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Neurotropic and Psychotropic Agents. VII.^{1a)} Synthesis and Pharmacological Properties of 2-(Alkoxyalkylamino)-3H-1,4-benzodiazepines

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The synthesis and pharmacological properties of some 2-(alkoxyalkylamino)-3H-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)-3H-1,4-benzodiazepine; 2-monoalkylamino-3H-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)-3H-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)-3H-1,4-benzodiazepines (I and II).

Compounds I were prepared from 7-chloro-5-(2-chlorophenyl)-2-methylthio-3H-1,4-benzodiazepine²⁾ and the corresponding methoxyalkylamines according to the procedures described in the literature.³⁾ 2-Dialkylamino-3H-1,4-benzodiazepines (II) were prepared by *N*-alkylation of 7-chloro-5-(2-chlorophenyl)-2-monoalkylamino-3H-1,4-benzodiazepines with corresponding alkyl or alkoxyalkyl halides in the presence of sodium hydride in *N,N*-dimethylformamide.⁴⁾

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) _m OR ₃			Alkylating ^{a)} agent	Reaction time (°C) (h)	mp (°C) (Solvent) ^{e)}	Yield (%)	Formula	Analysis (%)		
		R ₂	R ₃	m						Calcd	Found	
II-1	CH ₃	H	CH ₃	0	A	a)	111–112.5 (H–E)	38.4	C ₁₃ H ₁₇ Cl ₂ N ₃ O	59.68 (59.44)	4.73 4.68	11.60 11.47
II-2	CH ₃	H	CH ₂ C ₆ H ₅	0	A	b)	83.5–86.5 (H–CH–E)	42.1	C ₂₄ H ₂₁ Cl ₂ N ₃ O	65.76 (65.69)	4.83 4.75	9.59 9.71
II-3	CH ₃	CH ₃	CH ₂ C ₆ H ₅	0	A	5 3/4	115.5–117.5 (H–E)	24.6	C ₂₃ H ₂₃ Cl ₂ N ₃ O	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 ₂ N ₃ O	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 ₂ N ₃ O	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 ₂ N ₃ O	—	—	—
II-7	CH ₂ CH ₃	H	CH ₃	0	A	20 1.5	98.5–101 (H–E)	23.8	C ₁₉ H ₁₉ Cl ₂ N ₃ O	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 ₂ N ₃ O	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 ₂ N ₃ O	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 ₂ N ₃ O	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, R₃O(CH₂)_mCHCl; B, (CH₃)₂CHOCH₂CH₂Br; C, CH₃I.R₂

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 <i>p.o.</i>)	Anticonvulsant activity Anti-metrazole ED ₅₀ (mg/kg <i>p.o.</i>)
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) ED₅₀ > 125 mg/kg.

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

Experimental⁶⁾

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-benzodiazepine²⁾ (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 C₁₈H₁₇Cl₂N₃O: 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 CH₃O(CH₂)₃NH₂). *Anal.* Calcd for C₁₉H₁₉Cl₂N₃O: 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-benzodiazepine⁸⁾ (10.0 g) in dry dimethylformamide (DMF) (45 ml) with stirring under ice-H₂O 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-H₂O and extracted with AcOEt. The extract was washed with brine, dried over MgSO₄ 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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