POLYCYCLIC N-HETERO COMPOUNDS. XXVIII. SYNTHESIS AND ANTIDEPRESSIVE EVALUATION OF 4-SUBSTITUTED 9-CHLORO-6,7-DIHYDRO-5H-PYRIMIDO[5,4-d][1]BENZAZEPINE

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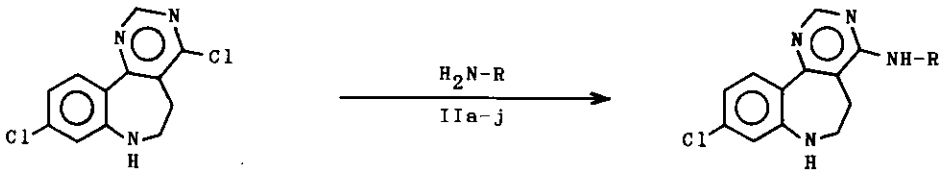
Abstract - 4-Substituted 9-chloro-6,7-dihydro-5H-pyrimido[5,4-d]-[1]benzazepines (IIIa-j) were synthesized by the reaction of 4,9-dichloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (I) with amines (IIa-j) and their antidepressive activities were investigated.

In our earlier study of the structure-activity relationship of antidepressive azasteroids, we reported that some 4-substituted 5,6-dihydrobenzo[h]-quinazolines[1] and 6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepines[2] exhibited anti-reserpine action, an indication of antidepressive activity. In a previous paper[3], we also reported the synthesis of 8-chloro-5,6-dihydro-4H-imidazo-[1',2':1,6]pyrimido[5,4-d][1]benzazepines, corresponding to a B-homo-6,11,13,15-tetraazasteroid. 4,9-Dichloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (I), a starting material of the above tetraazasteroids, seemed to be a useful intermediate for the preparation of 4-substituted 9-chloro-6,7-dihydro-5H-pyrimido-[5,4-d][1]benzazepines (III) to investigate an effect of 9-chloro atom of 4-substituted 6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepines. This paper deals with the synthesis of III and evaluation of their antidepressive activity.
As shown in Scheme 1, primary alkylamines (IIa-h) were allowed to react with I to obtain 4-alkylamino-9-chloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepines (IIIa-h). The 4-hydrazino derivative (IIIi) was prepared by the reaction of I with hydrazine hydrate in refluxing methanol. The 4-amino derivative (IIIj) could not be obtained in satisfactory yield by the reaction of I with an ammonia



I IIIa-j

IIa: R = $CH_2CH_2NMe_2$ f: R = $CH_2CH_2CH_2OMe$

b: R = $CH_2CH_2CH_2NMe_2$ g: R = $CH_2CH_2CH_2OH$

c: R = CH_2CH_2-N⟨O⟩ h: R = $CH_2CH(OH)CH_2OH$

d: R = $CH_2CH_2CH_2$-N⟨O⟩ i: R = NH_2

e: R = CH_2CH_2OMe j: R = H

Scheme 1

stream in ordinary organic solvents. However, IIIj was obtained in 50% yield when a solution of I in formamide was heated under an ammonia stream. Evaluation of the antidepressive activity of these compounds (III) was performed by the inhibition against reserpine-induced hypothermia in mice[4] and compared with that of control. Compounds IIIe and IIIg exhibited a antireserpine action.

Table I Effects of IIIe, IIIg, and XIb[3] on Reserpine-Induced Hypothermia in Mice

Compd.	Body temperature (°C) mean value ± SD				
	Before administration	Time after administration			
		30 min	1 h	2 h	4 h
saline	24.9 ± 0.3	26.2 ± 0.9	27.0 ± 0.9	28.2 ± 0.8	28.9 ± 0.6
IIIe	24.9 ± 0.8	27.7 ± 1.5	28.7 ± 1.7	30.8 ± 0.9*	32.6 ± 0.7*
IIIg	25.1 ± 0.7	27.3 ± 1.3	29.3 ± 1.0*	30.1 ± 1.2*	29.4 ± 1.9
XIb	24.7 ± 0.4	26.3 ± 1.0	27.3 ± 0.8	30.3 ± 1.3*	31.9 ± 1.2*

Five male ICR-JCL mice weighing 23 to 28 g were used in all experiments and test compounds (10 mg/kg, i.p.) were injected 18 hours following the administration of reserpine (2 mg/kg, i.p.) to mice.

* Significantly different from the control at $p<0.05$.

Table II Reaction Conditions, Appearrances, Melting Points, and Yields of III

Compd.	React. condition		Appearrance (Recryst. solv.)	Mp (°C)	Yield (%)
	Temp. (°C)	Time (h)			
IIIa	65	2	pale yellow prisms (acetonitrile)	128.5-130.5	85
IIIb	70-75	2	yellow oil		96
IIIc	75	2	pale yellow prisms (acetone)	194-196	77
IIId	70	2	pale yellow prisms (benzene)	172-173	81
IIIe	60-65	4	pale yellow needles (acetonitrile)	136.5-138	94
IIIf	65-70	2	pale yellow plates (diethyl ether)	126-127	89
IIIg	70	2	pale yellow prisms (acetone)	189-190.5	88
IIIh	refluxed in benzene	7	pale yellow prisms (as HCl salt) (ethanol-dioxane)	204-206	72
IIIi	refluxed in methanol	12	greenish yellow plates (methanol)	238-239.5	86
IIIj	a)	a)	pale yellow prisms (diluted ethanol)	189-192	50

a) refer to experimental section.

The B-homotetraazasteroids and related compounds in our earlier paper[3] in this Journal (compound No. in the literature: VIIIb, IXb, Xb, XIb, and XIIIb) were also screened, and 9-chloro-4-(2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido-[5,4-d][1]benzazepine (XIb) exhibited positive action. These positive data are shown in Table I.

Physical data of III are listed in Tables II, III, and IV.

EXPERIMENTAL

Mps were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Japan Spectroscopic

Table III Elemental Analyses and Ms and Ir Spectral Data of III

Compd.	Formula	Analysis (%) Calcd (Found)			Ms (m/z)[a]		Ir (cm^{-1})[b]
		C	H	N	M^+	Base peak	
IIIa	$C_{16}H_{20}ClN_5$	60.47	6.34	22.04	317	246	3320, 3280
		(60.20	6.26	21.86)			
IIIb	$C_{17}H_{22}ClN_5$	61.53	6.68	21.10	331	245	3300
		(61.27	6.81	20.88)			
IIIc	$C_{18}H_{22}ClN_5O$	60.08	6.16	19.46	359	246	3380, 3250
		(60.06	6.17	19.20)			
IIId	$C_{19}H_{24}ClN_5O$	61.04	6.47	18.73	373	245	3350, 3270
		(61.10	6.51	18.69)			
IIIe	$C_{15}H_{17}ClN_4O$	59.11	5.62	18.38	304	273	3380, 3290
		(59.00	5.54	18.08)			
IIIf	$C_{16}H_{19}ClN_4O$	60.28	6.01	17.57	318	273	3310, 3280
		(60.10	5.99	17.40)			
IIIg	$C_{15}H_{17}ClN_4O$	59.11	5.62	18.38	304	273	3360, 3120
		(59.28	5.70	18.12)			
IIIh	$C_{15}H_{17}ClN_4O_2 \cdot HCl$	50.43	5.07	15.68	320[c]	289	3285
		(50.18	5.04	15.46)			
IIIi	$C_{12}H_{12}ClN_5$	55.07	4.62	26.76	261	261	3310
		(55.06	4.48	26.49)			
IIIj	$C_{12}H_{11}ClN_4$	58.42	4.49	22.71	246	246	3400, 3320
		(58.50	4.43	22.66)			3170

a) a molecular ion showed a +2 isotope peak amounting to about one third of the intensity. b) in KBr pellet except for IIIb (neat); N-H and/or O-H. c) M - HCl; the molecular ion peak was not observed.

A-102 diffraction grating infrared spectrophotometer. The nmr spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard. The ms spectra were taken with a Shimadzu LKB-9000 instrument at 70 eV.

General Procedure for Preparation of 4-Alkylamino-9-chloro-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines (IIIa-g)

A mixture of 1 mM of I and 8 mM of an alkylamine (IIa-g) was heated under appropriate conditions (Table II). After evaporation of the alkylamine *in vacuo* the residue was basified with 10% Na_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was recrystallized from an appropriate solvent (Table II).

Table IV Nmr Spectral Data of III

Compd.	Nmr δ (J in Hz)
IIIa[a]	2.20 (6H, s, NMe_2), 2.39-2.77 (4H, m, 5-H and $C\underline{H}_2NMe_2$), 3.37-3.53 (4H, m, 6-H and $NHC\underline{H}_2$), 6.3 and 6.8[c], 6.69[d] (J = 8.4, 2.4), 6.84[e] (J = 2.4), 7.98[f] (J = 8.4), 8.36[g]
IIIb[b]	1.52-1.91 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.28 (6H, s, NMe_2), 2.32-2.83 (4H, m, 5-H and $C\underline{H}_2NMe_2$), 3.51-3.73 (4H, m, 6-H and $NHC\underline{H}_2$), 4.0 and 7.5[c], 6.69[e] (J = 2.1), 6.90[d] (J = 8.4, 2.1), 8.05[f] (J = 8.4), 8.55[g]
IIIc[a]	2.40-2.77 (8H, m, 5-H and $NHCH_2C\underline{H}_2N(C\underline{H}_2)_2$), 3.43-3.66 (8H, m, 6-H, $O(CH_2)_2$, and $NHC\underline{H}_2$), 3.8 and 6.2[c], 6.69[d] (J = 8.4, 2.4), 6.84[e] (J = 2.4), 8.00[f] (J = 8.4), 8.37[g]
IIId[b]	1.83 (2H, quin, J = 5.0, $CH_2C\underline{H}_2CH_2$), 2.46-2.78 (8H, m, 5-H and $NHCH_2CH_2C\underline{H}_2N(C\underline{H}_2)_2$), 3.49-3.80 (8H, m, 6-H, $NHC\underline{H}_2$ and $O(CH_2)_2$), 4.1 and 6.6[c], 6.68[e] (J = 2.1), 6.89[d] (J = 8.4, 2.1), 8.08[f] (J = 8.4), 8.56[g]
IIIe[a]	2.72[h] (J = 5.0), 3.28 (3H, s, OMe), 3.32-3.60 (6H, m, 6-H and CH_2CH_2O), 6.3 and 7.0[c], 6.71[d] (J = 8.4, 2.0), 6.84[e] (J = 2.0), 7.99[f] (J = 8.4), 8.38[g]
IIIf[b]	1.92 (2H, quin, J = 5.7, $CH_2C\underline{H}_2CH_2$), 2.63[h] (J = 5.7), 3.38 (3H, s, OMe), 3.47-3.71 (6H, m, 6-H and $C\underline{H}_2CH_2C\underline{H}_2$), 4.1 and 5.7[c], 6.69[e] (J = 2.1), 6.90[d] (J = 8.1, 2.1), 8.07[f] (J = 8.1), 8.57[g]
IIIg[a]	1.73 (2H, quin, J = 6.8, $CH_2C\underline{H}_2CH_2$), 2.72[h] (J = 5.1), 3.34-3.56 (6H, m, 6-H and $C\underline{H}_2CH_2C\underline{H}_2$), 4.5, 6.3, and 7.0 (each 1H, each br, D_2O exchangeable, 2 x NH and OH), 6.73[d] (J = 8.4, 2.0), 6.86[e] (J = 2.0), 8.01[f] (J = 8.4), 8.36[g]
IIIh[a,i]	2.94 (2H, br s, 5-H), 3.40-4.50 (10H, m, 6-H, $C\underline{H}_2C\underline{H}(OH)C\underline{H}_2OH$, and NH and/or OH; changed to 7H after addition of D_2O), 6.80[d] (J = 8.5, 2.0), 6.99[e] (J = 2.0), 7.51[f] (J = 8.5), 8.63[g], 8.94 (1H, br, D_2O exchangeable, NH or OH)
IIIi[a]	2.70[h] (J = 5.0), 3.1-4.5 (3H, br, D_2O exchangeable, 3 x NH), 3.44[j] (J = 5.0), 6.3[k], 6.71[d] (J = 8.1, 2.4), 6.84[e] (J = 2.4), 8.03[f] (J = 8.1), 8.45[g]
IIIj[a]	2.73[h] (J = 5.0), 3.49[j] (J = 5.0), 6.3[k], 6.63-6.74 (3H, m, 10-H and NH_2; changed to dd after addition of D_2O; J = 8.5, 2.5), 6.83[e] (J = 2.5), 7.98[f] (J = 8.5), 8.28[g]

a) in DMSO-d_6. b) in $CDCl_3$. c) each 1H, each br, D_2O exchangeable, 2 x NH. d) 1H, dd, 10-H. e) 1H, d, 8-H. f) 1H, d, 11-H. g) 1H, s, 2-H. h) 2H, t, 5-H. i) as HCl salt. j) 2H, t, 6-H. k) 1H, br, D_2O exchangeable, NH.

4-(2,3-Dihydroxypropylamino)-9-chloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (IIIh)

A solution of 0.27 g (1 mM) of I and 0.91 g (10 mM) of DL-3-amino-1,2-propanediol in 5 ml of dry dioxane was refluxed for 5 h. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml of 2N HCl and the solution was evaporated again. The residue was allowed to stand for several days in a refrigerator. The resulting crystals were recrystallized from EtOH-dioxane to give IIIh as monohydrochloride.

4-Hydrazino-9-chloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (IIIi)

A solution of 2.0 g (7.5 mM) of I and 2.3 ml (38 mM) of 85% $NH_2NH_2 \cdot H_2O$ in 200 ml of MeOH was refluxed for 12 h under nitrogen. The reaction mixture was evaporated to dryness and 10 ml of 0.5N NaOH was added to the residue. After cooling, the precipitated solid was filtered and recrystallized from MeOH to give 1.7 g (86%) of IIIi.

4-Amino-9-chloro-5,6-dihydro-5H-pyrimido[5,4-d][1]benzazepine (IIIj)

A mixture of 6.6 g (25 mM) of I and 60 ml of $HCONH_2$ was heated at 160-170 °C for 8 h under NH_3 stream. The reaction mixture was concentrated to *ca.* 20 ml and cooled. The precipitated crystals were collected and recrystallized from diluted EtOH to give 3.0 g (50%) of IIIj as pale yellow prisms.

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REFERENCES AND NOTES

1 T. Hirota, K. Kawanishi, K. Sasaki, and T. Namba, Chem. Pharm. Bull., 1986, 34, 3011.

2 T. Hirota, M. Fukumoto, and K. Sasaki, Heterocycles, 1986, 24, 1997.

3 T. Hirota, M. Fukumoto, K. Sasaki, T. Namba, and S. Hayakawa, Heterocycles, 1986, 24, 143.

4 B. M. Askew, Life Sci., 1963, 2, 725.

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