Notes

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Polycyclic *N*-Hetero Compounds. XXIII.[1] Synthesis and Antidepressive Activity of 4-Substituted 5,6-Dihydrobenzo[*h*]quinazolines

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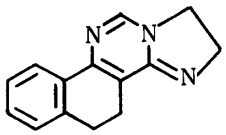
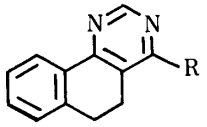
4-Alkylamino-5,6-dihydrobenzo[*h*]quinazolines (IIIa—k) were synthesized by the reaction of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (IIc) with primary alkylamines. Screening of 4-amino- (IIa), 4-hydroxy- (IIb), and 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (IId), as well as IIc and IIIa—k, for antireserpine action indicated that IId, IIIa, and IIIh exhibited effective antidepressant activity.

Keywords——benzo[*h*]quinazoline; 4-alkylaminobenzo[*h*]quinazoline; antidepressive activity; antireserpine activity; primary alkylamine

A 11,13,15-triazasteroidal compound, corresponding to 1,2,4,5-tetrahydrobenz[*h*]-imidazo[1,2-*c*]quinazoline (I)[2] exhibited antidepressive activity with moderate toxicity in mice.[3] During the course of this series of studies, we became interested in the possible anti-



I[2]



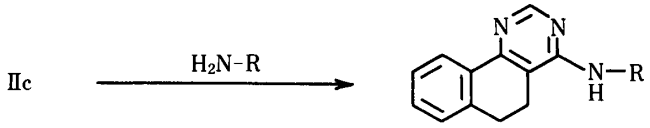
IIa : R=NH_2[2] IIc : R=Cl[2b]
IIb : R=OH[2] IId : R=$NHCH_2CH_2OH$[2]

Chart 1

depressive activity of starting materials of the above triazasteroid. 4-Amino- (IIa),[2] 4-hydroxy- (IIb),[2] and 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (IIc)[2b] did not exhibit antidepressive action, but 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (IId)[2] showed weak activity. This result prompted us to synthesize 4-substituted derivatives of 5,6-dihydrobenzo[*h*]quinazoline and to screen them for antidepressive activity. As shown in Chart 2, compound IIc was used as a starting material. Primary alkylamines were allowed to react with IIc to obtain 4-alkylamino-5,6-dihydrobenzo[*h*]quinazolines (IIIa—k) possessing a structure similar to IId.

Some data for the synthesized alkylamino derivatives (III) are listed in Table I.

The antidepressive activity of these 4-substituted benzo[*h*]quinazolines was screened by evaluating the inhibition of reserpine-induced hypothermia in mice[4] with respect to the control. In addition to IId, 4-(2-methoxyethylamino)- (IIIa) and 4-(2,3-dihydroxypropylamino)-5,6-dihydrobenzo[*h*]quinazoline (IIIh) exhibited effective action. However, other



IIIa–k

IIIa : R=$(CH_2)_2OMe$
IIIb : R=$(CH_2)_2NMe_2$
IIIc : R=$(CH_2)_2NEt_2$
IIId : R=$(CH_2)_2$N⟨ ⟩
IIIe : R=$(CH_2)_2$N⟨ O ⟩
IIIf : R=$(CH_2)_3OMe$
IIIg : R=$(CH_2)_3OEt$
IIIh : R=$CH_2CH(OH)CH_2OH$[5]
IIIi : R=$(CH_2)_3NMe_2$
IIIj : R=$(CH_2)_3N(CH_2CH_2OH)_2$ (as HCl salt)
IIIk : R=$(CH_2)_3$N⟨ O ⟩

Chart 2

TABLE I. Reaction Conditions, Appearance, Melting Points, and Yields of the Products

Compd.	Reaction time (h)	Appearance (Recryst. solv.)	mp (°C)	Yield (%)
IIIa	2	Colorless plates (Benzene–cyclohexane)	119—120	85
IIIb	3	Pale yellow granules (*n*-Hexane)	97—100	83
IIIc	5	Brown oil		90
IIId	2	Colorless granules (Cyclohexane)	127—129	85
IIIe	2	Pale yellow granules (Cyclohexane)	94—96	76
IIIf	3	Pale yellow scales (*n*-Hexane)	103—105	94
IIIg	3	Colorless fine needles (Benzene–*n*-hexane)	73—75	75
IIIi	3	Colorless needles (*n*-Hexane)	105—107	97
IIIj	13	Pale yellow granules (As HCl salt, EtOH–acetone)	185—188 (As HCl salt)	48
IIIk	3	Colorless granules (Benzene–*n*-hexane)	102—103	81

TABLE II. Effects of IId, IIIa, and IIIh on Reserpine-Induced Hypothermia in Mice

Compd.	Body temperature (°C) mean value ± S.D.				
	Before administration	Time after administration			
		30 min	1 h	2 h	4 h
Saline	22.2 ± 0.7	23.7 ± 0.8	25.4 ± 0.9	26.9 ± 1.3	28.8 ± 2.2
IId	21.9 ± 0.9	24.2 ± 0.9	26.1 ± 0.6	29.7 ± 0.8[a)]	29.6 ± 1.0
IIIa	22.3 ± 0.6	24.1 ± 0.7	25.7 ± 0.6	29.5 ± 0.9[a)]	31.8 ± 0.3[a)]
IIIh	22.3 ± 0.8	26.0 ± 1.4[a)]	27.1 ± 1.3	29.6 ± 1.2[a)]	29.5 ± 2.0

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 h after the administration of reserpine (2 mg/kg, i.p.). *a*) Significantly different from the control at $p < 0.05$.

compounds showed no noticeable activity. The effects of IId, IIIa, and IIIh on reserpine-induced hypothermia in mice are listed in Table II.

Further studies are in progress.

Experimental

Melting points 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 infrared (IR) absorption spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer. The nuclear magnetic resonance (NMR) spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm were measured relative to tetramethylsilane as an internal standard. The mass spectra (MS) were taken with a Shimadzu LKB-9000 instrument at 70 eV. Primary alkylamines used as reagents are commercially available.

General Procedure for Preparation of 4-Alkylamino-5,6-dihydrobenzo[*h*]quinazolines (III)——A mixture of 2 mmol (432 mg) of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (IIc)[2b] and 6 mmol of a suitable alkylamine was heated in a boiling water-bath until the starting material disappeared (checked by thin layer chromatography (TLC)). The mixture was cooled, *ca.* 50 ml of H_2O was added, and the whole was basified with 1 N NaOH. The resulting mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The resulting residue was recrystallized from an appropriate solvent (Table I).

Table III. Elemental Analyses of the Products and MS Spectral Data

Compd.	Formula	Analysis (%) Calcd (Found)			MS (*m/z*)
		C	H	N	
IIIa	$C_{15}H_{17}N_3O$	70.56	6.71	16.46	255 (M^+)
		(70.84	6.78	16.19)	
IIIb	$C_{16}H_{20}N_4$	71.61	7.51	20.88	268 (M^+)
		(71.79	7.57	20.65)	
IIIc	$C_{18}H_{24}N_4$	70.78	8.25	18.34	296 (M^+)
		(71.03	8.26	18.35)	
		(As $C_{18}H_{24}N_4 \cdot 1/2\,H_2O$)			
IIId	$C_{18}H_{22}N_4$	73.43	7.53	19.03	224 ($M-70$)[a]
		(73.22	7.57	18.78)	
IIIe	$C_{18}H_{22}N_4O$	69.65	7.14	18.05	310 (M^+)
		(69.60	7.21	17.86)	
IIIf	$C_{16}H_{19}N_3O$	71.34	7.11	15.60	269 (M^+)
		(71.17	7.13	15.62)	
IIIg	$C_{17}H_{21}N_3O$	72.05	7.47	14.83	283 (M^+)
		(71.89	7.53	14.80)	
IIIi	$C_{17}H_{22}N_4$	72.30	7.85	19.84	282 (M^+)
		(72.22	7.90	19.56)	
IIIj	$C_{19}H_{26}N_4O_2$	52.65	6.97	12.92	252 ($M-90$)[a]
		(52.85	6.89	12.99)	
		(As $C_{19}H_{26}N_4O_2 \cdot 2HCl \cdot H_2O$)			
IIIk	$C_{19}H_{24}N_4O$	70.34	7.46	17.27	324 (M^+)
		(70.13	7.47	17.23)	

a) Parent peak was not observed.

Elemental analyses of the products and instrumental data are listed in Tables III and IV.

4-[3-[*N*,*N*-Bis(2-hydroxyethyl)amino]-1-propylamino]-5,6-dihydrobenzo[*h*]quinazoline (as HCl Salt, IIIj)——The extract gave 673 mg of brown oily residue (free base of IIIj). The residue was dissolved in dry, alcohol-free $CHCl_3$ and dry HCl gas was bubbled into the solution for 10 min. After evaporation of the solvent, the resulting residue was purified by recrystallization.

Table IV. IR and NMR Spectral Data

Compd.	IR[a]	NMR δ (J in Hz)[b]
IIIa	3200	2.81 (4H, m), 3.41 (3H, s), 3.68 (4H, m), 5.10,[c] 7.31 (3H, m), 8.29 (1H, m), 8.64 (1H, s)
IIIb	3300	2.28 (6H, s), 2.57 (2H, t, J=6), 2.82 (4H, m), 3.58,[d] 5.47,[c] 7.27 (3H, m), 8.26 (1H, m), 8.61 (1H, s)
IIIc	3350	1.05 (6H, t, J=7), 2.74 (10H, m), 3.51,[e] 5.65,[c] 7.26 (3H, m), 8.28 (1H, m), 8.60 (1H, s)
IIId	3300	1.80 (4H, m), 2.73 (10H, m), 3.61,[d] 5.48,[c] 7.26 (3H, m), 8.26 (1H, m), 8.63 (1H, s)
IIIe	3300	2.60 (6H, m), 2.76 (4H, m), 3.66 (6H, m), 5.46,[c] 7.30 (3H, m), 8.26 (1H, m), 8.62 (1H, s)
IIIf	3250	1.95 (2H, m), 2.78 (4H, m), 3.40 (3H, s), 3.62,[f] 5.53,[c] 7.20 (3H, m), 8.26 (1H, m), 8.62 (1H, s)
IIIg	3280	1.25 (3H, t, J=7), 1.95 (2H, m), 2.85 (4H, m), 3.54 (2H, q, J=7), 3.65,[g] 5.73,[c] 7.30 (3H, m), 8.26 (1H, m), 8.62 (1H, s)
IIIi	3310	1.80 (2H, m), 2.30 (6H, s), 2.50 (4H, m), 2.93 (2H, t), 3.57 (2H, m), 7.21,[h] 8.24 (1H, m), 8.59 (1H, s)
IIIj	3350	1.81 (2H, m), 2.68 (6H, br t, J=5), 2.80 (4H, m), 3.57,[i] 5.31,[c] 7.21 (3H, m), 8.22 (1H, m), 8.57 (1H, s)
IIIk	3280	1.83 (2H, m), 2.51 (4H, t, J=4), 2.56 (2H, t, J=6), 2.81 (4H, m), 3.63,[e] 3.77 (4H, t, J=4), 6.40,[c] 7.31 (3H, m), 8.27 (1H, m), 8.62 (1H, s)

a) In KBr pellet, cm^{-1}, N–H. *b*) In $CDCl_3$. *c*) 1H, br; exchangeable with D_2O. *d*) 2H, q, J=6 Hz; changed to triplet on addition of D_2O, J=6 Hz. *e*) 2H, m; changed to triplet on addition of D_2O, J=6 Hz. *f*) 4H, m; changed to two triplets at 3.59 and 3.65 on addition of D_2O, each 2H, J=6 Hz. *g*) 4H, m; changed to two triplets at 3.50 and 3.65 on addition of D_2O, each 2H, J=6 Hz. *h*) 4H, m; changed to 3H on addition of D_2O. *i*) 8H, m; changed to 6H on addition of D_2O.

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References and Notes

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