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Neurotropic and Psychotropic Agents. VII.[1a] Synthesis and Pharmacological Properties of 2-(Alkoxyalkylamino)-3*H*-1,4-benzodiazepines

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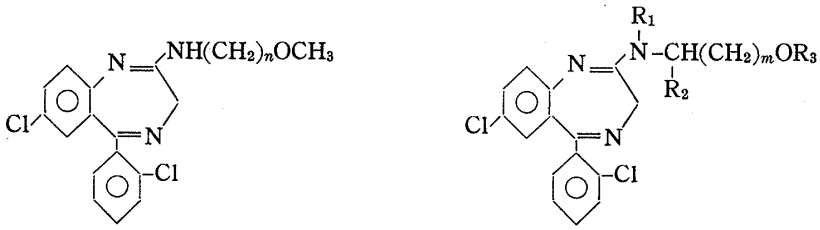
The synthesis and pharmacological properties of some 2-(alkoxyalkylamino)-3*H*-1,4-benzodiazepine derivatives (I and II) are described. Compounds I were prepared from the corresponding 2-methylthio-1,4-benzodiazepines and primary amines. Compounds II were prepared by alkylation of the corresponding 2-monoalkylamino-1,4-benzodiazepines with alkyl or alkoxyalkyl halides. The compounds (I and II) showed tranquilizing profiles like that of chlordiazepoxide in taming and anticonvulsant tests in mice.

Keywords——2-(alkoxyalkylamino)-3*H*-1,4-benzodiazepine; 2-monoalkylamino-3*H*-1,4-benzodiazepine; pharmacological test; taming effect in mice; anticonvulsant effect in mice

In the previous papers,[1] we described the synthesis and pharmacological properties of 2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine derivatives and 1-benzyloxymethyl-1,3-dihydro-1,4-benzodiazepin-2-one derivatives. In view of the pronounced central nervous system activities of these compounds, we thought it useful to study 2-(alkoxyalkylamino)-3*H*-1,4-benzodiazepines (I and II).

Compounds I were prepared from 7-chloro-5-(2-chlorophenyl)-2-methylthio-3*H*-1,4-benzodiazepine[2] and the corresponding methoxyalkylamines according to the procedures described in the literature.[3] 2-Dialkylamino-3*H*-1,4-benzodiazepines (II) were prepared by *N*-alkylation of 7-chloro-5-(2-chlorophenyl)-2-monoalkylamino-3*H*-1,4-benzodiazepines with corresponding alkyl or alkoxyalkyl halides in the presence of sodium hydride in *N*,*N*-dimethylformamide.[4]



I-1: $n=2$
I-2: $n=3$

II

Fig. 1

The physical data for 2-dialkylamino derivatives (II) thus obtained are summarized, together with the reaction conditions, in Table I.

Pharmacological Results

The 2-(alkoxyalkylamino) derivatives (I and II) prepared here were screened for usual central nervous system effects, taming and anticonvulsant activities, in laboratory animals according to the procedures described in the literature.[5] Compounds I and II showed tranquilizing profiles essentially like that of chlordiazepoxide (Table II). The compounds tested were less active in the mice-taming test than chlordiazepoxide, while compounds I-1, II-1, II-2, II-4, II-5, and II-9 showed more potent anti-metrazole activity in mice than chlordi-

Table I. 2-Dialkylamino-3*H*-1,4-benzodiazepines (II)

Compd.	R_1	$-CH(CH_2)_mOR_3$ (R_2)			Alkylating agent[d]	Reaction time		mp (°C) (Solvent)[c]	Yield (%)	Formula	Analysis (%) Calcd (Found)		
		R_2	R_3	m		(°C)	(h)				C	H	N
II-1	CH_3	H	CH_3	0	A	[a]		111—112.5 (H-E)	38.4	$C_{18}H_{17}Cl_2N_3O$	59.68 (59.44	4.73 4.68	11.60 11.47)
II-2	CH_3	H	$CH_2C_6H_5$	0	A	[b]		83.5—86.5 (H-CH-E)	42.1	$C_{24}H_{21}Cl_2N_3O$	65.76 (65.69	4.83 4.75	9.59 9.71)
II-3	CH_3	CH_3	$CH_2C_6H_5$	0	A	5	3/4	115.5—117.5 (H-E)	24.6	$C_{25}H_{23}Cl_2N_3O$	66.37 (66.48	5.12 5.07	9.29 9.24)
II-4	CH_3	H	CH_3	1	C	5	1.0	112—115 (H-E)	70.3	$C_{19}H_{19}Cl_2N_3O$	60.65 (60.59	5.09 5.04	11.17 11.26)
II-5	CH_3	H	$CH(CH_3)_2$	1	B	1	3.5	82.5—85 (H-P)	67.8	$C_{21}H_{23}Cl_2N_3O$	62.38 (62.40	5.73 5.70	10.39 10.29)
II-6	CH_3	H	CH_3	2	C	[a]		Oil	99.4	$C_{20}H_{21}Cl_2N_3O$	—	—	—
II-7	CH_2CH_3	H	CH_3	0	A	20	1.5	98.5—101 (H—E)	23.8	$C_{19}H_{19}Cl_2N_3O$	60.65 (60.53	5.09 4.98	11.17 11.09)
II-8	$CH(CH_3)_2$	H	CH_3	0	A	5	1.5	159.5—161 (E)	23.1	$C_{20}H_{21}Cl_2N_3O$	61.54 (61.33	5.42 5.45	10.77 10.54)
II-9		H	CH_3	0	A	20	1.5	68—82 (P)	21.3	$C_{20}H_{19}Cl_2N_3O$	61.86 (61.70	4.93 4.83	10.82 10.74)
II-10		H	CH_3	0	A	5	2.0	144.5—146.5 (H-E)	4.6	$C_{23}H_{25}Cl_2N_3O$	64.19 (64.28	5.86 5.71	9.76 9.83)

[a] Reacted at 5°C for 1 h, then at 20°C for 1 h.
[b] Reacted at 5°C for 20 min, then at 20°C for 20 min.
[c] H, *n*-hexane; E, ethanol; CH, cyclohexane; P, petroleum ether.
[d] A, $R_3O(CH_2)_mCHClR_2$; B, $(CH_3)_2CHOCH_2CH_2Br$; C, CH_3I.

Table II. Pharmacological Activities of 2-(Alkoxyalkylamino)-7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepines (I and II) in Mice

Compd.	Taming activity Anti-fighting ED_{50} (mg/kg *p.o.*)	Anticonvulsant activity Anti-metrazole ED_{50} (mg/kg *p.o.*)
I-1	3.99	1.83
I-2	18.23	6.32
II-1	5.26	4.02
II-2	7.86	4.98
II-3	34.57	16.00
II-4	3.50	1.65
II-5	8.00	1.99
II-6	6.57	5.66
II-7	23.78	6.76
II-8	34.57	9.95
II-9	3.99	3.51
II-10	*a*)	*a*)
Chlordiazepoxide	0.57	5.22
Diazepam	0.23	1.17

a) $ED_{50} > 125$ mg/kg.

azepoxide. Thus, introduction of an alkoxyalkylamino group did not improve these activities and led to a significant decrease in taming activity.

Experimental[6]

Solvents used were dried over molecular sieves 3A before use.

Benzyloxymethyl chloride,[7a] 2-isopropoxyethyl bromide,[7b] and 1-benzyloxyethyl chloride[1a] were prepared by the methods described in the literature.

7-Chloro-5-(2-chlorophenyl)-2-monoalkylamino-3*H*-1,4-benzodiazepines were prepared according to the method described in the literature.[3]

7-Chloro-5-(2-chlorophenyl)-2-(2-methoxyethylamino)-3*H*-1,4-benzodiazepine (I-1)——Compound I-1 was prepared from 7-chloro-5-(2-chlorophenyl)-2-methylthio-3*H*-1,4-benzodiazepine[2] (66.8 g) and 2-methoxyethylamine (500 ml) according to the method described in the literature.[3] Yield: 78.6%, mp 185—189°C (from EtOH). *Anal.* Calcd for $C_{18}H_{17}Cl_2N_3O$: C, 59.68; H, 4.73; N, 11.60. Found: C, 59.57; H, 4.72; N, 11.61.

7-Chloro-5-(2-chlorophenyl)-2-(3-methoxypropylamino)-3*H*-1,4-benzodiazepine was prepared by a similar method. Yield: 89.1%. mp 175.5—179°C (from $CH_3O(CH_2)_3NH_2$). *Anal.* Calcd for $C_{19}H_{19}Cl_2N_3O$: C, 60.65; H, 5.09; N, 11.17. Found: C, 60.64; H, 5.10; N, 11.16.

7-Chloro-5-(2-chlorophenyl)-2-(*N*-benzyloxymethyl-*N*-methylamino)-3*H*-1,4-benzodiazepine (II-2)——A 50% NaH dispersion in mineral oil (2.03 g) was added in small portions to a suspension of 7-chloro-5-(2-chlorophenyl)-2-methylamino-3*H*-1,4-benzodiazepine[8] (10.0 g) in dry dimethylformamide (DMF) (45 ml) with stirring under ice-H_2O cooling. After 40 min of stirring, benzyloxymethyl chloride (6.64 g) was added to the resulting solution at 5°C. After the mixture had been stirred for 20 min at 5°C, additional benzyloxymethyl chloride (1.30 g) was added with stirring. After being allowed to warm up to 20°C and then being stirred for 20 min, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on alumina with benzene. The first eluate gave II-2 (5.8 g).

Compounds prepared are summarized, together with the reaction conditions, in Table I.

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References and Notes

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