Anxiolytic Sedatives. 1. Synthesis and Pharmacology of Benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole Derivatives and Analogs

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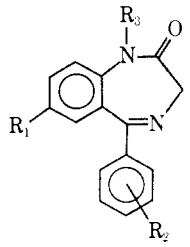
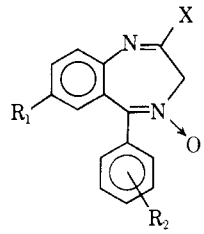
Benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole derivatives and analogs were synthesized to test their psychotropic properties. A majority of the compounds in this series were found to have an excellent anxiolytic sedative activity, and the relationship between their chemical structure and antibemegride activities was studied.

1,4-Benzodiazepine derivatives of the type Ia and Ib, synthesized by Sternbach, *et al.*,[1] have been shown to be very effective anxiolytic sedatives.[2] Thus, we turned our attention for development of psychotropic agents to

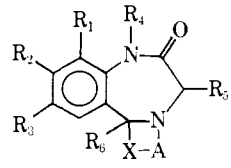


Ia



Ib

the synthesis of 1,4-benzodiazepine derivatives having the new tricyclic ring system of the type II (X = O or S; A = straight or branched alkylene). The methodology of the molecular modification stems from an earlier work[3] concerning a ring-fused chlorpromazine which showed a slight CNS-stimulating effect.



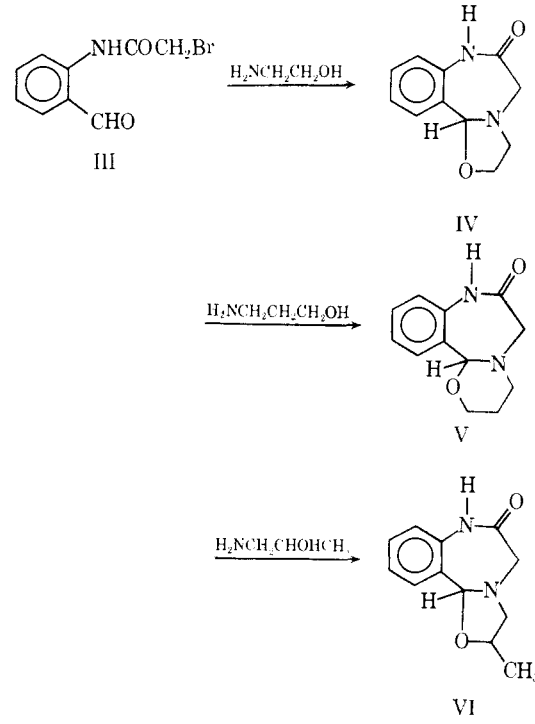
II

Chemistry.—Reaction of 2-bromoacetamidobenzaldehyde (III) with ethanolamine in MeOH gave the desired tricyclic compound IV.

Similar treatment of III with 3-aminopropanol or 1-amino-2-propanol afforded V or VI, respectively. These products IV, V, and VI did not display any psychotropic properties.

We then initiated the following syntheses for the purpose of studying the psychopharmacology of II in which R_6 was an aryl group. Treatment of 2-(α-bromoacylamino)benzophenone derivatives (VII, Y = Br) bearing various substituents with mercaptoethylamine or alkanolamine, such as ethanolamine, 3-aminopropanol, 1-amino-2-propanol, or 2-amino-1-propanol, afforded 2-(α-mercaptoethylamino- or alkanolaminoacylamino)benzophenone derivatives (VIII). In this preparation it was possible to use 2-(α-tosyloxyacylamino)benzophenone derivatives (VII, Y = *p*-$CH_3C_6H_4SO_2O$) as starting materials instead of 2-(α-bromoacylamino)benzophenone derivatives. Most of VII (Y = Br or *p*-$CH_3C_6H_4SO_2O$) used here were known and prepared as described in the literature.[4] Some of VIII were found to possess weak antibemegride activity.

SCHEME I



The ring-closure reaction of VIII in either the purified or the crude state to benzo[6,7]-1,4-diazepino[5,4-*b*]-oxazoles IX was accomplished by refluxing VIII in EtOH containing a small amount of AcOH.[5] The ring closure at room temp proceeded much more slowly than by refluxing. Compound IX could also be obtained directly from VII by refluxing with alkanolamine or

(1) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968), and ref cited therein.

(2) (a) L. H. Sternbach, L. O. Randall, and S. Gustafson, "Psychopharmacological Agents," Vol. 1–4, Academic Press, New York, N. Y., 1964, p 137; (b) S. J. Childress and M. I. Glucknan, *J. Pharm. Sci.*, **53**, 577 (1964); (c) L. H. Sternbach and L. O. Randall, "CNS Drugs, A Symposium Held at the Regional Research Laboratory, Hyderbad, India," CSIR, New Delhi, India, 1966, p 53; (d) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, *Drugs Affecting Centr. Nerv. Syst.*, **2**, 237 (1968).

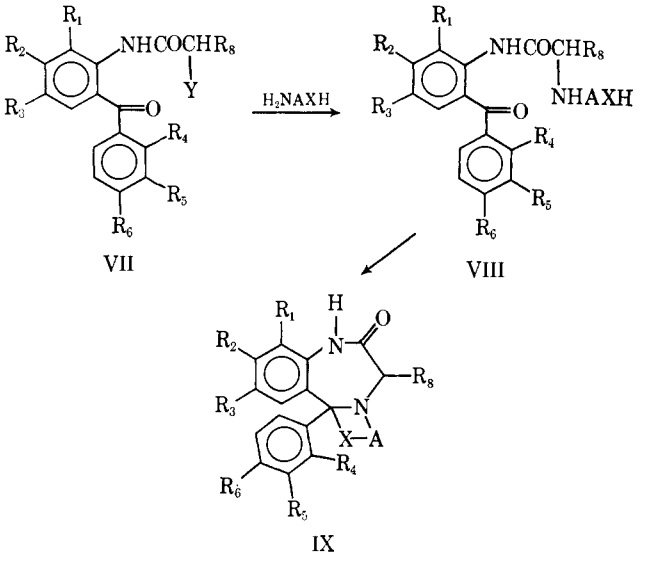
(3) (a) G. Sunagawa and T. Ichii, *Yukugaku Zasshi*, **79**, 1401 (1959); (b) T. Ichii, *ibid.*, **82**, 992, 999 (1962).

(4) L. H. Sternbach, R. I. Fryer, W. Metesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

(5) R. Tachikawa, H. Takagi, T. Miyadera, T. Kamioka, M. Fukunaga, and Y. Kawano, Japanese Patent Application, Nov 27, 1967; *Chem. Abstr.*, **71**, 124516 (1969).

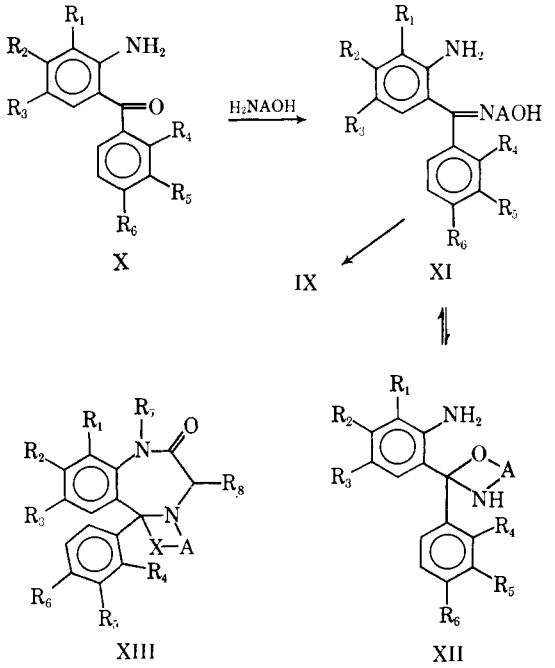
mercaptoethylamine in MeOH in the presence of anhyd NaOAc without isolation of the intermediate VIII.

SCHEME II



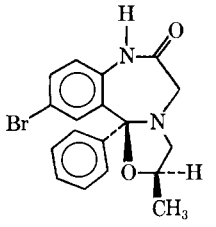
As an extension of the chemistry of IX, we investigated a new synthetic route to IX from 2-aminobenzophenone derivatives (X).[6] Heating X with alkanolamine at 170–200°, followed by removal of excess alkanolamine, afforded an oily condensation product which slowly gave rise to a crystalline anti Schiff base.[7] The oily condensation product would be a mixture of an oxazolidine XIIa and the Schiff base XIa (XII, XI, $R_1 = R_2 = R_4 = R_5 = R_6 = H$; $R_3 = Cl$; $A = CH_2CH_2$).

SCHEME III

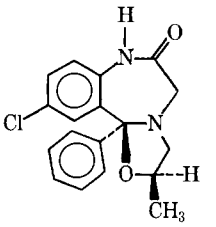


The reaction of α-bromoacyl halide or α-tosyloxyacyl halide with the oily condensation product or the crystalline Schiff base XI gave the same product IX (X = O) as previously synthesized.

When a branched alkanolamine such as 1-amino-2-propanol or 2-amino-1-propanol was used in the reaction with VII (R_8 = H), there should be 2 isomers of IX, trans and cis forms with respect to 2- or 3-Me and 11b-Ph groups. Theoretically, if R_8 in IX is an alkyl group, there should be 2 or 4 racemic isomers of IX in response to the kind of amine, straight alkanolamine (ethanolamine), or branched alkanolamine (1-amino-2-propanol, 2-amino-1-propanol), used in the reaction with VII. For example, IXa and IXb were shown by nmr spectra to exist as a mixture of cis and trans isomers in $CDCl_3$ from which the trans isomers were isolated. The stereochemistry determination was made by X-ray analyses. The *trans*-IXa isomerized rapidly in $CDCl_3$ at room temp to give an equilibrium mixture



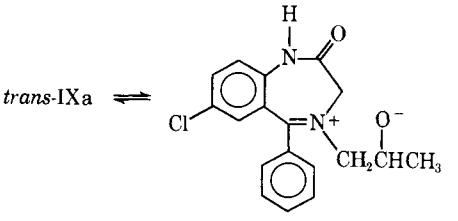
trans-IXb



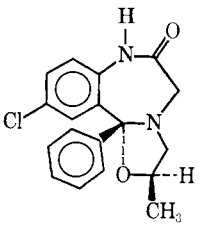
trans-IXa

of the trans and cis isomers (nearly 3:2, respectively). It seems probable that this isomerization proceeds *via* a quaternary iminium ion (XIV) as shown in Scheme IV.

SCHEME IV



XIV



cis-IXa

Some of the compounds IX were alkylated to yield XIII using NaOMe and alkylating agents such as MeI.

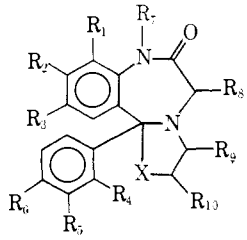
Pharmacology.—As was expected, IX and XIV, except for several derivatives, were found to have an excellent anxiolytic sedative activity.

The studies on antibemegride activity and acute toxicity of the above benzo[6,7]-1,4-diazepino[5,4-*b*]-oxazole or thiazole derivatives (XV) were carried out on groups of 10 or 20 male mice (ddy strain, weighing 20–25 g) at a minimum of 3 dose levels. The test compounds were given orally as suspensions in 0.85% saline soln containing 0.5% tragacanth 1 hr before adminis-

(6) R. Tachikawa, H. Takagi, T. Kamioka, T. Miyadera, M. Fukunaga, and Y. Kawano, Japanese Patent Application, Oct 24, 1968.

(7) (a) S. C. Bell, French Patent 1,369,044, 1964; *Chem. Abstr.*, **63**, 6920 (1965); (b) S. C. Bell, G. L. Conklin, and S. J. Childress, *J. Org. Chem.*, **29**, 2368 (1964).

tration of bemegride (30 mg/kg, sc) in 0.85% saline soln and the animals were observed for 30 min after bemegride injection. The antibemegride activity of XV was assessed by their ability to inhibit bemegride-



(X = O or S)

XV

induced convulsion. In the studies on acute toxicity, the compounds were also given orally, and the observation period after administration was 1 week. ED_{50} and LD_{50} values were calcd by the method of Litchfield and Wilcoxon.[8]

The results are summarized in Table III. The characteristics of the convulsion induced by bemegride are similar to those of pentylenetetrazole convulsion, and this anticonvulsant test is a very sensitive measure of the CNS-depressant effect. Some derivatives in this series, for example, XVa ($R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_8 = R_9 = H$;† $R_3 = Cl$; $R_{10} = CH_3$; X = O), retained antibemegride activity in a small dose which did not induce ataxia in the rotating rod test or muscular relaxation in the inclined plane test in mice.[9] Compound XVa, as well as several others in this series, showed marked taming effects on fighting mice, fighting hamsters, and aggressive rats in which olfactory bulbs were removed. In monkeys, XVa increased sociability and contentment and decreased hostility and excitability behavior. Compound XVa was also very potent against convulsion of the El-strain mouse as well as against convulsion induced by bemegride or pentylenetetrazole in mice but comparatively less potent against convulsion induced by strychnine or electroshock.[6]

As described above, XV had various effects comparable to psychotherapeutic drugs in various animal species; in order to simplify the study of the relationship between chemical structure and biological activity, we chose the results of antibemegride test in mice as an indicator. The substitutions of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and/or R_{10} in XV by alkyl groups tend to lower its antibemegride activity. However, the substitution of R_9 by Me enhances the activity very strongly. When R_3 is Cl, Br, or NO_2, and R_4 is Cl or F, the activity is also increased markedly. Thus, the most interesting substances with high potencies in this series are the compounds XV wherein R_3, R_4, and R_9 represent Cl or Br, Cl or F, and Me, respectively.

The acute toxicity of XV was generally very low, for example, LD_{50} value of XVa, XVb (R_3 = Br; R_{10} = CH_3; X = O), XVc (R_3 = Cl; R_{10} = H; X = O), XVd (R_3 = Br; R_{10} = H; X = O), XVe ($R_3 = NO_2$; R_{10} = H; X = O), XVf ($R_3 = R_4$ = Cl; R_{10} = H; X = O), or XVg (R_3 = Br; R_4 = Cl; $R_{10} = CH_3$; X = O) was 5200, 3600, 1700, 2200, 3200, 3300, or 3800 mg per kg po, respectively.

† In this section R_1, R_2, R_4, R_5, R_6, R_7, R_8, and R_9 are H except where indicated.

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

(9) H. Takagi, T. Kamioka, S. Kobayashi, Y. Suzuki, and R. Tachikawa, *Nippon Yakurigaku Zasshi*, **66**, 107 (1970).

Experimental Section[10]

2,3,5,6,7,11b-Hexahydrobenzo[6,7]1,4-diazepino[5,4-*b*]oxazol-6-one (IV).—A mixt of 2-bromoacetamidobenzaldehyde (1.55 g, 0.0064 mole) and ethanolamine (0.98 g, 0.016 mole) in 50 ml of abs MeOH was stirred for 5 hr at room temp. After standing overnight, the reaction mixt was heated under reflux for 7 hr. After cooling, the solvent was evapd under reduced pressure. The oily residue was dissolved in CH_2Cl_2, washed 3 times with H_2O, and dried (Na_2SO_4). Evapn of the solvent gave an oily substance (1.0 g) which was chromatographed on silica gel (30 g) and eluted with $CHCl_3$–MeOH (100:1) to afford 0.17 g of a solid. Recrystn from EtOH gave colorless needles, mp 159–161°. *Anal.* ($C_{11}H_{12}N_2O_2$) C, H, N. The ir spectrum showed an amide C=O at 1675 cm^{-1}, but no aldehyde band: uv λ_{max}^{EtOH} 240.5 mμ (ε 17700); nmr δ 3.01–4.30 (3 CH_2, m), 6.83–7.60 (4 H, aromatic protons, m), 8.09 (NH, *s*), 5.36 (CH, *s*).

2,3,6,7,8,12b-Hexahydrobenzo[6,7]-1,4-diazepino[5,4-*b*]-4*H*-oxazin-7-one (V).—A mixt of 2-bromoacetamidobenzaldehyde (2.0 g) and 3-aminopropanol (1.5 g) in 50 ml of abs MeOH was treated as described for the prepn of IV to give colorless needles (0.7 g) after recrystn from EtOH, mp 175–176°. *Anal.* ($C_{12}H_{14}N_2O_2$) C, H, N. The spectra (uv, ir, nmr) were as expected.

2-Methyl-2,3,5,6,7,11b-hexahydrobenzo[6,7]-1,4-diazepino-[5,4-*b*]oxazol-6-one (VI).—A mixt of 2-bromoacetamidobenzaldehyde (4.0 g) and 1-amino-2-propanol (3.0 g) in 60 ml of abs MeOH was treated as described for the preparation of IV to give colorless prisms (0.1 g) after recrystn from EtOH, mp 172–173°. *Anal.* ($C_{12}H_{14}N_2O_2$), C, H, N. The spectra (uv, ir, nmr) were as expected.

Syntheses of 2-(α-Bromoacylamino)benzophenone and 2-(α-Tosyloxyacylamino)benzophenone Derivatives (VII).—To a soln of 2-aminobenzophenone deriv (1 mole) and pyridine (1.2 moles) in 2.5 l. of anhyd toluene was added dropwise a soln of α-tosyloxy or α-bromoacyl halide (1.2 moles) in 500 ml of anhyd PhMe with stirring under ice-H_2O cooling. The reaction temp during the addn was maintained at 10–15°. Stirring was contd for 30 min at 3–5° and then for 2 hr at room temp. The reaction mixt was poured into 2.5 l. of ice water, the org layer was sepd, and the aq layer was extd with PhMe. The combined exts were washed successively with H_2O and satd NaCl soln until neutral to litmus and dried (Na_2SO_4). The solvent was distd under reduced pressure to give a solid. Recrystn from EtOH gave the product (Table I). The known, unlisted compounds were prepd in excellent yields (82–95%).

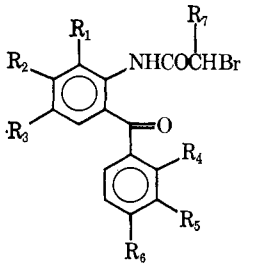
Syntheses of 2-(α-Alkanolaminoacylamino)benzophenone and 2-(α-Mercaptoethylaminoacylamino)benzophenone Derivatives (VIII).—Compd VII (1 mole) was added in small portions to a soln of alkanolamine or mercaptoethylamine (2.4 moles) in 1.5 l. of CH_2Cl_2 at 2–3° with stirring. Stirring was continued for 30 min at the same temp and then at room temp overnight. The reaction mixt was poured into 3 l. of ice H_2O, the org layer was sepd, and the aq layer was extd with CH_2Cl_2. The combined exts were washed 3 times with H_2O, dried (Na_2SO_4), and evapd under reduced pressure. The residual oil solidified on standing overnight. Recrystn from EtOH or Et_2O afforded the pure product (Table II).

Syntheses of Benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole Derivatives and Analogs (IX). Method A. From 2-(α-Alkanolaminoacylamino)benzophenone or 2-(α-Mercaptoethylaminoacylamino)benzophenone Derivatives (VIII).—A mixt of VIII (1 mole) and AcOH (2–3 ml) in 3 l. of EtOH was heated under reflux for 17 hr. After cooling, the solvent was evapd under reduced pressure, leaving a solid. Recrystn from EtOH or column chromatography, if necessary, afforded a pure product (Table III). In this ring-closure reaction, it was possible to use DMSO or an org acid with comparatively low mol wt instead of AcOH.

(10) Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data were obtained using Varian A-60 and HA-100 nmr, a Perkin-Elmer 221 spectrophotometer, and a Cary 14 CM-50 (Serial 1258) recording spectrophotometer. The nmr, ir, and uv spectra of all compounds were in agreement with the assigned structures. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE I

2-(α-BROMOACYLAMINO)BENZOPHENONE DERIVATIVES (VII)

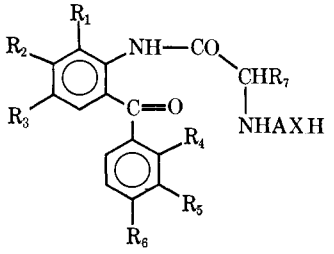


No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Mp, °C	Yield, %	Formula	Analyses[a]
1	Me	H	Me	H	H	H	H	160–162	91	$C_{17}H_{16}NO_2Br$	C, H, N, Br[b]
2	H	Me	Me	H	H	H	H	92.5–94	92	$C_{17}H_{16}NO_2Br$	C, H, N, Br
3	H	H	Cl	H	H	NO_2	H	151–153	83	$C_{15}H_{10}N_2O_4BrCl$	C, H, N, Br, Cl
4	H	H	Cl	H	Cl	H	H	126–128	91	$C_{15}H_{10}NO_2BrCl_2$	C, H, N, Br, Cl
5	H	H	Br	Cl	H	H	H	151–152	92	$C_{15}H_{10}NO_2Br_2Cl$	C, H, N, Br, Cl
6	H	H	Br	H	H	H	Me	117–119	89	$C_{16}H_{13}NO_2Br_2$	C, H, N, Br
7	Me	H	Me	H	H	H	Me	186–188	90	$C_{18}H_{18}NO_2Br$	C, H, N, Br
8	H	H	Cl	H	H	Cl	Me	115–116	92	$C_{16}H_{12}NO_2BrCl_2$	C, H, N, Br, Cl
9	H	H	Cl	H	H	H	Et	93.5–94	89	$C_{17}H_{15}NO_2BrCl$	C, H, N, Br, Cl
10	H	H	Cl	H	H	H	n-C_3H_7	60–63	93	$C_{18}H_{17}NO_2BrCl$	C, H, N, Br, Cl

[a] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [b] Br: calcd, 23.12; found, 23.59.

TABLE II

2-(ALKANOLAMINOACYLAMINO)BENZOPHENONE DERIVATIVES (VIII)



$R_1 = R_5 = R_7 = H$; X = O

No.	R_2	R_3	R_4	R_6	A(X)	Mp, °C	Yield, %	Formula	Analyses[a]
11	H	Cl	H	H	CH_2CH_2	121–123	86	$C_{17}H_{17}ClN_2O_3$	C, H, N, Cl
12	H	Br	H	H	$CH_2CH(CH_3)$	93–96	88	$C_{18}H_{19}BrN_2O_3$	C, H, N, Br
13	H	NO_2	H	H	$CH_2CH(CH_3)$	106–108.5	84	$C_{18}H_{19}N_3O_5$	C, H, N
14	Cl	Cl	H	H	$CH_2CH(CH_3)$	145.5–147	88	$C_{18}H_{18}Cl_2N_2O_3$	C, H, N, Cl
15	H	Cl	H	Cl	$CH_2CH(CH_3)$	116–118	86	$C_{18}H_{18}Cl_2N_2O_3$	C, H, N, Cl
16	H	Cl	Cl	Cl	$CH_2CH(CH_3)$	110.5–112	83	$C_{18}H_{17}Cl_3N_2O_3$	C, H, N, Cl
17	H	Cl	H	NO_2	$CH_2CH(CH_3)$	101–103	82	$C_{18}H_{18}ClN_3O_5$	C, H, N, Cl
18	H	Cl	Cl	H	CH_2CH_2	107–109	89	$C_{17}H_{16}Cl_2N_2O_3$	C, H, N, Cl
19	H	Cl	Me	H	$CH_2CH(CH_3)$	83–86	82	$C_{19}H_{21}ClN_2O_3$	C, H, N, Cl
20	H	Cl	Cl	H	$CH_2CH(CH_3)$	108–110	85	$C_{18}H_{18}Cl_2N_2O_3$	C, H, N, Cl
21	H	H	Cl	H	CH_2CH_2	89–91	79	$C_{17}H_{17}ClN_2O_3$	C, H, N, Cl

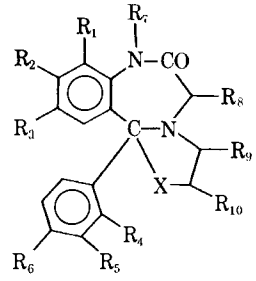
[a] Analytical results were within ±0.4% of the theoretical values.

Method B. By the Reaction of 2-(α-Bromoacylamino)benzophenone or 2-(α-Tosyloxyacylamino)benzophenone Derivatives (VII) with Alkanolamine or Mercaptoethylamine without Isolation of VIII.—The compd VII (1 mole) was added in small portions to a soln of alkanolamine or mercaptoethylamine (2.4 mmoles) in 1.5 l. of CH_2Cl_2 at 2–3° with stirring. Stirring was contd for 30 min at the same temp and subsequently overnight at room temp. The reaction mixt was poured into 3 l. of ice H_2O, the org layer was sepd, and the aq layer was extd with CH_2Cl_2. The combined exts were washed 3 times with H_2O, dried (Na_2SO_4), and evapd under reduced pressure. The residual oil was redissolved in 2 l. of EtOH contg 2–3 ml of AcOH and heated under reflux for 17 hr. After cooling, the solvent was evapd under reduced pressure to afford a solid. Recrystn from EtOH or column chromatography, if necessary, provided the product (Table III). In this case, it was also possible to use other catalysts as mentioned in method A in place of AcOH.

Method C. By the Reaction of 2-(α-Bromoacylamino)benzophenone or 2-(α-Tosyloxyacylamino)benzophenone Derivatives (VII) with Alkanolamine or Mercaptoethylamine in the Presence of NaOAc.—A mixt of VII (1 mole), alkanolamine, or mercaptoethylamine (1.2 moles) and NaOAc (1.2 moles) in 3–5 l. of MeOH was heated under reflux for about 17 hr. After cooling, the solvent was evapd under reduced pressure and the residue was extd with CH_2Cl_2 2 or 3 times. The combined exts were washed with H_2O and dried (Na_2SO_4). Evapn of the solvent and recrystn of the residue from EtOH afforded the product. The structure assignment was made by ir, uv, and nmr spectra.

TABLE III

BENZO[6,7]-1,4-DIAZEPINO[5,4-*b*]OXAZOLE OR -THIAZOLE DERIVATIVES (XV)



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	X	Mp, °C	Yield, % (method)	Formula	Analyses[a]	Antibemegride activity, ED_{50}, mg/kg (95% confidence limits)
22	H	H	Cl	H	H	H	H	H	H	H	O	175–176	64 (B)	$C_{17}H_{15}ClN_2O_2$	C, H, N, Cl	2.0 (1.5–2.7)
23	H	H	Br	H	H	H	H	H	H	H	O	190–191.5	59 (B)	$C_{17}H_{15}BrN_2O_2$	C, H, N, Br	1.6 (1.4–1.8)
24	H	H	NO_2	H	H	H	H	H	H	H	O	218–220 dec	53 (B)	$C_{17}H_{15}N_3O_4$	C, H, N	0.78 (0.6–1.01)
25	H	H	H	H	H	H	H	H	H	Me	O	174–176	58 (B)	$C_{18}H_{18}N_2O_2$	C, H, N	14.0 (10–19.6)
26	H	H	Cl	H	H	H	H	H	H	Me	O	186–188	72 (B)	$C_{18}H_{17}ClN_2O_2$	C, H, N, Cl	2.3 (1.6–3.4)
27	H	H	Br	H	H	H	H	H	H	Me	O	180–183	70 (A)	$C_{18}H_{17}BrN_2O_2$	C, H, N, Br	1.7 (1.3–2.3)
28	H	H	NO_2	H	H	H	H	H	H	Me	O	209 dec	52 (A)	$C_{18}H_{17}N_3O_4$	C, H, N	1.1 (0.65–1.9)
29	Me	H	Me	H	H	H	H	H	H	Me	O	273 dec	63 (B)	$C_{20}H_{22}N_2O_2$	C, H, N	>100
30	H	Me	Me	H	H	H	H	H	H	Me	O	172–174	66 (B)	$C_{20}H_{22}N_2O_2$	C, H, N	9.3 (7.6–11.4)
31	Cl	H	Cl	H	H	H	H	H	H	Me	O	226–228	64 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	>100
32	H	Cl	Cl	H	H	H	H	H	H	Me	O	196–197.5	65 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	37.4 (30–47)
33	Me	H	Cl	H	H	H	H	H	H	Me	O	254 dec	58 (B)	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	>100
34	H	H	Cl	H	H	H	H	H	Me	H	O	126–127	25 (B)	$C_{18}H_{17}ClN_2O_2$	C, H, N, Cl	0.44 (0.35–0.55)
35	H	H	Br	H	H	H	H	H	Me	H	O	126–127	26 (B)	$C_{18}H_{17}BrN_2O_2$	C, H, N, Br	0.41 (0.32–0.53)
36	H	H	NO_2	H	H	H	H	H	Me	H	O	182–183	23 (B)	$C_{18}H_{17}N_3O_4$	C, H, N	0.2 (0.13–0.32)
37	H	H	Cl	H	H	H	H	H	Et	H	O	154–156	28 (B)	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	
38	H	H	H	Cl	H	H	H	H	H	H	O	203–204	31 (A)	$C_{17}H_{15}ClN_2O_2$	C, H, N, Cl	
39	H	H	H	Cl	H	H	H	H	H	Me	O	195–196	58 (B)	$C_{18}H_{17}ClN_2O_2$	C, H, N, Cl	36.0 (25.7–50.4)
40	H	H	Cl	H	H	Cl	H	H	H	Me	O	187.5–189	63 (A)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	>100
41	H	H	Cl	H	Cl	H	H	H	H	H	O	165–167	67 (B)	$C_{17}H_{14}Cl_2N_2O_2$	C, H, N, Cl	47.0 (34.8–69.1)
42	H	H	Cl	H	Cl	H	H	H	H	Me	O	215 dec	58 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	>100
43	H	H	Cl	Cl	H	H	H	H	H	H	O	203–204 dec	59 (A)	$C_{17}H_{14}Cl_2N_2O_2$	C, H, N, Cl	0.23 (0.17–0.32)
44	H	H	Cl	Cl	H	H	H	H	H	Me	O	192 dec	65 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	0.36 (0.27–0.43)
45	H	H	Cl	Cl	H	H	H	H	Me	H	O	172–175	28 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	0.1 (0.07–0.15)
46	H	H	Cl	F	H	H	H	H	H	H	O	181–183	51 (B)	$C_{17}H_{14}ClFN_2O_2$	C, H, N, Cl, F	0.35 (0.25–0.49)
47	H	H	Cl	F	H	H	H	H	H	Me	O	199 dec	56 (B)	$C_{18}H_{16}ClFN_2O_2$	C, H, N, Cl, F	0.7 (0.58–0.84)
48	H	H	Cl	F	H	H	H	H	Me	H	O	165–167	27 (B)	$C_{18}H_{16}ClFN_2O_2$	C, H, N, Cl, F	0.11 (0.08–0.16)
49	H	H	Cl	Cl	H	Cl	H	H	H	Me	O	201.5 dec	68 (A)	$C_{18}H_{15}Cl_3N_2O_2$	C, H, N, Cl	>100
50	H	H	Cl	Me	H	H	H	H	H	Me	O	205 dec	63 (A)	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	8.0 (5.9–10.8)
51	H	H	Cl	H	H	NO_2	H	H	H	Me	O	193–195	55 (A)	$C_{18}H_{16}ClN_3O_4$	C, H, N, Cl	>100
52	H	H	Br	Cl	H	H	H	H	H	H	O	207 dec	61 (B)	$C_{17}H_{14}BrClN_2O_2$	C, H, N, Br, Cl	0.14 (0.11–0.18)
53	H	H	Br	Cl	H	H	H	H	H	Me	O	197 dec	64 (B)	$C_{18}H_{16}BrClN_2O_2$	C, H, N, Br, Cl	0.15 (0.12–0.19)
54	H	H	Br	Cl	H	H	H	H	Me	H	O	182–184	23 (B)	$C_{18}H_{16}BrClN_2O_2$	C, H, N, Br, Cl	0.1 (0.06–0.16)

55	H	H	Cl	H	H	H	H	Me	H	H	O	205–207	54 (B)	$C_{18}H_{17}ClN_2O_2$	C, H, N, Cl	6.4 (5.0–8.2)
56	H	H	Br	H	H	H	H	Me	H	H	O	204–205	62 (B)	$C_{18}H_{17}BrN_2O_2$	C, H, N, Br	5.9 (4.2–8.3)
57	Me	H	Me	H	H	H	H	Me	H	H	O	219–221	61 (B)	$C_{20}H_{22}N_2O_2$	C, H, N	>100
58	H	H	Cl	H	H	H	H	Me	H	Me	O	216–217	59 (B)	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	12.0 (7.1–20.1)
59	H	H	Cl	H	H	Cl	H	Me	H	H	O	204.5–205.5	65 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	>100
60	H	H	Cl	Cl	H	H	H	Me	H	H	O	222–224	70 (B)	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	0.45 (0.32–0.63)
61	H	H	Cl	Cl	H	H	H	Me	H	Me	O	220–223	62 (B)	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	2.8 (2.3–3.4)
62	H	H	Br	Cl	H	H	H	Me	H	H	O	216–217	59 (B)	$C_{18}H_{16}BrClN_2O_2$	C, H, N, Br, Cl	0.40 (0.34–0.47)
63	H	H	Cl	H	H	H	H	Et	H	H	O	183–184	58 (B)	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	>100
64	H	H	Cl	H	H	H	H	*n*-C_4H_9	H	H	O	173–175	51 (B)	$C_{21}H_{23}ClN_2O_2$	C, H, N, Cl	>100
65	H	H	Cl	H	H	H	Me	H	H	H	O	181–183	78	$C_{18}H_{17}ClN_2O_2$	C, H, N, Cl	4.5 (3.4–5.9)
66	H	H	Cl	H	H	H	Et	H	H	H	O	118–120	75	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	3.8 (2.8–5.1)
67	H	H	Cl	H	H	H	CH_2CH_2Cl	H	H	H	O	128–131	66	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	4.7 (3.0–7.3)
68	H	H	Cl	H	H	H	CH_2-*o*-ClC_6H_4	H	H	H	O	144–146	53	$C_{24}H_{20}Cl_2N_2O_2$	C, H, N, Cl	20.5 (16.5–25.4)
69	H	H	Br	H	H	H	Me	H	H	H	O	184–185.5	76	$C_{18}H_{17}BrN_2O_2$	C, H, N, Br	3.0 (2.1–4.2)
70	H	H	Br	H	H	H	Et	H	H	H	O	136–138	75	$C_{19}H_{19}BrN_2O_2$	C, H, N, Br	2.2 (1.1–3.1)
71	H	H	NO_2	H	H	H	Me	H	H	H	O	191–192 dec	62	$C_{18}H_{17}N_3O_4$	C, H, N	1.0 (0.7–1.4)
72	H	H	NO_2	H	H	H	Et	H	H	H	O	112–114	48	$C_{19}H_{19}N_3O_4$	C, H, N	2.2 (1.6–3.1)
73	Me	H	Me	H	H	H	Et	H	H	H	O	141–143	72	$C_{21}H_{24}N_2O_2$	C, H, N	
74	H	H	Cl	H	H	H	Me	H	H	Me	O	134–135	70	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	5.4 (3.4–8.6)
75	H	H	Cl	H	H	H	Et	H	H	Me	O	157–160	69	$C_{20}H_{21}ClN_2O_2$	C, H, N, Cl	4.2 (3.1–5.7)
76	H	H	Cl	H	H	H	$CH_2CH{=}CH_2$	H	H	Me	O	113–115	54	$C_{21}H_{21}ClN_2O_2$	C, H, N, Cl	6.2 (4.1–9.3)
77	H	H	Cl	H	H	H	*n*-C_4H_9	H	H	Me	O	121–122	58	$C_{22}H_{25}ClN_2O_2$	C, H, N, Cl	17.2 (10.9–27.2)
78	H	H	Cl	H	H	H	$CH_2C_6H_5$	H	H	Me	O	154–157	51	$C_{25}H_{23}ClN_2O_2$	C, H, N, Cl	7.1 (1.9–27.0)
79	H	H	Cl	H	H	H	CH_2-*p*-ClC_6H_4	H	H	Me	O	162–163.5	53	$C_{25}H_{22}Cl_2N_2O_2$	C, H, N, Cl	>100
80	H	H	Cl	H	H	H	CH_2-*o*-ClC_6H_4	H	H	Me	O	172–174	55	$C_{25}H_{22}Cl_2N_2O_2$	C, H, N, Cl	>100
81	H	H	Cl	H	H	H	CH_2-*p*-$NO_2C_6H_4$	H	H	Me	O	211 dec	36	$C_{25}H_{22}ClN_3O_4$	C, H, N, Cl	>100
82	H	H	Cl	H	H	H	$CH_2COC_6H_5$	H	H	Me	O	175–176	41	$C_{26}H_{23}ClN_2O_3$	C, H, N, Cl	>100
83	H	H	Br	H	H	H	Me	H	H	Me	O	149–150	71	$C_{19}H_{19}BrN_2O_2$	C, H, N, Br	4.6 (3.5–6.1)
84	H	H	NO_2	H	H	H	Me	H	H	Me	O	170–173	45	$C_{19}H_{19}N_3O_4$	C, H, N	2.4 (1.5–3.8)
85	Me	H	Me	H	H	H	Me	H	H	Me	O	136–138	69	$C_{21}H_{24}N_2O_2$	C, H, N	>100
86	Me	H	Cl	H	H	H	Me	H	H	Me	O	163–164	73	$C_{20}H_{21}ClN_2O_2$	C, H, N, Cl	>100
87	H	H	Cl	H	H	H	Me	H	Me	H	O	142–145	72	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	0.87 (0.4–1.9)
88	H	H	Cl	Cl	H	H	Me	H	H	H	O	154–155	68	$C_{18}H_{16}Cl_2N_2O_2$	C, H, N, Cl	0.52 (0.39–0.65)
89	H	H	Cl	Cl	H	H	Et	H	H	H	O	153–156	72	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	0.55 (0.36–0.84)
90	H	H	Cl	Cl	H	H	Me	H	Me	H	O	177.5–179	75	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	0.22 (0.15–0.23)
91	H	H	Br	Cl	H	H	Me	H	H	H	O	170–172	75	$C_{18}H_{16}BrCl_2N_2O_2$	C, H, N, Br, Cl	0.32 (0.21–0.49)
92	H	H	Br	Cl	H	H	Et	H	H	H	O	157–160	73	$C_{19}H_{18}BrClN_2O_2$	C, H, N, Br, Cl	0.50 (0.34–0.74)
93	H	H	Cl	H	H	Cl	Me	H	H	Me	O	164–166	75	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	>100
94	H	H	Cl	Cl	H	H	Me	H	H	Me	O	173–175	68	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	2.9 (2.2–3.6)
95	H	H	Br	Cl	H	H	Me	H	H	Me	O	188–189	65	$C_{19}H_{18}BrClN_2O_2$	C, H, N, Br, Cl	1.2 (0.8–1.9)
96	H	H	Cl	H	H	H	Et	Me	H	H	O	184–186	72	$C_{20}H_{21}ClN_2O_2$	C, H, N, Cl	
97	H	H	Cl	Cl	H	H	Me	Me	H	H	O	186–187	78	$C_{19}H_{18}Cl_2N_2O_2$	C, H, N, Cl	
98	H	H	Cl	H	H	H	Me	Me	H	Me	O	162–165	73	$C_{20}H_{21}ClN_2O_2$	C, H, N, Cl	
99	H	H	Cl	H	H	H	Me	Et	H	Me	O	155–158	64	$C_{21}H_{23}ClN_2O_2$	C, H, N, Cl	
100	H	H	Br	H	H	H	Me	Me	H	Me	O	159–161	59	$C_{20}H_{21}BrN_2O_2$	C, H, N, Br	
101	H	H	Cl	Cl	H	H	Me	Me	H	Me	O	199–201	79	$C_{20}H_{20}Cl_2N_2O_2$	C, H, N, Cl	
102	H	H	Cl	H	H	H	H	H	H	H	S	241–243 dec	10.5	$C_{17}H_{15}ClN_2OS$	C, H, N, S, Cl	8.3 (6.6–10.2)
103	H	H	Cl	H	H	H	H	Me	H	H	S	137–138	9.3	$C_{18}H_{17}ClN_2OS$	C, H, N, S, Cl	

TABLE III (*Continued*)

No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	X	Mp., °C	Yield, % (method)	Formula	Analyses[a]	Antibemegride activity, ED_{50}, mg/kg (65% confidence limits)
104												220–222	12	$C_{18}H_{17}ClN_2O_2$	C, H, N, Cl	3.8 (2.9–4.8)
105												170–172	46	$C_{19}H_{19}ClN_2O_2$	C, H, N, Cl	0.5 (0.39–0.63)
Cf. diazepam																2.7 (1.9–3.5)
chlordiazepoxide																

[a] Analytical results were within ±0.4% of the theoretical values.

Synthesis of Benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole Derivatives and Their Analogs (IX) from 2-Aminobenzophenone Derivatives (X) *via* Oily Condensation Products or Schiff Bases (XI).—A mixt of X (1 mole) and alkanolamine (4–6 moles) was heated at 170–200° for about 4 hr, and the excess alkanolamine was then removed slowly under reduced pressure. The residue was distd *in vacuo* to give the oily substance; ir 1613 (C=N), 1100, 1158, 1179 cm^{-1} (oxazolidine). *Anal.* ($C_{15}H_{15}N_2OCl$) C, H, N. The distillate solidified on standing at room temp for several days and was recrystd from C_6H_6 to afford the Schiff base (XI). The compd was assigned by the uv spectrum to be anti Schiff base.[7b] Whether or not the syn Schiff base existed in the oily product remained unsettled. To a soln of the oily product or XI (1 mole) and pyridine (2 moles) in 2 l. of dioxane, α-bromoacyl halide or α-tosyloxyacyl halide (1.2 moles) was added dropwise with stirring under ice-H_2O cooling. Stirring was contd for 30 min at 5–10° and for an addl 3 hr at room temp. At the end of the reaction, 2.5 l. of toluene and 2.5 l. of H_2O were added and the mixt was shaken. The org layer was sepd from the aq layer, dried (Na_2SO_4), and then concd under reduced pressure. The residue was recrystd from EtOH to give the desired product. In this prepn, it was possible to use an anhyd inorg base such as Na_2CO_3, K_2CO_3, or $NaHCO_3$, or an org tertiary amine, for example, picoline, quinoline, or Et_3N in place of pyridine.

Isolation, Structure Determination, and Isomerization of the Trans Isomers (IXa and IXb).—Recrystn of IXa and IXb from 70% aq EtOH gave the trans isomer as needles with an elongated *c* axis. The cell consts of IXb were calcd by oscillation and Weissenberg photographs to be $a = 16.34$ Å, $b = 8.88$ Å, $c = 13.89$ Å, and $\beta = 102°$. The crystals belong to the monoclinic system and the space group is $P2_1/c$. The mol structure was solved by the heavy-atom method with Sim's weighting scheme.[11] The parameters were refined by block diagonal least-squares procedure. After 8 cycles of these refinements, the *R* factor reached 12.3% which would be sufficient to discuss the chemical structure. The cell consts of IXa were estimated to be $a = 16.171$ Å, $b = 8.742$ Å, $c = 13.556$ Å, and $\beta = 102°$, whose values indicated that the crystal dimensions were isomorphous to those of the crystal of IXb. The reflection intensities of both crystals were also similar to each other. Therefore, it is concluded that the mol configurations of IXa and IXb are identical.

The nmr spectrum of the trans isomer of IXa in $CDCl_3$ at −30° showed a doublet at 1.38 ppm (3 H, $J = 6.5$ cps) due to the CH_3, an AB type quartet at 3.40 and 3.56 ppm (2 H, $J = 12$ cps) assigned to CH_2 between the NHC=O and the N in the 4 position, two triplets at 2.53 and 3.39 ppm (2 H, $J = 8.5$ cps) corresponding to the CH_2 of the oxazolidine ring, a multiplet at 4.0–4.60 ppm assignable to the CH adjacent to the O atom, a multiplet at 6.98 ppm (8 H) due to the H on the 2 arom rings, and an NHCO at 8.36 ppm. However, a doublet of low intensity due to the CH_3 of the cis isomer appeared at 1.25 ppm ($J = 6.5$ cps) after a few min at room temp and the proportion of the cis isomer increased by degrees until an equil mixt of the trans and cis isomers (nearly 3:2, respectively) in $CDCl_3$ was reached.

Alkylation of NH at the 7 Position of Benzo[6,7]-1,4-diazepino-[5,4-*b*]oxazole Derivative and Its Analog (IX).—The compd IX (1 mole) was mixed with NaOMe (1.2 moles) in MeOH at room temp and then MeOH was evapd under reduced pressure below 40°. To the residual oil was added 5 l. of DMF, and the mixt was stirred for 2 hr at room temp. The resulting MeOH was again evapd under reduced pressure at a low temp and then alkylating agent (2–3 moles) was added to the above mixt with stirring under ice-H_2O cooling. After standing overnight, the solvent was removed. The residue was dissolved in CH_2Cl_2, washed with H_2O, and dried (Na_2SO_4), and the solvent was evapd. The residual solid was recrystd from EtOH to give the product (Table III).

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(11) G. A. Sims, "Computing Methods and the Phase Problem in X-ray Crystal Analysis," R. Pepinsky, J. M. Robertson, and J. C. Speakman, Ed., Pergamon Press, Oxford, 1961, p 227.