with 6.6 mg of [^{3}H]methotrexate (33 μCi) and adjusted to pH 5.7. ECDI (20 mg) was added with rapid stirring and the reaction allowed to proceed at room temperature for 4 h. The mixture was then dialyzed exhaustively against PBS (phosphate-buffered saline; 0.15 M NaCl, 0.01 M phosphate, pH 8.2). A yellow precipitate which formed during the reaction could not be redissolved. A similar procedure was used for coupling the antibodies to methotrexate.

Mixed Anhydride Procedure. [^{3}H]Methotrexate (28 mg) (10 μCi) was suspended in 2 mL of acetic anhydride and heated at 100 °C for 30 min. The excess anhydride was then removed with a stream of dry nitrogen at 50 °C and the product redissolved immediately in 2 mL of dry dimethylformamide.

A solution of 60 mg of normal rabbit γ-globulin in 10 mL of water at pH 8.5 was treated with appropriate amounts of the above methotrexate "anhydride" at room temperature. After reacting for 18 h the mixture was exhaustively dialyzed against PBS. Tumor-specific anitsera were coupled in the same manner. The molecular ratios of γ-globulin to methotrexate ranged from about 1:15 for lowest dosage (10 mg/kg) to 1:120 for the highest dosage (80 mg/kg). Since there are a limited number of sites on the γ-globulin molecule where coupling could occur, there is some question as to how these high ratios were obtained. One possibility is that the drug underwent self-condensation to give a polymeric methotrexate. Such a derivative would probably be hydrolyzed in vivo to give monomeric drug so that the net effect is a method for coupling high ratios of methotrexate to γ-globulins.

Acknowledgment. This work was supported by National Cancer Institute Grant No. CA 12662 and The National Cancer Cytology Center and by an institutional grant IN-100A from the American Cancer Society.

References and Notes

(1) The abbreviations used are ECDI, 1-ethyl-3-(3-dimethylaminopropy)carbodiimide hydrochloride; PBS, 0.15 M NaCl–0.01 M phosphate, pH 8.2; MTX, methotrexate; Ab, antibody; NRS, normal rabbit serum.
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Synthesis and Central Nervous System Evaluation of Some 5-Alkoxy-3*H*-1,4-benzodiazepin-2(1*H*)-ones

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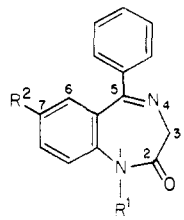
A series of 1-R-5-alkoxy-3*H*-1,4-benzodiazepin-2(1*H*)-ones was prepared and evaluated for central nervous system depressant activity. Several of these compounds, in particular, 7-chloro-5-ethoxy-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (2), gave a profile and activity level similar to diazepam when measured in mice.

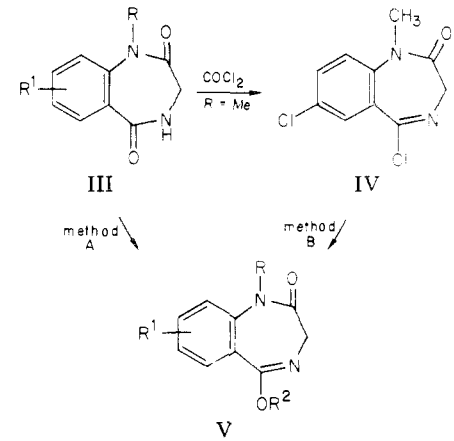
A considerable amount of medicinal chemistry has been carried out on the 1,4-benzodiazepine ring system since the finding that certain 5-aryl derivatives possess useful antianxiety activity in animals and man.[1] Among the more useful compounds developed to date are the 7-chloro-1-methyl (diazepam) and 7-nitro (nitrazepam) derivatives of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (I and II). The present work reports our findings on the central nervous system (CNS) activity of a series of compounds where the phenyl group in I and II has been replaced by an alkoxy or aryloxy group.[2]



I, $R^1 = CH_3$; $R^2 = Cl$
II, $R^1 = H$; $R^2 = NO_2$

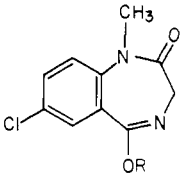
Chemistry. The synthesis of the 5-alkoxy- and 5-aryloxy-1-alkyl-3*H*-1,4-benzodiazepin-2(1*H*)-ones (V, Table

Scheme I



IV) was accomplished by the two methods given in Scheme I. Method A consisted of treating a 1-R-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (III) with a trialkyloxonium fluoroborate (Meerwein reagent) in an inert solvent. Method B involved the reaction of 5,7-dichloro-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)-one[3] (IV) with a so-

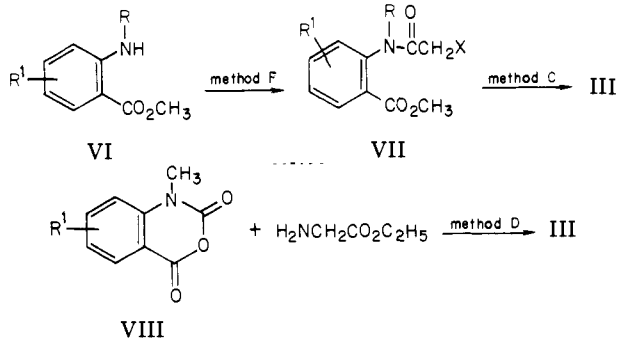
Table I. Neuropharmacological Data on 5-Alkoxy-7-chloro-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)-ones (V)



Compd	R	LD_{50},[a] mg/kg ip	Behavior[b] (ED_{50}, mg/kg ip)	N-SA[c] (ED_{50}, mg/kg ip)	Barbiturate[d] reinduction (RD_{50}, mg/kg ip)	Rotarod[e] (ND_{50}, mg/kg ip)	Amphetamine[f] interaction (% change at mg/kg ip)
1	CH_3	>200	Ataxia$_{50}$, 68.0; docility$_{50}$, 59.3; LRR_{50}, 300.0	>50	16.5		50%↓ at 50.0
2	C_2H_5	300	Ataxia$_{50}$, 45.3; docility$_{50}$, 42.8; LRR_{50}, 39.3	35.2	2.9	68.5	93%↓ at 18.8
3	CH_2CH_2Br			>102.4	>102.4		
4	CH_2CHCl_2			128.0	142.7		
5	CH_2CF_3			>102.4	>102.4		48%↓ at 51.2
6	$CH_2C_2H_5$	>400	Ataxia$_{50}$, 52.5; docility$_{50}$, 93.1; LRR_{50}, 78.1	38.2	19.2		50%↓ at 51.2
7	$CHCH_3(CF_3)$	300	Ataxia$_{50}$, 250.0; docility$_{50}$, 130.0; LRR_{50}, 288.0	100.0	>200.0	122.6	73%↓ at 100.0
8	$CH_2CH{=}CH_2$			63.9	54.4		55%↓ at 51.2
9	$CH_2C{\equiv}CH$	137.5	Ataxia$_{50}$, 22.7; docility$_{50}$, 20.8; LRR_{50}, 28.5	>25.0	22.9		44%↓ at 25.6
10	C_6H_5			50.1	>102.4		68%↓ at 51.2
11	$2\text{-}FC_6H_4$	650.0	Ataxia$_{50}$, 240.0; docility$_{50}$, 240.0; LRR_{50}, 428.0	>200.0	>200.0	146.0	45%↓ at 51.2
12	$4\text{-}Cl\text{-}2\text{-}CH_3C_6H_3$			>102.4	>102.4		36%↓ at 51.2

[a] Acute toxicity studies were carried out with paired male Royal Hart Wistar rats, 136–160 g, placed in 7 × 7 × 14 in. wire cages. The LD_{50} values were obtained 2 h postadministration of compounds using four rats per substance and estimated by probit analysis. [b] Analyses of behavior used a modification of the method of ref 4; LRR = loss of righting reflex; ten animals per dose. [c] N-SA = *N*-sulfamoylhexahydroazepine; methods of ref 6; ten animals were used per dose. [d] Modified method of ref 8 was used in which animals were administered compound immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time. [e] Method of ref 7; ten animals per dose, ND = neurological deficit. [f] Determined in mice using standard photocell activity cages manufactured by Woodward Research Corp., Herndon, Va.; dose of *dl*-amphetamine, 4.0 mg/kg ip; five mice per group.

Scheme II



dium alkoxide or aryloxide in refluxing benzene.

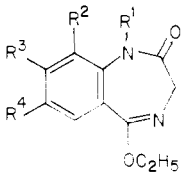
The methods of preparation of III (Table V) are given in Scheme II. Treatment of the methyl anthranilate VI with a haloacetyl halide gave the *N*-haloacetylanthranilates VII which were cyclized to III by ammonia in methanol (method C). Alternatively, the 1-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-diones VIII on treatment with ethyl glycinate hydrochloride in refluxing DMF gave III in 35–50% yield (method D). The 7-nitro- and 7-chloro-9-nitro-1-methyl derivatives of III were obtained by nitration (method E) of the appropriate dione.

Pharmacology. All derivatives of V and selected members of III were submitted to the battery of behavioral[4,5] and drug-interaction tests in mice given in Tables I–III. Anticonvulsant activity was determined by the antagonism to *N*-sulfamoylhexahydroazepine[6] (N-SA). General CNS-depressant activity was defined by the ability of substances to produce neurologic deficit on the rotarod[7] and by their abilities to reinduce "anesthesia" following recovery of loss of righting reflex obtained with hexobarbital.[8] Interaction with amphetamine-induced stimulation of locomotor activity was used to further define the CNS-depressant profile of compounds in the series.

Table I contains a listing of 7-chloro-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)-ones (V) where the 5 position contains a variety of alkoxy and aryloxy groups. The propargyl derivative **9** provided the most significant activity in the behavioral studies relative to the standard diazepam (Table II). Compound **2**, the 5-ethoxy analogue, gave the best anticonvulsant activity and showed reinduction of anesthesia following hexobarbital in the range of diazepam and nitrazepam. This substance also decreased amphetamine-induced stimulation at doses between those of diazepam and nitrazepam. Substitution of one or more halogen atoms in the ethyl group of **2** (compounds **3–5**) resulted in almost complete loss of activity whereas chain lengthening (**6** or **7**) or introduction of unsaturation (**8** and **9**) produced moderate to weak activity. The aryloxy derivatives **10–12** were devoid of any useful level of activity in the behavioral and drug-interaction tests.

The analogues given in Table II were prepared in an attempt to evaluate the effect of ring and N-substitution on compound **2**, the most interesting substance in Table

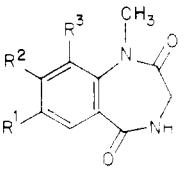
Table II. Neuropharmacological Data on 1-R-5-Ethoxy-3*H*-1,4-benzodiazepin-2(1*H*)-ones (V)



Compd	R^1	R^2	R^3	R^4	LD_{50},[a] mg/kg ip	Behavior[b] (ED_{50}, mg/kg ip)	N-SA[c] (ED_{50}, mg/kg ip)	Barbiturate[d] reinduction (RD_{50}, mg/kg ip)	Rotarod[e] (ND_{50}, mg/kg ip)	Amphetamine[f] interaction (% change at mg/kg ip)
2	CH_3	H	H	Cl	300.0	Ataxia$_{50}$, 45.3; docility$_{50}$, 42.8; LRR_{50}, 39.3	35.2	2.9	68.5	93%↓ at 18.8
13	C_2H_5	H	H	Cl	600.0	Ataxia$_{50}$, 100.0; docility$_{50}$, 100.0; LRR_{50}, 600.0	>75.0	21.8		5%↓ at 75.0
14	C_6H_5	H	H	Cl	650.0	Ataxia$_{50}$, 300.0; docility$_{50}$, 300.0; LRR_{50}, 300.0	>150.0	>150.0		50%↓ at 150.0
15	CH_3	H	Cl	H	600.0	Ataxia$_{50}$, 67.7; docility$_{50}$, 56.5; LRR_{50}, 74.4	29.9	38.4	61.8	50%↓ at 51.2
16	CH_3	H	H	NO_2	600.0	Ataxia$_{50}$, 42.5; docility$_{50}$, 11.3; LRR_{50}, 37.5	87.8	9.0	15.8	27%↓ at 51.2
17	CH_3	H	H	CH_3	300.0	Ataxia$_{50}$, 133.3; docility$_{50}$, 136.6; LRR_{50}, 140.6	>102.4	18.4	87.6	44%↓ at 51.2
18	CH_3	NO_2	H	Cl			>102.4	>102.4		19%↓ at 51.2
Diazepam					300.0	Ataxia$_{50}$, 21.9; docility$_{50}$, 4.1; LRR_{50}, 8.9	1.1	1.6	5.2	8%↓ at 50.0
Nitrazepam					733.4	Ataxia$_{50}$, 1.5; docility$_{50}$, 1.5; LRR_{50}, 1.5	1.0	0.8	0.5	50%↓ at 1.5

[a–f] See corresponding footnotes in Table I.

Table III. Neuropharmacological Data on 1-Methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-diones (III)



Compd	R^1	R^2	R^3	N-SA[a] (ED_{50}, mg/kg ip)	Barbiturate[b] reinduction (RD_{50}, mg/kg ip)	Amphetamine[c] interaction (% change at mg/kg ip)
19	Cl	H	NO_2	>102.4	>102.4	24%↓ at 51.2
20	Cl	H	H	>100.0	39.4	75%↓ at 100.0
21	H	Cl	H	>102.4	>102.4	30%↓ at 51.2
22	NO_2	H	H	>102.4	>102.4	51%↓ at 51.2
24	CH_3	H	H	>102.4	>102.4	62%↓ at 51.2

[a–c] See footnotes *c*, *d*, and *f*, respectively, in Table I.

I. Replacement of the nitrogen CH_3 group by a C_2H_5 (**13**) or C_6H_5 (**14**) group resulted in a marked decrease in activity. Substitution of the 7-Cl atom in **2** by a NO_2 (**16**) or CH_3 (**17**) group or shifting the Cl atom to position 8 (**15**) retained the general profile of activity but increased the barbiturate and amphetamine interaction values. Addition of a NO_2 group (**18**) at position 9 in compound **2** resulted in complete loss of activity.

The 1-methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-diones given in Table III were all devoid of any significant level of CNS-depressant activity.

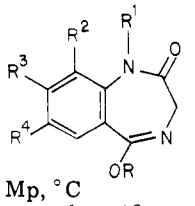
Experimental Section

Chemical Synthesis. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. For all compounds listed in Tables IV–VI ^1H NMR ($CDCl_3$ or Me_2SO-d_6) or IR (KBr) spectra were obtained on Varian Associates A-60 spectrometer or a Perkin-Elmer Infracord. In all cases the spectra were consistent with the assigned structure.

Analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of silica G with fluorescent indicator for all compounds reported in this paper. The analyses are within ±0.4% of the theoretical values.

1-R-5-Alkoxy-3*H*-1,4-benzodiazepin-2(1*H*)-ones (V). Method A. From 1-R-3,4-Dihydro-1*H*-1,4-benzodiazepine-2,5-diones (III). To a stirred solution of 44 g (0.20 mol) of 7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione in 250 mL of $CHCl_3$ there was added dropwise a solution of 68.4 g (0.40 mol) of triethyloxonium fluoroborate in 750 mL of CH_2Cl_2. After standing overnight at room temperature the mixture was washed with 500 mL of 50% K_2CO_3. The organic phase was separated, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from the appropriate solvent to give **2** (Table IV). In a similar manner there was

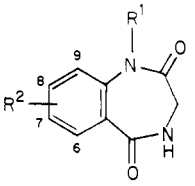
Table IV. 1-R-5-Alkoxy-3*H*-1,4-benzodiazepin-2(1*H*)-ones (V)



Compd[a]	Method[b]	Yield, %	Mp, °C (recrystn solvent)[c]	Emp formula	Analyses
1	A	60	114-115.5 (A)	$C_{11}H_{11}ClN_2O_2$	C, H, N
2	A	75	123 (A)	$C_{12}H_{13}ClN_2O_2$	C, H, Cl, N
3	B	40	110 (B)	$C_{12}H_{12}BrClN_2O_2$	C, H, Br, N
4	B	38	123 (B)	$C_{12}H_{11}Cl_3N_2O_2$	C, H, Cl
5	B	32	128 (B)	$C_{12}H_{10}ClF_3N_2O_2$	C, H, N
6	B	15	70 (B)	$C_{13}H_{15}ClN_2O_2$	C, H, Cl, N
7	B	38	95 (B)	$C_{13}H_{12}ClF_3N_2O_2$	C, H, N
8	B	28	64 (B)	$C_{13}H_{13}ClN_2O_2$	C, H, N
9	B	40	120 (B)	$C_{13}H_{11}ClN_2O_2$	C, H, Cl, N
10	B	55	111-113 (B)	$C_{16}H_{13}ClN_2O_2$	C, H, Cl, N
11	B	50	128 (B)	$C_{15}H_{12}FClN_2O_2$	C, H, Cl, N
12	B	55	179 (B)	$C_{17}H_{14}Cl_2N_2O_2$	C, H, Cl, N
13	A	46	91-93 (C)	$C_{13}H_{15}ClN_2O_2$	C, H, Cl, N
14	A	38	150.5-151.5 (C)	$C_{17}H_{15}ClN_2O_2$	C, H, Cl
15	A	65	95-97 (C)	$C_{12}H_{13}ClN_2O_2$	C, H, Cl, N
16	A	57	108-109 (A)	$C_{12}H_{13}N_3O_4$	C, H, N, O
17	A	46	87-89 (D)	$C_{13}H_{16}N_2O_2$	C, H, N
18	A	53	100-102 (E)	$C_{12}H_{12}ClN_3O_4$	C, H, Cl, N

[a] See Tables I and II for substituent pattern. [b] See Experimental Section. [c] A, CCl_4-pentane; B, Et_2O-pentane; C, EtOH; D, EtOAc; E, $CHCl_3$-pentane.

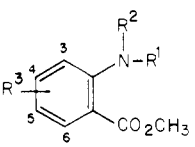
Table V. 3*H*-1,4-Benzodiazepine-2,5(1*H*,4*H*)-diones (III)



Compd	R^1	R^2	Method[a]	Yield, %	Mp, °C (recrystn solvent)[b]	Emp formula	Analyses
19	CH_3	7-Cl, 9-NO_2	E	56	237-238 (A)	$C_{10}H_5ClN_3O_4$	C, H, N
20	CH_3	7-Cl	C	35	174-175 (B)[c]	$C_{10}H_9ClN_2O_2$	C, H, Cl, N
21	CH_3	8-Cl	C	40	210-211 (C)[d]	$C_{10}H_9ClN_2O_2$	C, H, Cl, N
22	CH_3	7-NO_2	E	71	271-272 (A)	$C_{10}H_9N_3O_4$	C, H, N
23	C_2H_5	7-Cl	C	55	146-147 (D)	$C_{11}H_{11}ClN_2O_2$	C, H, Cl, N
24	CH_3	7-CH_3	D	50	170 (E)	$C_{11}H_{12}N_2O_2$	C, H, N
25	C_6H_5	7-Cl	E	35	203-205 (F)	$C_{15}H_{11}ClN_2O_2$	C, H, Cl

[a] See Experimental Section. [b] A, DMF; B, EtOH; C, $CHCl_3$-MeOH; D, EtOAc-EtOH; E, EtOH-CH_3COCH_3, F, EtOAc. [c] Lit.[9] mp 171.5-173.5 °C. [d] Lit.[9] mp 210-211.5 °C.

Table VI. *N*-Alkyl- and *N*-Alkyl-*N*-haloacetylanthranilates VI and VII



Compd	R^1	R^2	R^3	Method,[a] % yield	Mp or bp, °C (crystn solvent or mmHg)[b]	Emp formula	Analyses
26	CH_3	H	4-Cl	G, 65	130 (0.05)[c]	$C_9H_{10}ClNO_2$	
27	CH_3	H	5-Cl	G, 88	62.0-64.0 (A)[d]	$C_9H_{10}ClNO_2$	
28	C_2H_5	H	5-Cl	G, 78	47-49 (B)	$C_{10}H_{12}ClNO_2$	C, H, Cl
29	C_6H_5	H	5-Cl	H, 95	62.5-63.0 (C)	$C_{14}H_{12}ClNO_2$	C, H, Cl
30	CH_3	$COCH_2Cl$	4-Cl	F, 64	Oil	$C_{11}H_{11}Cl_2NO_3$	Cl
31	CH_3	$COCH_2Br$	5-Cl	F, 54	56.0-57.5 (D)	$C_{11}H_{11}BrClNO_3$	C, H, Br, N
32	C_2H_5	$COCH_2Br$	5-Cl	F, 49	Oil	$C_{12}H_{13}BrClNO_3$	C, H, Br, N
33	C_6H_5	$COCH_2Br$	5-Cl	F, 94	Oil	$C_{16}H_{13}BrClNO_3$	C, H, Br

[a] See Experimental Section. [b] A, MeOH; B, EtOAc; C, Et_2O-petroleum ether; D, Et_2O. [c] Lit., see ref 10. [d] Lit.[11] mp 63-64 °C.

prepared compounds **13–18** and from trimethyloxonium fluoroborate compound **1** (Table IV).

Method B. From 5,7-Dichloro-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (IV). A mixture of 10.0 g (0.09 mol) of 2-fluorophenol and 4.3 g (0.09 mol as NaH) of 50% NaH–mineral oil dispersion in 250 mL of dry C_6H_6 was stirred and refluxed until gas (H_2) evolution ceased. The reaction was then treated with 17.0 g (0.076 mol) of IV and reflux continued for 9 h. The mixture was then washed with 100 mL of 2 N NaOH and the C_6H_6 layer was separated, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was then chromatographed on silica gel (10 g per 1 g of substance) with $CHCl_3$–C_6H_6 (1:1) as eluent to give **11** (Table IV). In a similar manner there was obtained compounds **3–10** and **12** (Table IV).

1-R-3*H*-1,4-Benzodiazepine-2,5(1*H*,4*H*)-diones (III). Method C. Methyl *N*-R-*N*-Haloacetylanthranilates and Ammonia. A solution of 15 g of methyl 4-chloro-*N*-chloroacetyl-*N*-methylanthranilate (**30**) in 150 mL of anhydrous MeOH was saturated with NH_3 gas at room temperature and allowed to stand for 2 days. The solvent was removed in vacuo and the residue dissolved in C_6H_6 and chromatographed on silica gel (10 g per 1 g of substance; C_6H_6 eluent) to give **21** (Table V). Compounds **20**, **23**, and **25** (Table V) were prepared in a similar manner.

Method D. 1-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-diones and Ethyl Glycinate Hydrochloride. A mixture of 19.1 g (0.10 mol) of 1,6-dimethyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione, 13.9 g (0.10 mol) of ethyl glycinate hydrochloride, and 100 mL of anhydrous DMF was stirred and refluxed for 4 h. The solvent was removed in vacuo and the residue dissolved in $CHCl_3$, washed with 2 N HCl, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in C_6H_6 and chromatographed on silica gel (10 g per g of substance; C_6H_6–$CHCl_3$, 95:5 eluent) to give **24** (Table V).

Method E. 7-Nitro- and 7-Chloro-9-nitro-1-methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (22 and 19). A stirred solution of 33.4 g (0.18 mol) of 1-methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione in 500 mL of concentrated H_2SO_4 was cooled to an internal temperature of 0 °C and then treated portionwise with 16.7 g (0.20 mol) of $NaNO_3$ while maintaining the temperature below 5 °C. After an additional 2 h at 5 ± 5 °C the mixture was poured onto ca. 2 kg of ice–H_2O. The resultant solid was filtered off, washed with H_2O, and recrystallized from DMF to give **22** (Table V). Compound **19** was prepared in a similar manner by nitration of **20**.

Method F. Methyl *N*-Alkyl-*N*-haloacetylanthranilates (VII). A solution of 40.0 g (0.20 mol) of bromoacetyl bromide in 25 mL of CH_2Cl_2 was added dropwise to a stirred solution of 35.8 g (0.18 mol) of methyl 5-chloro-*N*-methylanthranilate (**27**) in 75 mL of CH_2Cl_2 at such a rate that the internal temperature was maintained at −5 ± 5 °C. After 0.5 h the mixture was treated dropwise with 100 mL of 2 N NaOH while maintaining the temperature at 0 ± 5 °C. The organic layer was separated and the aqueous layer washed with ca. 100 mL of $CHCl_3$. The combined organic phases were dried with $MgSO_4$ and filtered. The filtrate was distilled at atmospheric pressure to an oil bath temperature of 140 °C. The residue was treated at room temperature with ca. 200 mL of Et_2O and cooled in an ice bath. There was obtained **31** (Table VI). Compounds **32** and **33** were prepared in a similar manner and **30** was prepared from chloroacetyl chloride and **26**.

Method G. Methyl *N*-Alkylanthranilates (VI). A mixture of 100 g (0.473 mol) of 6-chloro-1-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione, 0.8 g of NaOH, and 600 mL of methanol was stirred and refluxed until CO_2 evolution ceased (ca. 25 h). The resultant solution was treated with charcoal, filtered, and concentrated to about one-third volume. There was obtained **27** (Table VI). Compounds **26** and **28** (Table VI) were obtained in a similar manner.

Method H. Methyl 5-Chloro-*N*-phenylanthranilate (29). To a freshly prepared solution of 7.25 g (0.315 mol) of sodium in 250 mL of anhydrous MeOH there was added dropwise a solution of 70 g (0.315 mol) of methyl 5-chlorosalicylate in 100 mL of anhydrous Et_2O. The mixture was stirred for 0.5 h, cooled in an ice bath, and then treated dropwise with a solution of 56 g (0.26 mol) of *N*-(α-chlorobenzylidene)aniline in 125 mL of anhydrous Et_2O at such a rate that the internal temperature did not exceed 20 °C. After an additional 3 h the mixture was concentrated in vacuo and the resultant white solid was treated with ca. 200 mL of H_2O and filtered. The remaining solid was crystallized from EtOH to give 75.4 g (80%) of methyl 3-chloro-6-[α-(phenylimino)benzyloxy]benzoate (**34**), mp 111.5–113 °C. Anal. ($C_{21}H_{16}ClNO_3$) C, H, Cl, N. A 1000-mL flask containing 200.5 g of **34** was heated to an internal temperature of 230 °C for ca. 10 min. An exothermic reaction then occurred to 275 °C for ca. 5 min. When the temperature dropped to 250 °C the mixture was heated to 300 °C for 5 min and then allowed to cool to room temperature. The solid was dissolved in 300 mL of hot EtOH and on cooling gave 152 g (76%) of methyl *N*-benzoyl-5-chloro-*N*-phenylanthranilate (**35**), mp 125.5–126.5 °C. Anal. ($C_{21}H_{16}ClNO_3$) C, H, N.

A solution containing 152.0 g (0.416 mol) of **35**, 600 g (15.0 mol) of NaOH, 1900 mL of EtOH, and 600 mL of H_2O was refluxed for ca. 18 h. The alcohol was removed in vacuo and the residue treated with ca. 1500 mL of H_2O and then dropwise with 1250 mL of cold concentrated HCl. The resultant solid was filtered off, washed with hot H_2O three times, and then recrystallized from EtOH to give 98 g (95%) of 5-chloro-*N*-phenylanthranilic acid (**36**), mp 205–207 °C. Anal. ($C_{13}H_{10}ClNO_2$) C, H, Cl, N.

A solution of 97 g (0.394 mol) of **36**, 54.5 g (0.394 mol) of anhydrous K_2CO_3, and 1000 mL of dry acetone was heated at reflux for ca. 1 h. The warm solution was treated dropwise with 49.7 g (0.394 mol) of $(CH_3)_2SO_4$ and then refluxed for 2 h. After cooling to room temperature the solids were filtered off and the filtrate was concentrated in vacuo. The residue was recrystallized twice to give **29** (Table VI).

6-Chloro-1-ethyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (37). A stirred solution of 30 g (0.15 mol) of 6-chloro-2*H*-3,1-benzoxazine-2,4(1*H*)-dione in 200 mL of anhydrous DMF was cooled to 5 °C and treated with 10.3 g (0.10 mol) of powdered anhydrous K_2CO_3. The mixture was stirred for ca. 0.5 h and then treated dropwise with 19.0 g (0.18 mol) of diethyl sulfate while maintaining the temperature at 5 ± 5 °C. The cooling was discontinued and after ca. 2 h of stirring, the mixture was poured into 500 g of ice–500 g of H_2O. The resultant solid was filtered off and recrystallized from EtOAc to 17.4 g (51%) of **37**, mp 148–150 °C. Anal. ($C_{10}H_8ClNO_3$) C, H, N, Cl.

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