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Neurotropic and Psychotropic Agents. IV.[1] Synthesis and Pharmacological Properties of 7-Chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine and Related Compounds[2]

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The synthesis and pharmacological properties of 7-chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine (III-1) and related compounds are described. Compound III-1 was prepared from the thiolactam (II-1) by treatment with 2-dimethylaminoethyl chloride in the presence of base in aqueous methanol and 7-chloro-5-(2-chlorophenyl)-2-methoxy-3*H*-1,4-benzodiazepine (IV) was obtained as a by-product. The latter (IV) was hydrolyzed in acid medium to give methyl (*E*)-[2-amino-5-chloro-α-(2-chlorophenyl)benzylidene]aminoacetate (*syn*-form) (XIX), which was converted into the 1,4-benzodiazepine (I-1) by further acid treatment. Compound XIX isomerized to the corresponding *anti*-form (XXII) on heating. Most of the compounds prepared had an effect similar to that of diazepam in causing taming and anticonvulsant effects in mice.

Keywords——2-substituted thio-3*H*-1,4-benzodiazepine; 2-alkoxy-3*H*-1,4-benzodiazepine; 1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione; hydrolysis of lactam ether; *syn-anti*-isomer of ketimine; pharmacological test; taming effect in mice; anticonvulsanr effect in mice

In the previous paper,[1] we described the synthesis of 8-chloro-10-(2-dimethylaminoethoxy)dibenzo[*b*,*f*]thiepin (Zotepine) and related compounds which have desirable properties as central nervous system (CNS) depressants.

As a part of our continuing studies of neurotropic and psychotropic agents, we were interested in 1,4-benzodiazepine derivatives with an dialkylaminoalkylthio group at the 2-position. In this report we describe the synthesis of 2-dialkylaminoalkylthio-3*H*-1,4-benzodiazepines (III), their CNS effects (anticonvulsant and taming activities), and their reactivities with electrophiles and nucleophiles.

Synthesis of 2-(2-Dialkylaminoalkylthio)-3*H*-1,4-benzodiazepines (III) and Related Compounds

A number of compounds (III) were prepared from thiolactams (II) according to the method shown in Chart 1. Thiation of the lactams (I) was achieved by treatment with phosphorus pentasulfide (P_2S_5) in a mixed solvent of chloroform and pyridine at 80°C to give the thiolactams (II).[3] The compounds III were prepared by alkylating the thiolactams (II) with alkyl

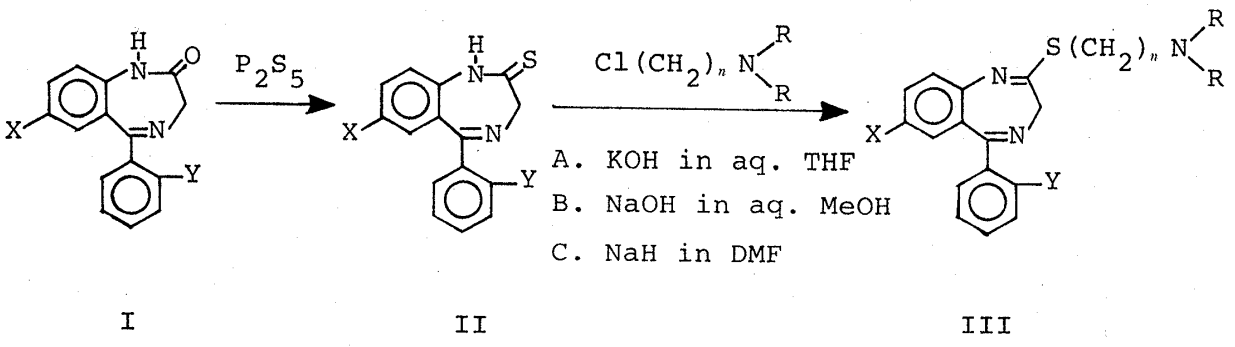


Chart 1

halides in the presence of potassium hydroxide in aqueous tetrahydrofuran (THF) (Method A), sodium hydroxide in aqueous methanol (Method B), or sodium hydride in *N*,*N*-dimethylformamide (DMF) (Method C) (Table I). Of these three methods, method A was especially useful for the preparation of III. The reaction of 1,4-benzodiazepine-2-thione (II-1) with 2-dimethylaminoethyl chloride (DMEC) hydrochloride (Method B) afforded 2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine (III-1, 48.0%) and 2-methoxy-1,4-benzodiazepine (IV) was also isolated in 16.1% yield. The structure of IV was confirmed by elemental analysis and spectral data.

In attempts to prepare 2-(2-bromoethylthio)-3*H*-1,4-benzodiazepine (VI), which should be useful as an intermediate for the preparation of III, the thiolactam (II-1) was allowed to react with 1,2-dibromoethane (Method C). The expected product (VI) was not obtained, but undesired products [V and (VII or VIII)][4] were isolated.

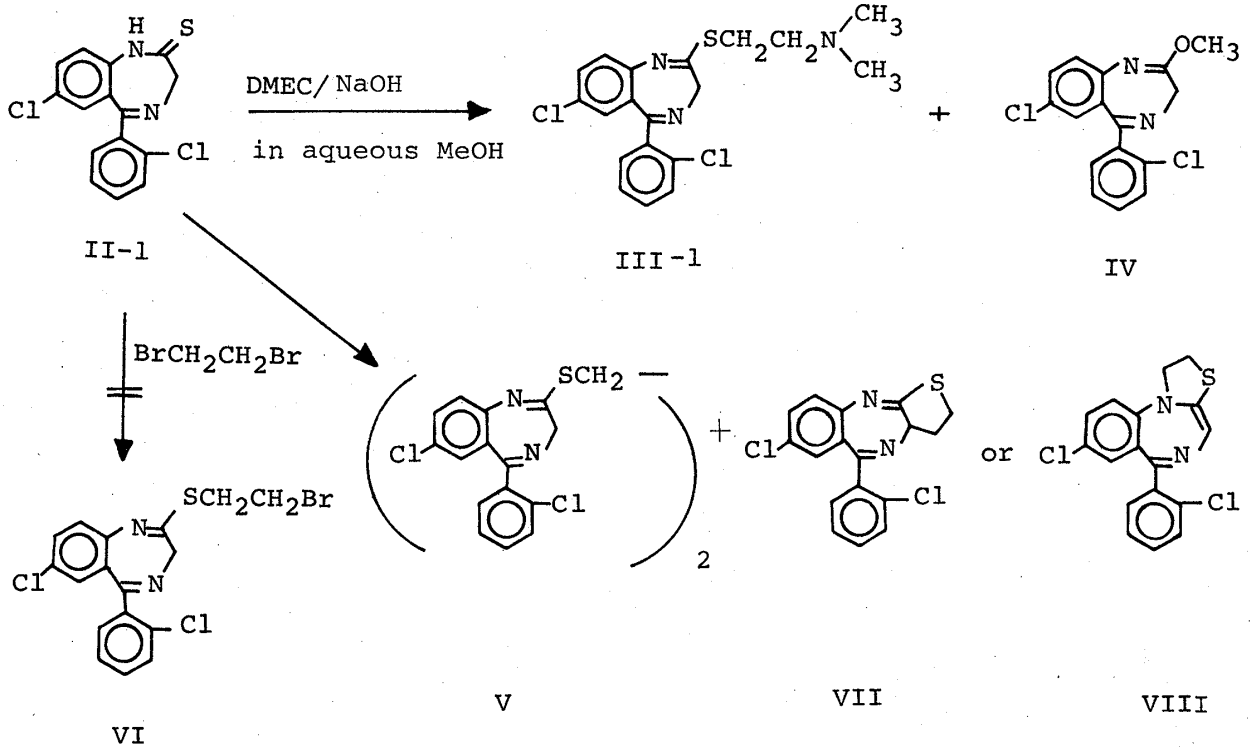


Chart 2

1-(2-Dimethylaminoethyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (X), an isomer of III-1, was prepared by the reaction of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (I-1) with freshly distilled DMEC in the presence of sodium hydride in DMF, followed by thiation of the resulting N^1-(2-dimethylaminoethyl) derivative (IX)[5] with P_2S_5 in refluxing pyridine.

4,5-Dihydro-3*H*-1,4-benzodiazepines were prepared as shown in Chart 4. First, reduction of II-1 was attempted. Although it was stable to catalytic hydrogenation[6] and lithium aluminum hydride ($LiAlH_4$) reduction,[7] II-1 was reduced to 1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine-2-thione (XI) in 31.1% yield by sodium cyanoborohydride ($NaBH_3CN$) in methanol under slightly acidic conditions[8] with recovery of some starting material (25%). However, XI was recovered unchanged on reaction with DMEC·HCl (Method A).

The N^4-methyl derivative (XVI) was prepared as follows. Methylation of I-1 with methyl iodide in refluxing acetonitrile gave the methiodide (XIII) in quantitative yield. It was smoothly reduced by sodium borohydride to the tetrahydro compound (XIV) in 59.5% yield.[9] Thiation of compound XIV with P_2S_5 gave the thiolactam XV, which was alkylated to the 2-(2-dimethylaminoethylthio) derivative (XVI) by DMEC·HCl treatment (Method A) in 79% yield.

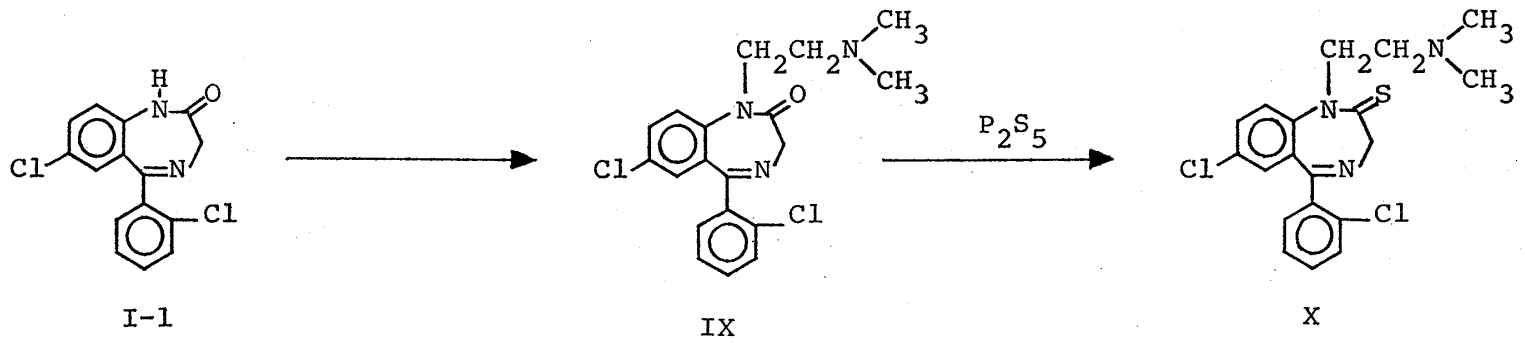


Chart 3

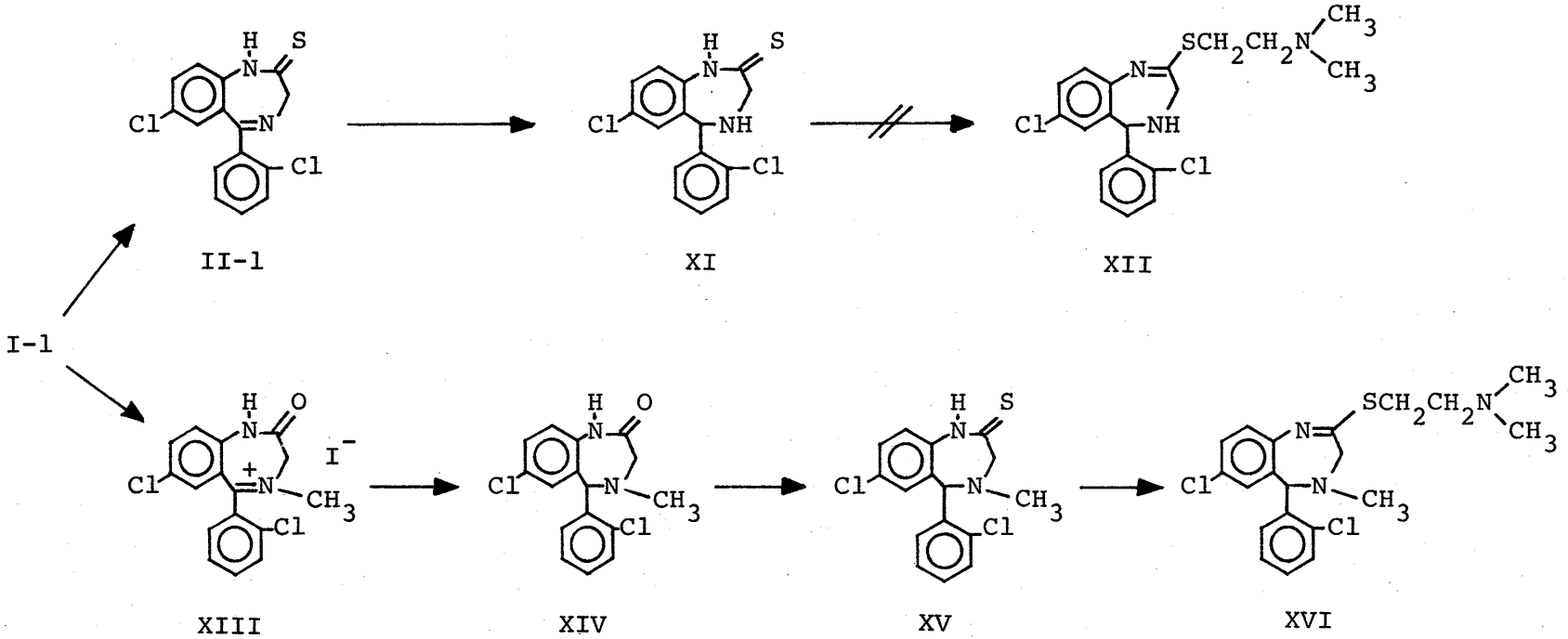


Chart 4

Reaction of Compounds III-1 and III-27 with Electrophiles and Nucleophiles

Compound III-1 was readily hydrolyzed by acid to give the lactam (I-1) in quantitative yield. While III-1 was stable to sodium hydroxide in aqueous THF, alkoxide anion caused solvolysis of the thioether group of III-1. Thus, treatment of III-1 with sodium hydroxide in aqueous methanol at 50°C gave IV and I-1 in 40% and 39% yields, respectively (Table III).

Under anhydrous conditions, the treatment of III-27[10] with sodium alkoxide in alcohol gave the corresponding 2-alkoxy-3*H*-1,4-benzodiazepine (IV, XVII, or XVIII) in high yield.

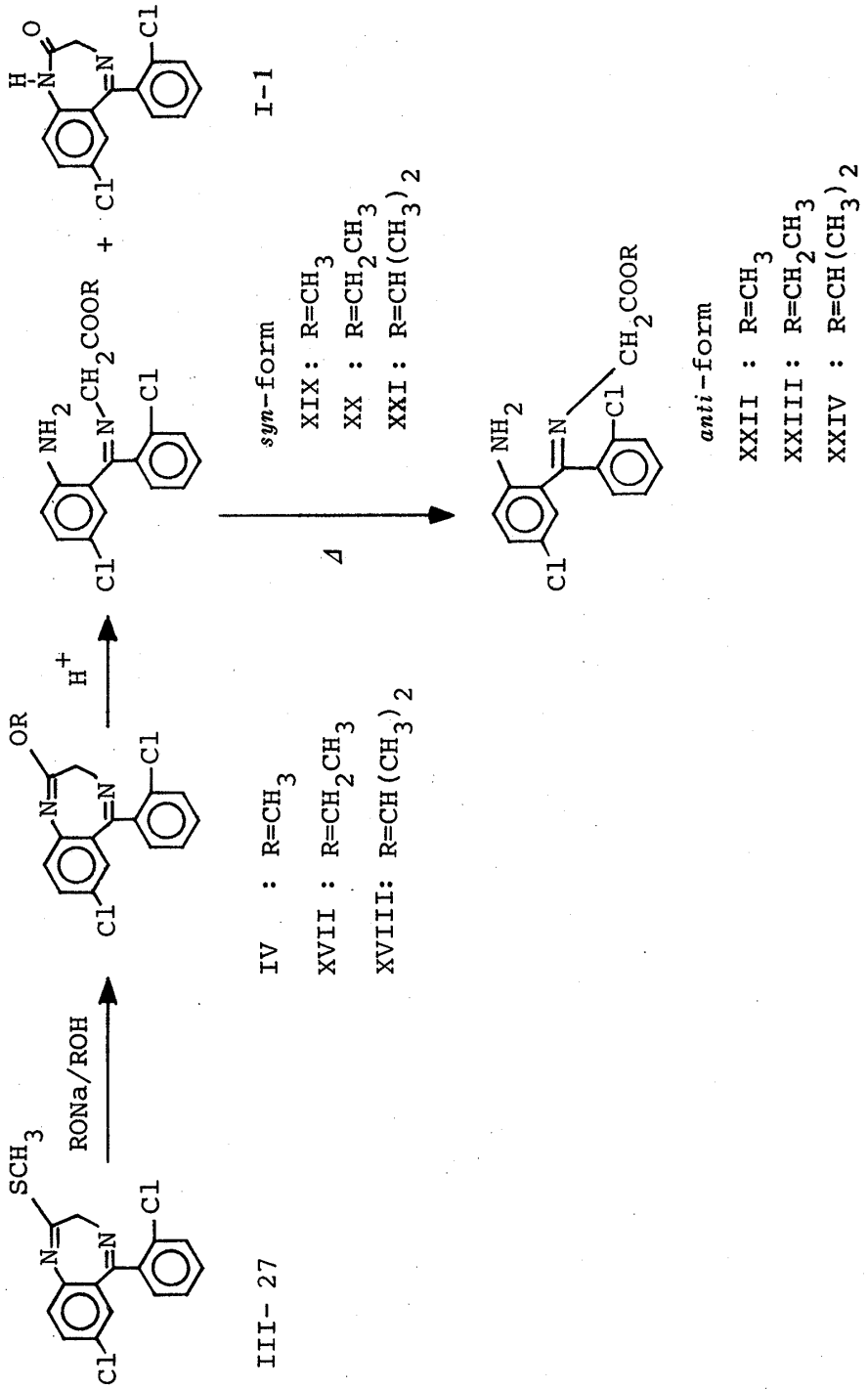
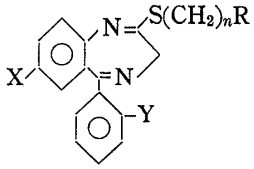
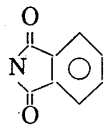


Chart 5

TABLE I. 2-Substituted Thio-3*H*-1,4-benzodiazepines (III)



	X	Y	*n*	R	Salt[a]	mp (°C) (Solvent)[b]	Method[c]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
III- 1	Cl	Cl	2	$N(CH_3)_2$	F	66—72 (Alc+H)			$C_{19}H_{19}Cl_2N_3S$	58.16 (58.36	4.88 4.84	10.71 10.52)
III- 2	Cl	Cl	2	$N(CH_3)_2$	MA	140—142 (EA)	A B C	67.7 48.0 62.2	$C_{19}H_{19}Cl_2N_3S\cdot C_4H_4O_4$	54.33 (54.23	4.56 4.57	8.27 8.27)
III- 3	Cl	Cl	2	$N(CH_3)_2$	FA	158—161 (IPA)	A	72.0	$C_{19}H_{19}Cl_2N_3S\cdot C_4H_4O_4$	54.33 (54.46	4.56 4.51	8.27 8.29)
III- 4	Cl	Cl	2	$N(Et)_2$	FA	158—160 (MIBK)	A	43.9	$C_{21}H_{23}Cl_2N_3S\cdot C_4H_4O_4$	55.97 (55.67	5.07 4.77	7.83 7.75)
III- 5	Cl	Cl	2	$N(Pr\text{-}iso)_2$	FA	156—158 (IPA)	A	55.8	$C_{23}H_{27}Cl_2N_3S\cdot C_4H_4O_4$	57.44 (57.33	5.54 5.47	7.44 7.48)
III- 6	Cl	Cl	2	$N(C_4H_9\text{-}n)_2$	FA	169—171 (MIBK)	A	58.2	$C_{25}H_{31}Cl_2N_3S\cdot C_4H_4O_4$	58.78 (58.72	5.95 5.96	7.09 6.92)
III- 7	Cl	Cl	2	$N(C_6H_{13}\text{-}n)_2$	FA	113—115 (E)	A	58.8	$C_{29}H_{39}Cl_2N_3S\cdot C_4H_4O_4$	61.10 (61.04	6.68 6.67	6.48 6.41)
III- 8	Cl	Cl	2		FA	184—188 (IPA)	A	55.0	$C_{21}H_{21}Cl_2N_3S\cdot C_4H_4O_4$	56.18 (56.15	4.72 4.71	7.86 7.90)
III- 9	Cl	Cl	2		FA	198—199 (M)	A	67.0	$C_{22}H_{23}Cl_2N_3S\cdot C_4H_4O_4$	56.93 (56.93	4.96 5.10	7.66 7.63)
III-10	Cl	Cl	2		FA	191—193 (Alc)	A	53.5	$C_{21}H_{21}Cl_2N_3OS\cdot C_4H_4O_4$	54.55 (54.40	4.58 4.39	7.63 7.65)
III-11	Cl	Cl	2		FA	170—171 (IPA)	B	66.4	$C_{23}H_{25}Cl_2N_3S\cdot C_4H_4O_4$	57.65 (57.76	5.20 5.31	7.47 7.40)
III-12	Cl	Cl	2[d]	$N(CH_3)_2$	FA	178—180 (IPA+E)	A	34.6	$C_{20}H_{21}Cl_2N_3S\cdot C_4H_4O_4$	55.17 (54.97	4.82 4.77	8.04 7.96)
III-13	Cl	Cl	3	$N(CH_3)_2$	FA	154—156 (IPA)	A C	71.0 41.0	$C_{20}H_{21}Cl_2N_3S\cdot C_4H_4O_4$	55.17 (54.99	4.82 4.68	8.04 7.93)
III-14	Cl	Cl	3		FA	148—151 (IPA)	A	54.8	$C_{22}H_{23}Cl_2N_3S\cdot C_4H_4O_4$	56.93 (56.90	4.96 4.70	7.66 7.92)
III-15	Cl	Cl	3		FA	110—112 (THF+E)	A	76.8	$C_{23}H_{25}Cl_2N_3S\cdot C_4H_4O_4$	57.65 (58.24	5.20 5.76	7.47 6.76)
III-16	Cl	Cl	3		FA	169—171 (IPA)	A	59.5	$C_{22}H_{23}Cl_2N_3OS\cdot C_4H_4O_4$	55.32 (55.08	4.82 4.79	7.45 7.28)
III-17	Cl	Cl	3		FA	164—167 (THF+E)	A	39.1	$C_{24}H_{27}Cl_2N_3S\cdot C_4H_4O_4$	58.33 (58.40	5.42 5.44	7.29 7.29)
III-18	Cl	Cl	6	$N(CH_3)_2$	MA	108—110 (EA)	A	64.9	$C_{23}H_{27}Cl_2N_3S\cdot C_4H_4O_4$	57.44 (57.42	5.54 5.57	7.44 7.37)
III-19	Cl	Cl	10	$N(CH_3)_2$	FA	53—58 (EA+E)	A	48.0	$C_{27}H_{35}Cl_2N_3S\cdot C_4H_4O_4$	59.99 (59.76	6.33 6.59	6.77 6.48)
III-20	Cl	F	2	$N(CH_3)_2$	FA	164—166 (IPA)	A	68.0	$C_{19}H_{19}ClFN_3S\cdot C_4H_4O_4$	56.15 (56.30	4.71 4.77	8.54 8.58)
III-21	Br	F	2	$N(CH_3)_2$	F	105—108 (E+H)	A	76.4	$C_{19}H_{19}BrFN_3S$	54.29 (54.12	4.56 4.65	10.00 9.33)
III-22	NO_2	Cl	2	$N(CH_3)_2$	MA	196—198 (M)	A	22.7	$C_{19}H_{19}ClN_4O_2S\cdot C_4H_4O_4$	53.23 (53.22	4.47 4.37	10.79 10.82)
III-23	Cl	H	2	$N(CH_3)_2$	FA	197—199 (M)	A	55.0	$C_{19}H_{20}ClN_3S\cdot C_4H_4O_4$	58.28 (58.59	5.10 5.13	8.87 9.01)
III-24	CF_3	H	2		FA	132—134 (Ac+E)	A	38.5	$C_{23}H_{24}F_3N_3S\cdot C_4H_4O_4$	59.22 (58.84	5.15 5.30	7.67 7.64)
III-25	NO_2	H	2	$N(CH_3)_2$	MA	131—134 (Alc+E)	C	48.5	$C_{19}H_{20}N_4O_2S\cdot C_4H_4O_4$	57.01 (56.97	4.99 4.88	11.56 11.62)

	X	Y	n	R	Salt[a]	mp (°C) (Solvent)[b]	Method[c]	Yeild (%)	Formula	Analysis (%) Calcd (Found) C	H	N
III-26	Cl	Cl	3		F	143—146 (MIBK+E)	A	77.0	$C_{26}H_{19}Cl_2N_3O_2S$	61.42 (61.72	3.77 3.61	8.27 8.21)
III-27	Cl	Cl	1	H	F	123—125[e] (Alc)	A	84.0	$C_{16}H_{12}Cl_2N_2S$	57.32 (57.24	3.61 3.57	8.36 8.32)
III-28	Cl	Cl	2	H	F	114—118 (Alc)	A	73.5	$C_{17}H_{14}Cl_2N_2S$	58.54 (58.50	4.04 3.98	8.02 8.13)
III-29	Cl	Cl	3	H	F	71—72 (H)	A	75.5	$C_{18}H_{16}Cl_2N_2S$	59.50 (59.45	4.44 4.30	7.71 7.70)
III-30	Cl	Cl	4	H	F	Oil	A	80.2	$C_{19}H_{18}Cl_2N_2S$	60.47 (60.24	4.81 4.82	7.42 7.28)
III-31	Cl	Cl	2	OEt	F	Oil	A	37.0	$C_{19}H_{18}Cl_2N_2OS$		——	
III-32	Cl	Cl	2	OCO- 	F	123—125 (B+H)	C	84.0	$C_{24}H_{18}Cl_2N_2O_2S$	61.41 (61.90	3.87 3.86	5.97 5.77)
III-33	Cl	Cl	2	SEt	F	76—77 (H)	A	63.5	$C_{19}H_{18}Cl_2N_2S_2$	55.74 (55.55	4.43 4.16	6.84 6.96)
III-34	Cl	Cl	1	COOH	F	191 (dec.) (E)	A	17.2	$C_{17}H_{12}Cl_2N_2O_2S$	53.83 (53.74	3.19 3.24	7.39 7.61)
III-35	Cl	Cl	1	$CONH_2$	F	73—75 (B)	C	85.0	$C_{17}H_{13}Cl_2N_3OS$	53.97 (53.89	3.46 3.40	11.11 10.82)
III-36	NO_2	F	2	$N(CH_3)_2$	FA	153—157 (Alc)	A	73.2	$C_{19}H_{19}FN_4O_2S$ $C_4H_4O_4$	54.97 (55.15	4.61 4.68	11.15 11.06)
III-37	Cl	OCH_3	2	$N(CH_3)_2$	MA	142—145 (Ac+EA)	A	70.0	$C_{20}H_{22}ClN_3OS \cdot C_4H_4O_4$	57.19 (56.82	5.20 5.05	8.34 8.29)

a) F, free base; FA, fumarate; MA, maleate.
b) B, benzene; Alc, ethanol; H, *n*-hexane; EA, ethyl acetate; IPA, isopropanol; MIBK, methyl isobutyl ketone; E, ether; M, methanol; THF, tetrahydrofuran; Ac, acetone.
c) A, KOH in aq. THF; B, NaOH in aq. MeOH; C, NaH in DMF.
d) $-SCH(CH_3)CH_2R$.
e) lit.[10] mp 118—120°C.

These products were hydrolyzed on mild acid treatment to the (2-amino-α-phenylbenzylidene)-aminoacetate derivatives with *syn*-configuration (Table IV). The *syn*-compounds were cyclized to the lactam (I-1) on further acid treatment, and isomerized quantitatively to the compounds with *anti*-configuration, on heating at 150°C. In contrast to the *syn*-compounds, the *anti*-compounds were not converted into the lactam (I-1) by acid treatment but were recovered unchanged.

α-Phenylbenzylideneaminoacetate derivatives obtained here were characterized on the basis of elemental analysis and spectral data and by comparison of their spectral data with those of ketimines described in the literature.[12b,c,13]

The above method therefore provides a useful route for the selective preparation of *syn*- or *anti*-(2-amino-α-phenylbenzylidene)aminoacetates.[11] The other methods hitherto reported always gave a mixture of both stereisomers.[12]

Pharmacological Results

All of the compounds prepared here were screened for usual central nervous system effects, anticonvulsant and taming activities, in laboratory animals according to the produres described in the literature.[14] The results are summarized in Table II together with those for reference compounds. Most of the substituted 1,4-benzodiazepine derivatives described in the present report had an effect similar to that of diazepam in causing taming and anticonvulsant effects in mice. Compounds (III-2, III-21, and III-22) having a 2-fluorophenyl or 2-chlorophenyl

substituent in the 5-position were generally more potent than those (III-23 and III-25) having a phenyl group in the 5-position, as described in the literature.[15] Compound V showed no pronounced activity.

Of the α-phenylbenzylideneaminoacetate derivatives, the *syn*-form XIX was comparable in potency to III-2, while the *anti*-form XXII was found to be inactive at the dose tested 10 mg/kg, *p.o.*). This may be explained as resulting from the conversion of the *syn*-form XIX into the lactam I-1 in the gastrointestinal tract.

Table II. Pharmacological Properties of 2-Substituted Thio-1,4-benzodiazepines and Related Compounds in Mice

Compound	Taming activity Anti-fighting ED_{50} (mg/kg, *p.o.*)	Anticonvulsant activity Anti-metrazole ED_{50} (mg/kg, *p.o.*)	Compound	Taming activity Anti-fighting ED_{50} (mg/kg, *p.o.*)	Anticonvulsant activity Anti-metrazole ED_{50} (mg/kg, *p.o.*)
III- 2	0.66	1.60	III-25	5.61	5.10
III- 3	0.92	1.64	III-26	*a*)	*a*)
III- 4	2.80	2.25	III-28	2.96	20.8
III- 5	0.99	3.29	III-31	1.18	3.42
III- 6	0.37	4.71	III-32	91.3	96.5
III- 7	0.82	8.00	III-33	19.7	13.6
III- 8	1.14	0.79	III-34	0.74	3.67
III- 9	1.01	4.58	III-35	1.59	1.27
III-10	1.24	1.00	I-1	0.14	0.28
III-11	1.58	1.27	V	*a*)	*a*)
III-12	0.31	1.75	X	5.33	12.29
III-13	0.43	0.93	XVI	9.57	52.71
III-18	0.16	2.08	XIX	0.79	0.71
III-19	0.54	3.09	XXII	*b*)	*b*)
III-21	0.38	0.90	Chlordiazepoxide	0.57	5.22
III-22	0.24	1.47	Diazepam	0.23	1.17
III-23	2.59	6.84	Nitrazepam	0.06	0.73

a) Ineffective at a dose of 500 mg/kg.
b) Ineffective at a dose of 10 mg/kg.

Experimental[16]

Commercial chemicals were used without further purification. 1,4-Benzodiazepin-2-ones (I) and 1,4-benzodiazepine-2-thiones (II) used in the present work were prepared by the methods described in the literature.[3,6b,13a,17]

7-Chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine (III-1) and Its Maleate (III-2)——Method A: DMEC·HCl (16.9 g) was added to a mixture of II-1[3] (25 g), 10% KOH (130 ml), and THF (17 ml) at room temperature. The mixture was stirred for 1.5 h, diluted with brine and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give an oily product, which was converted in a usual way into the corresponding maleate (III-2, 26.8 g). Infrared (IR) ν_{max}^{Nujol} cm^{-1}: 2400, 1700, 1600, 1580. ^{1}H-nuclear magnetic resonance (NMR) ($CDCl_3$) δ: 2.85 (6H, s, $N(CH_3)_2$), 3.37 (4H, s, S–CH_2–CH_2–N), 4.20 (2H, s, C_3–CH_2–), 6.27 (2H, s, $\rangle C{=}C\langle$), 7.0—7.5 (7H, m, Ar–H).

Method B: A mixture of II-1 (2.5 g), DMEC·HCl (1.7 g), 10% NaOH (10 ml), and MeOH (10 ml) was stirred at room temperature for 2.5 h. The resulting oil obtained on work-up as above was chromatographed in benzene over alumina. The first eluate gave 2-methoxy-3*H*-1,4-benzodiazepine (IV, 0.4 g, 16.1%) as colorless prisms, mp 76—80°C (from *n*-hexane). *Anal.* Calcd for $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79; N, 8.78. Found: C, 60.25; H, 3.75; N, 8.67. IR ν_{max}^{Nujol} cm^{-1}: 1635, 1605, 1590. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s, OCH_3), 4.13 (2H, s, –CH_2–), 7.0—7.6 (7H, m, Ar–H). The subsequent eluate gave III-1 as an oily product, which was converted into the maleate (III-2, 1.90 g).

Method C: A 50% NaH dispersion in mineral oil (1.2 g) was added in small portions to a solution of II-1 (6.4 g) in dry DMF (50 ml) with stirring under ice-cooling. The mixture was stirred for 20 min at room temperature and then allowed to react with freshly distilled DMEC (3.3 g) for 1 h at room temperature.

The resulting oil obtained on work-up as described in method A was chromatographed in benzene over alumina to give the maleate (III-2, 6.3 g).

The compound (III-2) obtained by methods B and C was identical with the authentic sample prepared by method A.

The compounds (III) prepared by these methods are listed in Table I.

1,2-Bis[[7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]thio]ethane (V) and (VII or VIII)——II-1 (25.6 g) was allowed to react with 1,2-dibromoethane (44.8 g) in the presence of a 50% NaH dispersion in mineral oil (4.4 g) in DMF for 5 h at room temperature. The crude product obtained on work-up as described in method A was chromatographed in benzene over alumina. The first eluate gave VII (or VIII) (1.2 g, 4.3%), mp 231—234°C (from iso-PrOH). *Anal.* Calcd for $C_{17}H_{12}Cl_2N_2S$: C, 58.80; H, 3.48; N, 8.07; Cl, 20.42; S, 9.23. Found: C, 58.63; H, 3.24; N, 7.98; Cl, 20.50; S, 9.11. IR ν_{max}^{Nujol} cm^{-1}: 1625, 1600, 1565. The subsequent eluate gave V (3.0 g, 11.3%) as colorless prisms, mp 173—175°C (from EtOH). *Anal.* Calcd for $C_{32}H_{22}Cl_4N_4S_2$: C, 57.49; H, 3.32; N, 8.38. Found: C, 57.54; H, 3.17; N, 8.23. IR ν_{max}^{Nujol} cm^{-1}: 1600, 1575. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (4H, s, S–CH_2–CH_2–S), 4.25 (4H, s, C_3–CH_2–×2), 7.0—7.6 (14H, m, Ar–H).

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-1-(2-dimethylaminoethyl)-2*H*-1,4-benzodiazepine-2-thione (X)——P_2S_5 (2.95 g) was added to a solution of IX[5] (5.0 g) in dry pyridine (50 ml). The mixture was heated for 4 h under reflux, cooled, then poured into H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give an oil, which was chromatographed in AcOEt over silica gel to give X (3.5 g, 67.1%), mp 128—130°C (from EtOH). *Anal.* Calcd for $C_{19}H_{19}Cl_2N_3S$: C, 58.16; H, 4.88; N, 10.71. Found: C, 57.91; H, 4.71; N, 10.63. IR ν_{max}^{Nujol} cm^{-1}: 1605, 1595, 1560. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (6H, s, $N(CH_3)_2$), 2.70 (2H, m, –CH_2–N<), 4.16 and 5.44 (each 1H, d, J=12 Hz, C_3–CH_2–), 4.20 and 4.80 (each 1H, m, N^1–CH_2–), 7.0—7.8 (7H, m, Ar–H).

7-Chloro-5-(2-chlorophenyl)-2,3-dihydro-4-methyl-2-oxo-1*H*-1,4-benzodiazepinium Iodide (XIII)——A mixture of I-1[17] (15.3 g) and CH_3I (10 ml) in dry CH_3CN (100 ml) was stirred at 60°C for 4 h. The reaction mixture was concentrated *in vacuo* to give XIII (20.8 g, 92.8%), mp 198—200°C (dec.) (from CH_3CN). *Anal.* Calcd for $C_{16}H_{13}Cl_2IN_2O$: C, 42.98; H, 2.93; N, 6.27. Found: C, 42.76; H, 3.02; N, 6.10. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1640, 1620, 1590, 1560. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (3H, s, N^4–CH_3), 4.73 and 4.83 (each 1H, d, J=12 Hz, C_3–CH_2–), 7.1—8.1 (7H, m, Ar–H), 12.06 (1H, bs, –NHCO–).

7-Chloro-5-(2-chlorophenyl)-4-methyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (XIV)——$NaBH_4$ (4.5 g) was added in small portions to a chilled suspension of XIII (20.6 g) in EtOH (400 ml) over 30 min with stirring. The mixture was allowed to warm up to room temperature, stirred for 4 h, concentrated *in vacuo* and then diluted with H_2O. The resulting precipitate was collected, washed with H_2O, and dried to give XIV (8.8 g, 59.5%), mp 232—235°C (from EtOH–acetone). *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2O$: C, 59.83; H, 4.39; N, 8.72. Found: C, 59.92; H, 4.22; N, 8.65. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1590. ^{1}H-NMR (DMSO-d_6) δ: 2.36 (3H, s, N^4–CH_3), 3.10 and 3.42 (each 1H, d, J=14 Hz, C_3–CH_2–), 4.71 (1H, s, C_5–CH<), 6.4—7.8 (7H, m, Ar–H), 10.23 (1H, bs, –NHCO–).

7-Chloro-5-(2-chlorophenyl)-4-methyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine-2-thione (XV)——P_2S_5 (25 g) was added to a solution of XIV (26.5 g) in a mixed solvent of dry $CHCl_3$ (170 ml) and dry pyridine (170 ml) at room temperature. After being stirred for 30 min, the mixture was allowed to warm up to 80°C and was then stirred for an additional 3 h. After the mixture had cooled, the supernatant was separated and concentrated *in vacuo* to give an oil, which was chromatographed in $CHCl_3$ over silica gel to give XV (14.1 g, 50.7%), mp 157—160°C (from benzene). *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2S$: C, 56.98; H, 4.18; N, 8.31. Found: C, 56.87; H, 4.23; N, 8.18. IR ν_{max}^{Nujol} cm^{-1}: 3150, 3100, 1600, 1580, 1520. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, N^4–CH_3), 3.45 and 3.88 (each 1H, d, J=14 Hz, –C_3–CH_2–), 4.92 (1H, s, C_5–CH<), 6.4—7.9 (7H, m, Ar–H), 10.4 (1H, s, –NHCO–).

7-Chloro-5-(2-chlorophenyl)-4,5-dihydro-2-(2-dimethylaminoethylthio)-4-methyl-3*H*-1,4-benzodiazepine (XVI)——A mixture of XV (4.5 g), DMEC·HCl (2.6 g), 10% KOH (26 ml) and THF (10 ml) was stirred at room temperature for 2 h. The resulting oil obtained on work-up as described in method A gave an oily product (XVI), which was converted into the corresponding maleate (5.5 g, 78.6%), mp 143—146°C (from iso-PrOH). *Anal.* Calcd for $C_{20}H_{23}Cl_2N_3S \cdot C_4H_4O_4$: C, 54.96; H, 5.19; N, 8.01. Found: C, 54.84; H, 5.23; N, 7.85. IR ν_{max}^{Nujol} cm^{-1}: 2350, 1700, 1620, 1600 (sh), 1580. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, N^4–CH_3), 2.95 (6H, s, $N(CH_3)_2$), 3.2—3.8 (6H, m, –CH_2–CH_2– and C_3–CH_2), 4.50 (1H, s, C_5–CH<), 6.30 (2H, s, $^{H}\!>\!=\!<\!^{H}$), 6.4—7.9 (7H, m, Ar–H).

Reactions of III-1 with Base and Acid——The results are summarized in Table III. A typical procedure is as follows. A mixture of III-1 (2.0 g), 10% NaOH (10 ml), and MeOH (10 ml) was stirred at 50°C for 4 h. The crude product obtained on work-up as described in method A was chromatographed in $CHCl_3$ over alumina. The first eluate gave IV (0.65 g, 40%), mp 76—80°C (from *n*-hexane). The subsequent eluate gave I-1 (0.60 g, 39%), mp 199—200°C (from *n*-hexane) (lit.[17a] mp 199—201°C).

Preparation of IV, XVII, and XVIII from III-27. 7-Chloro-5-(2-chlorophenyl)-2-methoxy-3*H*-1,4-benzodiazepine (IV)——A solution of III-27[10] (1.7 g) in MeOH was treated with MeONa [prepared from Na (140 mg) and dry MeOH (30 ml)] at 50°C for 30 min. The mixture was concentrated, diluted with H_2O and

Table III. Reaction of III-1 with Base or Acid

Solvent	Conditions Base or Acid used	°C	h	Products (%) IV	Products (%) I-1
aq. MeOH	NaOH	50	4	40	39
aq. MeOH	NaOH	RT	1	92.2	5
aq. THF	NaOH	50	4	No-reaction	
aq. DMSO	NaOH	RT	6	—	quant.
aq. MeOH	HCl	RT	1	—	quant.

Abbreviations: aq. = aqueous, RT = room temperature, quant. = quantitative.

extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to give IV (1.5 g, 92.7%), mp 76—80°C (from *n*-hexane).

2-Ethoxy-3*H*-1,4-benzodiazepine (XVII)[18] and 2-Isopropoxy-3*H*-1,4-benzodiazepine (XVIII) were prepared according to the procedure described for IV.

XVII: An oil. IR ν_{max}^{film} cm^{-1}: 1640, 1605, 1590. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, CH_3), 4.09 (2H, s, C_3–CH_2–), 4.32 (2H, q, J=7 Hz, –CH_2–), 7.0—7.6 (7H, m, Ar–H).

XVIII: An oil. IR ν_{max}^{film} cm^{-1}: 1640, 1605, 1595. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=6 Hz, $C(CH_3)_2$), 4.05 (2H, s, C_3–CH_2–), 5.23 (1H, septet, J=6 Hz, –CH<), 7.0—7.5 (7H, m, Ar–H).

Preparation of XIX, XX, and XXI. Methyl (*E*)-[2-Amino-5-chloro-α-(2-chlorophenyl)benzylidene]-aminoacetate (XIX, *syn*-Form)——A 5% HCl solution (47 ml) was added dropwise to a solution of IV (10 g) in MeOH (200 ml) at −70°C. After being allowed to warm up to −20°C and being stirred for 2.5 h, the mixture was poured into chilled saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The resulting residue was chromatographed in a 20: 1 mixture of $CHCl_3$ and MeOH over silica gel to give XIX (5.3 g, 50.2%), mp 112—117°C (from *n*-hexane–EtOH). *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2O_2$: C, 56.99; H, 4.18; N, 8.31. Found: C, 56.91; H, 4.10; N, 8.33. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3370, 3250, 1740, 1635, 1605, 1590. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s, $COOCH_3$), 3.90 (2H, bs, NH_2), 4.32 (2H, bs, –CH_2CO–), 6.6—7.6 (7H, m, Ar–H). Ultraviolet (UV) λ_{max}^{EtOH} nm (ε): 244 (16100), 332 (2240).

The subsequent eluate was concentrated to give I-1 (2.8 g, 29.3%), mp 199—200°C (from *n*-hexane) (lit.[17a] mp 199—201°C).

Compounds XX and XXI were obtained by the procedure described for XIX.

Table IV. Reaction of 2-Alkoxy-3*H*-1,4-benzodiazepines with HCl

Compound	Conditions Solvent	°C	h	Products (yield, %) XIX, XX, or XXI		I-1	
IV	aq. MeOH	−20	2.5	XIX	50.2	I-1	29.3
XVII	aq. EtOH	−20	2.5	XX	51.7	I-1	37.5
XVIII	aq. iso-PrOH	−20	2.5	XXI	45.7	I-1	37.6

aq. = aqueous.

XX (51.7%), mp 114—115°C (from *n*-hexane–EtOH). *Anal.* Calcd for $C_{17}H_{16}Cl_2N_2O_2$: C, 58.13; H, 4.59; N, 7.98. Found: C, 57.92; H, 4.53; N, 7.95. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3370, 3250, 1755, 1635, 1620, 1590, 1570. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=8 Hz, CH_3), 3.92 (2H, s, NH_2), 4.14 (2H, q, J=8 Hz, –OCH_2–), 4.26 (2H, bs, –CH_2CO–), 6.5—7.6 (7H, m, Ar–H). UV λ_{max}^{EtOH} nm (ε): 245 (16000), 331 (2150). And I-1 (37.5%), mp 199—200°C (from *n*-hexane).

XXI (45.7%), mp 85—87°C (from *n*-hexane–EtOH). *Anal.* Calcd for $C_{18}H_{18}Cl_2N_2O_2$: C, 59.19; H, 4.97; N, 7.67. Found: C, 59.50; H, 5.10; N, 7.49. IR ν_{max}^{Nujol} cm^{-1}: 3460, 3350, 1740, 1630, 1600, 1590. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, d, J=6 Hz, $C(CH_3)_2$), 3.93 (2H, s, NH_2), 4.30 (2H, s, –CH_2CO–), 5.08 (1H, septet, J=6 Hz, –CH<), 6.6—7.8 (7H, m, Ar–H). UV λ_{max}^{EtOH} nm (ε): 245 (14900), 322 (1970). And I-1 (37.6%), mp 199—200°C (from *n*-hexane).

Conversion of *syn*-Form into *anti*-Form——Compounds XIX and XX were heated for 10 min at 150°C to give the *anti*-forms XXII and XXIII, respectively. Compound XXI was heated for 3 min at the same temperature to give an *anti*-form (XXIV). The products obtained were recrystallized from EtOH. The

conversion yields of *syn*-form into *anti*-form were quantitative. The physical data for the compounds obtained are as follows.

XXII: mp 138—141°C. *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2O_2$: C, 56.99; H, 4.18; N, 8.31. Found: C, 56.72; H, 3.94; N, 8.44. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3250, 1740, 1610, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s, $COOCH_3$), 3.97 and 4.05 (each 1H, d, J=19 Hz, $-CH_2CO-$), 6.87 (2H, bs, NH_2), 6.6—7.6 (7H, m, Ar–H). UV λ_{max}^{EtOH} nm (ε): 232 (29400), 259 (6130), 370 (5810).

XXIII: mp 144—146°C. *Anal.* Calcd for $C_{17}H_{16}Cl_2N_2O_2$: C, 58.13; H, 4.59; N, 7.98. Found: C, 58.00; H, 4.50; N, 7.92. IR ν_{max}^{Nujol} cm^{-1}: 3470, 3280, 1740, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7 Hz, CH_3), 3.83 and 4.04 (each 1H, d, J=18 Hz, $-CH_2CO-$), 4.12 (2H, q, J=7 Hz, $-CH_2-$), 6.82 (2H, bs, NH_2), 6.6—7.6 (7H, m, Ar–H). UV λ_{max}^{EtOH} nm (ε): 233 (29200), 258 (6240), 370 (5710).

XXIV: mp 168—170°C. *Anal.* Calcd for $C_{18}H_{18}Cl_2N_2O_2$: C, 59.19; H, 4.97; N, 7.67. Found: C, 59.06; H, 4.87; N, 7.67. IR ν_{max}^{Nujol} cm^{-1}: 3480, 3280, 1735, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, d, J=6 Hz, $C(CH_3)_2$), 3.80 and 4.40 (each 1H, d, J=19 Hz, $-CH_2CO-$), 5.03 (1H, septet, J=6 Hz, $-CH<$), 6.90 (2H, bs, NH_2), 6.5—7.6 (7H, m, Ar–H). UV λ_{max}^{EtOH} nm (ε): 232 (29100), 260 (6030), 370 (5670).

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