[Chem. Pharm. Bull. 21(11)2382—2390(1973)]

UDC 547.892.04 : 615.21.011.5

Heterocycles. VI.[1] Syntheses of 4*H*-*s*-Triazolo[4,3-*a*][1,4]benzodiazepines, Novel Tricyclic Psychosedatives

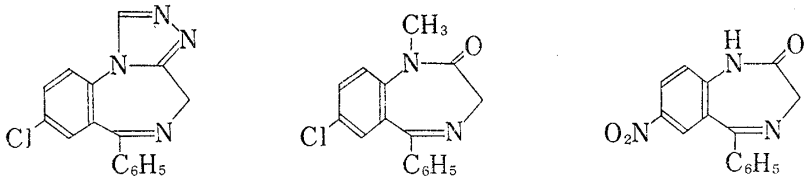
Kanji Meguro, Hiroyuki Tawada, Hiroshi Miyano, Yoshiaki Sato, and Yutaka Kuwada

Chemical Research Laboratories, Central Research Division, Takeda Chemical Industries, Ltd.[2]

(Received January 19, 1973)

A variety of 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (VII) which are highly active in central nervous system depression was synthesized with the aim of investigating structure–activity relationships.

A great number of 1,4-benzodiazepine derivatives has been synthesized[3] and some of them are widely used clinically as tranquillizers, anticonvulsants, hypnotics, *etc.* Chemical studies in this area, however, have been directed mainly toward simple modifications of the 1,4-benzodiazepine skeleton. We reported in the preceding paper[1] the synthesis of 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (D-40TA) possessing a novel tricyclic ring system. This compound was found, by Nakajima, *et al.*[4] in the Biological Research Laboratories of this Division, to have superior activities in central nervous system depression over the known 1,4-benzodiazepines (*e.g.* diazepam and nitrazepam).



D-40TA diazepam nitrazepam

Chart 1

We prepared a variety of *s*-triazolo[4,3-*a*][1,4]benzodiazepine derivatives with the aim of investigating structure–activity relationships and for the development of useful drugs for clinical purpose. This paper is concerned with general methods for the synthesis of 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines.

2-Hydrazino-1,4-benzodiazepines (VI) were easily prepared from 2-amino-1,4-benzodiazepines (I) or 1,4-benzodiazepine-2-thiones (II) by the reaction with hydrazine hydrate according to the method reported in the preceding paper.[1] Synthesis of the starting materials, 2-amino-3*H*-1,4-benzodiazepines (I, X≠O), which involves cyclization of 2-amino-α-phenylbenzylideneaminoacetonitriles (III) had been reported in a previous paper.[5] Other starting compounds (I) (X=O) and (II) which include some new compounds were prepared from 2-chloromethylquinazoline 3-oxides (IV) and 1,4-benzodiazepin-2-ones (V), respectively, by

1) Part V: K. Meguro and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2375 (1973). For the preliminary communication of the Part V see *idem*, *Tetrahedron Letters*, **1970**, 4039.
2) Location: *Juso, Higashiyodogawa-ku, Osaka.*
3) For the most recent review see L.H. Sternbach, *Angew. Chem. Int. Ed. Eng.*, **10**, 34 (1971).
4) R. Nakajima, C. Hattori, and Y. Nagawa, *Japan. J. Pharmacol.*, **21**, 489 (1971); R. Nakajima, Y. Take, R. Moriya, Y. Saji, T. Yui, and Y. Nagawa, *ibid.*, **21**, 497 (1971).
5) K. Meguro, H. Tawada, and Y. Kuwada, *Yakugaku Zasshi*, **93**, 1253 (1973).

known methods.[6] Compound (Vd) (R_1=Cl, R_2=H, R_4=$CH_2CH(CH_3)_2$) was obtained by fusion of 2-(2-amino-5-chloro-α-phenylbenzylideneamino)ethanol[7] with L-leucine ethyl ester hydrochloride in the presence of 2-methylimidazole[8] as a mixture of (±)- and (+)-form. The (±)-form was used for the preparation of IId.

Compound (VI) was cyclized to 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (VII) on treatment with orthoesters in good yields. The cyclization was generally performed in ethanol in the presence of sulfuric acid as an acid catalyst, but in some cases where R_1 is a nitro or a trifluoromethyl group, it was better to use *p*-toluenesulfonic acid as the catalyst in chloroform. VII was also prepared by heating monoacylhydrazino compounds (VIII), which were obtained by acylation of VI with one mole equivalent of acylating agents, at their melting points or in boiling pyridine. Compound (VIII) was synthesized more easily by direct reaction of I with monoacylhydrazines in methanol or ethanol in the presence of acetic acid at room temperature. When formylhydrazine was used in this reaction, the cyclized compound (VII) was obtained in addition to VIII.

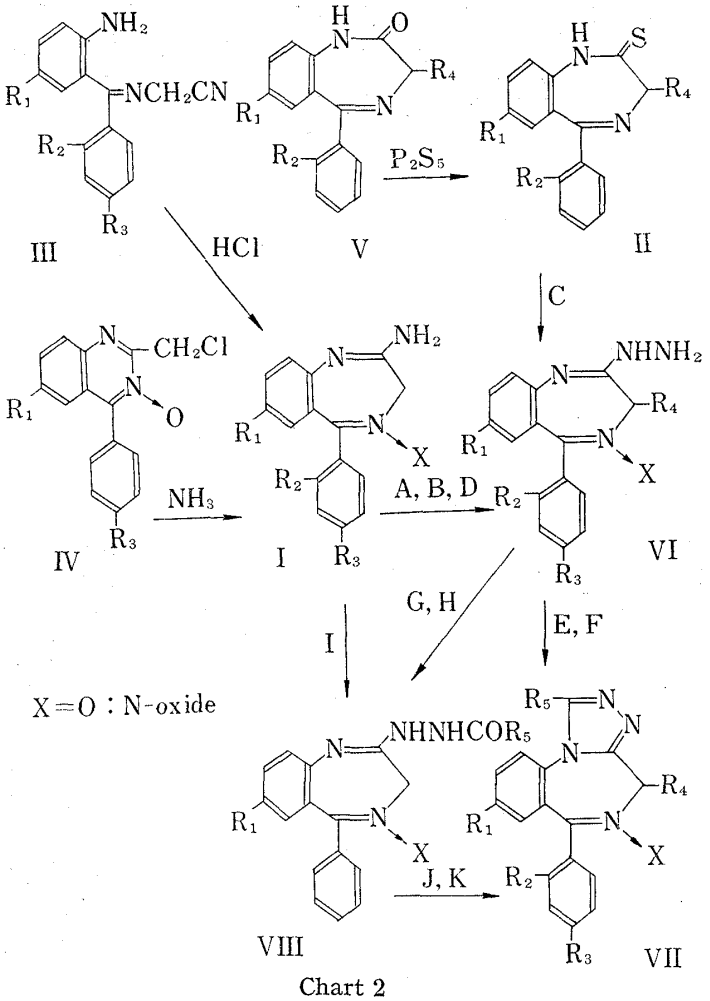


Chart 2

Compound (VIII) showed a positive ferric chloride test (blue) and exhibited, in the nuclear magnetic resonance (NMR) spectrum, two separate signals due to the acyl protons. The methyl signals of 2-(2-acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (VIIIa-2 in Table III), for instance, appeared at δ 1.89 and 2.06 in the ratio 3: 2 in dimethylsulfoxide-d_6 and coalesced into a single peak at 100°. These facts suggested that VIII is present in a mixture of two tautomers in solution, probably keto and enol in the acylhydrazino group.

Other methods for cyclizing VI to VII were investigated using VIa (Chart 3). When VIa was treated with formic acid or with formamide and sulfuric acid, VIIa-1 was obtained. On formylation with N-formyl-2-methylimidazole followed by heating in pyridine, VIa also afforded VIIa-1. Fusion of VIa and amidine hydrochlorides with 2-methylimidazole gave VIIa-1 and VIIa-2. When VIa was acetylated with acetic anhydride and sulfuric acid,

6) For I (X=O) see *a*) L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961); *b*) L.H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *ibid.*, **26**, 4488 (1961); *c*) L.H. Sternbach, R.I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963); *d*) G. Saucy and L.H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962). For II see *e*) G.A. Archer and L.H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).

7) *a*) S.C. Bell, G.L. Conklin, and S.J. Childress, *J. Org. Chem.*, **29**, 2368 (1964); *b*) see ref. 5.

8) This method is a modification of our fusion method for the preparation of 1,4-benzodiazepin-2-ones; K. Meguro and Y. Kuwada, *J. Takeda Res. Lab.*, **30**, 9 (1971).

VIIa-2 was obtained in one step. Reaction of VIa with ethyl acetimidate hydrochloride in chloroform in the presence of 2-methylimidazole at room temperature gave an amidrazone (IX) in high yield and it was converted into VIIa-2 on heating to the melting point. When the same reaction was carried out in the absence of 2-methylimidazole, however, VIIa-2 was obtained as the major product (60%) in addition to IX (19%). This suggests that an α-ethoxyethylidene compound (X) formed preferably as an intermediate rather than IX under these conditions. Compound (X) could then cyclize to VIIa-2 easily as it may indeed be the intermediate in the reaction of VIa with ethyl orthoacetate. Compound IX was also obtained by reaction of VIa with acetamidine hydrochloride under mild conditions.

A 5,6-dihydro compound (XIII) was obtained by a similar route as illustrated in Chart 4. Compound (XIII) gave VIIa-1 on bromination with N-bromosuccinimide followed by treatment with sodium methoxide.

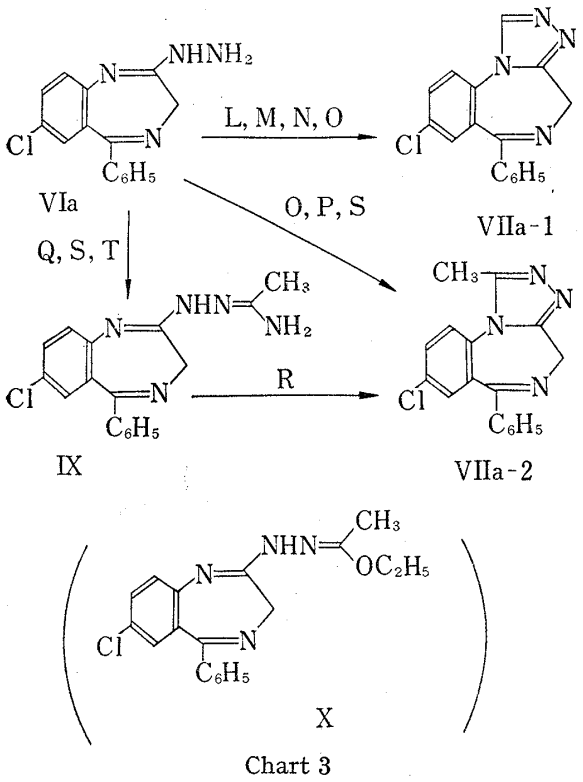


Chart 3

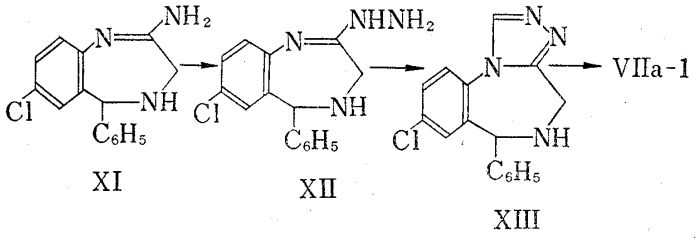


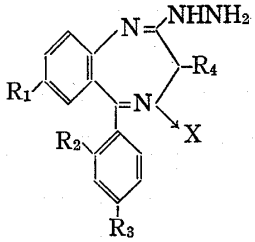
Chart 4

Compounds (VI), (VII) and (VIII) prepared are shown in Tables I, II and III, respectively. Acetonides of VI prepared by recrystallization from acetone are also shown in Table I.

Recently, Hester, *et al.*[9] reported independently a synthesis of 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines which involves the reaction of 1,4-benzodiazepine-2-thiones with monoacylhydrazines followed by cyclization.

Pharmacological data of most of VII except 5-oxides have been published by Nakajima, *et al.*[4] prior to the report of Hester, *et al.*[9b] The data on the 5-oxides will be published elsewhere in near future.

TABLE I. 2-Hydrazino-3*H*-1,4-benzodiazepines (VI)



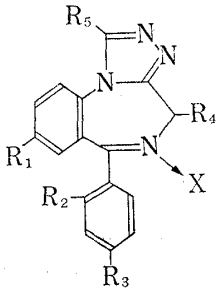
Compd.	R_1	R_2	R_3	R_4	X	Recrystn.[a] from	mp, °C[b]	Method[c]	Yield %	Formula[d]	Acetonide mp, °C	Reference[e]
a	Cl	H	H	H		Dic–B	202—204 (d)	[f]	72—81	$C_{15}H_{13}N_4Cl$	184.5—185.5[f]	a, b

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

Compd.	R_1	R_2	R_3	R_4	X	Recrystn.[a] from	mp, °C[b]	Method[c]	Yield %	Formula[d]	Acetonide mp, °C	Reference[e]
b	Cl	H	CH_3O	H		Ch–B	214—220	A	80	$C_{16}H_{15}ON_4Cl$	[g]	a
c	Cl	Cl	H	H		Ch–H	220—223(d)	A	91	$C_{15}H_{12}N_4Cl_2$	167—168	a
								C	99			b
d	Cl	H	H	$(CH_3)_2$-$CHCH_2$		Ch–H	168—169	C	65	$C_{19}H_{21}N_4Cl$	189—190	c
e	H	H	H	H		Dic–B	116—118	B[h]	74	$C_{15}H_{14}N_4 \cdot 1/3C_6H_6$	[g]	a
f	CH_3	H	H	H		Ch–Eth	240—241(d)	A[h]	95	$C_{16}H_{16}N_4$	194—195	a
g	CH_3O	H	H	H		Ch–Eth	110—120	A[h]	77	$C_{16}H_{16}ON_4$	[g]	a
h	NO_2	H	H	H		—	amorph.[i]	B	—	—	203—205	a
i	CF_3	H	H	H		Ch–H	133—135(d)	B	94	$C_{16}H_{13}N_4F_3$	[g]	a
j	Cl	H	H	H	O	Ch–Eth	262—263(d)	[f]	94	$C_{15}H_{13}ON_4Cl$	223—224[f]	d
k	Cl	H	CH_3O	H	O	Ch–B	>300	B	90	$C_{16}H_{15}O_2N_4Cl$	[g]	c
l	Cl	H	Cl	H	O	Ch–H	>300	A	90	$C_{15}H_{12}ON_4Cl_2$	211—213	c
m	NO_2	H	H	H	O	[j]	266(d)	D	87	$C_{15}H_{13}O_3N_5$	244—245	e
n	CF_3	H	H	H	O	Ch–B	285—287(d)	B	98	$C_{16}H_{13}ON_4F_3$	224—225	f

a) Dic: dichloromethane, B: benzene, Ch: chloroform, H: *n*-hexane, Eth: ethyl ether
b) (d) shows decomposition.
c) See experimental section.
d) Satisfactory elementary analyses (±0.4% for C, H, N) were obtained.
e) Ref. to the starting materials I or II. a: ref. 5, b: ref. 6*e*, c: new compounds. For the preparation see experimental section, d: ref. 6*a*, e: ref. 6*c*, f: ref. 6*d*.
f) See ref. 1.
g) Not prepared.
h) The reaction was conducted with ice-cooling.
i) Crude amorphous powder obtained was used *per se* in the next reaction.
j) Analyzed without recrystn.

TABLE II. 4*H*-*s*-Triazolo[4,3-*a*][1,4]benzodiazepines (VII)

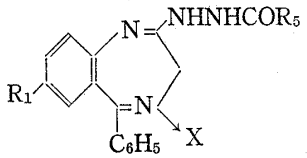


Compd.	R_1	R_2	R_3	R_4	R_5	X	Recrystn.[a] from	mp,[b] °C	Method[c]	Yield,[d] %	Formula[e]	Lit. mp,[f] °C
a-1	Cl	H	H	H	H		Ac–H	226—227	E[g]	87	$C_{16}H_{11}N_4Cl$	228—229
									J	82		
									K	81		
									L	72		
									M	40		
									N	77		
									O	76		

Compd.	R_1	R_2	R_3	R_4	R_5	X	Recrystn.[a] from	mp,[b] °C	Method[c]	Yield,[d] %	Formula[e]	Lit. mp,[f] °C
a-2[h]	Cl	H	H	H	CH_3		Ac–H	225.5—226.5	E	92	$C_{17}H_{13}N_4Cl$	228—228.5
									J	83		
									O	37		
									P	49		
									R	91		
									S	60		
a-3	Cl	H	H	H	C_2H_5		Ac	229—230	E	94	$C_{18}H_{15}N_4Cl$	231.5—232.5
									K	88		
a-4[i]	Cl	H	H	H	C_6H_{13}		Ac–H_2O	75— 78	J	87	$C_{22}H_{23}N_4Cl\cdot 2H_2O$	
a-5	Cl	H	H	H	C_6H_5		EAc	193—194	K	89	$C_{22}H_{15}N_4Cl$	193.5—194.5
a-6	Cl	H	H	H	$C_6H_5CH_2$		EAc	190—192	K	78	$C_{23}H_{17}N_4Cl$	192.5—193.5
b-1	Cl	H	CH_3O	H	H		EAc	216—217	E	67	$C_{17}H_{13}ON_4Cl$	
b-2	Cl	H	CH_3O	H	CH_3		Ch–Met	268—269	E	76	$C_{18}H_{15}ON_4Cl$	
c-1	Cl	Cl	H	H	H		Alc	259—259.5	E	96	$C_{16}H_{10}N_4Cl_2$	
c-2	Cl	Cl	H	H	CH_3		Ch–H	223—224	E	95	$C_{17}H_{12}N_4Cl_2$	223—225
d-1	Cl	H	H	$(CH_3)_2$-CHCH$_2$	H		B–H	140.5—141.5	E	86	$C_{20}H_{19}N_4Cl$	
e-1	H	H	H	H	H		Ac–H	201—202	E	81	$C_{16}H_{12}N_4$	
e-2	H	H	H	H	CH_3		Met–EAc	226—227	E	86	$C_{17}H_{14}N_4$	230—231
f-1	CH_3	H	H	H	H		EAc	177—178	E	75	$C_{17}H_{14}N_4$	
f-2	CH_3	H	H	H	CH_3		EAc	211—212	E	76	$C_{18}H_{16}N_4$	
g-1	CH_3O	H	H	H	H		EAc	209—210	E	69	$C_{17}H_{14}ON_4$	
g-2	CH_3O	H	H	H	CH_3		EAc	196—197	E	69	$C_{18}H_{16}ON_4$	
h-1	NO_2	H	H	H	H		THF	270—271	F	41[j]	$C_{16}H_{11}O_2N_5$	
h-2	NO_2	H	H	H	CH_3		Ac	229—230	F	30[j]	$C_{17}H_{13}O_2N_5$	231.5—232.5
									K	80		
i-1	CF_3	H	H	H	H		EAc	258—260	F	58	$C_{17}H_{11}N_4F_3$	
i-2[i]	CF_3	H	H	H	CH_3		Ac–H_2O	112—113	F	39	$C_{18}H_{13}N_4F_3\cdot 1/5H_2O$	135—137[k]
j-1	Cl	H	H	H	H	O	Ch–Met	267—268(d)	E[g]	97	$C_{16}H_{11}ON_4Cl$	
									L	78		
j-2	Cl	H	H	H	CH_3	O	Met–Eth	273—274(d)	E	94	$C_{17}H_{13}ON_4Cl$	
									J	72		
j-3	Cl	H	H	H	C_2H_5	O	Met	273—274(d)	E	92	$C_{18}H_{15}ON_4Cl$	
k-1	Cl	H	CH_3O	H	H	O	Ch–Met	285—286	E	87	$C_{17}H_{13}O_2N_4Cl$	
k-2	Cl	H	CH_3O	H	CH_3	O	Ch–Met	286—287	E	89	$C_{18}H_{15}O_2N_4Cl$	
l-2	Cl	H	Cl	H	CH_3	O	DMF–H_2O	302—303(d)	E	85	$C_{17}H_{12}ON_4Cl_2$	
m-1	NO_2	H	H	H	H	O	DMF–H_2O	274—275(d)	E	84	$C_{16}H_{11}O_3N_5$	
n-2	CF_3	H	H	H	CH_3	O	Met–H_2O	141—143(d)	E	64	$C_{18}H_{13}ON_4F_3$	

a) Ac: acetone, H: *n*-hexane, EAc: ethyl acetate, Ch: chloroform, Met: methanol, Alc: ethanol, B: benzene, THF: tetrahydrofuran, Eth: ethyl ether, DMF: N,N-dimethylformamide
b) (d) shows decomposition.
c) See experimental section.
d) Yields for method J—S are from a single experiment and no attempts were made to obtain optimum yields.
e) Satisfactory elementary analyses (±0.3% for C, H, N) were obtained.
f) Hester, *et al.* (see ref. 9).
g) See ref. 1.
h) This compound is also referred to as D-65MT (see ref. 4).
i) hygroscopic
j) Overall yield based on Ih.
k) Reported for anhydrous crystals.

Table III. 2-(2-Acylhydrazino)-3*H*-1,4-benzodiazepines (VIII)



Compd.	R_1	R_5	X	Recrystn.[a] from	mp (decomp.) °C	Method[b]	Yield %	Formula[c]
a-1	Cl	H		Met	161—162	I	54[d]	$C_{16}H_{13}ON_4Cl \cdot 1/2CH_3OH$
a-2	Cl	CH_3		Ch–Met	202—204[e]	G	81	$C_{17}H_{15}ON_4Cl$
						I	84	
a-3	Cl	C_2H_5		Ch–Met	186—187	G	94	$C_{18}H_{17}ON_4Cl$
a-4	Cl	C_6H_{13}		DMF–H_2O	224—225	H	93	$C_{22}H_{25}ON_4Cl$
						I[f]	97	
a-5	Cl	C_6H_5		Ch–Met	207—208	H	79	$C_{22}H_{17}ON_4Cl$
						I	89	
a-6	Cl	$C_6H_5CH_2$		DMF–H_2O	224—225	H	90	$C_{23}H_{19}ON_4Cl$
						I	90	
h-2	NO_2	CH_3		DMF–H_2O	184—185	I[g]	82	$C_{17}H_{15}O_3N_5 \cdot 1/2H_2O$
j-2	Cl	CH_3	O	DMF–H_2O	256—258	G[h]	71	$C_{17}H_{15}O_2N_4Cl$
						I	73	

a) Met: methanol, Ch: chloroform, DMF: N,N-dimethylformamide
b) See experimental section.
c) Satisfactory elementary analyses (±0.3% for C, H, N) were obtained.
d) In addition, compd. VIIa—l was obtained in 28% yield from the mother liquor.
e) lit.[9] mp 199—200° (decomp.)
f) Enanthylhydrazine (mp 82—84°) was prepd. by the reaction of ethyl enanthate with hydrazine hydrate.
g) This reaction was carried out in ethanol.
h) This reaction was carried out in THF in the presence of triethylamine as a base.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The structures of all compounds were supported by infrared (IR), ultraviolet (UV), and NMR spectra. When a compound was prepared by separate routes, the product was identified by a comparison of IR spectrum each other. Extracted solutions were dried over Na_2SO_4 and all solvents were evaporated on a rotary evaporator under water aspirator pressure.

6-Chloro-2-chloromethyl-4-(4-methoxyphenyl)quinazoline 3-Oxide (IVk)——2-Amino-5-chloro-4′-methoxybenzophenone oxime[10] (2.8 g) was treated with chloroacetyl chloride (1.5 ml) in AcOH (40 ml) and then with dry HCl gas at 70° for 3 hr. The mixture was allowed to stand at room temperature overnight and evaporated. The residue was partitioned between aq. $NaHCO_3$ and $CHCl_3$. After the usual treatment of the $CHCl_3$ layer the product was crystallized from ether to yield IVk (2.8 g, 84%). Recrystallization from EtOH gave yellowish needles, mp 151—152°. *Anal.* Calcd. for $C_{16}H_{12}O_2N_2Cl_2$: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.73; H, 3.56; N, 8.26.

2-Amino-7-chloro-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-Oxide (Ik)——A suspension of IVk (14.5 g) in saturated NH_3/MeOH (400 ml) was stirred for 4 hr, concentrated and diluted with H_2O. The precipitate was collected by filtration and washed with H_2O and acetone to yield Ik (7.3 g, 54%). Recrystallization from acetone gave colorless needles, mp 237—238°. *Anal.* Calcd. for $C_{16}H_{14}O_2N_3Cl$: C, 60.86; H, 4.47; N, 13.31. Found: C, 61.07; H, 4.48; N, 13.18.

2-Amino-7-chloro-5-(4-chlorophenyl)-3*H*-1,4-benzodiazepine 4-Oxide (Il)——A mixture of 6-chloro-2-chloromethyl-4-(4-chlorophenyl)quinazoline 3-oxide[6b] (IVl, 5.1 g) and saturated NH_3/MeOH (100 ml) was stirred for two days. The precipitated crystals were collected to yield Il (3.7 g, 72%). Additional Il (0.7 g, 14.5%) was recovered from the mother liquor. The combined crystals were recrystallized from dimethylformamide (DMF)–H_2O to give colorless needles, mp 252—254° (decomp.). *Anal.* Calcd. for $C_{15}H_{11}ON_3Cl_2$: C, 56.26; H, 3.46; N, 13.32. Found: C, 56.34; H, 3.22; N, 13.13.

10) This compound prepared by the usual method (see ref. 6*b*) is not reported and showed mp 158—162°.

(±)- And (+)-7-Chloro-1,3-dihydro-3-isobutyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Vd)——A mixture of 2-(2-amino-α-phenylbenzylideneamino)ethanol[5] (27.5 g), L-leucine ethyl ester hydrochloride (58.7 g) and 2-methylimidazole (24.6 g) was heated at 130° for 30 min. After cooling, the fused material was dissolved in EtOH (500 ml) and treated with 4N NaOH (150 ml) at room temperature for 2 hr. After acidification with AcOH the mixture was concentrated, diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with aq. $NaHCO_3$ and H_2O and dried. Evaporation of the solvent left an oil which was crystallized from EtOH to yield (±)-Vd (11 g, 34%), mp 205—208°. Recrystallization from EtOH gave yellowish prisms, mp 212.5—213.5°. $[\alpha]_D^{20}$ 0° (c=1.0, EtOH). *Anal.* Calcd. for $C_{19}H_{19}ON_2Cl$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.55; H, 5.92; N, 8.51.

The mother liquor was evaporated and the residue purified by column chromatography [silica gel 600 g, acetone–*n*-hexane (3: 7, v/v)] to obtain (+)-Vd (12.5 g, 39%). Recrystallization from *n*-hexane gave colorless prisms, mp 160—161°. $[\alpha]_D^{22}$ +157.6° (c=1.0, EtOH). *Anal.* Calcd. for $C_{19}H_{19}ON_2Cl$: C, 69.83; H, 5.86; N, 8.57. Found: C, 70.05; H, 5.84; N, 8.47.

(±)-7-Chloro-1,3-dihydro-3-isobutyl-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (IId)——Thiation of (±)-Vd (8.2 g) with P_2S_5 (11.1 g) in boiling dry pyridine (50 ml) for 2 hr followed by treatment in the usual manner[6e] gave IId (3.7 g, 43%). Recrystallization from EtOH afforded yellow prisms, mp 170—171.5°. *Anal.* Calcd. for $C_{19}H_{19}N_2ClS$: C, 66.56; H, 5.59; N, 8.17. Found: C, 66.34; H, 5.65; N, 7.91.

2-Hydrazino-3*H*-1,4-benzodiazepines (VI, Table I)——Some selected examples of the method for the preparation are as follows.

7-Chloro-2-hydrazino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine (VIb)——Method A: To a stirred mixture of Ib (3.0 g), MeOH (50 ml) and AcOH (0.6 ml) was added dropwise $N_2H_4 \cdot H_2O$ (1.5 ml). The mixture was stirred at room temperature for 30 min, poured into ice–water (100 ml) and extracted with $CHCl_3$. The organic extract was washed with H_2O, dried and evaporated. The residue was recrystallized from $CHCl_3$–benzene to give VIb as colorless crystals (2.5 g, 80%), mp 214—220°. *Anal.* Calcd. for $C_{16}H_{15}ON_4Cl$: C, 61.05; H, 4.80; N, 17.80. Found: C, 60.93; H, 4.67; N, 17.83.

2-Hydrazino-5-phenyl-7-trifluoromethyl-3*H*-1,4-benzodiazepine (VIi)——Method B: To a stirred mixture of Ii (9.1 g), EtOH (150 ml) and AcOH (3.6 ml) was added dropwise $N_2H_4 \cdot H_2O$ (4.5 ml). The mixture was stirred at room temperature for 30 min and the product was isolated in a similar manner to that described in method A. Recrystallization from $CHCl_3$–*n*-hexane gave a colorless crystalline powder (8.9 g, 94%), mp 133—135° (decomp.). *Anal.* Calcd. for $C_{16}H_{13}N_4F_3$: C, 60.37; H, 4.12; N, 17.60. Found: C, 60.05; H, 3.96; N, 17.40.

7-Chloro-5-(2-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (VIc)——Method C: To a stirred suspension of IIc[6e] (3.21 g) in MeOH (50 ml) was added $N_2H_4 \cdot H_2O$ (1.5 ml) and the mixture was stirred at room temperature for 30 min. The resulting solution was poured into ice–water and the product was isolated in a similar manner to that described in method A. Recrystallization from $CHCl_3$–*n*-hexane gave pale yellow crystals (3.15 g, 99%), mp 220—223° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}N_4Cl_2$: C, 56.44; H, 3.79; N, 17.55. Found: C, 56.73; H, 3.57; N, 17.23.

2-Hydrazino-7-nitro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (VIm)——Method D: A mixture of Im (9.0 g), $N_2H_4 \cdot H_2O$ (7.5 ml), EtOH (300 ml), and AcOH (5.4 ml) was heated on a water bath (95°) with vigorous shaking. As soon as a clear solution was obtained (*ca.* 5 min) the stirred solution was cooled with ice. After stirring was continued for 20 min, the precipitate was collected by filtration, washed with EtOH and ether, and dried to yield yellow crystals (8.1 g, 87%), mp 226° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_3N_5$: C, 57.87; H, 4.21; N, 22.50. Found: C, 57.98; H, 4.01; N, 22.26.

4*H*-*s*-Triazolo[4,3-*a*][1,4]benzodiazepines (VII, Table II)——Some examples of the method for the preparation are as follows.

8-Chloro-1-ethyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (VIIa—3)——Method E: To a stirred mixture of VIa (1.4 g), ethyl orthopropionate (4 ml) and EtOH (50 ml) was added dropwise conc. H_2SO_4 (0.5 ml) and the mixture was stirred at room temperature for 30 min. After neutralization with aq. $NaHCO_3$ the solvent was evaporated and the precipitated crystals were collected, and washed with H_2O and ether to give VIIa—3 (1.5 g, 94%). Recrystallization from acetone gave colorless prisms, mp 229—230°. *Anal.* Calcd. for $C_{18}H_{15}N_4Cl$: C, 66.97; H, 4.68; N, 17.36. Found: C, 67.18; H, 4.48; N, 17.53.

6-Phenyl-8-trifluoromethyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (VIIi—1)——Method F: To a stirred and cooled solution of VIi (3.2 g) in $CHCl_3$ (50 ml) was added in portions *p*-toluenesulfonic acid hydrate (7.6 g) at below 10°. The mixture was then stirred at room temperature for 2.5 hr, washed with aq. $NaHCO_3$ and H_2O, and dried. Evaporation followed by addition of ether gave crystals (1.9 g, 58%), mp 246—251°. Recrystallization from AcOEt afforded colorless plates, mp 258—260°. *Anal.* Calcd. for $C_{17}H_{11}N_4F_3$: C, 62.19; H, 3.38; N, 17.07. Found: C, 61.99; H, 3.46; N, 16.89.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine 5-Oxide (VIIj—2)——Method J: A suspension of 2-(2-acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (VIIIj—2, 343 mg) in pyridine (3 ml) was refluxed for 4 hr and the solvent was evaporated. The residue was recrystallized from MeOH to give colorless needles (233 mg, 72%), mp 272—274°.

8-Chloro-1,6-diphenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (VIIa—5)——Method K: 2-(2-Benzoylhydrazino)-6-chloro-5-phenyl-3*H*-1,4-benzodiazepine (VIIIa—5, 3.9 g) was heated at 215° under a water

aspirator pressure for about 15 min. The fused material was recrystallized from AcOEt to give colorless needles (3.3 g, 89%), mp 193—194°. *Anal.* Calcd. for $C_{22}H_{15}N_4Cl$: C, 71.25; H, 4.08; N, 15.11. Found: C, 71.11; H, 4.10; N, 14.98.

8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (VIIa—1)——Method L: A solution of VIa (284 mg) in 99% HCOOH (2 ml) was allowed to stand at room temperature overnight, after which it was concentrated and neutralized with aq. $NaHCO_3$. The product was isolated by extraction with $CHCl_3$ and recrystallized from acetone–*n*-hexane to give colorless plates (212 mg, 72%), mp 226—227°.

Method M: To a suspension of VIa (284 mg) in $HCONH_2$ (4 ml) was added conc. H_2SO_4 (0.1 ml) and the mixture was allowed to stand at room temperature for 6 hr then heated at 95° for 30 min. After dilution with H_2O followed by neutralization with $NaHCO_3$ the product was isolated and recrystallized to give colorless plates (117 mg, 40%), mp 224—226°.

Method N: To a stirred and cooled suspension of N,N'-carbonylbis(2-methylimidazole) (178 mg) in dry tetrahydrofuran (THF) (2.5 ml) was added dropwise a solution of 99% HCOOH (46 mg) in dry THF (2 ml) and the mixture was stirred for 30 min with cooling.[11] To this was then added dropwise a solution of VIa (284 mg) in dry THF (4 ml) and the mixture was stirred with cooling for 30 min then at room temperature for 30 min. The solvent was evaporated and the residue heated in boiling pyridine (1.5 ml) for 45 min. After evaporation of the pyridine the residue was partitioned between $CHCl_3$ and H_2O. The product was obtained from the $CHCl_3$ layer as crystals (227 mg, 77%). Recrystallization gave colorless plates of mp 227—228°.

Method O: A mixture of VIa (284 mg), formamidine hydrochloride (240 mg) and 2-methylimidazole (250 mg) was heated at 160° for 10 min. The fused material was partitioned between $CHCl_3$ and H_2O, and the product isolated from the organic phase was recrystallized to give colorless plates (222 mg, 76%), mp 226—227°.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (VIIa—2)——Method P: To a stirred suspension of VIa (284 mg) in Ac_2O (5 ml) was added conc. H_2SO_4 (0.1 ml) and the resulting solution was allowed to stand at room temperature overnight. The solution was poured into H_2O, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The product was isolated and recrystallized from acetone–*n*-hexane to give colorless needles (150 mg, 49%), mp 224—225°.

Method R: 2-[2-(*α*-Amino)ethylidenehydrazino]-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (IX, 350 mg) was heated to over 200°. When generation of ammonia ceased after about 10 min, the fused material was recrystallized to give colorless needles (300 mg, 90%), mp 225.5—226.5°.

Method S: To a stirred solution of VIa (1.4 g) in $CHCl_3$ (30 ml) was added ethyl acetimidate hydrochloride (1.2 g) and the turbid solution was stirred overnight. This was then washed with H_2O until the washings did not have a yellow color. From the $CHCl_3$ layer, VIIa—2 was isolated and recrystallized to give colorless needles (0.9 g, 60%), mp 225.5—226.5°.

The above washings were made alkaline with aq. $NaHCO_3$ and extracted with $CHCl_3$. From the extract compound (IX) was obtained as yellow crystals (0.3 g, 19%), mp 190—193° (decomp.).

2-(2-Acylhydrazino)-3*H*-1,4-benzodiazepines (VIII, Table III)——Some examples of the method for the preparation are as follows.

2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (VIIIa—2)——Method G: To a stirred solution of VIa (1.4 g) in $CHCl_3$ (30 ml) was added Ac_2O (0.47 ml) and the mixture was stirred for 1 hr. This was then washed with aq. $NaHCO_3$ and H_2O and dried. Evaporation of the solvent left crystals which were recrystallized from $CHCl_3$–MeOH to give colorless crystals (1.3 g, 81%), mp 202—204° (decomp.). *Anal.* Calcd. for $C_{17}H_{15}ON_4Cl$: C, 62.48; H, 4.63: N, 17.15. Found: C, 62.38; H, 4.44; N, 17.23.

2-(2-Benzoylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (VIIIa—5)——Method H: To a stirred and ice-cooled solution of VIa (1.4 g) in dry THF (25 ml) was added dropwise benzoyl chloride (0.62 ml). The mixture was then stirred at room temperature for 2 hr and diluted with aq. $NaHCO_3$. The precipitate was collected and recrystallized from $CHCl_3$–MeOH to give colorless needles (1.5 g, 79%), mp 207—208° (decomp.). *Anal.* Calcd. for $C_{22}H_{17}ON_4Cl$: C, 67.95; H, 4.41; N, 14.41. Found: C, 67.87; H, 4.20; N, 14.49.

2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (VIIIj—2)——Method I: A mixture of Ij (286 mg), monoacetylhydrazine (296 mg), MeOH (5 ml) and AcOH (0.12 ml) was stirred for 6 hr and the precipitate was collected by filtration to give colorless crystals (250 mg, 73%). Recrystallization from DMF–H_2O afforded fine needles of mp 256—258° (decomp.).

2-[2-(*α*-Amino)ethylidenehydrazino]-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (IX)——Method Q: To a stirred solution of VIa (1.4 g) and 2-methylimidazole (0.8 g) in $CHCl_3$ (30 ml) was added ethyl acetimidate hydrochloride (0.9 g) and the mixture was stirred for 15 min. This was then washed with H_2O, dried and evaporated. The residue was recrystallized from acetone to give yellowish needles (1.4 g, 88%), mp 199—200° (decomp.). *Anal.* Calcd. for $C_{17}H_{16}N_5Cl$: C, 62.67; H, 4.95; N, 21.50. Found: C, 62.64; H, 4.84; N, 21.32.

11) For the preparation of N-formylimidazole see H.A. Staab and B. Polenski, *Ann. Chem.*, **655**, 95 (1962).

Method T: A mixture of VIa (284 mg), 2-methylimidazole (250 mg), acetamidine hydrochloride (280 mg) and $CHCl_3$ (10 ml) was stirred for 24 hr, washed with H_2O and dried. Evaporation of the solvent left 260 mg of crystals which were dissolved in MeOH and filtered to remove insoluble material. After evaporation of the MeOH from the filtrate, the residue was recrystallized from acetone to give yellow needles (130 mg, 40%), mp 199—200° (decomp.).

7-Chloro-4,5-dihydro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (XII)——By analogous procedure to Method A, XII was obtained from 2-amino-7-chloro-4,5-dihydro-5-phenyl-3*H*-1,4-benzodiazepine (XI)[12] in 70% yield. Recrystallization from benzene gave colorless needles, mp 223—224°. This was chracterized after recrystallization from acetone as its acetonide, colorless needles, mp 183—184° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}N_4Cl$: C, 66.15; H, 5.86; N, 17.14. Found: C, 66.48; H, 5.75; N, 17.32.

8-Chloro-5,6-dihydro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (XIII)——By analogous procedure to method E, XIII was obtained from XII in 65% yield. Recrystallization from AcOEt–iso-Pr_2O gave colorless crystals of mp 168—169°. *Anal.* Calcd. for $C_{16}H_{13}N_4Cl$: C, 64.75; H, 4.42; N, 18.88. Found: C, 64.42; H, 4.45; N, 18.58.

Conversion of XIII to VIIa—1——A mixture of XIII (148 mg), CCl_4 (5 ml) and N-bromosuccinimide (98 mg) was refluxed for 40 min and the solvent was evaporated. The residue was treated with 1N NaOMe/MeOH (0.6 ml) under reflux for 20 min and diluted with H_2O. The mixture was extracted with $CHCl_3$ and the extract was washed with H_2O and dried. After removal of the solvent the residue was recrystallized from AcOEt to give VIIa—1 as colorless plates (28 mg, 19%), mp 225—226°.

Acknowledgement We are very grateful to Dr. S. Tatsuoka, Director of this Division, for his encouragement throughout this work. Thanks are also due to the members of the Analytical Section of these Laboratories for microanalyses and UV and NMR spectral measurements.

12) Part IV of this Series: K. Meguro, H. Natsugari, H. Tawada, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2366 (1973).