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Diazepines. IV.[1] Synthesis and Biological Action of 6-Phenyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-ones

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A series of 6-phenyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-ones (**1**) was synthesized starting from 2-nitrodiphenylamines (**9**) and was evaluated for CNS activity. Bromoacetylation of **9** to N-bromoacetyl-2-nitrodiphenylamines (**10**) and subsequent treatment of **10** with sodium cyanide gave N-cyanoacetyl-2-nitrodiphenylamines (**11**) which were also prepared directly from **9** by cyanoacetylation. The reduction of the nitro group of **11** to give 2-amino-N-cyanoacetyldiphenylamines (**12**) followed by cyclization of **12** with HCl afforded 4-amino-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (**13**). Treatment of **13** with propargylamine in the presence of *p*-toluenesulfonic acid or with α-bromoketone gave **1**. Some of **1** were also synthesized by treatment of **13** with α-aminoaldehyde acetal to the amidine derivatives **14** followed by their cyclization in formic acid. Although the ED_{50} for the antipentetrazole activity of 8-chloro-2-ethyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-one (**1h**) was 5.5 mg/kg, the ratio of antipentetrazole to muscle relaxant activity and that of taming to muscle relaxant activity of **1h** were fairly large compared with those of diazepam.

Keywords——imidazobenzodiazepinone; aminobenzodiazepinone; tranquilizer; diazepine; benzodiazepine; amidine; central nervous system depressant; imidazole

Our continued interest in tricyclic diazepine compounds possessing useful central nervous system (CNS) action prompted us to investigate the synthesis and the biological action of 6-phenyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-ones (**1**)[3] on the basis of the following: (1) 1-phenyl-1*H*-1,5-benzodiazepin-2,4(3*H*,5*H*)-dione derivatives (**2a**,**b**)[4,5] and 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-one (**3**)[6] show a partly analogous CNS action as diazepam (**4**) and 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[1,2-*a*][1,4]-benzodiazepine (**5**),[7] respectively, indicating a bioisosterism of the moieties **6** and **7**;[8] (2) the synthesis and the CNS action of 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine derivatives (**8**) have recently been reported.[9,10]

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2) Location: *Asahigaoka, Hino, Tokyo, 191, Japan.*
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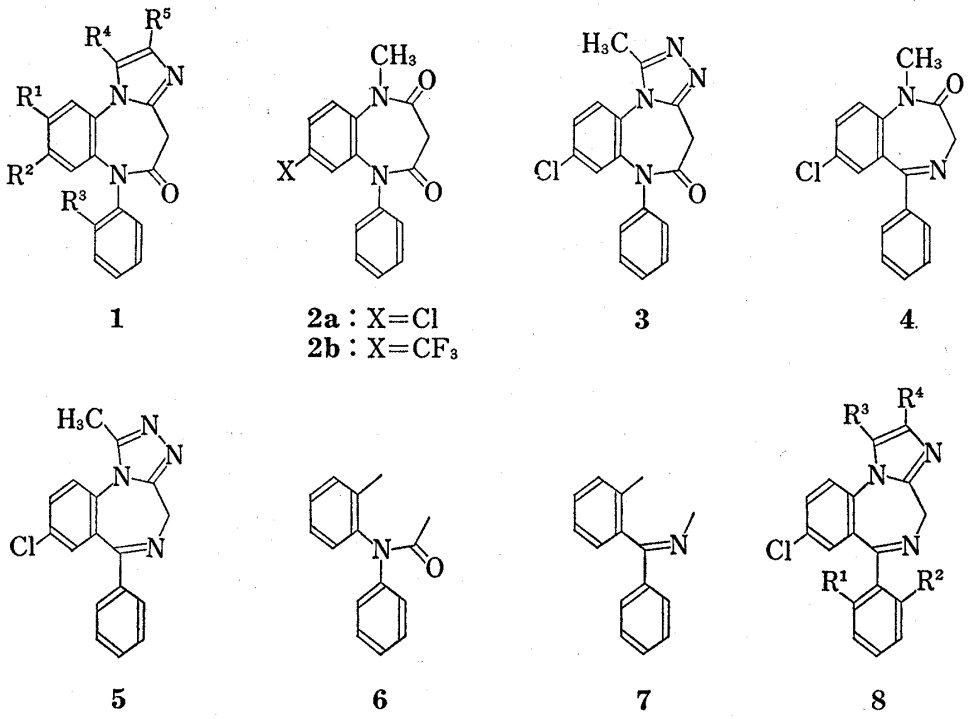


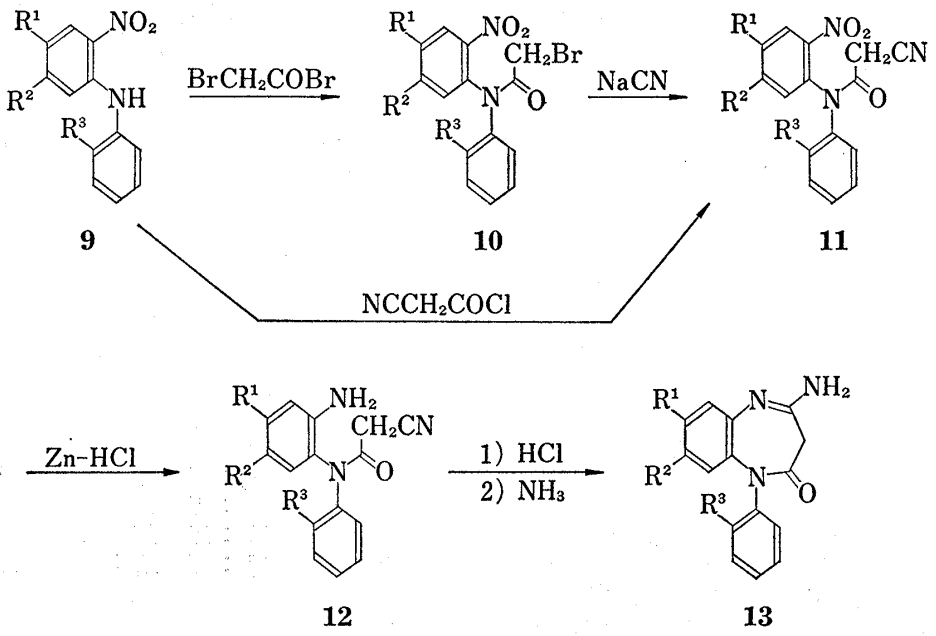
1 **2a** : X=Cl **3** **4**
2b : X=CF_3

5 **6** **7** **8**

Chart 1

Chemistry

4-Amino-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (**13a—c**), the intermediates for the synthesis of **1**, were prepared *via* the route shown in Chart 2. Acylation of 2-nitrodiphenylamines (**9**) with bromoacetyl bromide to N-bromoacetyl-2-nitrodiphenylamines (**10**) and subsequent treatment of **10** with sodium cyanide gave N-cyanoacetyl-2-nitrodiphenylamines (**11**) which could also be obtained directly from **9** by cyanoacetylation with cyanoacetyl chloride.



9 **10** **11**

12 **13**

9—13a : $R^1=R^2=R^3=H$
9—13b : $R^1=R^3=H$, $R^2=Cl$
9—13c : $R^1=H$, $R^2=Cl$, $R^3=F$

Chart 2

The rates of the bromoacetylation and of the cyanoacetylation are both considerably influenced by the substituent(s) on **9**. Thus, whereas the bromoacetylation of 2-nitrodiphenylamine (**9a**) proceeded smoothly in refluxing benzene to give N-bromoacetyl-2-nitrodiphenylamine (**10a**) in 97% yield after a reaction period of 18 hr, the conversion of 5-chloro-2-nitrodiphenylamine (**9b**) to N-bromoacetylated compound (**10b**) needed stronger conditions, *e.g.* heating in toluene at 105° (under further stronger conditions, namely, in refluxing toluene, the yield was lowered by side-reactions). In the case of 5-chloro-2′-fluoro-2-nitrodiphenylamine (**9c**), even the latter reaction condition was not strong enough, and N-bromoacetylated compound (**10c**) was obtained by heating at 90° a mixture of **9c** and bromoacetyl bromide in a molar ratio of 1: 10 without a solvent for 4 days. The yields and the physical, analytical, and spectral data of **10** so obtained are listed in Tables I and II. Similarly the cyanoacetylation of **9b** was slower than that of **9a**.

Selective reduction of the nitro group of **11** to yield 2-amino-N-cyanoacetyldiphenylamines (**12**) was effected by treatment with zinc-hydrochloric acid in acetone. During an attempted purification of crude 2-amino-N-cyanoacetyldiphenylamine (**12a**) by silica gel column chromatography it was converted to 2-cyanomethyl-1-phenylbenzimidazole[11] (**15**) as determined by analysis and spectral data (see Experimental), so crude **12a—c** were employed without purification in the next step. Cyclization of crude **12a—c** with gaseous hydrogen chloride afforded **13a—c**. 4-Amino-1-phenyl-7-trifluromethyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (**13d**) was prepared by the method described earlier.[8]

The imidazo compounds **1** were synthesized from **13** by Methods E, F, and G (Chart 3):

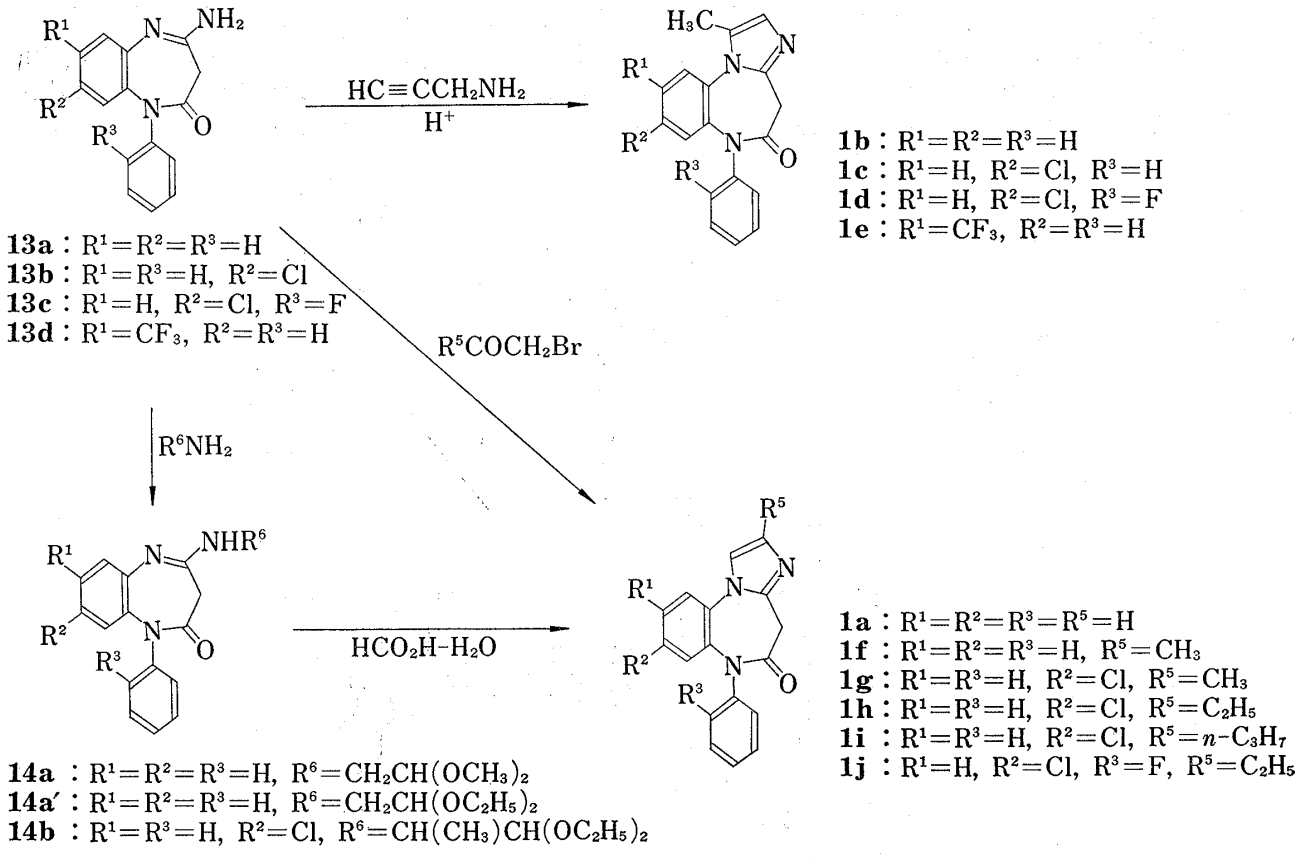


Chart 3

11) C.R. Ganelin, H.F. Ridley, and R.G.W. Spickett, *J. Heterocyclic Chem.*, **3**, 278 (1966).

Method E, treatment of **13** with propargylamine in boiling butanol using *p*-toluenesulfonic acid as the catalyst; Method F, treatment of **13** with an appropriate α-bromoketone in boiling ethanol or butanol in the presence of N,N-diisopropylethylamine; Method G, treatment of **13** with an aminoacetaldehyde dialkyl acetal in boiling butanol with *p*-toluenesulfonic acid as the catalyst to give 4-[(2,2-dialkoxyethyl)amino]-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (**14**) followed by heating at reflux a solution of **14** in 99% formic acid.

In the case of Method F, the compounds **1** were anticipated to have the alkyl substituent at C-2 rather than at C-1 from our previous study[10] on a similar reaction leading to 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines, and it was unambiguously confirmed by the fact that the reaction of **13b** with bromoacetone gave the same imidazobenzodiazepine as that prepared by Method G using 2-aminopropionaldehyde diethyl acetal.

Compounds **1** were characterized by elemental analyses and mass, infrared (IR), and nuclear magnetic resonance (NMR) spectral data (Tables V and VI). In NMR spectroscopy the imidazole ring proton of **1g** (C_1–H) resonates at a lower magnetic field than that (C_2–H) of **1c** [$\delta > 7.00$ (overlapped with the signal of protons on two benzene rings) *vs.* 6.93], and regarding the methyl proton signal of **1g** and **1c** the opposite is observed (δ 2.30 *vs.* 2.38). These can be attributed to the anisotropic deshielding effect of the benzene ring of the benzodiazepine skeleton on the C_1–H and the C_1–CH_3. The difference of the chemical shifts of the C_1–H of **1f** and of the C_2–H of **1b** ($\delta > 6.97$ and 6.92, respectively) and the difference concerning the C_2–CH_3 (**1f**) and the C_1–CH_3 (**1b**) (δ 2.30 and 2.41, respectively) can also be ascribed to a similar anisotropic effect. The C-4 protons of **1** appeared as an AB quartet of δ_{AB} of 0.45—0.54, whereas the corresponding methylene protons of the bicyclic benzodiazepines **13** and **14** showed as a singlet (**13a,b** and **14a,a',b**) or an AB quartet of δ_{AB} of only 0.10 (**13c**).

Pharmacology

Compounds **1b**—**e**, **g**—**j** were subjected to tests designed to detect CNS activity, and the results are shown in Table VII. The compounds without a chlorine atom at C-8 (R^2=H) (**1b,e**) were almost inactive. In the compound with a chlorine atom at C-8, introduction of the ethyl group at C-2 (R^5=C_2H_5) (**1h,j**) produced the most active pharmacologically in this series, while replacement of the ethyl group with the methyl or propyl group (**1g** and **1i**) considerably decreased the overall activities. On the other hand, introduction of the methyl group at C-1 (**1c**) instead of C-2 (**1g**) produced a compound whose activity is closer to **1h**. The effect of introduction of a fluorine atom at the *ortho*-position of the C-6 phenyl group (R^3=F (**1d,j**) was scarcely observed. The compound **1h** is several times less potent in the CNS activities than diazepam. On the contrary, the ratio of antipentetrazol to muscle relaxant activity and that of taming to muscle relaxant activity of **1h** are fairly large compared with those of diazepam.

Experimental

Melting points were obtained on a Yanagimoto hot-stage apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-500 spectrophotometer. NMR data were obtained on a JEOL JNM-MH-100 spectrometer except in the case otherwise noted, and chemical shifts are recorded in parts per million (δ) with tetramethylsilane as an internal standard (s=singlet; t=triplet; q=quartet; m=multiplet; bs=broad singlet; ar-H=protons on benzene rings). Mass spectra (MS) were run on a LKB 9000 spectrometer at 70 eV.

Evaporation of the solvent is done under reduced pressure.

Chemistry

Preparation of N-Bromoacetyl-2-nitrodiphenylamines (10, Tables I and II)——General Method A: The preparation of **10** by the coupling of a 2-nitrodiphenylamine (**9**) with bromoacetyl bromide is exemplified by the synthesis of N-bromoacetyl-5-chloro-2-nitrodiphenylamine (**10b**). A stirred solution of 5-chloro-2-nitrodiphenylamine (**9b**) (12.0 g of 98% purity, 47.3 mmol) and bromoacetyl bromide (19.5 g, 96.6 mmol) in dry toluene (80 ml) was heated in an oil bath at 105° under N_2 for 24 hr, cooled, and evaporated. The residue was dissolved in EtOAc (150 ml), and the solution was washed successively with H_2O, saturated aq.

$NaHCO_3$ solution, and aq. NaCl solution, and dried over Na_2SO_4. The solvent was evaporated, and the residue was crystallized with ether–hexane to give 16.0 g (92% yield) of **10b**, mp 138—140°. The physical, analytical, and spectral data are shown in Tables I and II.

Preparation of N-Cyanoacetyl-2-nitrodiphenylamines (11, Tables I and II)——General Method B: The preparation of **11** by the treatment of **10** with NaCN is exemplified by the synthesis of 5-chloro-N-cyanoacetyl-2′-fluoro-2-nitrodiphenylamine (**11c**). To a stirred, ice-cold solution of NaCN (452 mg, 9.22 mmol) in N,N-dimethylformamide (DMF) (4 ml) was added a solution of N-bromoacetyl-5-chloro-2′-fluoro-2-nitrodiphenylamine (**10c**) (2.90 g, 7.47 mmol) in DMF (10 ml) over a period of 10 min. After stirring for 1 hr, the mixture was diluted with EtOAc (300 ml). The EtOAc solution was washed successively with four 40-ml portions of H_2O, saturated aq. $NaHCO_3$ solution, and aq. NaCl solution, and dried over Na_2SO_4. The solvent was evaporated, and the residue was crystallized with ether to give 2.30 g (92% yield) of **11c**, mp 169—172°. The physical, analytical, and spectral data are shown in Tables I and II.

General Method C: The preparation of **11** by the coupling of **9** with cyanoacetyl chloride is exemplified by the synthesis of 5-chloro-N-cyanoacetyl-2-nitrodiphenylamine (**11b**). To a stirred solution of **9b** (10.0 g, 40.2 mmol) in dry benzene (100 ml) was added cyanoacetyl chloride (8.0 g, 77.3 mmol), and the mixture was heated at reflux for 4.5 days, cooled to room temperature, and filtered. The solid collected was mixed with Celite No. 545 (Koso Chemical) (8 g) and extracted with benzene using a Soxhlet apparatus to give 2.0 g of **11b**. On the other hand, the filtrate was evaporated, and the residue was taken in CH_2Cl_2. The insoluble solid (0.27 g) was collected by filtration and found to be **11b** from the spectral data. The filtrate was evaporated, and the residue was chromatographed on silica gel. Elution with benzene gave 5.28 g of **9b** and that with benzene–EtOAc (95: 5) gave 0.69 g of **11b** (2.97 g of **11b** in total, 49% yield based on converted **9b**). The physical, analytical, and spectral data are shown in Tables I and II.

Table I. N-Bromoacetyl-2-nitrodiphenylamines (**10**) and N-Cyanoacetyl-2-nitrodiphenylamines (**11**)

Compd. No.	Method	Yield[a] (%)	Recrystn. solvent[b]	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
10a	A	97[c]	M–H	100 —101	$C_{14}H_{11}BrN_2O_3$	50.17 (50.40)	3.31 (3.18)	8.36 (8.24)
10b	A	92	M–H	140 —141	$C_{14}H_{10}BrClN_2O_3$	45.50 (45.65)	2.73 (2.63)	7.58 (7.59)
10c	A	50[d]	M–H	148.5—150	$C_{14}H_9BrClFN_2O_3$	43.38 (43.19)	2.34 (2.30)	7.23 (7.45)
11a	B C	95 81[e]	EA–B	174.5—175.5	$C_{15}H_{11}N_3O_3$	64.05 (64.37)	3.94 (3.70)	14.94 (14.79)
11b	B C	94 49[f]	M–H	196.5—197.5	$C_{15}H_{10}ClN_3O_3$	57.07 (57.03)	3.19 (3.02)	13.31 (13.03)
11c	B	92	M–H	173 —175	$C_{15}H_9ClFN_3O_3$	53.99 (54.05)	2.72 (2.81)	12.59 (12.24)

a) Yield of crude material before recrystallization; no efforts were made to optimize yields.
b) M=CH_2Cl_2; H=hexane; EA=EtOAc; B=benzene.
c) Reaction conditions: heating at reflux in dry benzene for 18 hr.
d) Reaction conditions: heating at 90 ° for 4 days using 10 equivalents of $BrCH_2COBr$ without a solvent.
e) Based on converted **9a**; 26% of **9a** was recovered.
f) Based on converted **9b**; 53% of **9b** was recovered.

Table II. Spectral Data of **10** and **11**

Compd. No.	IR ν_{max}^{KBr} cm^{-1}	NMR δ (in $CDCl_3$)
10a	1672, 1527, 1355	3.83 (2H, s, CH_2), 7.15—8.00 (9H, m, ar-H)
10b	1673, 1527, 1345	3.82 (2H, s, CH_2), 7.17—8.00 (8H, m, ar-H)
10c	1684, 1520, 1340	3.80 (2H, s, CH_2), 7.00—8.10 (7H, m, ar-H)
11a	2265, 1679, 1525, 1371, 1346	3.41 (2H, s, CH_2), 7.12—8.03 (9H, m, ar-H)
11b	2265, 1687, 1521, 1367, 1347	3.41 (2H, s, CH_2), 7.18—8.02 (8H, m, ar-H)
11c	2265, 1687, 1519, 1494, 1366, 1353	3.43 (2H, s, CH_2), 7.10—8.10 (7H, m, ar-H)

Preparation of 4-Amino-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (13, Tables III and IV)——General Method D: The preparation of **13** by the reduction of **11** followed by cyclization is exemplified by the synthesis of 4-amino-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (**13a**). To a stirred, ice-cold solution of N-cyanoacetyl-2-nitrodiphenylamine (**11a**) (3.00 g, 10.7 mmol) in acetone (30 ml) was added conc. HCl (10 ml), and then added Zn-dust (3.00 g) portionwise over 10 min. After stirring for 1 hr the mixture was filtered, and the filtrate was concentrated to *ca.* 10 ml, diluted with EtOAc (50 ml) and H_2O (30 ml), and neutralized by addition of solid Na_2CO_3 under cooling in an ice-bath. The organic layer was separated, washed with aq. NaCl solution, and dried over Na_2SO_4. The solution was concentrated to *ca.* 25 ml. To the solution was introduced HCl (gas) over 30 min with stirring under cooling in an ice-bath, and the mixture which had started to generate colorless precipitates was allowed to stand at room temperature in the flask closed with stoppers for 3 days. Dry ether (20 ml) was added to the mixture, and the generated solid was collected by filtration and stirred with 10% aq. NH_3 (40 ml) to give 1.15 g (43% yield) of **13a**, which was collected by filtration and dried. The physical, analytical, and spectral data are shown in Tables III and IV.

Preparation of 6-Phenyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-ones (1) (Tables V and VI)——General Method E: The preparation of **1** by the reaction of **13** with properglyamine is exemplified by the synthesis of 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-one (**1d**). A

Table III. 4-Amino-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (**13**) and 4-[(2,2-Dialkoxyethyl)amino]-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (**14**)

Compd. No.	Method	Yield[a] (%)	Recrystn. solvent[b]	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
13a	D	43[c]	A–B	251—252	$C_{15}H_{13}N_3O$	71.70 (71.84)	5.22 (5.05)	16.72 (16.43)
13b	D	32[c]	M–P	247—249[d]	$C_{15}H_{12}ClN_3O$	[e]		
13c	D	35[c]	M–H	264—266[f]	$C_{15}H_{11}ClFN_3O$	[g]		
14a	G[h]	90	M–H	171—172	$C_{19}H_{21}N_3O_3$	67.24 (67.14)	6.24 (6.23)	12.38 (12.39)
14a′	G[h]	90	M–H	150—151	$C_{21}H_{25}N_3O_3$	68.64 (68.75)	6.86 (6.82)	11.44 (11.59)
14b	G[h]	73	M–H	171—173	$C_{22}H_{26}ClN_3O_3$	63.53 (63.63)	6.30 (6.32)	10.10 (9.74)

a) Yield of crude material before recrystallization; no efforts were made to optimize yields.
b) A=acetone; B=benzene; M=CH_2Cl_2; P=diisopropyl ether; H=hexane.
c) Based on **11**.
d) Lit.[8] mp 242—243°
e) MS M^+ Calcd.: 285.067. Found: 285.069 ±0.009.
f) Lit.[8] mp 258—259°
g) MS M^+ Calcd.: 303.058. Found: 303.040 ±0.018.
h) Compound **14** was prepared by the first reaction of Method G.

Table IV. Spectra Data of **13** and **14**

Compd. No.	IR ν_{max}^{KBr} cm^{-1}	NMR δ (in $CDCl_3$)
13a	3300, 3050, 1684, 1654, 1616, 1586	3.32 (2H, bs, CH_2), 5.7 (2H, bs, NH_2), 6.84—7.57 (9H, m, ar-H)
14a	3290, 1660, 1621, 1590, 1569	3.25 (2H, s, CH_2CO), 3.39 (6H, s, $2\times OCH_3$), 3.61 (2H, m, NCH_2), 4.59 (1H, t, J=5.5 Hz, O-CH-O), 5.71 (1H, broad, NH), 6.67—7.49 (9H, m, ar-H)
14a′	3290, 1658, 1618, 1588, 1563	1.19 (6H, t, J=7.0 Hz, $2\times CH_3$), 3.20 (2H, s, CH_2CO), 3.36—3.79 (6H, m, $2\times OCH_2$ and NCH_2), 4.68 (1H, t, J=5.5 Hz, O-CH-O), 5.49 (1H, broad, NH), 6.70—7.43 (9H, m, ar-H)
14b	3330, 1663, 1621, 1592, 1567	1.14—1.28 (9H, m, $2\times CH_2\underline{CH_3}$ and $NCHC\underline{H_3}$), 3.19 (2H, s, CH_2CO), 3.41—3.87 (4H, m, $2\times O\underline{CH_2}CH_3$), 4.15—4.58 (2H. m, NCHCH⟨), 5.37—5.53 (1H, broad, NH), 6.77—7.53 (7H, m, ar-H)

solution of 4-amino-8-chloro-1-(2-fluorophenyl)-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (**13c**) (200 mg, 0.659 mmol), propargylamine (182 mg, 3.30 mmol), and *p*-toluenesulfonic acid monohydrate (10 mg) in BuOH (5 ml) was heated at reflux for 3 hr. The mixture was evaporated, and the residue was taken up in benzene. The solution was washed successively with saturated aq. $NaHCO_3$ solution, H_2O, and saturated aq. NaCl solution and dried over Na_2SO_4. The material obtained on evaporation of the solvent was chromatographed on silica gel. Elution wish benzene–EtOAc (3: 2) gave 81 mg (36% yield) of **1d**, mp 183—186°. The physical, analytical, and spectral data are shown in Tables V and VI.

General Method F: The preparation of **1** by the reaction of **13** with an α-bromoketone is exemplified by the synthesis of 8-chloro-2-ethyl-6-phenyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-one (**1h**). A stirred solution of 4-amino-8-chloro-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (**13b**) (520 mg, 1.82 mmol), 1-bromo-2-butanone (2.09 g, 13.8 mmol), and N,N-diisopropylethylamine (357 mg) in EtOH (15 ml) was heated at reflux for 7 hr. The mixture was evaporated, and the residue was taken up in EtOAc. The EtOAc solution was washed successively with saturated aq. $NaHCO_3$ solution and aq. NaCl solution, and dried over Na_2SO_4. The oil obtained on evaporation of the solvent was chromatographed on silica gel. Elution with benzene–EtOAc (4: 1) gave 130 mg (21% yield) of **1h**, mp 171—173°. The physical, analytical, and spectral data are shown in Tables V and VI.

General Method G: The preparation of **1** by the reaction of **13** with an aminoacetaldehyde dialkyl acetal to give 4-[2,2-dialkoxyethyl)amino]-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-ones (**14**) followed by their cyclization in formic acid is exemplified by the synthesis of 8-chloro-2-methyl-6-phenyl-4*H*-imidazo-[1,2-*a*][1,5]benzodiazepin-5(6*H*)-one (**1g**).

i) 8-Chloro-4-[(2,2-diethoxy-1-methylethyl)amino]-1-phenyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (14b)——To a mixture of **13b** (143 mg, 0.500 mmol), 2-aminopropionaldehyde diethyl acetal (200 mg, 1.36 mmol), and BuOH (2 ml) was added *p*-toluenesulfonic acid monohydrate (92 mg), and the mixture was heated at reflux for 16 hr. The material obtained on evaporation of BuOH was taken up in CH_2Cl_2 (10 ml), and the insoluble material was removed by filtration. The filtrate was washed successively with saturated aq. $NaHCO_3$ solution and aq. NaCl solution, and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2–EtOAc (3: 2) gave 179 mg of pale brown crystals, which were washed with ether–hexane to give 152 mg (73% yield) of **14b** as colorless crystals, mp 170—172°. The physical, analytical, and spectral data are shown in Tables III and IV.

ii) Cyclization of 14b to 1g——A mixture of **14b** (180 mg, 0.433 mmol) and 99% formic acid (2 ml) was heated at reflux for 1 hr. The material obtained on evaporation of the mixture was dissolved in CH_2Cl_2

Table V. 6-Phehyl-4*H*-imidazo[1,2-*a*][1,5]benzodiazepin-5(6*H*)-ones (**1**)

Compd. No.	Method	Yield[a] (%)	Recrystn. solvent[b]	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
1a	G	84[c]	M-M1-H	108	$C_{17}H_{13}N_3O$	*d*)		
1b	E	94	M-H	206—207	$C_{18}H_{15}N_3O$	74.72 (74.63)	5.23 (5.33)	14.52 (14.83)
1c	E	33	M-H	204—205	$C_{18}H_{14}ClN_3O$	66.77 (66.54)	4.36 (4.20)	12.98 (12.72)
1d	E	36	M-H	186.5—188	$C_{18}H_{13}ClFN_3O$	63.26 (63.01)	3.83 (3.66)	12.29 (12.65)
1e	E	35	M-H	182—183	$C_{19}H_{14}F_3N_3O$	63.86 (63.54)	3.95 (3.99)	11.76 (11.67)
1f	F	18	M-H	195—195.5	$C_{18}H_{15}N_3O$	74.72 (74.95)	5.23 (5.01)	14.52 (14.41)
1g	G F	67[e] 14	E-H	199.5—200.5	$C_{18}H_{14}ClN_3O$	66.77 (66.95)	4.36 (4.17)	12.98 (13.01)
1h	F	21	M-H	173—174	$C_{19}H_{16}ClN_3O$	67.56 (67.70)	4.77 (4.75)	12.44 (12.45)
1i	F	25	M-H	185—187	$C_{20}H_{18}ClN_3O$	68.28 (68.17)	5.16 (4.98)	11.94 (11.77)
1j	F	10	M-H	180.5—182	$C_{19}H_{15}ClFN_3O$	64.14 (63.97)	4.25 (4.14)	11.81 (11.34)

a) Yield of material isolated by silica gel column chromatography; no efforts were made to optimize yields.
b) M=CH_2Cl_2; Ml=MeOH; H=hexane; E=ether.
c) Yield from **14a**.
d) MS M^+ Calcd: 275.106. Found: 275.105±0.008; *m/e* (relative intensity): 275(93), 248(M^+ −HCN, 76), 246(93), 77 (54), 32(67), 31(100).
e) Yield from **14b**.

(15 ml), and the solution was treated with saturated aq. $NaHCO_3$ solution. The organic layer was separated, washed with aq. NaCl solution, and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2–EtOAc (1: 2—1: 4) gave 94 mg (67% yield) of **1g** as colorless crystals, mp 199—200.5°. The physical, analytical, and spectral data are shown in Tables V and VI.

Table VI. Spectral Data of **1**

Compd. No.	IR ν_{max}^{KBr} cm^{-1}	NMR δ (in $CDCl_3$)
1a	1670, 1500, 1427, 1328, 1311	ν_A 4.08 and ν_B 3.59 (2H, ABq, J=13.5 Hz, CH_2CO), 6.69—7.48 (11H, m, C_1-H, C_2-H, and ar-H)
1b	1677, 1498, 1413, 1330, 1314, 1298	2.41 (3H, s, CH_3), ν_A 4.00 and ν_B 3.53 (2H, ABq, J=13.5 Hz, CH_2CO), 6.92 (1H, s, C_2-H), 7.02—7.46 (9H, m, ar-H)
1c	1690, 1496, 1426, 1402, 1329, 1311	2.38 (3H, s, CH_3), ν_A 4.02 and ν_B 3.52 (2H, ABq, J=13.5 Hz, CH_2CO), 6.93 (1H, s, C_2-H), 7.06—7.50 (8H, m, ar-H)
1d[a]	1692, 1498, 1423, 1402, 1322, 1304	2.33 (3H, s, CH_3), ν_A 4.00 and ν_B 3.55 (2H, ABq, J= 14.0 Hz, CH_2CO), 6.90 (1H, s, C_2-H), 7.00—7.60 (7H, m, ar-H)
1e	1694, 1448, 1318	2.42 (3H, s, CH_3), ν_A 4.05 and ν_B 3.51 (2H, ABq, J=13.9 Hz, CH_2CO), 6.96 (1H, s, C_2-H), 7.00—7.70 (8H, m, ar-H)
1f	1676, 1498, 1419, 1331, 1302	2.30 (3H, s, CH_3), ν_A 4.05 and ν_B 3.56 (2H, ABq, J=13.5 Hz, CH_2CO), 6.97—7.51 (10H, m, C_1-H and ar-H)
1g	1692, 1496, 1398, 1322, 1297	2.30 (3H, s, CH_3), ν_A 4.02 and ν_B 3.54 (2H, ABq, J=13.2 Hz, CH_2CO), 7.00—7.50 (9H, m, C_1-H and ar-H)
1h	1681, 1496, 1429, 1401, 1329, 1298	1.28 (3H, t, J=7.4 Hz, CH_3), 2.66 (2H, q, J=7.4 Hz, $C\underline{H}_2CH_3$), ν_A 4.06 and ν_B 3.54 (2H, ABq, J=13.6 Hz, CH_2CO), 6.96—7.50 (9H, m, C_1-H and ar-H)
1i	1686, 1496, 1430, 1401, 1326	1.00 (3H, t, J=7.4 Hz, CH_3), 1.73 (2H, sextet, J= 7.4 Hz, $C\underline{H}_2CH_3$), 2.61 (2H, t, J=7.4 Hz, $C\underline{H}_2CH_2$-CH_3), ν_A 4.07 and ν_B 3.56 (2H, ABq, J=14.0 Hz, CH_2CO), 7.00—7.50 (9H, m, C_1-H and ar-H)
1j	1686, 1496, 1430, 1401, 1332	1.28 (3H, t, J=7.5 Hz, CH_3), 2.67 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), ν_A 4.08 and ν_B 3.59 (2H, ABq, J= 14.0 Hz, CH_2CO), 6.95—7.50 (8H, m, C_1-H and ar-H)

a) The NMR spectrum of this compound was recorded on a Varian EM 360 spectrophotometer.

Table VII. CNS Activities[a] of **1**

Compd. No.	Anticonvulsant activity		Taming activity Fighting mouse	Muscle-relaxant activity Inclined screen	Motor incoordinating Rotating rod	Sedation Potentiation of thiopental
	Pentetrazole	Maximal electroshock				
1b	>100	>100	>100	>100	>100	100
1c	10	60	5.5	30	38	2.0
1d	17.5	>100	5.5	30	38	13.5
1e	>100	>100	>100	>100	>100	100
1g	86	>100	>30	>30	>100	30
1h	5.5	50	3.6	55	25	1.8
1i	14.2	55	27	54	>100	4.4
1j	5.5	>30	4.1	10	18	0.8
Diazepam	0.8	10.0	1.5	1.0	4.5	0.24

a) Values are ED_{50}'s expressed in mg/kg.

2-Cyanomethyl-1-phenylbenzimidazole (15)——Compound **11a** (1.01 g, 3.59 mmol) was dissolved in acetone (20 ml), and conc. HCl (5 ml) was added. To the resulting solution was added Zn-dust (1.00 g) with stirring under cooling in an ice-bath over a period of 1 min. After stirring for an additional 30 min, the solid was filtered off, and the filtrate was evaporated to remove acetone. To the residue was added H_2O (50 ml), and the mixture was made alkaline by adding portionwise solid Na_2CO_3, and extracted with EtOAc. The combined extracts were washed with saturated aq. $NaHCO_3$ solution and aq. NaCl solution, and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on silica gel. Elution with benzene–EtOAc (9: 1) gave 659 mg (79% yield) of **15** as colorless crystals. Recrystallization from ether–hexane gave colorless prisms, mp 122.5—123.5° (lit.,[11] mp 121—123°). IR ν_{max}^{KBr} cm^{-1}: 2265, 1597, 1497, 1452. NMR ($CDCl_3$) δ: 3.90 (2H, s, CH_2), 7.06—7.91 (9H, m, ar-H). *Anal.* Calcd. for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.33; H, 4.63; H, 18.06.

4-Amino-1-phenyl-7-trifluoromethyl-2*H*-1,3-dihydro-1,5-benzodiazepin-2-one (13d)——The title compound was prepared according to the method described in literature.[8] However, after the imino-chloride had been formed in dioxane, tetrahydrofuran (THF) was added so as to make the ratio of dioxane-THF (2: 1), and the mixture was cooled to −30°. To the stirred, cold mixture (slurry) was introduced NH_3 gas, which raised the temperature of the mixture to 10°. Without adding THF, the mixture could not be cooled enough to control the temperature from vigorous heat generation during the NH_3 introduction.

Pharmacology

Methods——Groups of 6 male ddY mice weighing 18—24 g were used. All the test compounds suspended in 5% arabic gum solution were administered orally. A top dose up to 100 mg/kg was selected arbitrarily in each test. The ED_{50}'s of the test compounds were calculated by the method of Litchfield-Wilcoxon.[12]

Anticonvulsant Activity (Pentetrazole)——Mice were challenged with subcutaneous injection of 125 mg/kg of pentetrazole 1 hr after administration of the test compound. The absence of clonic and tonic convulsions for 30 min after the injection of pentetrazole was taken as a measure of antipentetrazole activity.

Anticonvulsant Activity (Maximal Electroshock)——The mice similarly pretreated with the test compound were delivered maximal electroshock of rectangular current of 100 Hz, 1 msec, and 30 mA for 0.2 sec through ear clips. Prevention of tonic hind limb extension was taken as a positive anti-electroconvulsive shock activity.

Taming Activity——According to the method of Tedeschi, *et al.*,[13] a pair of mice were stimulated by rectangular current of 4.5 Hz, 200 msec, and 3 mA for 3 min which was applied through a grid to the feet of the animals. Three pairs of mice per dose which showed several fighting episodes for 3 min were submitted to the test 30, 60, and 90 min after administration of the test compound. The absence of fighting episode was taken as a measure of taming activity in fighting mice induced by electro-foot shock.

Muscle-relaxant Activity——The mice which could stay for more than 30 sec at a certain place on a 70° inclined wooden board were submitted to this test 30, 60, and 90 min after administration of the test compound. The muscle relaxant activity was regarded as positive when the mouse slided down more than several mm within 30 sec after being placed on the inclined board.

Motor Incoordinating Activity——Groups of 5 mice were used. The mice which could stay on the rotating rod (3.0 cm in diameter, 5.5 rpm) for more than 3 min were submitted to this test 30, 60, and 90 min after administration of the test compound. The motor incoordinating activity was regarded as positive when the mouse fell down from the rotating rod within 3 min in two successive trials.

Potentiation of Thiopental Hypnosis——Mice were given intraperitonealy 55 mg/kg of thiopental-Na 1 hr after administration of the test compound. The potentiating activity was determined from the number of mice which slept two times longer than the control mice which were administered vehicle.

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