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Neurotropic and Psychotropic Agents. VI.[1] 1-Alkoxymethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones[2]

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1-Alkoxymethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (II) were prepared by two methods: one was direct alkylation of 1,4-benzodiazepin-2-ones (I) with alkoxymethyl chlorides and the other was *via* 2-[*N*-(alkoxymethyl)phthalimidoacetamido]benzophenones (IV) which were prepared from the corresponding 2-(phthalimidoactamido)benzophenones (III) and alkoxymethyl chlorides. Certain compounds prepared had comparable activity to diazepam and chlorodiazepoxide in taming and anticonvulsant tests in mice.

Keywords——1-alkoxymethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one; 2-(phthalimidoacetamido)benzophenone; benzyloxymethyl chloride; pharmacological test; taming effect in mice; anticonvulsant effect in mice

Substituents at the 1-position of 1,4-benzodiazepine are known to enhance the pharmacological activity of these compounds and the effect of substituent at this position has been studied very extensively.[3] Although the 1-methoxymethyl-1,4-benzodiazepine derivatives are already known,[4] no information is available on the effect of a benzyloxymethyl group in the

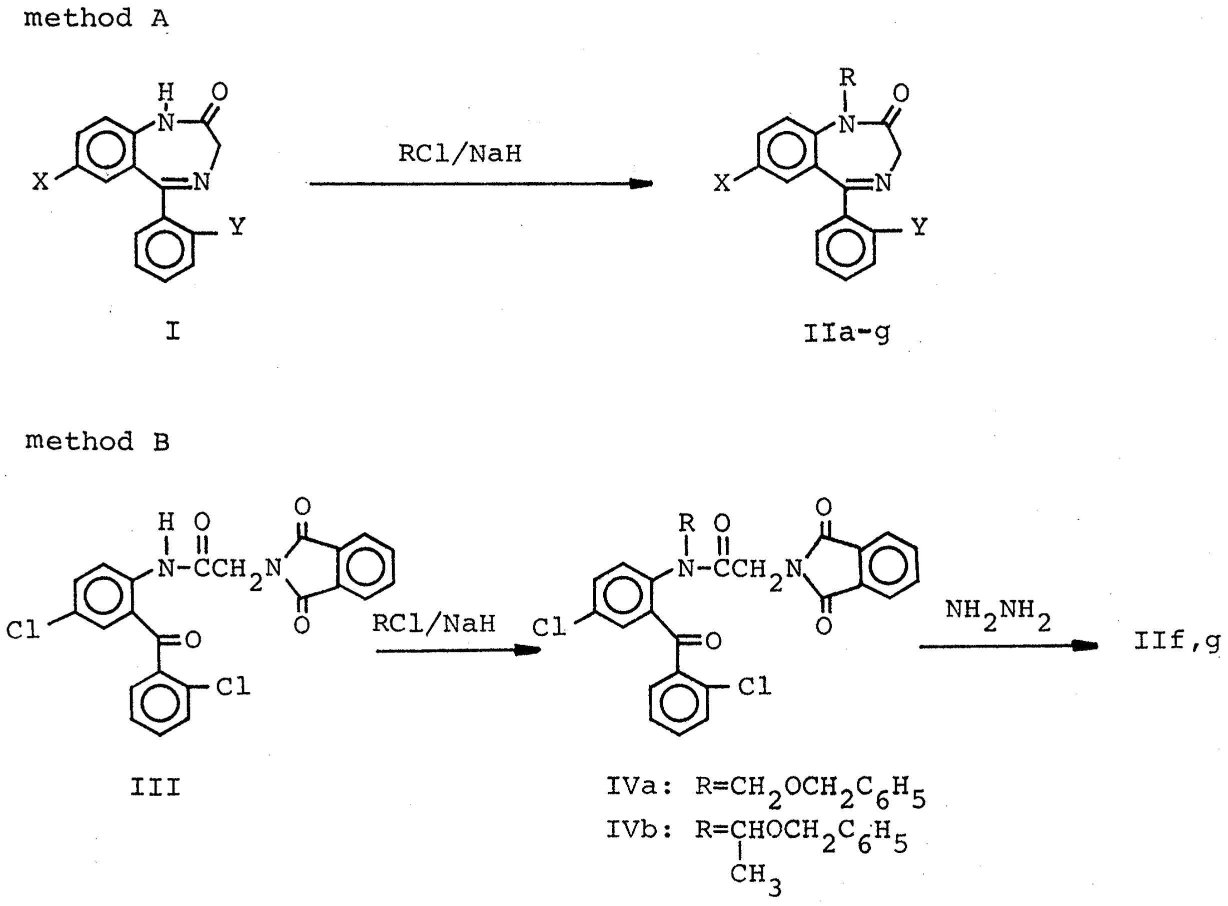
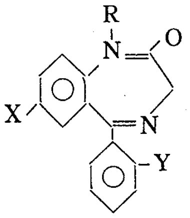


Chart 1

1-position on the biological activity. In the present paper, we describe the synthesis and pharmacological properties of some new 1-benzyloxymethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (II).

Two general methods for the preparation of the 1-benzyloxymethyl derivatives (II) were employed. Method A was a direct alkylation of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (I)[5] with benzyloxymethyl chlorides according to the method described in the literature.[4]

TABLE I. 1-Alkoxymethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (II)



Compd.	X	Y	R	Method	Yield (%)	mp (°C) (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
II-a[b]	NO_2	H	CH_2OCH_3			$C_{17}H_{15}N_3O_4$				
II-b	$SOCH_3$	H	CH_2OCH_3	A	54.9	Amorphous powder	$C_{18}H_{18}N_2O_3S$			
II-c	CF_3	H	CH_2OCH_3	A	53.2	122—123.5 (H)	$C_{18}H_{15}F_3N_2O_2$	62.07 (61.90	4.34 4.35	8.04 7.99)
II-d	NO_2	H	$CH_2OCH_2C_6H_5$	A	62.5	156—158 (E)	$C_{23}H_{19}N_3O_4$	68.82 (69.08	4.77 4.54	10.47 10.38)
II-e	NO_2	H	$CH_2OCH_2C_6H_4Cl$-*p*	A	16.5	146—147 (E)	$C_{23}H_{18}ClN_3O_4$	63.38 (63.60	4.16 4.01	9.64 9.44)
II-f	Cl	Cl	$CH_2OCH_2C_6H_5$	A B	38.3 60.7	103.5—106 (Et-P)	$C_{23}H_{18}Cl_2N_2O_2$	64.95 (64.79	4.27 4.20	6.59 6.36)
II-g	Cl	Cl	$\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{OCH_2C_6H_5}$	A B	34.0 53.5	120—122 (E—H)	$C_{24}H_{20}Cl_2N_2O_2$	65.61 (65.47	4.59 4.50	6.38 6.37)

a) B, benzene; E, ethanol; H, *n*-hexane; Et, ether; P, petroleum ether.
b) reference 4.

TABLE II. Pharmacological Activities of 1-Alkoxymethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (II) in Mice

Compd.	Anticonvulsant activity[a] (*p.o.*) Anti-electroshock	Taming activity[a] (*p.o.*) Anti-fighting
IIa	+++	++++
IIb	+	±
IIc	++	++
IId	+	+
IIe	±	±
IIf	+	+++
IIg	+	+++
Diazepam	++	+++
Chloridazepoxide	++	++

a) ++++ indicates 80% inhibition at a dose of 2 mg/kg.
+++ indicates 80% inhibition at a dose of 8 mg/kg.
++ indicates 80% inhibition at a dose of 32 mg/kg.
+ indicates 80% inhibition a dose of 125 mg/kg.
± indicates 80% inhibition at a dose of 500 mg/kg.

Method B consisted of alkylation of the 2-(phthalimidoacetamido)benzophenone (III), followed by construction of the 1,4-benzodiazepine ring.[6)] Acylation of 2-amino-5,2′-dichlorobenzophenone with phthalimidoacetyl chloride afforded III, which was alkylated with benzyloxymethyl chlorides in the presence of sodium hydride to give 2-[*N*-(benzyloxymethyl)phthalimidoacetamido]benzophenones (IV) in good yields. When the reaction was carried out with a base such as sodium amide, potassium *tert*-butoxide, triethylamine, or Triton B instead of sodium hydride, the compounds IV were produced in poor yields. Treatment of the alkylated phthalimido derivatives (IV) with hydrazine hydrate in refluxing ethanol effected removal of the phthalimido group and subsequent cyclization of the resulting amino derivatives to give II in good yields. Method B gave II in better yields than method A.

Pharmacological Properties

Most of the compounds were found to be active when screened for taming and anticonvulsant effects in mice. The methods used in these test have been described in the literature.[7)] The results are listed in Table II with the data for the reference compounds, diazepam and chlordiazepoxide. Compound IIa was more active than the reference compounds. Compounds IIc, IIf, and IIg were comparable in potency to the reference compounds. Compound IIb having a methylsulfinyl group at the 7-position was less active than compounds IIa and IIc and the reference compounds. As regards the substituents on the 1-position, introduction of the benzyloxymethyl group, which is bulkier than the methoxymethyl group, led to a slight decrease in both activities.

Experimental

All melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected.

1,3-Dihydro-2*H*-1,4-benzodiazepin-2-ones (I)[5)] and the phthalimido derivative (III)[6d)] were prepared according to the methods described in the literature. Benzyloxymethyl chloride,[8a)] *p*-chlorobenzyloxymethyl chloride,[8b)] and 1-benzyloxyethyl chloride were prepared according to the method of Hill and Keach.[8a)] Solvents used were dried over molecular sieves 3A overnight before use.

Preparation of 1-Benzyloxymethyl-7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (IIf) and Related Compounds——Method A: A 50% NaH dispersion in mineral oil (3.0 g) was added in small portions to a solution of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[5d)] (15.2 g) in dry tetrahydrofuran (THF) (200 ml) and the mixture was stirred for 1 h under reflux. Benzyloxymethyl chloride (10 g) was added dropwise to the resulting solution over 10 min with stirring. After being stirred for 3 h under ice-H_2O cooling and then standing overnight at room temperature, the mixture was concentrated *in vacuo*. The resulting residue was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed in benzene over alumina to give IIf (8.1 g).

Method B: Preparation of IIf from IVa——A mixture of IVa (970 mg) and 100% $NH_2NH_2 \cdot H_2O$ (250 mg) in EtOH (50 ml) was refluxed for 1 h with stirring, then concentrated *in vacuo*. Ice-H_2O was added to the resulting residue and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The resulting residue was triturated with *n*-hexane to give IIf (440 mg).

2-[*N*-(Benzyloxymethyl)phthalimidoacetamido]-5,2′-dichlorobenzophenone (IVa)——A 50% NaH dispersion mineral oil (150 mg) was added in small portions to a mixture of III (1.36 g) and benzyloxymethyl chloride (700 mg) in dry THF (50 ml) at room temperature with stirring. After being stirred for 2 h, the mixture was concentrated *in vacuo*. The resulting gum was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated *in vacuo*. The resulting residue was triturated with Et_2O to give IVa (0.91 g, 52.7%), mp 135—136.5°C (from EtOH). *Anal.* Calcd for $C_{31}H_{22}Cl_2N_2O_5$: C, 64.93; H, 3.87; N, 4.89; Cl, 12.37. Found: C, 64.64; H, 3.66; N, 4.83; Cl, 12.45.

IVb was prepared by a method similar to that used for IVa. Yield: 34.3%, mp 167—169°C (from EtOH). *Anal.* Calcd for $C_{32}H_{24}Cl_2N_2O_5$: C, 65.42; H, 4.12; N, 4.77; Cl, 12.07. Found: C, 65.19; H, 4.08; N, 4.70; Cl, 12.12.

Compounds II prepared by Methods A and B are listed in Table I.

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