to that described for the preparation of **23b**. The resulting oil was chromatographed on an alumina column. Elution with Et_2O gave **26c** as an oil: TLC (alumina, Et_2O–petroleum ether 1:1) showed a single spot. Treatment of a solution of **26c** in Et_2O with ethereal HCl precipitated 1.9 g (18%) of **26c**·HCl, mp 134 °C dec. Anal. ($C_{31}H_{37}NO_6S$·HCl·H_2O) C, H, N.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-(1-hydroxy-2-methylsulfonylethyl)benzyl Alcohol (27). The amino ketone **26c**·HCl was treated with $NaBH_4$ in a manner similar to that described for the preparation of **24a**. The crude product was chromatographed on an alumina column. Initial fractions of the eluent (Et_2O) removed impurities. Elution with MeOH–EtOAc (1:9) and evaporation of the solvent gave 0.24 g (16%) of **27** as an oil: TLC (alumina, Et_2O) showed a single spot.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(1-hydroxy-2-methylsulfonylethyl)benzyl Alcohol (1i). The amino alcohol **27** (240 mg) was hydrogenated over 10% Pd/C at ambient temperature and an initial H_2 pressure of 3.5 kg/cm^2 to give 160 mg of **1i**. A solution of **1i** in EtOH was treated with fumaric acid (0.5 mol equiv). Addition of EtOAc precipitated the salt. Recrystallization from EtOH–EtOAc gave 100 mg (55%) of **1i** hemifumarate: mp 152 °C dec; mass spectral data supported the assigned structure. Anal. ($C_{15}H_{25}NO_5S$·0.5$C_4H_4O_4$·H_2O) C, H, N.

Dimethyl 4-Benzyloxyisophthalate (28b). A solution of **28a**[13] (2.0 g, 7.35 mmol) in 100 mL of MeOH and 0.1 mL of concentrated H_2SO_4 was refluxed for 18 h and then evaporated. The residue was dissolved in Et_2O. The Et_2O solution was washed with 5% $NaHCO_3$, dried, and concentrated. The residue was recrystallized from EtOH to give 1.2 g (55%) of **28b**: mp 103–104 °C; TLC (silica gel, Et_2O–petroleum ether 3:7) showed a single spot. Anal. ($C_{17}H_{18}O_5$) C, H.

4-Benzyloxyisophthalyl Alcohol (29). A suspension of $LiAlH_4$ (600 mg) in 30 mL of Et_2O was refluxed with a solution of **28b** (1.1 g, 3.67 mmol) in 30 mL of Et_2O and 5 mL of THF for 3 h. Excess $LiAlH_4$ was decomposed by *cautious* dropwise addition of 1.2 mL of H_2O and 1 mL of 2.5 N NaOH. Insoluble material was removed by filtration, and the filtrate was evaporated. The residue was recrystallized from Me_2CO–hexane to give 0.55 g (61%) of **29**: mp 90–92 °C; TLC (silica gel, Et_2O) showed a single spot. Anal. ($C_{15}H_{18}O_3$) C, H.

4-Benzyloxyisophthalaldehyde (30). A solution of **29** (300 mg, 1.23 mmol) in 50 mL of CH_2Cl_2 was refluxed with activated MnO_2 (3 g) for 1.5 h. After the mixture was filtered, the filtrate was evaporated to give 270 mg (92%) of crystalline **30**: mp 104–105 °C; TLC (silica gel, Et_2O–petroleum ether 2:3) showed a single spot. Anal. ($C_{15}H_{14}O_3$) C, H.

Bis[2,4-(2-*tert*-butylamino-1-hydroxyethyl)phenol] (1j). A solution of **30** (5.16 g, 0.0215 mol) in $CHCl_3$ (100 mL), AcOH (9 mL), and *tert*-butyl isocyanide (14 g) was refluxed for 48 h. The solution was washed with 5% $NaHCO_3$ and H_2O and dried. The solvent was evaporated and the residue was chromatographed on a silica gel column (eluted with Et_2O). Evaporation of the initial fractions gave 5.4 g of crude acetoxyamide **31a**.

A solution of crude **31a** (5.4 g) in 150 mL of MeOH and 45 mL of 2.5 N HCl was refluxed for 2.5 h, and the MeOH was then evaporated. The aqueous solution was extracted with Et_2O. The extract was washed with 5% $NaHCO_3$ and H_2O and dried. Evaporation of the solvent gave 3.7 g (39% from **30**) of the hydroxyamide **31b** as a foam: TLC (silica gel, Et_2O) showed a single spot.

To 90 mL of a 1 M solution of diborane in THF was added a solution of **31b** (3.7 g, 8.4 mmol) in 50 mL of THF. The mixture was refluxed for 2 h. The chilled solution was treated *cautiously* with 20 mL of MeOH and 20 mL of 3 N HCl, and the THF was evaporated. The aqueous solution was made alkaline with 2.5 N NaOH and extracted with Et_2O. The extract was treated with ethereal HCl, and the precipitated HCl salt was extracted into H_2O. The aqueous extract was washed with Et_2O, made alkaline with 2.5 N NaOH, and extracted with Et_2O. The extract was dried and evaporated to give 1.73 g (50%) of the ethanolamine **32** as an oil: TLC (silica gel, MeOH–Et_2O 1:19) showed a major component and two minor impurities.

A solution of **32** (1.2 g, 2.9 mmol) in 100 mL of EtOH was hydrogenated over 10% Pd/C (1.0 g) at 3.5 kg/cm^2 for 10 min. The mixture was filtered and the filtrate was evaporated. The residue in 30 mL of EtOH was treated with fumaric acid (1 mol equiv). The salt crystallized on dilution with EtOAc (20 mL) and cooling. Four recrystallizations from MeOH–EtOAc gave 0.24 g (19%) of **1j** hemifumarate: mp 243 °C dec; mass spectral data supported the assigned structure. Anal. ($C_{18}H_{32}N_2O_3$·$C_4H_4O_4$) H, N; C: calcd, 59.98; found, 61.37.

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Central Nervous System Activity of a Novel Class of Annelated 1,4-Benzodiazepines, Aminomethylene-2,4-dihydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-ones[1]

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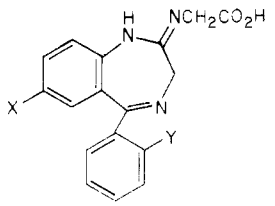
The synthesis and CNS activity of a novel class of annelated 1,4-benzodiazepines, the aminomethylene-2,4-dihydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepines, are described. An investigation of the structure–activity relationships in the series derived from 8-chloro-2,4-dihydro-2-dimethylaminomethylene-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]-benzodiazepin-1-one (**10**) led to the synthesis of a group of compounds with potent minor tranquillizer activity.

The 1,4-benzodiazepines are a remarkable class of compounds with potent minor tranquillizer, muscle-relaxant, anticonvulsant, and sedative–hypnotic activity, whose pharmacological and clinical eminence is attested

Table I. N-5-Aryl-3H-1,4-benzodiazepin-2-ylglycines



Compd no.	X	Y	Yield, %	Mp, °C	Analyses or Formula[a]
IIIa	Cl	H	77	215-220	C, H, N, Cl
IIIb	NO_2	H	65	151-154	$C_{17}H_{14}N_4O_4$
IIIc	Cl	Cl	87	136-139	$C_{17}H_{13}Cl_2N_3O_2$
IIId	Cl	F	88	147-150	$C_{17}H_{13}ClFN_3O_2$
IIIe	NO_2	Cl	83	158-161	$C_{17}H_{13}ClN_4O_4$
IIIf	NO_2	F	45	144-147	$C_{17}H_{13}FN_4O_4$

[a] These compounds were amorphous solids which except for IIIa were found not to give accurate C, H, and N analyses. The structures were therefore established by IR, NMR, and accurate mass spectral data.

by the large number of reviews and books which have been published describing their properties.[2] Recently, two groups[3,4] have described the synthesis of a novel series of annelated 1,4-benzodiazepines, namely, 6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepines, which showed similar pharmacological profiles to the benzodiazepines from which they were derived but which were an order of magnitude more potent. This paper describes the synthesis of another annelated system, the aminomethylene-2,4-dihydro-1H-imidazo[1,2-a][1,4]benzodiazepin-1-ones, together with preliminary central nervous system (CNS) results for the series.

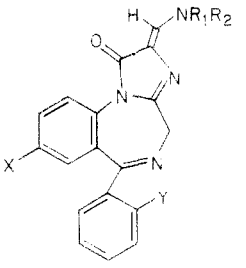
Chemistry. The synthetic route used to prepare these compounds is shown in Scheme I. The 5-aryl-1,3-dihydro-7-substituted-2H-1,4-benzodiazepine-2-thiones IIa-f[5] were condensed with glycine in aqueous ethanol to give the previously unreported amino acids IIIa-f (Table I). Dicyclohexylcarbodiimide in dry methylene chloride cyclized these acids to the imidazolobenzodiazepines IVa-f which were found to be oils unstable to hydrolytic solvents whose structures could be established by IR and NMR spectra. These compounds were not otherwise characterized but were immediately condensed either with dimethylformamide dialkyl acetal or with an amide-$POCl_3$ complex to give the stable, crystalline dimethylaminomethylene-2,4-dihydro-5-aryl-1H-imidazo[1,2-a][1,4]-benzodiazepin-1-ones Va-f (Table II). The dimethylamino group of V, being part of a vinylogous amide structure, was readily displaced by a variety of primary and secondary amines, usually in dry toluene under reflux, to give the more active derivatives Ia-f.

These compounds, and their precursors V, could exist in isomeric forms with the amino group on the exocyclic methylene bond lying cis or trans to the carbonyl group. The NMR spectrum of a freshly prepared solution of the NHMe derivative (compound 2) showed the presence of two isomers in a ratio which slowly changed over several weeks until eventually the original minor component predominated. The spectral changes were consistent with the production of an isomer containing a stronger hydrogen bond, presumably the cis form. The spectrum of the NMe_2 derivative (compound Va) showed originally the presence of only one isomer and did not change with time. It was concluded that in the absence of any possible hydrogen bonding, this compound and related tertiary amines existed entirely in the trans form. Such a conclusion agrees with the results of literature studies of less complex compounds.[6]

Results and Discussion

In order to obtain an overall minor tranquillizer profile of these compounds, a battery of seven pharmacological

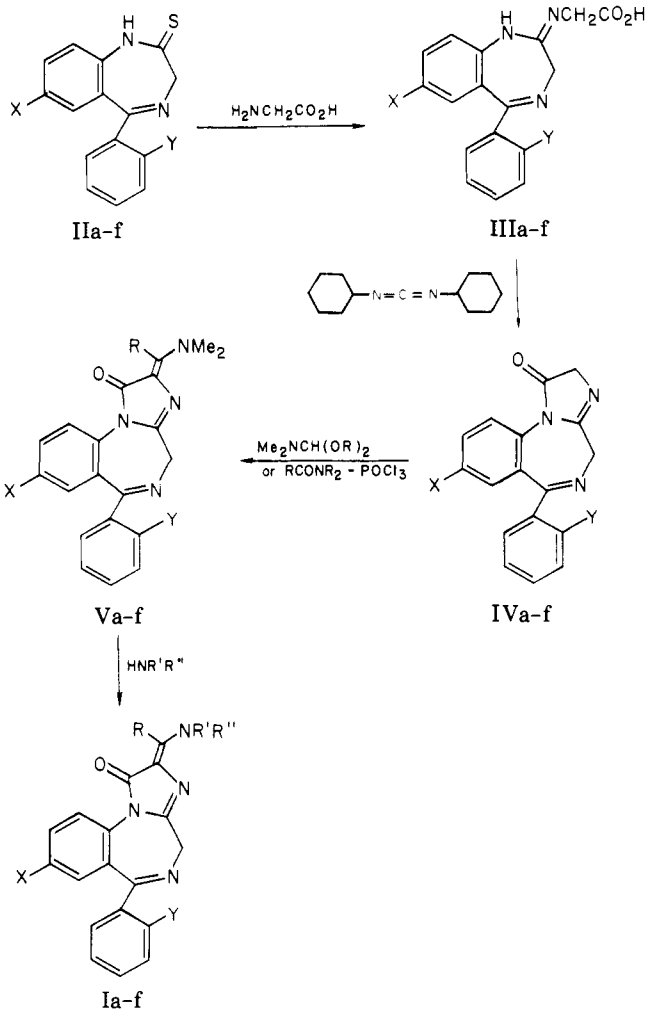
Table II. 2-Alkylaminomethylene-2,4-dihydro-6-aryl-1H-imidazo[1,2-a][1,4]benzodiazepin-1-ones



Compd no.	X	Y	R_1	R_2	Method	Yield, %	Mp, °C	Crystn solvent	Analyses
Va (10)	Cl	H	Me	Me	E	97[a]	264-265	EtOAc-MeOH	C, H, N, Cl
Vb	NO_2	H	Me	Me	E	83[a]	227-228	EtOAc-MeOH	C, H, N
Vc	Cl	Cl	Me	Me	E	53[a]	282-284	EtOAc-MeOH	C, H, N, Cl
Vd	Cl	F	Me	Me	E	63[a]	257-260	EtOAc-MeOH	C, H, N, Cl
Ve	NO_2	Cl	Me	Me	E	77[a]	253-255	EtOAc-MeOH	C, H, N, Cl
Vf	NO_2	F	Me	Me	E	76[a]	228-231	EtOAc-MeOH	C, H, N
1	Cl	H	H	H	A	98[b]	265-267	MeOH-EtOAc	C, H, N, Cl
2	Cl	H	H	Me	B	88[b]	233-235	Et_2O	C, H, N, Cl
3	Cl	H	H	Et	B	93[b]	234-236	CH_2Cl_2-Et_2O	C, H, N, Cl
4	Cl	H	H	n-Pr	C	96[b]	153-155	CH_2Cl_2-Et_2O	C, H, N, Cl
5	Cl	H	H	n-Bu	C	93[b]	165-167	$CHCl_3$-Et_2O	C, H, N, Cl
6	Cl	H	H	t-Bu	D	93[b]	230-232	$CHCl_3$-Et_2O	C, H, N, Cl
7	Cl	H	H	C_6H_{11}	C	87[b]	143-145	$CHCl_3$-Et_2O	C, H, N, Cl
8	Cl	H	H	CH_2CH_2OH	C	85[b]	223-225	$CHCl_3$-Et_2O	C, H, N, Cl
9	Cl	H	H	$CH_2CH_2NEt_2$	C	70[b]	113-116	C_6H_6-petr ether	C, H, N, Cl
11	Cl	H	Me	$CH_2CH_2NMe_2$	C	52[b]	152-155	Et_2O	C, H, N, Cl
12	Cl	Cl	H	CH_2CH_3	C	82[c]	235-237	MeOH-Et_2O	C, H, N, Cl
13	Cl	Cl	H	$CH_2CH_2CH_3$	C	94[c]	227-229	MeOH-Et_2O	C, H, N, Cl

[a] From IIIa-f. [b] From compound 10. [c] From IIIc.

Scheme I



a, X = Cl; Y = H
b, X = NO_2; Y = H
c, X = Cl; Y = Cl
d, X = Cl; Y = F
e, X = NO_2; Y = Cl
f, X = NO_2; Y = F

tests was used. Antianxiety activity was measured by the antagonism of foot-shock--induced aggression, anticonvulsant activity by the degree of protection against convulsions induced by pentylenetetrazole, maximal electroshock, and strychnine, sedative activity by the potentiation of hexobarbital and chlorprothixene induced loss of righting reflex, and muscle relaxation by the rotary drum test. Table III shows these results and the acute toxicities (in mg/kg) for all tested compounds and also includes the data for a representative benzodiazepine, chlordiazepoxide.

The first active compound to be synthesized was the dimethylamino derivative Va (R = H, compound **10**) which showed some activity in the antiaggression, antielectroshock, and antipentylenetetrazole tests. To maximize the activity of this structure it was decided to first optimize the substitution pattern on the exocyclic methylene group and then attempt to further improve activity by varying the substitution on the 6-aryl group and the C-8 position according to structure–activity relationships already established for the 1,4-benzodiazepines.[7]

Consequently, the dimethylamino group was displaced by ammonia and a range of primary amines to give compounds **1–9**. From Table III it can be seen that while there was not a uniform order of potency over all tests, the overall minor tranquillizer potency appeared to peak around the *n*-propyl and *n*-butyl substituent (compounds **4** and **5**). Interestingly, derivative **8** whose hydroxyethyl group has a π value close to that of methyl[8] was much more potent than **2** and the much reduced activity of the diethylaminoethyl derivative **9** may then be due to unfavorable steric or lipophilic interactions due to the two ethyl groups. The addition of an *o*-chloro atom to the 5-phenyl group has been shown[7] to increase the activity of the 1,4-benzodiazepines so the 6-*o*-chlorophenyl analogues of **3** and **4**, namely, **12** and **13**, were prepared. However, the results were disappointing and for this series showed no consistent increase in activity over the unsubstituted compounds. Indeed in the rotating drum test **12** and **13** were significantly less active than **3** and **4**, while **13** was also less active than **4** in three other tests.

Attention was then switched to the heterocyclic derivatives **14–26** (Table IV), wherein it was quickly established that the greatest activity lay in the *N'*-alkylpiperazines with the peak activity residing in the *N'*-ethyl and *N'*-propyl derivatives. That the activity-enhancing effect of an *N'*-alkyl group was not merely due to lipophilicity was indicated by the results of the *N'*-allyl (**20**), *N'*-cyclopropylmethyl (**21**), and *N'*-isopropyl (**22**) derivatives. Compound **20** should have a *p* value intermediate between that of **17** and **18** but was less active than either in all tests, while **21** and **22** should have the same *p* values as **18** but were also less active in all tests. These results indicated that the optimum substituent at this position also requires a degree of conformational flexibility. The lower level of activity of the morpholino derivative **14** and the virtual lack of activity of the piperidino **25** and thiomorpholino **26** derivatives indicated the necessity for the presence of the *N'*-alkyl group for optimum activity. From this stage of the work it was evident that the greatest activity in the series lay with the *N'*-methyl, ethyl, and propyl piperazides, while the lower activity of the ethylidene derivative **36** (Table V) indicated that the smaller steric requirement of the methylene group was optimal.

Having established the requirements around the exocyclic methylene group for optimal activity, a further series of compounds containing either an *N'*-methyl- or *N'*-ethylpiperazine group was prepared to evaluate the effect of varying the substitution on C-8 and on the C-6 phenyl ring. Firstly, it was concluded that as there was little change in activity when the C_8-chlorine was replaced by a nitro group (compound **27**) the overall activity was insensitive to the precise nature of this electron-withdrawing substituent. Secondly, a group of compounds bearing either a fluorine or a chlorine atom on the ortho position of the C-6 phenyl ring (**28–35**) was prepared and it was found that in all the tests (with the exception of **32** and **33** in the potentiation of hexobarbital) these derivatives showed enhanced activities over the parent structures **16** and **17**, with the general level of activity being very high. The potency of these compounds combined with their low toxicity indicated that all of these compounds had a very favorable therapeutic ratio. Determining which of a series of compounds such as **28–35** is the most active overall is something of a problematical exercise since not one of the compounds is more active than any other in all tests and many of the differences in ED_{50} values are not statistically significant. Accordingly, a number of these compounds are currently being further evaluated with a view to possible future clinical use.

Experimental Section

Chemistry. All melting points are uncorrected and were obtained on a Kofler hot-stage apparatus. NMR spectra were recorded on a Perkin-Elmer R12 60-MHz instrument and shift

Table III. Pharmacological Activity in the Mouse[a] (ED_{50}, mg/kg po)

Compd no.	Antiaggression	Antielectroshock	Antipentylene-tetrazole	Antistrychnine	Potentiation of hexobarbital	Potentiation of chlorprothixene	Rotary drum	Acute toxicity
Chlordiazepoxide	7.0 (4.6-10.64)	8.0 (5.92-10.8)	1.9 (1.1-3.23)	5.0 (3.5-7.0)	64.0 (45.7-89.6)	4.0 (2.1-7.6)	6.8 (5.03-9.18)	>1000
1		>50	7.1 (6.0-8.37)	>50	1.65 (0.95-2.8)	4.3 (2.15-8.6)	>50	>1000
2	5.3 (4.1-6.4)			>50	>50	>50		>1000
3	1.45 (0.87-2.39)	>10 < 30	4.0 (2.9-5.4)	>50	7.2 (5.21-9.9)	>10	1.8 (0.9-3.6)	>1000
4	0.92 (0.65-1.28)	4.0 (2.96-5.4)	1.55 (1.03-2.32	>50	3.9 (2.4-6.2)	2.6 (1.85-3.64)	2.8 (1.8-4.56)	>1000
5	3.35 (2.52-4.43)	12.5 (7.35-21.25)	1.15 (0.85-1.55)	17 (10.62-27.2)	0.66 (0.45-0.96)	1.8 (1.12-2.88)	24 (9.6-60.0)	>1000
6	1.1 (0.61-1.98)	19 (14.1-25.6)	3.25 (2.8-4.2)	>50	5.0 (3.4-7.2)	14.0 (8.23-23.8)	14.5 (6.9-30.4)	>1000
7	1.4 (0.87-2.24)	8.5 (5.66-12.75)	2.35 (1.23-4.46)	15.0 (10.4-21.6)	8.3 (3.7-18.7)	6.2 (3.64-10.54)		>1000
8	1.5 (0.96-2.32)	9.5 (5.7-15.6)		16.0 (8-32)	3.6 (1.8-7.2)		2.6	>1000
9	>20	>50	16.0 (11.8-21.6)	>50	>50	>50	>50	>1000
10	14 (10.9-17.9)	42 (34.4-57.2)	>5 < 10	>50	>50	>50	>50	>1000
11		>50		>50	>50	>50	>50	>1000
12	1.0 (0.62-1.6)	18 (10.5-30.6)	0.39 (0.13-1.2)	25	0.27 (0.07-0.94)	9.6 (6.4-14.4)	11.5 (7.9-16.6)	>1000
13	2.4 (1.7-3.3)	>30	1.0 (0.58-1.7)	>25	0.06	5.6 (4.0-7.8)	8.0	>1000
14	2.4 (1.4-4.1)	7.0 (3.18-15.4)	2.3 (1.79-2.94)	>50	>50	20.3 (11.94-34.51)	29 (20.7-40.6)	>1000
15	>20	>50	1.95 (1.3-2.9)	>50	7.5 (5.5-10.12)	23 (12.4-42.6)	>50	>1000
16	2.65 (2.03-3.44)	2.1 (1.54-2.85)	0.9 (0.64-1.26)	7.1 (6.01-8.37)	4.9 (1.42-6.95)	4.6 (3.4-6.2)	4.2 (1.86-9.45)	>1000
17	0.94 (0.58-1.5)	2.2 (1.51-3.19)	0.48 (0.32-0.72)	5.5 (4.23-7.15)	1.1 (0.38-2.8)	5.0 (3.7-6.75)	1.6 (1.14-2.24)	>1000
18	1.3 (1.07-1.39)	2.7 (1.92-3.78)	>1 < 2	6.4 (4.5-8.9)	3.6 (2.1-6.12)	3.2 (1.88-5.44)	1.1 (0.61-1.98)	>1000
19	1.5 (0.83-2.7)	20.5 (15.2-27.6)	>2 < 3	24.0 (14.11-40.8)	44	>50	9.0 (6.42-12.6)	>1000
20	2.3 (1.58-3.33)	13.5 (9.31-19.57)	21 (1.5-2.94)	>50	25	18.0 (7.2-45)	13.0 (6.5-26)	>1000
21	4.65 (4.07-5.3)	10.5 (7-15.75)	3.5	30 (15.8-57)	30 (12.5-72)	25 (14.7-42.5)	6.2	>1000
22	2.1 (1.5-2.94)	7.0 (5.6-8.75)	1.25	5.8 (2.8-12.2)	6.6 (5.3-8.3)	6.4 (4.6-9.0)	12 (6-24)	>1000
23	>50	>50	26 (16.77-40.3)	>50	>50	>50	>50	>1000
24	>20					>50		>1000
25	>20	>50	16.0 (9.41-27.2)	>50	>1 < 2.5	>50		>1000

26	>20	>50	>50	>50	>50	>50	>50	>1000	
27	2.2	4.2	0.92	6.6	3.6	4.5	8.6	>1000	
	(1.83–2.64)	(2.62–6.72)	(0.68–1.23)	(5.28–8.25)	(2.11–6.12)	(3.46–5.85)	(7.16–10.32)		
28	0.2	2.1	0.165	1.8	0.074	1.6	0.78	>1000	
	(0.12–0.31)	(1.31–3.36)	(0.09–0.29)	(1.38–2.34)	(0.032–0.17)	(1.9–2.14)	(0.55–1.09)		
29	0.34	0.27	0.115	1.25	0.21	1.35	2.6	>1000	
	(0.23–0.49)	(0.14–0.51)	(0.08–0.14)	(0.88–1.42)	(0.1–0.42)	(1.28–1.41)	(1.36–4.94)		
30	0.42	0.76	0.028	0.41	1.0	1.1	2.2	>1000	
	(0.28–0.63)	(0.41–1.33)	(0.01–0.04)	(0.26–0.63)	(0.62–1.6)	(0.55–2.2)	(0.88–5.5)		
31	0.26	1.2	0.13	0.46	0.8	1.6	1.5	>1000	
	(0.15–0.44)	(0.69–2.04)	(0.07–0.24)	(0.23–0.92)	(0.47–1.36)	(1.25–2.04)	(0.29–2.5)		
32	0.5	2.2	0.087	2.3	2.5	1.2	0.56	>1000	
	(0.42–0.60)	(1.62–2.97)	(0.05–0.13)	(1.53–3.43)	(1.38–4.5)	(0.8–1.8)	(0.28–1.12)		
33	0.48	1.55	0.155	1.6	2.8	2.35	0.7	>1000	
	(0.32–0.72)	(1.06–2.24)	(0.11–0.2)	(1.0–2.56)	(1.6–4.9)	(1.5–3.66)	(0.31–1.54)		
34	0.34	2.8	0.15	2.8	0.8	0.99	0.46	>1000	
	(0.21–0.54)	(1.9–4.1)	(0.1–0.2)	(1.64–4.76)	(0.61–1.0)	(0.66–1.48)	(0.25–0.82)		
35	0.64	2.6	0.18	3.75	0.72	4.0	0.37	>1000	
	(0.41–0.99)	(1.85–3.6)	(0.1–0.3)	(2.41–5.81)	(0.57–0.9)	(3.03–5.28)	(0.21–0.62)		
36	>20	14	4.0	>50	5.2	>50	>50	>1000	
		(8.75–22.4)	(2.6–6.0)		(3.5–7.8)				
37	20	>50					>50	>1000	
38			>50	>50	>50			>1000	
39	>20		>50	>50	>50		>50	>1000	

[a] The figures in parentheses are 95% confidence limits.

values are recorded in τ units. Infrared spectra were recorded as KBr disks on a Pye-Unicam SP 1000 spectrophotometer. Elemental analyses were performed by CHN Analysis Ltd., Alpha House, Countesthorpe Road, South Wigston, Leicester LE8 2PJ, England.

Method A. 2-Aminomethylene-8-chloro-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (1). Compound **10** (2.1 g) was suspended in dry MeOH (100 mL), the mixture cooled to −70 °C (dry ice–acetone), and dry NH_3 passed through for 15 min. The solution was allowed to warm to room temperature, stirred for a further 2 days, and evaporated. The residue was recrystallized from MeOH–EtOAc to give **1**: 1.9 g (98%); mp 265–267 °C; IR (KBr) ν_{NH2} 3320, 3180, $\nu_{C=O}$ 1690, 1665, $\nu_{C=N}$ 1640, 1625 cm^{-1}; NMR (Me_2SO-d_6) 5.81, 5.12 (2 H, q, J = 12 Hz, C_4-CH_2), 2.2–2.8 (8 H, m, ArH + =CH), 1.95 (1 H, d, J = 8 Hz, C_{10}-H). Anal. ($C_{18}H_{13}ClN_4O$) C, H, Cl, N.

Method B. 8-Chloro-2,4-dihydro-2-methylaminomethylene-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (2). Compound **10** (1.0 g) was suspended in dry MeOH (50 mL) and cooled in an ice bath, and $MeNH_2$ (liquid from an inverted cylinder) was run in for 5 min. The cold solution was stirred for 1 h, warmed to room temperature, stirred for 1 h, and evaporated, and the residue was recrystallized from Et_2O to give **2**: 850 mg (88%); mp 233–235 °C; IR ν_{NH} 3300, $\nu_{C=O}$ 1690, $\nu_{C=N}$ 1620 cm^{-1}; NMR ($CDCl_3$) 6.82, 6.85 (2 unequal doublets, J = 5 Hz, giving 2 singlets on D_2O shake, 3 H, NMe), 5.85, 5.03, 5.86, 4.98 (2 unequal quartets, J = 12.3 Hz, 2 H, C_4-CH_2), 2.3–2.7 (m, 9 H, ArH + =CH), 2.0 (d, J = 9.0 Hz, 1 H, C_{10}-H). Anal. ($C_{19}H_{15}ClN_4O$) C, H, N, Cl.

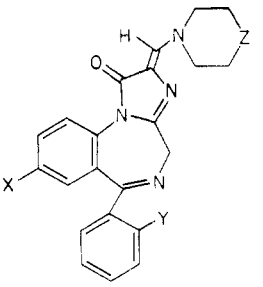
Method C. 8-Chloro-2-*n*-propylaminomethylene-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (4). A solution of compound **10** (2.2 g) in dry toluene (50 mL) was treated with *N*-propylamine (10 mL), refluxed for 3 h, and evaporated to give a gum which crystallized from CH_2Cl_2–Et_2O to give **4**: 2.2 g (96%); mp 153–155 °C; IR ν_{NH} 3230, $\nu_{C=O}$ 1700, $\nu_{C=N}$ 1630 cm^{-1}; NMR ($CDCl_3$) 8.3–9.2 (5 H, m, $-CH_2CH_3$), 6.4–6.8 (2 H, m, $-NCH_2-$), 5.02, 5.90 (2 H, q, J = 12 Hz, C_4-CH_2), 2.3–2.8 (8 H, m, ArH + =CH), 2.00 (1 H, d, J = 8 Hz, C_{10}-H). Anal. ($C_{21}H_{19}ClN_4O$) C, H, N, Cl.

Method D. 8-Chloro-2-*tert*-butylaminomethylene-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (6). A solution of compound **10** (2.3 g) in *tert*-butylamine (15 mL) and EtOH (20 mL) was refluxed for 12 h and evaporated and the residual gum crystallized from $CHCl_3$–Et_2O to give **6**: 2.3 g (93%); mp 230–232 °C; IR ν_{NH} 3320, $\nu_{C=O}$ 1690, $\nu_{C=N}$ 1640 cm^{-1}; NMR ($CDCl_3$) 8.67 [9 H, s, $C(CH_3)_3$], 5.03, 5.90 (2 H, q, J = 12 Hz, C_4-H_2), 2.3–2.9 (8 H, m, ArH + =CH), 1.99 (1 H_2, d, J = 9 Hz, C_{10}-H). Anal. ($C_{22}H_{21}ClN_4O$) C, H, N, Cl.

Method E. 8-Chloro-2,4-dihydro-2-dimethylaminomethylene-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (10). (a) *N*-7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-ylglycine. A suspension of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (15 g), glycine (20 g), and Na_2CO_3 (20 g) in EtOH (350 mL)–H_2O (150 mL) was stirred and refluxed for 5 h, poured into H_2O (1 L), and filtered to remove a small amount of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ extract was discarded; the aqueous layer was adjusted to pH 4 with 2 N HCl and extracted with $CHCl_3$ (3 × 200 mL). Solid precipitated out of the extracts and was filtered off to give compound IIIa (11.3 g). Evaporation of the $CHCl_3$ solution gave a further 2.0 g: overall yield 13.3 g (77%); mp 215–220 °C (EtOH); IR ν_{OH} 2700–2600 (broad), $\nu_{C=O}$ 1700, $\nu_{C=N}$ 1670 cm^{-1}; NMR (Me_2SO-d_6) 6.04 (2 H, s, CH_2), 2.5–3.0 (9 H, m, ArH + 3H). Anal. ($C_{17}H_{14}ClN_3O_2$) C, H, N, Cl.

(b) 8-Chloro-2,4-dihydro-2-dimethylaminomethylene-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (10). Compound IIIa (11.0 g) was suspended in dry CH_2Cl_2 (300 mL), DCC (7.2 g) was added, and the suspension was stirred at 40 °C for 2 h, cooled to 0 °C, filtered, and evaporated to give 8-chloro-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one, compound IVa, as a brown oil. IVa (ca. 2.5 g) was dissolved in dry benzene (60 mL), dimethylformamide diethyl acetal (1.5 g) and triethylamine (1.0 mL) were added, the solution was stirred at room temperature for 1 h and evaporated, and the residue was crystallized from EtOAc–MeOH to give **10** (97%):

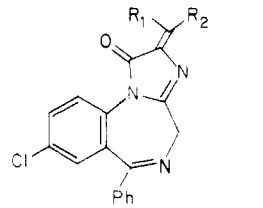
Table IV. 2-(Heterocyclic methylene)-6-aryl-2,4-dihydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-ones



Compd no.	X	Y	Z	Method	Yield, %	Mp, °C	Crystn solvent	Analyses
14	Cl	H	O	C	93	223-224	MeOH-EtOAc	C, H, N, Cl
15	Cl	H	NH	C	85	233-235	$CHCl_3$-Et_2O	C, H, N, Cl
16	Cl	H	NMe	C	87	255-256	MeOH-EtOAc	C, H, N, Cl
17	Cl	H	NEt	C	78	183-184	CH_2Cl_2-Et_2O	C, H, N, Cl
18	Cl	H	NPr	C	60	148-152	EtOAc-Et_2O	C, H, N, Cl
19	Cl	H	NBu	C	84	186-187	MeOH	C, H, N, Cl
20	Cl	H	$NCH_2CH{=}CH_2$	C	86	187-188	MeOH	C, H, N, Cl
21	Cl	H	NCH_2-c-C_3H_5	F	82	202-204	MeOH	C, H, N, Cl
22	Cl	H	N-*i*-Pr	F	72	146-148	EtOAc	C, H, N, Cl
23	Cl	H	NPh	C	67	206-208	MeOH-EtOAc	C, H, N, Cl
24	Cl	H	NCHO	G	89	235-237	CH_2Cl_2-Et_2O	C, H, N, Cl
25	Cl	H	CH_2	C	73	249-250	MeOH-Et_2O	C, H, N, Cl
26	Cl	H	S	C	86	255-258	CH_2Cl_2-Et_2O	C, H, N, S
27	NO_2	H	NMe	C	87	284-286	$CHCl_3$-Et_2O	C, H, N
28	Cl	Cl	NMe	C[a]	83	247-248	MeOH-Et_2O	C, H, N, Cl
29	Cl	F	NMe	C[b]	78	249-251	CH_2Cl_2-Et_2O	C, H, N, Cl
30	NO_2	Cl	NMe	C[c]	61	214-215	$CHCl_3$-Et_2O	C, H, N, Cl
31	NO_2	F	NMe	C[d]	75	303-306	$CHCl_3$-Et_2O	C, H, N
32	Cl	Cl	NEt	C[a]	71	243-245	CH_3OH	C, H, N, Cl
33	Cl	F	NEt	C[b]	46	235-237	CH_3OH	C, H, N, Cl
34	NO_2	Cl	NEt	C[c]	89	265-267	CH_2Cl_2-Et_2O	C, H, N, Cl
35	NO_2	F	NEt	C[d]	70	262-264	EtOAc-petr ether	C, H, N

[a] From compound Vc. [b] From compound Vd. [c] From compound Ve. [d] From compound Vf.

Table V. 2-(Substituted methylene)-6-phenyl-2,4-dihydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-ones



Compd no.	R_1	R_2	Method	Yield, %	Mp, °C	Crystn solvent	Analyses
36	Me	c-$N(CH_2CH_2)_2NMe$	H	38	193-195	EtOAc	C, H, N, Cl
37	———	$C_5H_{11}N$-Me ———	I	62	271-272	CH_2Cl_2-Et_2O	C, H, N, Cl
38	H	Ph	E	57	232-234	EtOAc-C_6H_6	C, H, N, Cl
39	H	C_6H_4-*p*-NMe_2	E	44	264-265	$CHCl_3$-Et_2O	C, H, N

mp 264–265 °C; IR $\nu_{C=O}$ 1690 cm^{-1}; NMR ($CDCl_3$) 6.82 (3 H, s, NMe), 6.48 (3 H, s, NMe), 5.00, 5.90 (2 H, q, J = 12 Hz, C_4-H_2), 2.4–2.85 (8 H, m, ArH + =CH), 2.00 (1 H, d, J = 8 Hz, C_{10}-H). Anal. ($C_{20}H_{17}ClN_4O$) C, H, N, Cl.

Method F. 8-Chloro-2-(4-cyclopropylmethylpiperazin-1-ylmethylene)-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (21). Compound **15** (1.5 g), cyclopropylmethyl bromide (1.5 g), and Na_2CO_3 (3.0 g) were heated in CH_3CN (25 mL)–CH_2Cl_2 (5 mL) for 6 h, poured into saturated $NaHCO_3$ (100 mL), and extracted with $CHCl_3$ (2 × 100 mL). The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated to give a residue, crystallization of which from MeOH gave **21**: 1.4 g (82%); mp 202–204 °C; IR $\nu_{C=O}$ 1695, $\nu_{C=N}$ 1630 cm^{-1}; NMR ($CDCl_3$) 9.0–9.9 (5 H, m, cyclopropyl), 7.74 (2 H, d, J = 6 Hz, $-CH_2-$), 7.3–7.5 [4 H, m, $(CH_2)_2N$], 6.4–6.7 (2 H, m, CH_2N), 5.4–5.7 (2 H, m, CH_2N), 5.00, 5.90 (2 H, q, J = 12 Hz, C_4-H_2), 2.86 (1 H, s, =CH), 2.2–2.8 (7 H, m, ArH), 1.99 (1 H, d, J = 8 Hz, C_{10}-H). Anal. ($C_{26}H_{26}ClN_5O$) C, H, N, Cl.

Method G. 8-Chloro-2-(4-formylpiperazin-1-ylmethylene)-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (24). To a solution of carbonyldiimidazole (1.6 g) in dry CH_2Cl_2 (75 mL) was added HCO_2H (0.5 g) followed, after 15 min, by compound **15** (1.36 g). After a further 30 min the solution was washed with saturated $NaHCO_3$ solution and H_2O, dried ($MgSO_4$), and evaporated to give a pale yellow oil. This was dissolved in $CHCl_3$ and washed through neutral alumina (100 g) to give a colorless oil which crystallized from CH_2Cl_2–Et_2O to give **24**: 1.3 g (89%); mp 235–237 °C; IR $\nu_{C=O}$ 1690, 1680, $\nu_{C=N}$ 1625 cm^{-1}; NMR ($CDCl_3$) 6.1–6.6 (6 H, m, $-CHCH_2NCH_2CH-$), 5.5–5.8 (2 H, m, $-CHNCH-$), 5.01–5.90 (2 H, q, J = 12 Hz, C_4-H_2), 2.87 (1 H, s, =CH), 2.3–2.8 (7 H, m, ArH), 2.03 (1 H, d, J = 8 Hz, C_{10}-H), 1.92 (1 H, s, CHO). Anal. ($C_{23}H_{20}ClN_5O_2$) C, H, N, Cl.

Method H. 8-Chloro-2-[1-(4-methylpiperazin-1-yl)-ethylidene]-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]-benzodiazepin-1-one (36). (a) 8-Chloro-2-(1-dimethylaminoethylidene)-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one. To a stirred solution of compound IVa (1.0 g) and *N*,*N*-dimethylacetamide (400 mg) in dry CH_2Cl_2 (40 mL) at 0 °C was added $POCl_3$ (740 mg) dropwise over 15 min.

The solution was stirred at room temperature for 20 h, washed with saturated $NaHCO_3$ solution and H_2O, dried ($MgSO_4$), and evaporated to give on crystallization from $CHCl_3$–Et_2O 8-chloro-2-(1-dimethylaminoethylidene)-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one: 580 mg (50%); mp 251–252 °C.

(b) 8-Chloro-2-[1-(4-methylpiperazin-1-yl)ethylidene]-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one. A solution of the above compound (2.3 g) in *N*-methylpiperazine (15 mL) was stirred at 120 °C under a N_2 atmosphere for 9 h, cooled, and poured into saturated NaCl solution. The precipitate was filtered off, dissolved in $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and evaporated to give **36** (38%): mp 193–195 °C (EtOAc); IR $\nu_{C=O}$ 1660, $\nu_{C=N}$ 1615 cm^{-1}; NMR ($CDCl_3$) 7.72 (3 H, s, NCH_3), 7.50 (4 H, m, CH_2NCH_2), 7.33 (3 H, s, CH_3C=), 5.7–6.0 (5 H, m, one H of C_4 + CH_2NCH_2), 5.03 (1 H, d, J = 12 Hz, one H of C_4), 2.3–2.7 (7 H, m, ArH), 1.96 (1 H, d, J = 8 Hz, C_{10}-H). Anal. ($C_{24}H_{24}ClN_5O$) C, H, N, Cl.

Method I. 8-Chloro-2-(1-methyl-2-piperidylidene)-2,4-dihydro-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-one (37). To a stirred solution of compound IVa (3.0 g) and 1-methyl-2-piperidone (1.6 g) in dry CH_2Cl_2 (90 mL) held at 0 °C was added $POCl_3$ (2.2 g) dropwise over 15 min. The solution was allowed to warm to room temperature, stirred for a further 24 h, and poured into $NaHCO_3$ solution, the organic layer was separated, washed with H_2O, and dried ($MgSO_4$), and the residue was recrystallized from CH_2Cl_2–Et_2O to give **37**: 2.3 g (62%); mp 271–272 °C; IR $\nu_{C=O}$ 1655 cm^{-1}; NMR ($CDCl_3$) 8.24 (4 H, m, $-CH_2CH_2-$), 6.70 (4 H, m, $-CH_2C$= and CH_2N), 6.35 (3 H, s, NMe), 5.00, 5.90 (2 H, q, J = 12 Hz, C_4-CH_2-), 2.3–2.7 (7 H, m, ArH), 1.91 (1 H, d, J = 8 Hz, C_{10}-H). Anal. ($C_{23}H_{21}ClN_4O$) C, H, N, Cl.

Pharmacology. All the tests were performed on male CD-1 mice (Charles River) weighing 18–22 g with the compound being dosed orally as a solution or suspension in distilled water. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[9] A detailed discussion of the pharmacology of the series will be published elsewhere.[10]

Antiaggressive Activity. Thirty minutes after oral dosing with either vehicle alone or vehicle plus test compounds, pairs of mice were placed under an inverted 1-L pyrex beaker on a metal grid connected to a Palmer square wave stimulator. The feet of the mice were electrically stimulated with 90-V pulses of 5-ms duration at a frequency of 2 pulses/s for 2 min. This procedure provokes fighting in the control mouse and the ED_{50} of a test compound is that dose which causes a 50% reduction in the number of fights of that batch of mice over the control group.

Anticonvulsant Test against Maximal Electroshock. This was a modification of the method of Keasling et al.[11] using a Ugile Basile ECT apparatus delivering shocks with a pulse width of 0.2 ms at a frequency of 100 Hz for 0.2 s at a current of 55 mA.

Anticonvulsant Test against Pentylenetetrazole Convulsions. This was a modification of the method of ref 4b using a dose of 130 mg/kg of pentylenetetrazole.

Anticonvulsant Test against Strychnine Convulsions. Thirty minutes after dosing with either vehicle alone or vehicle plus test compound, mice were given 1 mg/kg of strychnine and then housed individually in observation boxes. The number of mice exhibiting tonic convulsions within 15 min of the strychnine challenge was noted, and the results for the tonic phase were expressed as a percentage reduction of the control value. From a constructed dose–response line, the doses protecting 50% of the mice against tonus were established.

Potentiation of Hexobarbital. Two groups of mice received an ip dose of hexobarbital (150 mg/kg) followed by either vehicle alone or vehicle plus test compound orally. The number of mice which exhibited loss of righting reflex for 30 s after dosing was noted and a dose–response curve constructed.

Potentiation of Chlorprothixene. This was conducted as above using a dose of chlorprothixene (12.5 mg/kg) ip.

Rotary Drum Test. Thirty minutes after dosing with either vehicle alone or vehicle plus test compound, groups of mice were placed on a 30-cm diameter rotating drum revolving at 1 revolution/min, facing against its direction of movement. The number of mice falling off within a 2-min period was noted.

Acute Toxicity. Oral acute toxicity tests were conducted using groups of ten mice with mortality being assessed at 24 h.

References and Notes

(1) Presented in part at the Vth International Symposium on Medicinal Chemistry, Paris, July 1976.

(2) (a) See, for example, G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968); (b) S. Garattini, E. Mussini, and L. O. Randall, Ed., "The Benzodiazepines", Raven Press, New York, N.Y., 1973; (c) D. J. Greenblatt and R. I. Shader, Ed., "Benzodiazepines in Clinical Practice", Raven Press, New York, N.Y., 1974; (d) G. Zbinden and L. O. Randall, *Adv. Pharmacol.*, **5**, 213 (1967); (e) L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning in "Psychopharmacological Agents", Vol. III, M. Gordon, Ed., Academic Press, New York, N.Y., 1974, p 175.

(3) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).

(4) (a) J. B. Hester, D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971); (b) J. B. Hester, A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).

(5) (a) For IIa–d, see G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964); (b) for IIe see ref 4b; (c) for IIf see J. B. Hester and A. R. Hanze, U.S. Patent 3933794 (1976).

(6) See, for example, a study of aminomethylene derivatives of 2-phenylpyrrolone which showed that monosubstituted aminomethylene derivatives exist in the cis form and disubstituted in the trans form: L. N. Kurkoskaya, N. N. Shapet'ko, N. B. Sokolova, and I. Ya. Kirtko, *Zh. Org. Khim.*, 11 (5), 1091–1101 (1975); *Chem. Abstr.*, **83**, 96135k (1975).

(7) See ref 2b, Chapter 1.

(8) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).

(9) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

(10) T. G. Johns, G. W. L. James, D. C. Piper, and R. D. N. Birtley, unpublished results.

(11) H. H. Keasling, E. L. Schumann, and W. Veldhamp, *J. Med. Chem.*, 8, 548 (1965).