.4	>800	10
37	>400	50	37	>800	10
38	500	100	1.75	520	2
39	>200		0.75	315	0.10
40	>400		68	>800	
41	250	>100	93	>800	20
42	200	100	>800	360	10
Bromazepam	30	10	0.8	34	0.2
Diazepam	30	10	1.4	22	0.2

2-Nitro-5-chloroaniline (1).[17] A solution of 288 g (1.5 mol) of 2,4-dichloronitrobenzene (Aldrich Co.) in 3 L of liquid NH_3 was heated in an autoclave at 100 °C for 16 h. The residue obtained from evaporation of NH_3 was dissolved in CH_2Cl_2, washed with H_2O, and concentrated to crystallize **1** (250.7 g, 97%, mp 119–122 °C dec). Recrystallization of **1** from MeOH raised the melting point to 126.5–127 °C (lit.[17] 127.5–128 °C): MS *m/e* 172 (M^+).

2-Bromo-4-chloronitrobenzene (2).[11] To a solution of 242 g (1.4 mol) of **1** in 3.5 L of 5 M H_2SO_4, chilled in an ice bath, was added over a 45-min period a solution of 194 g (2.8 mol) of $NaNO_2$ in 1.5 L of H_2O. After 1.5 h, a cold solution of 832 g (7.6 mol) of KBr in 2.6 L of H_2O was added, followed by 267 g (4.2 mol) of copper powder. The ice bath was removed and the reaction mixture was stirred at room temperature for 16 h. Addition of 5 L of H_2O followed by steam distillation afforded 198 g (59%) of **2**, mp 46–50 °C. Recrystallization from hexane yielded yellow needles: mp 49–50 °C (lit.[11] 49 °C); MS *m/e* 235 (M^+).

4-Pyrimidinecarboxylic Acid (6).[8] A solution of 75 g (0.8 mol) of 4-methylpyrimidine and 134 g (1.21 mol) of SeO_2[9] in 850 mL of pyridine was heated to 50–60 °C for 2 h and then heated at 80–85 °C for 3.5 h. The heating was discontinued and the reaction allowed to cool while stirring overnight. After filtration and concentration, the residue was dissolved in 500 mL of H_2O, filtered to remove the last traces of SeO_2, and concentrated to give, in two crops, 79.0 g (80%) of **6**, mp 226–230 °C dec (lit.[8] 234–235 °C dec). This material was used without recrystallization.

Methyl 4-Pyrimidinecarboxylate (7).[10] A well-stirred suspension of 31 g (0.25 mol) of the acid **6** in a mixture of 200 mL each of CH_2Cl_2 and Et_2O was treated with an excess of ethereal diazomethane. The solution was stirred (1 h), filtered, and concentrated to give 25.7 g (74%) of **7**: mp 63–68 °C dec; IR (Nujol) 1730 cm^{-1} (ester).

4-(5-Chloro-2-nitrobenzoyl)pyrimidine (14). A vigorously stirred, cooled (−90 °C) solution of 220 mL of 1.4 M C_6H_5Li (0.306 mol) in 300 mL of THF–Et_2O–hexane (2:1:1 by volume, referred to in all these experiments as TEH) was treated with a solution of 70.95 g (0.3 mol) of **2** in 500 mL of chilled TEH. The solution was left to stir 1 h, and a chilled solution of 41.4 g (0.30 mol) of ester **7** in 800 mL of TEH was added over 30 min while maintaining the reaction temperature throughout at −90 to −100 °C. After 40 min of stirring, the reaction mixture was poured slowly into 1 L of H_2O. The mixture was extracted with three 250-mL portions of CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried, and concentrated to give about 100 g of black oil which was dissolved in C_6H_6 and applied to a column of 180 g of silica gel. Elution with C_6H_6–EtOAc (2:1) gave 24.7 g (31%) of **14**, R_f 0.61 (silica gel, in the same solvent). A sample for analyses, mp 93–94 °C dec, was obtained by recrystallization from CH_2Cl_2–hexane: IR (KBr) 1685 (CO), 1530, 1515, and 1330 cm^{-1} (NO_2); MS *m/e* 263 (M^+). Anal. ($C_{11}H_6ClN_3O_3$) C, H, Cl, N.

2-Amino-5-chlorophenyl 4-Pyrimidinyl Ketone (15). A solution of 19.7 g (0.0745 mol) of **14** in 750 mL of EtOH containing 0.65 g of 10% Pd/C was hydrogenated for 3 days in a Parr apparatus (20 psi or less). Filtration and concentration gave a red product which was dissolved in in 1.0 L of CH_2Cl_2 and stirred with 78.2 g (0.9 mol) of MnO_2 (Winthrop Laboratories) for 22 h, then filtered, and concentrated. The red oil was taken up in 1 L of CH_2Cl_2. Hexane (400 mL) was added and the solution cooled to crystallize 7.6 g (43%) of **15**, mp 151.5–153.5 °C dec. A sample for analyses, mp 154–155.5 °C dec, was obtained by recrystallization from CH_2Cl_2–hexane: IR ($CHCl_3$) 3415 and 3280 (NH_2) and 1630 cm^{-1} (CO); MS *m/e* 233 (M^+). Anal. ($C_{11}H_8ClN_3O$) C, H, Cl, N.

5-Chloro-2-nitrophenyl 2-Pyrazinyl Ketone (16). Following the procedure described for **14**, 6.9 g (50 mmol) of methyl 2-pyrazinecarboxylate[12] (**9**) afforded, after an identical isolation procedure, 6.3 g (47%) of **16**: mp 180–181 °C dec (CH_2Cl_2–hexane); R_f 0.6 [silica gel, C_6H_6–EtOAc (2:1)]; IR (KBr) 1690 (CO), 1510 and 1340 cm^{-1} (NO_2). Anal. ($C_{11}H_6ClN_3O_3$) C, H, Cl, N.

2-Amino-5-chlorophenyl 2-Pyrazinyl Ketone (17). A solution of 16.3 g (62 mmol) of **16** and 16.5 g of 10% Pd on carbon in 250 mL of cyclohexene and 250 mL of THF was heated to reflux for 28 h. Solids were removed by filtration. Concentration of the filtrate afforded 10.3 g (72%) of **17**, mp 149–155 °C. A sample for analyses, mp 160.5–161.5 °C (CH_2Cl_2–hexane), was prepared by chromatography on 100 g of silica gel, using C_6H_6–EtOAc (2:1; R_f 0.41) as eluent: IR (KBr) 3430 and 3300 (NH_2) and 1630 cm^{-1} (CO); MS *m/e* 233 (M^+). Anal. ($C_{11}H_8ClN_3O$) C, H, Cl, N.

α-(2-Nitrophenyl)-3,6-dimethylpyrazine-2-methanol (18). To a stirred, chilled (−50 °C) solution of 117.5 g (0.50 mol) of 2-iodo-3,6-dimethylpyrazine[14] (**11**) in 2.5 L of Et_2O was added 0.55 mol of *n*-C_4H_9Li in hexane over a 20-min period. The tan solution was stirred for 10 min and then treated with a solution of 75.2 g (0.5 mol) of *o*-nitrobenzaldehyde in 700 mL of Et_2O over a 30-min period, while maintaining the temperature of the reaction at −50 to −55 °C. After a further period of stirring (2 h), the mixture was allowed to warm to room temperature and quenched by addition of 2 L of 1 N HCl. The aqueous layer was extracted with two 500-mL portions of CH_2Cl_2. The combined organic phases were washed with H_2O and brine, dried, and concentrated. The residual red-brown oil was adsorbed on a column of 1.32 kg of silica gel. Elution with CH_2Cl_2–EtOAc (1:2) afforded 58.1 g (45%) of **18**: mp 127–128 °C (CH_2Cl_2–hexane); IR (KBr) 3160 (OH) and 1520 and 1350 cm^{-1} (NO_2); MS *m/e* 259 (M^+). Anal. ($C_{13}H_{13}N_3O_3$) C, H, N.

3-(2-Nitrobenzoyl)-2,5-dimethylpyrazine (19). To a stirred solution of 51.8 g (0.20 mol) of **18** in 500 mL of glacial AcOH was added 40 g (0.4 mol) of CrO_3 over a 20-min period, while maintaining the reaction temperature between 60 and 65 °C. After stirring for 1 h at this temperature, the mixture was cooled and added to 1 L of ice water. Extraction with CH_2Cl_2 afforded 32.7 g (63%) of **19**: mp 117–119 °C (CH_2Cl_2–hexane); IR (KBr) 1690 (CO) and 1520 and 1345 cm^{-1} (NO_2); MS *m/e* 257 (M^+). Anal. ($C_{13}H_{11}N_3O_3$) C, H, N.

2-Aminophenyl 2,5-Dimethylpyrazin-3-yl Ketone (20). A solution of 10.3 g (40 mmol) of **19** in 400 mL of THF, containing 10.3 g of 10% Pd/C, was hydrogenated for a period of 5.5 h in a Parr apparatus at 50 psi. Filtration and concentration gave 9.5 g of red oil which was separated on a column of 850 g of silica gel with C_6H_6–EtOAc (2:1) as eluent. Concentration of the fractions containing **20** [TLC on silica gel, C_6H_5–EtOAc (2:1), R_f 0.4] afforded a yield of 2.6 g (28%), mp 108–109 °C. A sample suitable for analyses, mp 99–100.5 °C, was prepared by sublimation at 75 °C (0.05 mmHg): IR (KBr) 3430 and 3305 (NH_2) and 1635 cm^{-1} (CO); MS *m/e* 227 (M^+). Anal. ($C_{13}H_{13}N_3O$) C, H, N.

2-Amino-5-bromophenyl 2,5-Dimethylpyrazin-3-yl Ketone

(21). To a cold stirred solution of 11.4 g (50 mmol) of **20** in 120 mL of HOAc was added dropwise 65 mL (54 mmol) of 1 M Br_2 in HOAc. The resulting suspension was stirred at room temperature for 2 h. The solids which formed were collected and washed with cold HOAc followed by Et_2O. The solids were dissolved in CH_2Cl_2, washed with 3 N NaOH followed by H_2O, then dried, and evaporated. Crystallization of the residue from EtOH–H_2O gave 7.1 g (47%) of **21**, mp 147–150 °C. Recrystalliaztion (EtOH–H_2O) afforded yellow plates: mp 158–160 °C; NMR ($CDCl_3$) δ 2.46 (s, 3, CH_3), 2.54 (s, 3, CH_3), 6.50 (br, 2, NH_2), 6.58 (d, J = 9 Hz, 1), 7.18 (d, J = 2.5 Hz, 1), 7.23–7.38 (m, 1), and 8.42 ppm (s, 1); MS m/e 305 (M^+). Anal. ($C_{13}H_{12}BrN_3O$) C, H, N.

2-(2-Pyrimidyl)-2-(2-chlorophenyl)acetonitrile (22). To a solution of 54.4 g (0.36 mol) of *o*-chlorophenylacetonitrile in 900 mL of dry THF, 17.2 g of 50% NaH in mineral oil (0.36 mol) was added and the mixture heated to reflux for 30 min. A solution of 41.1 g (0.36 mol) of 2-chloropyrimidine in 200 mL of dry THF was added during 10 min to the refluxing solution and heating was continued for an additional 3 h. After cooling, 100 mL of H_2O was added and THF evaporated. The aqueous residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried, and concentrated to dryness. Extraction of the residue twice with 375-mL portions of hot hexane removed 9.4 g of an oil. The residue slowly crystallized from C_6H_6–hexane to yield 23 g (28%) of **22**, mp 79–81 °C. From the hexane extracts on seeding, an additional 3.2 g of **22** was obtained. Recrystallization of a sample from hexane gave colorless rhombs: mp 81–82 °C; IR ($CHCl_3$) 2250 cm^{-1} (CN). Anal. ($C_{12}H_8ClN_3$) C, H, N.

2-(2-Chlorobenzoyl)pyrimidine (23). To a solution of 3.0 g (13 mmol) of **22** in 250 mL of dry THF, 0.78 g of a 50% suspension of NaH in mineral oil was added. The mixture was stirred, heated to reflux for 2 h, and cooled to room temperature and a rapid stream of dry air was bubbled in for 15 h. At this time, 30 mL of 33% aqueous MeOH was added cautiously, followed by about 200 mL of H_2O. THF was evaporated and the precipitated solid (1.7 g, 50%, mp 124–127 °C) was collected. Extraction of the filtrate with CH_2Cl_2 afforded an additional 0.15 g of **23**, mp 120–123 °C. Recrystallization from C_6H_6–hexane gave colorless plates: mp 127–129 °C; IR ($CHCl_3$) 1695 cm^{-1} (CO). Anal. ($C_{11}H_7ClN_2O$) C, H, N.

2-(2-Chloro-5-nitrobenzoyl)pyrimidine (24). To a solution of 11.9 g (55 mmol) of **23** in 60 mL of concentrated H_2SO_4, chilled to 0 °C, a mixture of 3.1 mL of 90% HNO_3 and 7.7 mL of concentrated H_2SO_4 was added dropwise over 1 h. Stirring was continued at 0 °C for an additional 1 h and for 1 h at room temperature. The mixture was poured onto ice and made basic by addition of dilute aqueous NH_3. The solid that precipitated weighed 13.8 g (95%), mp 143–146 °C. Recrystallization from C_6H_6 yielded light yellow rhombs: mp 147–149 °C; IR ($CHCl_3$) 1705 (CO), 1535, 1370 cm^{-1} (NO_2). Anal. ($C_{11}H_6ClN_3O_3$) C, H, N.

2-(2-Amino-5-nitrobenzoyl)pyrimidine (25). A mixture of 25 g (95 mmol) of **24** in 600 mL of dioxane and 600 mL of concentrated aqueous NH_3 was heated for 5 h in an autoclave at 100 °C and 100 psi of initial ammonia pressure. The reaction mixture was concentrated to remove dioxane. The solid that formed was separated by filtration and suspended in a mixture of 50 mL of 3 N HCl and 500 mL of ethanol and stirred for 16 h at room temperature. The yellow solid that resulted was separated by filtration and dried. It weighed 14.2 g (62%), mp 239–240 °C. Recrystallization from EtOH or MeCN gave yellow needles: mp 267–268 °C; IR (KBr) 3450, 3330 (NH_2), 1640 (CO), 1550, 1302 cm^{-1} (NO_2). Anal. ($C_{11}H_8N_4O_3$) C, H, N.

2-(2-Acetamido-5-nitrobenzoyl)pyrimidine (26). A mixture of 1.0 g (4 mmol) of **25** in 50 mL of acetic anhydride was heated to reflux for 2 h and then concentrated to dryness under reduced pressure. The residue was triturated with H_2O, collected, and dried to give 0.9 g (86%) of crude **26**, mp 200–206 °C. Extraction with C_6H_6 separated a small amount of insoluble material. Repeated crystallization of the C_6H_6 soluble material from EtOH gave fine needles: mp 221–222 °C; IR ($CHCl_3$) 1710 (CO), 1660 (amide CO), 1563, 1511, 1504, 1350 cm^{-1} (NO_2). Anal. ($C_{13}H_{10}N_4O_4$) C, H, N.

4′-Amino-2′-(α-hydroxy-2-pyrimidinylmethyl)acetanilide (27). A solution of 2.86 g (10 mmol) or **26** in 250 mL of DMF containing about 10–20 g of Raney nickel was hydrogenated at atmospheric pressure and room temperature. About 40 mmol of H_2 was absorbed. After filtration to remove catalyst and concentration to dryness, the residue crystallized from EtOH to give 0.9 g (35%) of colorless prisms, mp 192–194 °C. Recrystallization gave a pure sample of mp 182–184 °C. The melting point does not appear to be very characteristic of the purity of the substance: IR (KBr) 3350 (NH), 3250 (OH), 1685 (amide CO), 1520 (amide II, NO_2, br), 1375 cm^{-1} (NO_2). Anal. ($C_{13}H_{14}N_4O_2$) C, H, N.

4′-Chloro-2′-(α-hydroxy-2-pyrimidinylmethyl)acetanilide (28). A solution of 6.0 g (23 mmol) of **27** in 48 mL of 3 N HCl was cooled to −10 °C and, while stirring, a solution of 1.76 g (25.5 mmol) of $NaNO_2$ in 8 mL of H_2O was added dropwise. Stirring was continued for another 5 min at −10 °C; then the cold reaction mixture was added dropwise to a suspension of 5.1 g of CuCl in 32 mL of 9 N HCl while maintaining the temperature at −10 °C. The addition was over a 30-min period; then the reaction was allowed to warm to room temperature. After dilution with 90 mL of H_2O, the temperature was raised to 35 °C for 2 h. The reaction mixture was made basic by addition of concentrated aqueous NH_3. Extraction wth CH_2Cl_2 afforded 3.6 g (66%) of **28** as colorless prisms: mp 144–146 °C (C_6H_6–hexane); IR ($CHCl_3$) 3450 (OH), 3300 (NH), 1690 (amide CO), 1567 cm^{-1} (amide II). Anal. ($C_{13}H_{12}ClN_3O_2$) C, H, Cl, N.

4′-Chloro-2′-(2-pyrimidinylcarbonyl)acetanilide (29). To a solution of 0.50 g (1.8 mmol) of **28** in 10 mL of glacial AcOH, a solution of 0.18 g (1.8 mmol) of chromic acid in 1 mL of H_2O was added. A brown solid separated almost immediately. The mixture was heated with stirring for 1 h at 50–55 °C and cooled, and several drops of EtOH were added to destroy excess chromic acid. The mixture was made slightly basic with aqueous NH_3. Extraction with CH_2Cl_2 afforded 0.30 g (60%) of **29**, mp 151–153 °C, obtained as pale yellow rods from EtOH: IR ($CHCl_3$) 3330 (NH), 1695 (amide CO), 1660 (CO), 1563 cm^{-1} (amide II). Anal. ($C_{13}H_{10}ClN_3O_2$) C, H, N.

2-(2-Amino-5-chlorobenzoyl)pyrimidine (30). A solution of 1.0 g (36 mmol) of **29** in a mixture of 50 mL of 6 N HCl and 50 mL of EtOH was heated to reflux for 15 min. Concentration under reduced pressure removed most of the ethanol. Ice was added to the acidic residue and it was made alkaline by addition of concentrated aqueous NH_3. Extraction with CH_2Cl_2 afforded a gum which was dissolved in Et_2O and adsorbed on a bed of Florisil. Elution of the bed with EtOAc afforded 0.30 g (36%) of yellow prisms (cyclohexane): mp 129–131 °C; IR ($CHCl_3$) 3510, 3350 (NH_2), 1640 cm^{-1} (CO). Anal. ($C_{11}H_8ClN_3O$) C, H, N.

2-Bromo-4′-chloro-2′-(4-pyrimidinylcarbonyl)acetanilide (31). A solution of the amino ketone (10–50 mmol) in C_6H_6 or CH_2Cl_2 was stirred at 0 °C with sufficient dilute NaOH or Na_2CO_3 to maintain an alkaline aqueous layer throughout the reaction. Bromoacetyl bromide (1.5 equiv) was added slowly, followed by stirring at room temperature for 2 h. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated.

Following this procedure, a dark semisolid (17 g) was obtained from 10.9 g (47 mmol) of **15**. The mixture was dissolved in a small volume of CH_2Cl_2 and applied to a column of 300 g of silica gel. Elution with 10% EtOAc in CH_2Cl_2 and crystallization from CH_2Cl_2–hexane afforded 7.3 g (44%) of **31**: mp 149–150.5 °C dec (R_f 0.33, silica gel, 10% EtOAc in CH_2Cl_2); IR (KBr) 3240 (NH), 1685 and 1525 (amide), and 1640 cm^{-1} (ketone). Anal. ($C_{13}H_9BrClN_3O_2$) C, H, Br, Cl, N.

2-Bromo-4′-chloro-2′-(2-pyrazinoyl)acetanilide (32). Following the general procedure described under **31**, 5.8 g (24.8 mmol) of amino ketone **17** afforded a dark semisolid mixture which on trituration with hexane yielded 5.5 g (59%) of **32**, mp 112–114 °C dec. Recrystallization from CH_2Cl_2–hexane raised the melting point to 114–115 °C dec; IR (KBr) 3300 (NH) 1685 and 1530 (amide), and 1655 cm^{-1} (ketone). Anal. ($C_{13}H_9BrClN_3O_2$) C, H, Br, Cl, N.

2,4′-Dibromo-2′-(2,5-dimethylpyrazin-3-ylcarbonyl)acetanilide (33). Following the general procedure described under **31**, 3.06 g (10 mmol) of **21** afforded 3.65 g (85%) of **33** as yellow needles (C_6H_6–hexane): mp 160–162 °C; IR (KBr) 3220 (NH), 1675 and 1515 (amide), and 1648 cm^{-1} (ketone); NMR ($CDCl_3$) δ 2.58 (s, 6, $2CH_3$), 4.04 (s, 2, CH_2), 7.46 (d, J = 2.5 Hz, 1, 5′-H), 7.72 (dd, J = 9 and 2.5 Hz, 1, 3′-H), 8,53 (s, 1, CH), 8.68 (d, J =

9 Hz, 1, 2′-H), and 11.91 ppm (br s, 1, NH). Anal. ($C_{15}H_{13}Br_2N_3O_2$) C, H, N.

2-Bromo-4′-chloro-2′-(2-pyrimidinylcarbonyl)acetanilide (34). To a solution of 0.5 g (2 mmol) of **30**, in 10 mL of glacial HOAc, 0.43 g (2.2 mmol) of bromoacetyl bromide was added. On standing for 16 h at room temperature, the oil that had separated soon after mixing, crystallized. It was separated by filtration to give 0.9 g of a product, mp 200–202 °C dec. Trituration with EtOH yielded light yellow crystals of **34**, mp 151–153 °C. Further crystallization from EtOH did not alter the melting point: IR ($CHCl_3$) 3280 (NH), 1692 (amide CO) 1667 (CO), 1580, 1563 cm^{-1}. Anal. ($C_{13}H_9BrClN_3O_2$) C, H, N.

7-Chloro-1,3-dihydro-5-(4-pyrimidinyl)-2*H*-1,4-benzodiazepin-2-one (35). A solution of 7.3 g (20.6 mmol) of **31** in 100 mL of CH_2Cl_2 and 300 mL of liquid NH_3 was allowed to reflux under a dry ice condenser for 5 h. Ammonia was allowed to evaporate. Some solids were removed by filtration. The residue from evaporation of CH_2Cl_2 was dissolved in 200 mL of MeOH containing 4 mL of HOAc and heated under reflux for 5 h. Solvents were evaporated. Partitioning of the residue between H_2O and CH_2Cl_2 followed by drying and evaporation of the CH_2Cl_2 layer afforded 2.9 g (51%) of **35**, mp 256–257 °C dec. After recrystallization from EtOAc, the mp was 254.5–256 °C dec: IR (KBr) 3170 (NH), 1680 and 1670 cm^{-1} (CO); NMR ($CDCl_3$) 4.24 (s, 2, CH_2), 7.19 (d, J = 8.5 Hz, 1, 9-H), 7.36 (d, J = 2.5 Hz, 1, 6-H), 7.42 (dd, 1, 8-H), 7.99 (dd, J = 5 and 1.5 Hz, 1, 6′-H), 8.84 (d, J = 5 Hz, 1, 5′-H), 9.12 (d, J = 1.5 Hz, 1, 2′-H), and 10.55 ppm (s, 1, NH); MS m/e 272 (M^+). Anal. ($C_{13}H_9ClN_4O$) C, H, N.

7-Chloro-1,3-dihydro-5-(2-pyrazinyl)-2*H*-1,4-benzodiazepin-2-one (36). Following the procedure described for **35**, 2.0 g (5.6 mmol) of bromoacetanilide **32** afforded 1.3 g (84%) of **36**: mp 184–185 °C dec (CH_3OH); IR (KBr) 3220 (NH) and 1707 cm^{-1} (CO); NMR (Me_2SO-d_6) 4.27 (s, 2, CH_2), 7.23 (d, J = 9 Hz, 1, 9-H), 7.37 (d, J = 2.5 Hz, 1, 6-H), 7.53 (dd, J = 9 and 2.5 Hz, 1, 8-H), 8.54 (d, J = 2.5 Hz, 1, 6′-H), 8.64 (d, J = 2.5 Hz, 1, 5′-H), 9.15 (s, 1, 3′-H), and 10.58 ppm (s, 1, NH); MS m/e 272 (M^+). Anal. ($C_{13}H_9ClN_4O$) C, H, Cl, N.

7-Bromo-1,3-dihydro-5-(2,5-dimethylpyrazin-3-yl)-2*H*-1,4-benzodiazepin-2-one (37). To about 500 mL of liquid NH_3 was added an ice-cold solution of 6.7 g (15.4 mmol) of bromoacetanilide **33** in 100 mL of THF. The solution was stirred under refluxing NH_3 for 5 h. Ammonia and THF were evaporated. The residue was dissolved in 250 mL of EtOH and heated to reflux 16 h. On cooling, crystalline **37** was collected in three crops (3.5 g, 47%, mp 262–264 °C). Recrystallization from EtOH afforded pale yellow prisms: mp 264–266 °C; IR (KBr) 1680 cm^{-1} (lactam); UV max (2-PrOH) 228 nm (ε 32 400), 282 (9380), and 314 (3120); MS m/e 344 (M^+). Anal. ($C_{15}H_{13}BrN_4O$) C, H, N.

7-Chloro-5-(2-pyrimidinyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (38). Following the procedure described for **37**, 1.1 g of **34** afforded 0.30 g (36%) of **38** as colorless rods ($CHCl_3$–hexane): mp 241–242 °C; IR (KBr) 1690 (amide) and 1563 cm^{-1}. Anal. ($C_{13}H_9ClN_4O$) C, H, N.

7-Chloro-1,3-dihydro-1-methyl-5-(2-pyrimidinyl)-2*H*-1,4-benzodiazepin-2-one (39). A solution of compound **42** (15 g, 55 mmol) in glacial HOAc (240 mL) was stirred at 25 °C and treated dropwise with Jones reagent[18] (0.10 mol of CrO_3) during 4.5 h. The solution was stirred for 16 h and was then poured into ice–water (1 L) and made basic with 10 N NaOH. The product mixture was isolated by extraction with CH_2Cl_2 and was obtained as a dark-colored gum (11 g). Purification was effected by filtration of a CH_2Cl_2 solution of the crude product through a column of neutral Woelm alumina (activity I, 110 g). Evaporation of the eluates afforded a dark colored gum (8.3 g) which was extracted with hot C_6H_6. The C_6H_6 soluble material was adsorbed on a column of 75 g of neutral Woelm alumina (activity III). The C_6H_6 eluate (1.2 L) was discarded. Elution with CH_2Cl_2 gave 1.39 g of a yellow gum. Trituration of the gum with ether, followed by crystallization from CH_2Cl_2–ether–hexane, gave cream prisms: mp 157–159 °C (1.05 g, 6.6%); IR ($CHCl_3$) 1680 cm^{-1} (CO). Anal. ($C_{14}H_{11}ClN_4O$) C, H. A similarly low yield (6.7%) was obtained when ruthenium tetraoxide[15] was used as oxidant.

2,3-Dihydro-7-nitro-5-(2-pyrimidinyl)-1*H*-1,4-benzodiazepine (40). A mixture of 2-(2-chloro-5-nitrobenzoyl)pyrimidine (**24**, 446.2 g, 1.70 mol), ethylenediamine (510 g, 8.5 mol), and anhydrous pyridine (1700 mL) was stirred and heated on the steam bath for 5 h. Most of the solvents were removed by concentration under reduced pressure, followed by successive codistillation with xylene and toluene. The resulting tarry residue was mixed with MeOH (200 mL) and 3 N HCl (2.5 L). The solution was allowed to stand for 2 h at room temperature and was then cooled and made basic with 5 N NaOH. The crude product precipitated and was collected, washed with H_2O, and dried. Purification was effected by addition of Woelm activity I neutral alumina (1 kg) to a slurry of the product in methanol, followed by evaporation of the solvent. The dried mixture of product and alumina was then continuously extracted with hot CH_2Cl_2, in a Soxhlet extractor, until no further product was recovered in the extract (4–5 days were required). Filtration of the extract gave the purified product (130.7 g, mp 222–224 °C); further crops were obtained by concentration of the filtrates; the total yield of product having mp 215–231 °C was 195 g (43%). This material was sufficiently pure to be used in the methylation step. Recrystallization from EtOH–C_6H_6–hexane or EtOH–CH_2Cl_2–hexane afforded bright yellow rhombs: mp 230–232 °C dec; IR ($CHCl_3$) 3440 (NH), 1632 (C=N), and 1535 and 1320 cm^{-1} (NO_2). Anal. ($C_{13}H_{11}N_5O_2$) C, H, N.

2,3-Dihydro-1-methyl-7-nitro-5-(2-pyrimidinyl)-1*H*-1,4-benzodiazepine (41). A solution of **40** (147.7 g, 0.55 mol) and $NaOCH_3$ (33.0 g, 0.61 mol) in anhydrous DMF (1300 mL) was stirred for 1 h at room temperature and was then treated dropwise with a solution of dimethyl sulfate (77.0 g, 0.61 mol) in dry DMF (260 mL) during 2 h, maintaining the temperature of the reaction mixture at 0–5 °C by cooling in an ice bath. Stirring was continued for 24 h at room temperature, and then the mixture was poured into ice water (6 L). Dry ice was added until the mixture was approximately neutral (pH 5–6); the crude product was isolated by extraction with CH_2Cl_2 and was obtained as a crystalline solid (156.8 g). This material was extracted with cold CH_2Cl_2; unchanged starting material **40** (20.9 g, mp 228–230 °C dec, 14% recovery) was removed by filtration. The filtrates were passed through a bed of Woelm activity III neutral alumina (785 g). The CH_2Cl_2 eluate was evaporated, and the resulting residue (94.0 g) was crystallized from C_6H_6–hexane to give 82.0 g (61% based on unrecovered **40**) of **41**, mp 179–181 °C. Recrystallization from CH_2Cl_2–hexane afforded yellow rods: mp 181–183 °C dec; IR ($CHCl_3$) 1635 cm^{-1} (C=N). Anal. ($C_{14}H_{13}N_5O_2$) C, H, N.

7-Chloro-2,3-dihydro-1-methyl-5-(2-pyrimidinyl)-1*H*-1,4-benzodiazepine (42). A suspension of compound **41** (72 g, 0.25 mol) in MeOH (1400 mL) was hydrogenated at atmospheric temperature and pressure, over an alcohol-washed Raney nickel catalyst (5 teaspoonsful, activity ca. W-2). Hydrogen uptake ceased after 3 h (3.2 mol). Removal of the catalyst and solvent afforded the crude 7-aminobenzodiazepine as a noncrystalline residue. This material was purified by filtration of a CH_2Cl_2 solution through a column of Woelm neutral alumina, activity III (350 g). Evaporation of the eluates afforded a brown foam (62.9 g, 98% yield), which was used directly in the next step.

A solution of the brown foam in 3 N HCl (483 mL, 1.45 mol), at −5 to −10 °C, was treated slowly with a solution of $NaNO_2$ (20.4 g, 0.296 mol) in H_2O (100 mL), followed by slow addition to a suspension of CuCl (52.8 g, 0.534 mol) in a mixture of concentrated HCl (250 mL) and H_2O (125 mL). The mixture was diluted with H_2O (500 mL) and heated at 35 (1.5 h) and 40 °C (2 h) until N_2 evolution ceased. The mixture was made basic with concentrated aqueous NH_3, and the product was isolated by extraction with CH_2Cl_2. This material was purified by filtration of a CH_2Cl_2 solution through a column of Woelm neutral alumina, activity III (315 g). Evaporation of the eluates afforded **42** as a tan-colored crystalline residue (23.4 g), which was recrystallized from benzene–hexane to give 22.5 g (34%) of **42**, mp 106–109 °C. Recrystallization from CH_2Cl_2–petroleum ether afforded yellow needles: mp 107–109 °C; IR ($CHCl_3$) 1630 cm^{-1} (C=N); MS m/e 272 (M^+). Anal. ($C_{14}H_{13}ClN_4$) C, H, N.

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Compounds with Gastric Antisecretory Activity. 1. Phenoxyalkylamines

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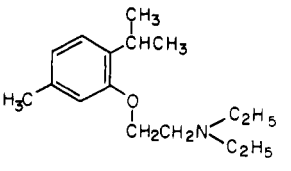
A series of *o*-alkylphenoxyalkylamines, derived from classical H_1 antagonists, has been found to inhibit histamine-induced gastric acid secretion. The most potent compound was *trans*-1-[2-[2-[2-(1-adamantyl)vinyl]-phenoxy]ethyl]pyrrolidine (**54**). The *o*-acylphenol **23** required for the preparation of **54** was obtained by the novel reaction of 1-bromoadamantane (**21**) with 4-hydroxycoumarin (**20**) using diethyl phosphonate as solvent. The product **22** was then hydrolyzed under basic conditions to give **23** in high yield. **54** was not an H_2 antagonist and its mode of action remains unknown. The compound had no significant anticholinergic, antiinflammatory, anticonvulsant, sedative, or H_1-antihistaminic activity.

Since the discovery of the first compound with histamine blocking activity, 929F (I), by Bovet and Staub[1] in 1937, it has been appreciated that compounds of this type do not oppose the gastric secretory actions of histamine. In 1966 Ash and Schild[2] proposed the symbol H_1 for those receptors that were blocked by the antihistamines known at that time. They stressed that further classification of the histamine receptors in the stomach, uterus, and heart must await the discovery of specific antagonists.

The classification of histamine receptors into H_1 and H_2 types is now firmly established following the discovery of selective H_2 agonists and antagonists by Black, Ganellin, and co-workers[3-5] in 1972. Concurrent with this discovery we had been seeking antagonists of histamine-induced gastric acid secretion. We now wish to report a series of compounds, derived from H_1 antagonists, which are capable of antagonizing histamine-induced gastric acid secretion. These compounds, however, are not H_2 antagonists, and their mode of action is at present unknown.

The starting point for our work was the H_1-antihistamine I. Following its discovery in 1937, all synthetic modifications on this compound have been directed toward optimizing H_1-receptor activity. We found that replacement of the isopropyl group of I by large alkyl groups yielded compounds that were capable of inhibiting gastric acid secretion.



I

Chemistry. The majority of compounds listed in Tables II and III were synthesized from the appropriate *o*-alkylphenol **2** as outlined in Scheme I. Treatment of **2** with sodium hydride in an inert solvent such as DMF afforded the alkali metal phenolate which was allowed to react with a dialkylaminoalkyl halide to give the desired product **9** (method A). Alternatively, the phenolate was allowed to react with dibromopropane to give **4** which was then allowed to react with either primary or secondary amines to give **9** (method B). A variation of this route was the reaction of **2** with ethyl chloroacetate to give the ester **3**, followed by hydrolysis, formation of the acyl chloride, and reaction with the appropriate amine to yield the amide. This was then reduced with $LiAlH_4$ to the desired product **9** (method C).

The vinyl compounds of Table IV were prepared in a straightforward manner by treating the metal phenolate of **1** with a dialkylaminoethyl halide to give **5** which was then reduced to the alcohol and dehydrated to give **8** (method D). An alternative route commencing from salicylaldehyde afforded the ether **6**, which upon reaction with an alkyl Grignard gave the alcohol **7**. This was either dehydrated with mild acid or treated with thionyl chloride and warmed to give the vinyl compound **8** (method E).

The *o*-alkylphenols (Table I) were obtained by standard methods. The most favored route involved reacting salicylaldehyde methyl ether with the appropriate alkyl Grignard followed by hydrogenolysis of the secondary alcohol. Demethylation to the phenol was then effected by either pyridine hydrochloride or 48% HBr in acetic acid.

When the position para to the phenolic hydroxyl bore a substituent, the Fries or Friedel–Crafts methods of obtaining the *o*-acylphenols **1** were employed. Reduction to the alkylphenol **2** was then effected by the Clemmensen