POLYCYCLIC N-HETERO COMPOUNDS. XXVI[1]. SYNTHESIS OF 4-SUBSTITUTED 6,7-DIHYDRO-5H-PYRIMIDO-[5,4-d][1]BENZAZEPINE

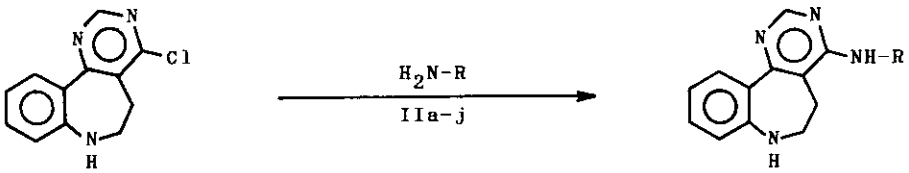
Takashi Hirota*, Masami Fukumoto, and Kenji Sasaki

Faculty of Pharmaceutical Sciences, Okayama University
Tsushima, Okayama 700, Japan

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

In our study of the structure-activity relationship of antidepressive aza-steroids, some 4-alkylamino-5,6-dihydrobenzo[h]quinazolines exhibited anti-reserpine action, an indication of antidepressive activity[2]. In a previous paper[3], we reported the synthesis of 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-Chloro-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 6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepines (III) that are regarded as ring system analogs of the 5,6-dihydrobenzo[h]quinazo-lines[2]. This paper deals with the synthesis of III and investigation of their antidepressive activity.

As shown in Scheme 1, primary alkylamines (IIa-h) were allowed to react with I to obtain 4-alkylamino-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 stream in ordinary organic solvents. However, IIIj was obtained in 45% yield when a solution of I in formamide was heated under an ammonia stream. Analogous



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

reaction in an autoclave also afforded IIIj in 87% yield. Physical data of III are listed in Tables I, II, and III.

The antidepressive activity of these compounds (III) was screened by the inhibition against reserpine-induced hypothermia in mice[4] and compared with that of control. Compound IIIi exhibited a weak antireserpine action. The B-homotetraazasteroids and related compounds in our earlier paper[3] in this Journal (compound No. in the literature: VIIIa, IXa, Xa, XIa, and XIIIa) were also screened, but did not exhibit any noticeable activity.

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 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.

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

Compd.	React. Condition		Appearrance (Recryst. Solv.)	Mp (°C)	Yield (%)
	Temp. (°C)	Time (h)			
IIIa	65-70	2	pale yellow prisms (ethyl acetate)	145-146	52
IIIb	60-70	2	yellow oil		98
IIIc	70	2	pale yellow prisms (diethyl ether)	142-143	94
IIId	55	3	pale yellow needles (benzene)	146-147	93
IIIe	60-65	4	pale yellow prisms (dichloromethane)	82-83	47
IIIf	65-70	2	yellow oil		95
IIIg	70	2	pale greenish yellow prisms (ethanol)	174-175	93
IIIh	a)	7	pale yellow prisms[b] (as 2HCl salt)	215-217	81
IIIi	c)	6	greenish yellow plates (methanol)	193-194	86
IIIj	d)	d)	pale yellow plates (ethyl acetate)	194-195	87

a) refluxed in benzene. b) not recrystallized. c) refluxed in methanol. d) method B.

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

A mixture of 1 mM of I and 7 mM of an alkylamine (IIa-g) was heated under appropriate conditions (Table I). 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 I).

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

A solution of 403 mg (1.74 mM) of I and 0.40 ml (5.22 mM) of DL-3-amino-1,2-propanediol in 2 ml of dry benzene was refluxed for 7 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

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

Compd.	Formula	Analysis (%) Calcd (Found)			Ms (m/z)		Ir (cm^{-1})[a]
		C	H	N	M^+	Base Peak	
IIIa	$C_{16}H_{21}N_5$	67.82	7.47	24.71	283	212	3300
		(67.61	7.51	24.46)			
IIIb	$C_{17}H_{23}N_5$	68.66	7.79	23.55	297	211	3320
		(68.41	7.82	23.36)			
IIIc	$C_{18}H_{23}N_5O$	66.44	7.12	21.52	325	212	3350, 3220
		(66.30	7.11	21.36)			
IIId	$C_{19}H_{25}N_5O$	67.23	7.42	20.63	339	211	3370, 3260
		(67.03	7.48	20.45)			
IIIe	$C_{15}H_{18}N_4O$	66.65	6.71	20.73	270	239	3380, 3310
		(66.49	6.71	20.64)			
IIIf	$C_{16}H_{20}N_4O$	67.58	7.09	19.70	284	239	3340
		(67.30	7.13	19.45)			
IIIg	$C_{15}H_{18}N_4O$	66.65	6.71	20.73	270	239	3330, 3280
		(66.66	6.82	20.44)			3210
IIIh	$C_{15}H_{18}N_4O_2 \cdot 2HCl$	50.15	5.61	15.60	286[b]	255	3340, 3220,
		(49.95	5.55	15.51)			3000-2300
IIIi	$C_{12}H_{13}N_5$	63.42	5.77	30.82	227	227	3420, 3310,
		(63.47	5.65	30.79)			3280, 3190
IIIj	$C_{12}H_{12}N_4$	67.90	5.70	26.40	212	212	3410, 3300,
		(67.83	5.65	26.31)			3130

a) in KBr pellet except for IIIb and IIIf (neat); N-H and/or O-H. b) M - 2HCl; parent peak was not observed.

overnight in a refrigerator. The resulting crystals were washed with 10 ml of cold MeOH and dried.

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

A solution of 5.0 g (21.6 mM) of I and 6.2 ml (108 mM) of 85% $NH_2NH_2 \cdot H_2O$ in 200 ml of MeOH was refluxed for 6 h under nitrogen. The reaction mixture was evaporated to dryness and 30 ml of 0.5N NaOH was added to the residue. After trituration, the solid was filtered and recrystallized from MeOH to give 4.22 g (86%) of IIIi.

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

Method A: A mixture of 7.01 g (30.3 mM) of I and 10 ml of $HCONH_2$ was heated at 160-165 °C for 8 h under NH_3 stream. After cooling, the precipitated crystals

Table III Nmr Spectral Data of III

Compd.	Nmr δ (J in Hz)
IIIa[a]	2.26 (6H, s, NMe_2), 2.49-2.73 (4H, m, 5-H and $C\underline{H}_2NMe_2$), 3.40-3.77 (4H, m, 6-H and $C\underline{H}_2CH_2NMe_2$), 3.9 and 5.5[c], 6.70[d] (J = 7.5, 1.8), 7.17 (2H, m, 9- and 10-H), 8.08[e] (J = 7.5, 2.0), 8.60[f]
IIIb[a]	1.78 (2H, m, $C\underline{H}_2CH_2NMe_2$), 2.28 (6H, s, NMe_2), 2.38-2.67 (4H, m, 5-H and $C\underline{H}_2NMe_2$), 3.4 and 7.4[c], 3.62 (4H, m, 6-H and $NHC\underline{H}_2$), 6.68[d] (J = 7.5, 1.8), 6.96[g] (J = 7.5, 1.8), 7.21[h] (J = 7.5, 2.4), 8.04[e] (J = 7.5, 2.4), 8.58[f]
IIIc[a]	2.46-2.76 (8H, m, 5-H and $N(CH_2)_3$), 3.50-3.77[i], 5.6[j], 6.72[d] (J = 7.5, 1.5), 6.98[g] (J = 7.5, 1.5), 7.24[h] (J = 7.5, 2.0), 8.11[e] (J = 7.5, 2.0), 8.63[f]
IIId[a]	1.84 (2H, quin, J = 6.0, $CH_2C\underline{H}_2CH_2$), 2.50 (4H, t, J = 6.0, $N(CH_2)_2$), 2.65 (4H, m, 5-H and $NHCH_2CH_2C\underline{H}_2N$=), 3.61 (4H, m, 6-H and $NHC\underline{H}_2$), 3.71 (4H, t, J = 6.0, $O(CH_2)_2$), 3.9 and 6.7[c], 6.72[d] (J = 7.7, 1.2), 6.98[g] (J = 7.7, 1.2), 7.23[h] (J = 7.7, 1.8), 8.09[e] (J = 7.7, 1.8), 8.61[f]
IIIe[a]	2.67[k] (J = 5.7), 3.40 (3H, s, OMe), 3.67 (6H, m, 6-H and CH_2CH_2O), 3.8 and 5.2[c], 6.71[d] (J = 8.1, 1.5), 6.97[g] (J = 8.1, 1.5), 7.21[h] (J = 8.1, 2.0), 8.08[e] (J = 8.1, 2.0), 8.61[f]
IIIf[a]	1.93 (2H, quin, J = 5.9, $CH_2C\underline{H}_2CH_2$), 2.63[k] (J = 5.7), 3.37 (3H, s, OMe), 3.62[l], 5.7[j], 6.71[d] (J = 7.7, 1.4), 6.97[g] (J = 7.7, 1.4), 7.22[h] (J = 7.7, 1.9), 8.07[e] (J = 7.7, 1.9), 8.60[f]
IIIg[a]	1.74 (2H, quin, J = 6.6, $CH_2C\underline{H}_2CH_2$), 2.70[k] (J = 5.3), 3.46 (6H, m, 6-H and $C\underline{H}_2CH_2C\underline{H}_2O$), 4.4, 5.8, and 6.9 (each 1H, each br, D_2O exchangeable, 2 x NH and OH), 6.73 (2H, m, 8- and 10-H), 7.14[h] (J = 8.0, 1.5), 7.93[e] (J = 8.0, 1.5), 8.38[f]
IIIh[b,m]	2.92 (2H, br s, 5-H), 3.41-3.83[n], 6.90-7.79[o], 8.79[f], 9.45 (1H, br, D_2O exchangeable, NH or OH)
IIIi[b]	2.68[k] (J = 5.1), 3.1-4.5 (3H, br, D_2O exchangeable, 3 x NH), 3.49[p] (J = 5.1), 5.8[j], 6.64 and 6.81 (each 1H, each m, 8- and 10-H), 7.14[h] (J = 8.1, 1.7), 7.97[e] (J = 8.1, 1.7), 8.45[f]
IIIj[b]	2.71[k] (J = 5.0), 3.53[p] (J = 5.0), 5.9[j], 6.63-6.79[q], 7.15 (1H, m, 9-H), 7.95[e] (J = 7.8, 1.5), 8.29[f]

a) in $CDCl_3$. b) in DMSO-d_6. c) each 1H, each br, D_2O exchangeable, 2 x NH. d) 1H, dd, 8-H. e) 1H, dd, 11-H. f) 1H, s, 2-H. g) 1H, td, 10-H. h) 1H, td, 9-H. i) 9H, m, 6-H, $O(CH_2)_2$, $NHC\underline{H}_2$, and NH; changed to 8H after addition of D_2O. j) 1H, br, D_2O exchangeable, NH. k) 2H, t, 5-H. l) 7H, m, 6-H, $C\underline{H}_2CH_2C\underline{H}_2O$, and NH; changed to 6H after addition of D_2O. m) as 2HCl salt. n) 8H, m, 6-H, CH_2CHCH_2, and NH (or OH); changed to 7H after addition of D_2O. o) 8H, m, 8-, 9-, 10-, and 11-H and 4 x NH (and/or OH); changed to 4H after addition of D_2O. p) 2H, t, 6-H. q) 4H, m, 8- and 10-H and NH_2; changed to 2H after addition of D_2O.

were collected and recrystallized from diluted EtOH to give 2.90 g (45%) of IIIj as pale yellow prisms, mp 194–195 °C.

Method B: A mixture of 463 mg (2 mM) of I, 38 mg (0.2 mM) of $CuCl_2 \cdot 2H_2O$, 13 mg (0.2 mM) of Cu powder, and 80 ml of EtOH in an autoclave was saturated with NH_3 gas under cooling (NaCl-ice). The mixture was heated at 120 °C for 10 h. After cooling, the reaction mixture was saturated with NH_3 gas again and heated at 170 °C for an additional 14 h. After cooling, the contents was poured into a flask and the autoclave was rinsed with hot EtOH. The combined hot EtOH suspension was filtered and the filtrate was evaporated to dryness. The residue was recrystallized.

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