

to that described for the preparation of **23b**. The resulting oil was chromatographed on an alumina column. Elution with Et<sub>2</sub>O gave **26c** as an oil: TLC (alumina, Et<sub>2</sub>O-petroleum ether 1:1) showed a single spot. Treatment of a solution of **26c** in Et<sub>2</sub>O with ethereal HCl precipitated 1.9 g (18%) of **26c**·HCl, mp 134 °C dec. Anal. (C<sub>31</sub>H<sub>37</sub>NO<sub>6</sub>·S·HCl·H<sub>2</sub>O) C, H, N.

**α-(N-Benzyl-tert-butylaminomethyl)-4-benzyloxy-3-(1-hydroxy-2-methylsulfonyl)ethyl)benzyl Alcohol (27)**. The amino ketone **26c**·HCl was treated with NaBH<sub>4</sub> 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<sub>2</sub>O) 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<sub>2</sub>O) showed a single spot.

**α-tert-Butylaminomethyl-4-hydroxy-3-(1-hydroxy-2-methylsulfonyl)ethyl)benzyl Alcohol (1i)**. The amino alcohol **27** (240 mg) was hydrogenated over 10% Pd/C at ambient temperature and an initial H<sub>2</sub> pressure of 3.5 kg/cm<sup>2</sup> 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<sub>15</sub>H<sub>25</sub>NO<sub>5</sub>·S·0.5C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

**Dimethyl 4-Benzyloxyisophthalate (28b)**. A solution of **28a**<sup>13</sup> (2.0 g, 7.35 mmol) in 100 mL of MeOH and 0.1 mL of concentrated H<sub>2</sub>SO<sub>4</sub> was refluxed for 18 h and then evaporated. The residue was dissolved in Et<sub>2</sub>O. The Et<sub>2</sub>O solution was washed with 5% NaHCO<sub>3</sub>, 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<sub>2</sub>O-petroleum ether 3:7) showed a single spot. Anal. (C<sub>17</sub>H<sub>18</sub>O<sub>5</sub>) C, H.

**4-Benzyloxyisophthalyl Alcohol (29)**. A suspension of LiAlH<sub>4</sub> (600 mg) in 30 mL of Et<sub>2</sub>O was refluxed with a solution of **28b** (1.1 g, 3.67 mmol) in 30 mL of Et<sub>2</sub>O and 5 mL of THF for 3 h. Excess LiAlH<sub>4</sub> was decomposed by cautious dropwise addition of 1.2 mL of H<sub>2</sub>O 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<sub>2</sub>CO-hexane to give 0.55 g (61%) of **29**: mp 90–92 °C; TLC (silica gel, Et<sub>2</sub>O) showed a single spot. Anal. (C<sub>15</sub>H<sub>18</sub>O<sub>3</sub>) C, H.

**4-Benzyloxyisophthalaldehyde (30)**. A solution of **29** (300 mg, 1.23 mmol) in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> was refluxed with activated MnO<sub>2</sub> (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<sub>2</sub>O-petroleum ether 2:3) showed a single spot. Anal. (C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>) C, H.

**Bis[2,4-(2-tert-butylamino-1-hydroxyethyl)phenol] (1j)**. A solution of **30** (5.16 g, 0.0215 mol) in CHCl<sub>3</sub> (100 mL), AcOH (9 mL), and tert-butyl isocyanide (14 g) was refluxed for 48 h. The solution was washed with 5% NaHCO<sub>3</sub> and H<sub>2</sub>O and dried. The solvent was evaporated and the residue was chromatographed on a silica gel column (eluted with Et<sub>2</sub>O). Evaporation of the initial fractions gave 5.4 g of crude acetoxamide **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<sub>2</sub>O. The extract was washed with 5% NaHCO<sub>3</sub> and H<sub>2</sub>O and dried. Evaporation of the solvent gave 3.7 g (39% from **30**) of the hydroxamide **31b** as a foam: TLC (silica gel, Et<sub>2</sub>O) 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<sub>2</sub>O. The extract was treated with ethereal HCl, and the precipitated HCl salt was extracted into H<sub>2</sub>O. The aqueous extract was washed with Et<sub>2</sub>O, made alkaline with 2.5 N NaOH, and extracted with Et<sub>2</sub>O. The extract was dried and evaporated to give 1.73 g (50%) of the ethanolamine **32** as an oil: TLC (silica gel, MeOH-Et<sub>2</sub>O 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<sup>2</sup> 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<sub>18</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) H, N; C: calcd, 59.98; found, 61.37.

## References and Notes

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## Central Nervous System Activity of a Novel Class of Annelated 1,4-Benzodiazepines, Aminomethylene-2,4-dihydro-1H-imidazo[1,2-a][1,4]benzodiazepin-1-ones<sup>1</sup>

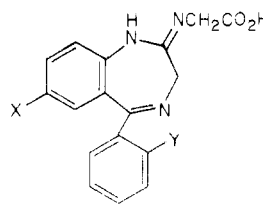
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The synthesis and CNS activity of a novel class of annelated 1,4-benzodiazepines, the aminomethylene-2,4-dihydro-1H-imidazo[1,2-a][1,4]benzodiazepines, are described. An investigation of the structure-activity relationships in the series derived from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

The 1,4-benzodiazepines are a remarkable class of compounds with potent minor tranquilizer, muscle-re-

laxant, anticonvulsant, and sedative-hypnotic activity, whose pharmacological and clinical eminence is attested

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


Compd no.	X	Y	Yield, %	Mp, °C	Analyses or Formula <sup>a</sup>
IIIa	Cl	H	77	215-220	C, H, N, Cl
IIIb	NO <sub>2</sub>	H	65	151-154	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub>
IIIc	Cl	Cl	87	136-139	C <sub>17</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub>
IIId	Cl	F	88	147-150	C <sub>17</sub> H <sub>13</sub> ClFN <sub>4</sub> O <sub>2</sub>
IIIe	NO <sub>2</sub>	Cl	83	158-161	C <sub>17</sub> H <sub>13</sub> ClN <sub>4</sub> O <sub>4</sub>
IIIf	NO <sub>2</sub>	F	45	144-147	C <sub>17</sub> H <sub>13</sub> FN <sub>4</sub> O <sub>4</sub>

<sup>a</sup> 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.<sup>2</sup> Recently, two groups<sup>3,4</sup> have described the synthesis of a novel series of annelated 1,4-benzodiazepines, namely, 6-phenyl-4*H*-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-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-ones, together with preliminary central nervous system (CNS) results for the series.

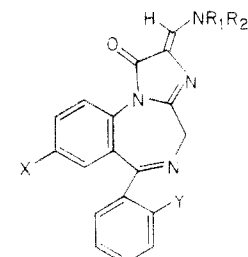
**Chemistry.** The synthetic route used to prepare these compounds is shown in Scheme I. The 5-aryl-1,3-dihydro-7-substituted-2*H*-1,4-benzodiazepine-2-thiones IIa-f<sup>5</sup>

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 imidazobenzodiazepines 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<sub>3</sub> complex to give the stable, crystalline dimethylamino-methylene-2,4-dihydro-5-aryl-1*H*-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<sub>2</sub> 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.<sup>6</sup>

## Results and Discussion

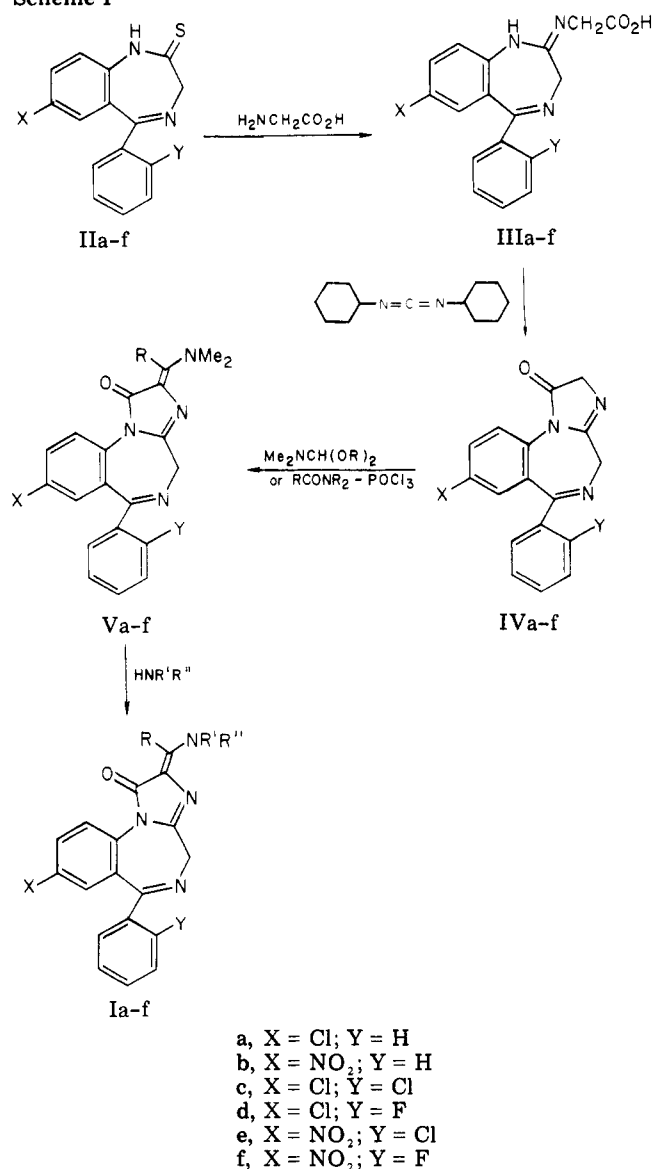
In order to obtain an overall minor tranquilizer profile of these compounds, a battery of seven pharmacological

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


Compd no.	X	Y	R <sub>1</sub>	R <sub>2</sub>	Meth- od	Yield, %	Mp, °C	Crystn solvent	Analyses
Va (10)	Cl	H	Me	Me	E	97 <sup>a</sup>	264-265	EtOAc-MeOH	C, H, N, Cl
Vb	NO <sub>2</sub>	H	Me	Me	E	83 <sup>a</sup>	227-228	EtOAc-MeOH	C, H, N
Vc	Cl	Cl	Me	Me	E	53 <sup>a</sup>	282-284	EtOAc-MeOH	C, H, N, Cl
Vd	Cl	F	Me	Me	E	63 <sup>a</sup>	257-260	EtOAc-MeOH	C, H, N, Cl
Ve	NO <sub>2</sub>	Cl	Me	Me	E	77 <sup>a</sup>	253-255	EtOAc-MeOH	C, H, N, Cl
Vf	NO <sub>2</sub>	F	Me	Me	E	76 <sup>a</sup>	228-231	EtOAc-MeOH	C, H, N
1	Cl	H	H	H	A	98 <sup>b</sup>	265-267	MeOH-EtOAc	C, H, N, Cl
2	Cl	H	H	Me	B	88 <sup>b</sup>	233-235	Et <sub>2</sub> O	C, H, N, Cl
3	Cl	H	H	Et	B	93 <sup>b</sup>	234-236	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
4	Cl	H	H	<i>n</i> -Pr	C	96 <sup>b</sup>	153-155	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
5	Cl	H	H	<i>n</i> -Bu	C	93 <sup>b</sup>	165-167	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N, Cl
6	Cl	H	H	<i>t</i> -Bu	D	93 <sup>b</sup>	230-232	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N, Cl
7	Cl	H	H	C <sub>6</sub> H <sub>11</sub>	C	87 <sup>b</sup>	143-145	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N, Cl
8	Cl	H	H	CH <sub>2</sub> CH <sub>2</sub> OH	C	85 <sup>b</sup>	223-225	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N, Cl
9	Cl	H	H	CH <sub>2</sub> CH <sub>2</sub> NEt <sub>2</sub>	C	70 <sup>b</sup>	113-116	C <sub>6</sub> H <sub>6</sub> -petr ether	C, H, N, Cl
11	Cl	H	Me	CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	C	52 <sup>b</sup>	152-155	Et <sub>2</sub> O	C, H, N, Cl
12	Cl	Cl	H	CH <sub>2</sub> CH <sub>3</sub>	C	82 <sup>c</sup>	235-237	MeOH-Et <sub>2</sub> O	C, H, N, Cl
13	Cl	Cl	H	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	C	94 <sup>c</sup>	227-229	MeOH-Et <sub>2</sub> O	C, H, N, Cl

<sup>a</sup> From IIIa-f. <sup>b</sup> From compound 10. <sup>c</sup> From IIIc.

Scheme I



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.<sup>7</sup>

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 tranquilizer potency appeared to peak

around the *n*-propyl and *n*-butyl substituent (compounds 4 and 5). Interestingly, derivative 8 whose hydroxyethyl group has a  $\pi$  value close to that of methyl<sup>8</sup> 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<sup>7</sup> 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<sub>8</sub>-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<sub>50</sub> values are not statistically significant. Accordingly, a number of these compounds are currently being further evaluated with a view to possible future clinical use.

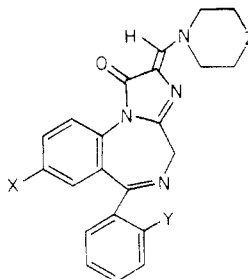
## Experimental Section

**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

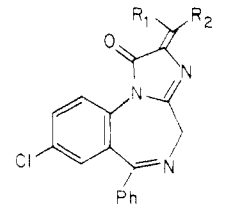
Table III. Pharmacological Activity in the Mouse<sup>a</sup> (ED<sub>50</sub>, mg/kg po)

Compd no.	Antiagression	Antielectroshock	Antipentylenetetrazole	Antistrychnine	Potentiation of hexobarbital	Potentiation of chlorprothixene	Rotary drum	Acute toxicity
Chlordiazepoxide								
1	7.0 (4.6-10.64)	8.0 (5.92-10.8) >50	1.9 (1.1-3.23) 7.1 (6.0-8.37)	5.0 (3.5-7.0) >50	64.0 (45.7-89.6) 1.65 (0.95-2.8) >50	4.0 (2.1-7.6) 4.3 (2.15-8.6) >50	6.8 (5.03-9.18) >50	>1000 >1000 >1000
2	5.3 (4.1-6.4)							>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								
12	1.0 (0.62-1.6)	18 (10.5-30.6)	0.39 (0.13-1.2)	>50	>50	>50	>50	>1000
13	2.4 (1.7-3.3)	>30	1.0 (0.58-1.7)	25 (10.62-27.2)	0.27 (0.07-0.94)	9.6 (6.4-14.4)	11.5 (7.9-16.6)	>1000
14	2.4 (1.4-4.1)	7.0 (3.18-15.4)	2.3 (1.79-2.94)	>50	0.06	5.6 (4.0-7.8)	8.0	>1000
15	>20	>50	1.95 (1.3-2.9)	>50	>50	20.3 (11.94-34.51)	29 (20.7-40.6)	>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)	7.5 (5.5-10.12)	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							>1000
25	>20	>50	16.0 (9.41-27.2)	>50	>1 < 2.5	>50		>1000



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 <sub>3</sub> -Et <sub>2</sub> O	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 <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
18	Cl	H	NPr	C	60	148-152	EtOAc-Et <sub>2</sub> O	C, H, N, Cl
19	Cl	H	NBu	C	84	186-187	MeOH	C, H, N, Cl
20	Cl	H	NCH <sub>2</sub> CH=CH <sub>2</sub>	C	86	187-188	MeOH	C, H, N, Cl
21	Cl	H	NCH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	F	82	202-204	MeOH	C, H, N, Cl
22	Cl	H	N- <i>i</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 <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
25	Cl	H	CH <sub>2</sub>	C	73	249-250	MeOH-Et <sub>2</sub> O	C, H, N, Cl
26	Cl	H	S	C	86	255-258	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, S
27	NO <sub>2</sub>	H	NMe	C	87	284-286	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N
28	Cl	Cl	NMe	C <sup>a</sup>	83	247-248	MeOH-Et <sub>2</sub> O	C, H, N, Cl
29	Cl	F	NMe	C <sup>b</sup>	78	249-251	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
30	NO <sub>2</sub>	Cl	NMe	C <sup>c</sup>	61	214-215	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N, Cl
31	NO <sub>2</sub>	F	NMe	C <sup>d</sup>	75	303-306	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N
32	Cl	Cl	NEt	C <sup>a</sup>	71	243-245	CH <sub>3</sub> OH	C, H, N, Cl
33	Cl	F	NEt	C <sup>b</sup>	46	235-237	CH <sub>3</sub> OH	C, H, N, Cl
34	NO <sub>2</sub>	Cl	NEt	C <sup>c</sup>	89	265-267	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
35	NO <sub>2</sub>	F	NEt	C <sup>d</sup>	70	262-264	EtOAc-petr ether	C, H, N

<sup>a</sup> From compound Vc. <sup>b</sup> From compound Vd. <sup>c</sup> From compound Ve. <sup>d</sup> 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 <sub>1</sub>	R <sub>2</sub>	Method	Yield, %	Mp, °C	Crystn solvent	Analyses
36	Me	<i>c</i> -N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> NMe	H	38	193-195	EtOAc	C, H, N, Cl
37	—	C <sub>5</sub> H <sub>11</sub> N-Me	I	62	271-272	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, Cl
38	H	Ph	E	57	232-234	EtOAc-C <sub>6</sub> H <sub>6</sub>	C, H, N, Cl
39	H	C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NMe <sub>2</sub>	E	44	264-265	CHCl <sub>3</sub> -Et <sub>2</sub> O	C, H, N

mp 264-265 °C; IR  $\nu_{\text{C=O}}$  1690 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) 6.82 (3 H, s, NMe), 6.48 (3 H, s, NMe), 5.00, 5.90 (2 H, q, *J* = 12 Hz, C<sub>4</sub>-H<sub>2</sub>), 2.4-2.85 (8 H, m, ArH + =CH), 2.00 (1 H, d, *J* = 8 Hz, C<sub>10</sub>-H). Anal. (C<sub>20</sub>H<sub>17</sub>ClN<sub>4</sub>O) 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<sub>2</sub>CO<sub>3</sub> (3.0 g) were heated in CH<sub>3</sub>CN (25 mL)-CH<sub>2</sub>Cl<sub>2</sub> (5 mL) for 6 h, poured into saturated NaHCO<sub>3</sub> (100 mL), and extracted with CHCl<sub>3</sub> (2 × 100 mL). The organic layer was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), and evaporated to give a residue, crystallization of which from MeOH gave 21: 1.4 g (82%); mp 202-204 °C; IR  $\nu_{\text{C=O}}$  1695,  $\nu_{\text{C=N}}$  1630 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) 9.0-9.9 (5 H, m, cyclopropyl), 7.74 (2 H, d, *J* = 6 Hz, -CH<sub>2</sub>-), 7.3-7.5 [4 H, m, (CH<sub>2</sub>)<sub>2</sub>N], 6.4-6.7 (2 H, m, CH<sub>2</sub>N), 5.4-5.7 (2 H, m, CH<sub>2</sub>N), 5.00, 5.90 (2 H, q, *J* = 12 Hz, C<sub>4</sub>-H<sub>2</sub>), 2.86 (1 H, s, =CH), 2.2-2.8 (7 H, m, ArH), 1.99 (1 H, d, *J* = 8 Hz, C<sub>10</sub>-H). Anal. (C<sub>26</sub>H<sub>26</sub>ClN<sub>5</sub>O) 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]benzo-**

**diazepin-1-one (24).** To a solution of carbonyldiimidazole (1.6 g) in dry CH<sub>2</sub>Cl<sub>2</sub> (75 mL) was added HCO<sub>2</sub>H (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<sub>3</sub> solution and H<sub>2</sub>O, dried (MgSO<sub>4</sub>), and evaporated to give a pale yellow oil. This was dissolved in CHCl<sub>3</sub> and washed through neutral alumina (100 g) to give a colorless oil which crystallized from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O to give 24: 1.3 g (89%); mp 235-237 °C; IR  $\nu_{\text{C=O}}$  1690, 1680,  $\nu_{\text{C=N}}$  1625 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) 6.1-6.6 (6 H, m, -CHCH<sub>2</sub>NCH<sub>2</sub>CH-), 5.5-5.8 (2 H, m, -CHNCH-), 5.01-5.90 (2 H, q, *J* = 12 Hz, C<sub>4</sub>-H<sub>2</sub>), 2.87 (1 H, s, =CH), 2.3-2.8 (7 H, m, ArH), 2.03 (1 H, d, *J* = 8 Hz, C<sub>10</sub>-H), 1.92 (1 H, s, CHO). Anal. (C<sub>23</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>2</sub>) 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<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0 °C was added POCl<sub>3</sub> (740 mg) dropwise over 15 min.

The solution was stirred at room temperature for 20 h, washed with saturated  $\text{NaHCO}_3$  solution and  $\text{H}_2\text{O}$ , dried ( $\text{MgSO}_4$ ), and evaporated to give on crystallization from  $\text{CHCl}_3\text{-Et}_2\text{O}$  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  $\text{N}_2$  atmosphere for 9 h, cooled, and poured into saturated  $\text{NaCl}$  solution. The precipitate was filtered off, dissolved in  $\text{CHCl}_3$ , washed with  $\text{H}_2\text{O}$ , dried ( $\text{MgSO}_4$ ), and evaporated to give 36 (38%): mp 193–195 °C ( $\text{EtOAc}$ ); IR  $\nu_{\text{C=O}}$  1660,  $\nu_{\text{C=N}}$  1615  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ ) 7.72 (3 H, s,  $\text{NCH}_3$ ), 7.50 (4 H, m,  $\text{CH}_2\text{NCH}_2$ ), 7.33 (3 H, s,  $\text{CH}_3\text{C=}$ ), 5.7–6.0 (5 H, m, one H of  $\text{C}_4 + \text{CH}_2\text{NCH}_2$ ), 5.03 (1 H, d,  $J = 12$  Hz, one H of  $\text{C}_4$ ), 2.3–2.7 (7 H, m, ArH), 1.96 (1 H, d,  $J = 8$  Hz,  $\text{C}_{10}\text{-H}$ ). Anal. ( $\text{C}_{24}\text{H}_{24}\text{ClN}_5\text{O}$ ) 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  $\text{CH}_2\text{Cl}_2$  (90 mL) held at 0 °C was added  $\text{POCl}_3$  (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  $\text{NaHCO}_3$  solution, the organic layer was separated, washed with  $\text{H}_2\text{O}$ , and dried ( $\text{MgSO}_4$ ), and the residue was recrystallized from  $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$  to give 37: 2.3 g (62%); mp 271–272 °C; IR  $\nu_{\text{C=O}}$  1655  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ ) 8.24 (4 H, m,  $-\text{CH}_2\text{CH}_2-$ ), 6.70 (4 H, m,  $-\text{CH}_2\text{C=}$  and  $\text{CH}_2\text{N}$ ), 6.35 (3 H, s, NMe), 5.00, 5.90 (2 H, q,  $J = 12$  Hz,  $\text{C}_4\text{-CH}_2-$ ), 2.3–2.7 (7 H, m, ArH), 1.91 (1 H, d,  $J = 8$  Hz,  $\text{C}_{10}\text{-H}$ ). Anal. ( $\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}$ ) 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.  $\text{ED}_{50}$  values were calculated by the method of Litchfield and Wilcoxon.<sup>9</sup> A detailed discussion of the pharmacology of the series will be published elsewhere.<sup>10</sup>

**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  $\text{ED}_{50}$  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.<sup>11</sup> 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.
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- (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 II f see J. B. Hester and A. R. Hanze, U.S. Patent 3933 794 (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).