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Polycyclic N-Hetero Compounds. VI.[1] Synthesis of 11,13,15-Triazasteroidal Compounds and Correction of the Structures of Its Intermediates

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11,13,15-Triazasteroidal compounds, that is, 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]-quinazolines (IV) were synthesized by the new route. Its intermediates (VII, VIII) were compared with the previous intermediates (II, III). II and III were corrected to II′ and III′ respectively.

In the previous paper,[3] we reported synthesis of 11,13,15-triazasteroidal compounds (IV) from 4-amino-5,6-dihydrobenzo[*h*]quinazolines (I), as shown in Chart 1, by the successive reactions with ethylene chlorohydrin, phosphorus tribromide, and aq. sodium carbonate. However, the compounds (IV) were lately synthesized by an alternative pathway, and the reported structures of the intermediates (II, III) were decided to be incorrect. The present paper deals with the new synthetic route of the compounds (IV) and the correct structures of the previous intermediates. The new synthetic route is shown in Chart 2, and the intermediates (VII, VIII) were compared with the previous intermediates (II, III) respectively.

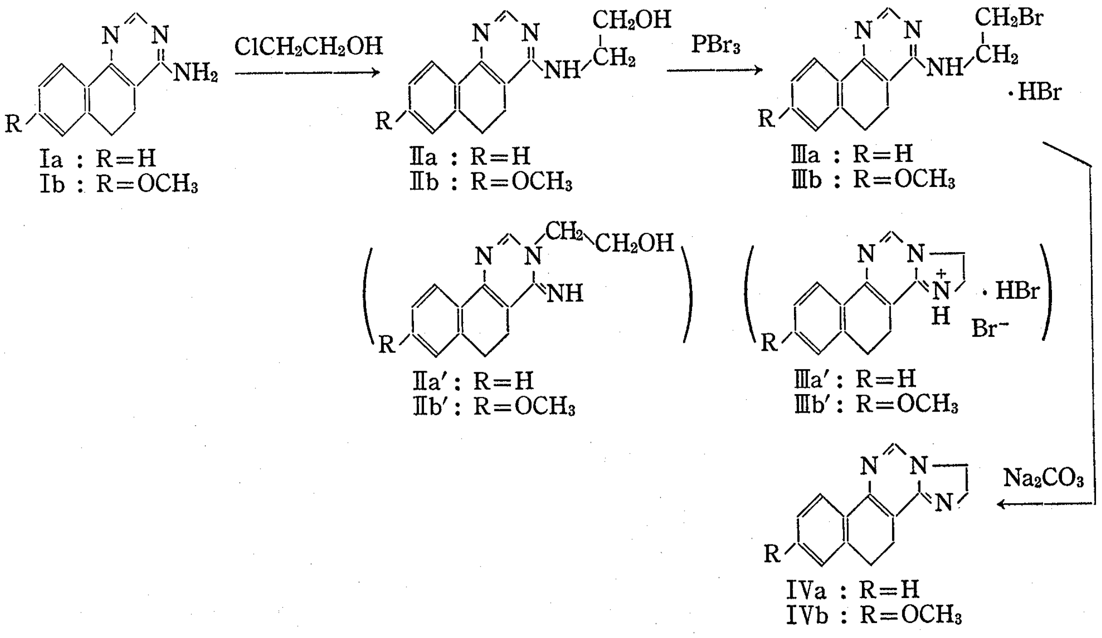

Chart 1

As the result, since VII and VIII are not identical with II and III, the structures of II and III will be corrected.

As starting materials, 4-amino-5,6-dihydrobenzo[*h*]quinazoline (Ia) and 4-amino-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (Ib) were used as same as the previous paper. At

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[1] Part V: T. Koyama, T. Hirota, Y. Shinohara, and S. Ohmori, *Chem. Pharm. Bull.* (Tokyo), 23, 497 (1975).

[2] Location: *1-1, Tsushima naka 1-chome, Okayama, 700, Japan.*

[3] T. Koyama, T. Hirota, T. Yoshida, H. Hara, and S. Ohmori, *Chem. Pharm. Bull.* (Tokyo), 22, 1451 (1974).

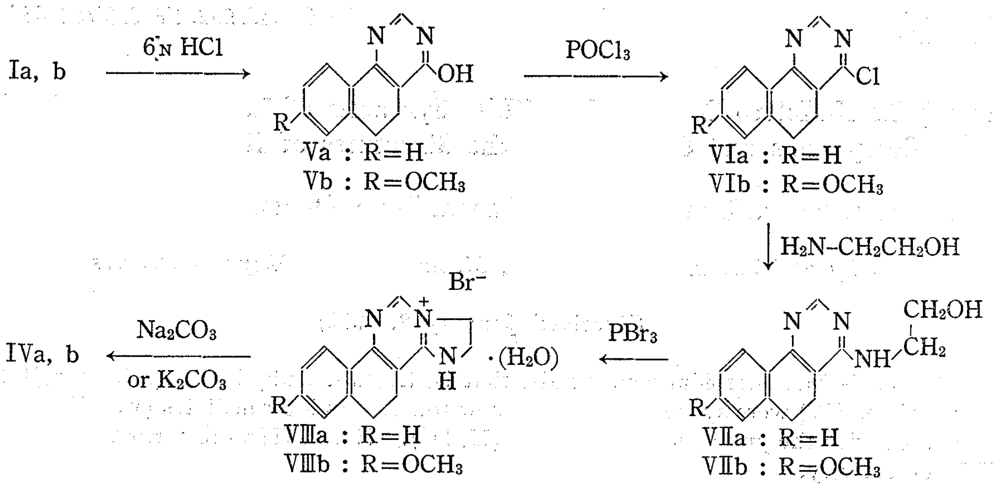
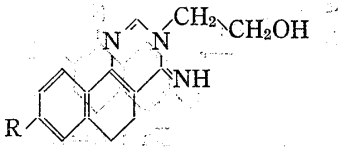


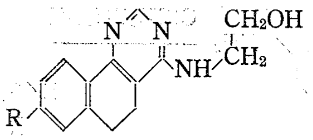
Chart 2

first, according to the method of Rosowsky and Modest[4] I were refluxed with 6N HCl, and the resulted 4-hydroxy-5,6-dihydrobenzo[*h*]quinazolines (V) were heated with phosphoryl chloride in order to convert OH to Cl. Treatment of 4-chloro-5,6-dihydrobenzo[*h*]quinazolines (VI) with ethanolamine gave 4-*β*-hydroxyethylamino-5,6-dihydrobenzo[*h*]quinazolines (VII). The position of hydroxyethyl group admits of no doubt from the synthetic method. Elemental analyses of VII agreed with $C_{14}H_{15}ON_3$ (VIIa) and $C_{15}H_{17}O_2N_3$ (VIIb) but data of mp, infrared (IR) spectra, nuclear magnetic resonance (NMR) spectra, and thin-layer chromatography (TLC) differ from the previous compounds (II) (refer to Table I). Although mp of IIb and VIIb are much closed, mixed mp depressed considerably.

TABLE I.



IIa′ : R=H
IIb′ : R=OCH3



VIIa : R=H
VIIb : R=OCH3

	VIIa	II′a		VIIb	II′b
Recryst. solvent	dil. EtOH	C_6H_6–EtOH	Recryst. solvent	C_6H_6–EtOH	C_6H_6–EtOH
mp	159–161°	189–190°	mp	179–180°	179–179.5°
				(mixed mp: depression)	
	NMR (in $CDCl_3$, δ values)			NMR (in $CDCl_3$, δ value)	
C-5, 6	2.58, 2.93 (each 2H, bt)	2.54, 2.89 (each 2H, bt)	C-5, 6	2.59, 2.95 (each 2H, bt)	2.58, 2.92 (each 2H, bt)
C-1′, 2′	3.67, 3.82 (each 2H, m)	3.91, 4.11 (each 2H, m)	C-1′, 2′	3.70, 3.83 (each 2H, m)	3.93, 4.18 (each 2H, m)
NH, OH		5.44, 6.22 (each 1H, b)	OCH_3	3.84 (3H, s)	3.84 (3H, s)
			NH, OH		3.0–4.5 (2H, b)
C-7, 8, 9	7.30 (3H, m)	7.24 (3H, m)	C-7	6.77 (1H, d)	6.78 (1H, d)
C-10	8.20 (1H, dd)	8.01 (1H, dd)	C-9	6.89 (1H, dd)	6.89 (1H, dd)
C-2	8.53 (1H, s)	7.80(1H, s)	C-10	8.20 (1H, d)	8.04 (1H, d)
			C-2	8.53 (1H, s)	7.84 (1H, s)

s: singlet, d: doublet, t: triplet, m: multiplet, b: broad

Brown, *et al.*[5] reported that pyrimidine ring nitrogen was alkylated by the methylation of 4-aminopyrimidine or 2-aminopyrimidine with methyl iodide. Therefore, it is possible that 3-*β*-hydroxyethyl-4-imino-3,4,5,6-tetrahydrobenzo[*h*]quinazolines (II′) were formed from I and ethylene chlorohydrin.

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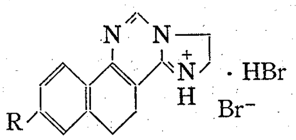
[4] A. Rosowsky and E.J. Modest, *J. Org. Chem.*, **31**, 2607 (1966).

[5] D.J. Brown, E. Hoerger, and S.F. Mason, *J. Chem. Soc.*, **1955**, 4035.

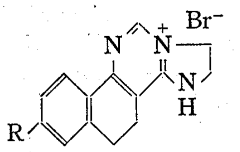
It is remarkable in chemical shift of singlet proton signal of 2-position in NMR spectra that in previous compounds (II) it appeared at δ 7.80 (IIa) and δ 7.84 (IIb), but in present compounds (VII) it appears in the lower field at δ 8.53. The chemical shift of the latter (δ 8.53) agreed with usual value of 2-position proton signal of pyrimidine ring in NMR. This is suggested that pyrimidine ring of the previous compounds (II) are tinged with more double bond character than aromaticity, therefore, hydroxyethyl group of the previous compounds combined at pyrimidine ring nitrogen, that is, the structures of the previous compounds (II) are corrected to (II′) (If hydroxyethyl group combined at 1-position, following cyclization to imidazo[1,2-*c*]quinazoline could not occur.).

On heating VII with phosphorus tribromide afforded 1,2,4,5-tetrahydrobenz[*h*]imidazo-[1,2-*c*]quinazolinium bromide monohydrate (VIII), and its NMR spectra in dimethyl sulfoxide-d_6 closely similar to that of the previous compounds (III) (refer to Table II). Both mass spectra showed the same parent peaks, IIIa and VIIIa at *m*/*e* 223, IIIb and VIIIb at *m*/*e* 253, and similar fragmentations to that of the cyclized pure 11,13,15-triazasteroidal compounds (IV) and at *m*/*e* 80, 82, the peak of HBr appeared strongly. Therefore, it is reasonable that the previous compounds (III) have structures of already cyclized compounds (III′).

TABLE II.



IIIa′ : R=H
IIIb′ : R=OCH₃



VIIIa : R=H
VIIIb : R=OCH₃

	VIIIa	III′a		VIIIb	III′b
Recryst. solvent	H_2O	dil. EtOH	Recryst. solvent	dil. EtOH	dil. EtOH
mp	above 280°	295—300° (decomp.)	mp	274—276°	260—263° (decomp.)
	NMR (in Me_2SO-d_6, δ value)			NMR (in Me_2SO-d_6, δ value)	
C-4, 5	2.88 (4H, m)	2.93 (4H, m)	C-4, 5	2.88 (4H, m)	2.88 (4H, m)
C-1, 2	3.99, 4.69 (each 2H, bt)	3.88, 4.75 (each 2H, bt)	OCH_3	3.86 (3H, s)	3.85 (3H, s)
C-6, 7, 8	7.42 (3H, m)	7.50 (3H, m)	C-1, 2	4.01, 4.77 (each 2H, bt)	3.89, 4.72 (each 2H, bt)
C-9	8.13 (1H, dd)	8.18 (1H, dd)	C-6	7.01 (1H, d)	7.01 (1H, d)
C-11	8.83 (1H, s)	8.85 (1H, s)	C-8	7.05 (1H, dd)	7.04 (1H, dd)
NH	10.07 (1H, b)	8.96 (1H, b)	C-9	8.13 (1H, d)	8.13 (1H, d)
			C-11	8.77 (1H, s)	8.78 (1H, s)
			NH	9.90 (1H, b)	8.97 (1H, b)

refer to the footnote of Table I

Treatment of these III′ or VIII with aq. sodium carbonate or aq. potassium carbonate afforded the same 11,13,15-triazasteroidal compounds respectively, and its mp, IR, NMR, and TLC agreed with each other, and mixed mp did not depress.

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. IR spectra were taken on a Japan Spectroscopic Company DS-301 spectrometer in KBr disk. Mass spectra were taken on a Shimadzu-LKB 9000 spectrometer with a direct inlet system.

4-Hydroxy-5,6-dihydrobenzo [*h*] quinazoline (Va)——After treatment of 1.00 g of Ia with 40 ml of hot 6N HCl for 30 hr, resulting solution was cooled and the deposited crystals were filtered. The filtrate was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with sat. NaCl solution, dried over anhydro. Na_2SO_4, and $CHCl_3$ was evaporated. The solid residue and the above filtered crystals were combined and recrystallized from benzene to give 963 mg (94%) of Va as colorless feathers, mp 245—246°. *Anal.* Calcd. for $C_{12}H_{10}ON_2$: C, 72.73; H, 5.05; N, 14.14. Found: C, 72.71; H, 5.09; N, 14.07. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}:

3100—2300 (broad), 1660, 1637. NMR ($CDCl_3$): 2.91 (4H, bs, CH_2CH_2), 7.35 (3H, m, C_7,C_8,C_9-H), 8.18 (1H, bd, J=*ca.* 8 Hz, C_{10}–H), 8.20 (1H, s, C_2–H), 13.20 (1H, b, OH, or NH).

4-Chloro-5,6-dihydrobenzo[*h*]quinazoline (VIa)——A mixture of 12.83 g of Va and 150 ml of $POCl_3$ was refluxed for 2.5 hr and then the cooled reaction mixture was poured into ice water carefully. The solution was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with sat. NaCl solution, dried over anhydro. Na_2SO_4, and $CHCl_3$ was washed with sat. NaCl solution, dried over anhydro. Na_2SO_4, and $CHCl_3$ was evaporated. The crystalline residue was recrystallized from cyclohexane to give 12.0 g (85.7%) of VIa as colorless plates, mp 82—83°. Beilstein test: positive. *Anal.* Calcd. for $C_{12}H_9N_2Cl$: C, 66.51; H, 4.16; N, 12.93. Found: C, 66.45; H, 4.10; N, 12.91. NMR ($CDCl_3$): 3.03 (4H, bs, CH_2CH_2), 7.35 (3H, m, C_7,C_8,C_9-H), 8.34 (1H, m, C_{10}-H), 8.87 (1H, s, C_2-H).

4-β-Hydroxyethylamino-5,6-dihydrobenzo[*h*]quinazoline (VIIa)——A mixture of 0.40 g of VIa and 1.0 g of ethanolamine was heated at 130—140° for 3 hr and then ice water was poured into the cooled mixture. The deposited crystals were collected and recrystallized from dil. EtOH to give 0.27 g (61%) of VIIa as colorless needles, mp 159—160°. *Anal.* Calcd. for $C_{14}H_{15}ON_3$: C, 69.69; H, 6.27; N, 17.42. Found: C, 70.04; H, 6.29; N, 17.19. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3260 (broad) (O–H, N–H).

1,2,4,5-Tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolinium bromide (VIIIa)——A mixture of 200 mg of VIIa, 3 ml of PBr_3 and 5 ml of dry benzene was refluxed for 2 hr and then volatile liquid was evaporated *in vacuo*. The solid residue was recrystallized from H_2O to give 98 mg (31%) of VIIIa as colorless feathers, mp above 280°. Pale yellow precipitate formed with $AgNO_3$. *Anal.* Calcd. for $C_{14}H_{16}ON_3Br$ (monohydrate): C, 52.19; H, 4.97; N, 13.05. Found: C, 52.59; H, 4.94; N, 13.30. Mass Spectrum: *m/e* (M^+)=223.

1,2,4,5-Tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (IVa)——a) When the mother liquid of recrystallization of VIIIa was made alkaline with Na_2CO_3, yellow crystals were deposited. They were collected and recrystallized from benzene–cyclohexane to give 57.5 mg of IVa as yellow needles, mp 127—128°, identical with the material from the method of the previous paper[3] (mixed mp, IR, NMR, and TLC).

b) An aqueous solution of 64 mg of VIIIa was made alkaline with Na_2CO_3 and then resulting yellow crystals were collected. After washing with cold H_2O, recrystallization from benzene–cyclohexane gave 35 mg (80%) of IVa as yellow needles, mp 127—128°, identical with the material from the method of the previous paper[3] (mixed mp, IR, NMR, and TLC).

4-Hydroxy-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (Vb)——A mixture of 3.0 g of fine powdered Ib and 500 ml of 6N HCl was refluxed for 40 hr and then excess HCl was evaporated *in vacuo*. The resulted solid was dissolved in hot water and neutralized with $NaHCO_3$. The deposited solid was collected and recrystallized from EtOH to give 2.5 g (83%) of Vb as colorless needles, mp 273.5—275°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.30; H, 5.30; N, 12.27. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3100—2300 (broad), 1660, 1642. Mass Spectrum: *m/e* (M^+)=228. NMR ($CDCl_3$): 2.87 (4H, bs, CH_2CH_2), 3.85 (3H, s, OCH_3), 6.81 (1H, d, J=2 Hz, C_7–H), 6.89 (1H, dd, J=8 Hz, J=2 Hz, C_9–H), 8.12 (1H, d, J=8 Hz, C_{10}–H), 8.16 (1H, s, C_2–H).

4-Chloro-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (VIb)——A solution of 705 mg of Vb and 20 ml of $POCl_3$ was refluxed for 2.5 hr, cooled at room temperature and then the reaction mixture was poured into ice water carefully. The aq. solution was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with sat. NaCl solution, dried over anhydro. Na_2SO_4, and $CHCl_3$ was evaporated. The solid residue was recrystallized from cyclohexane to give 649 mg (85%) of VIb as colorless needles, mp 107—108°. *Anal.* Calcd. for $C_{13}H_{11}ON_2Cl$: C, 63.29; H, 4.46; N, 11.36. Found: C, 63.46; H, 4.47; N, 11.37. NMR ($CDCl_3$): 3.00 (4H, bs, CH_2CH_2), 3.86 (3H, s, OCH_3), 6.79 (1H, d, J=2.5 Hz, C_7–H), 6.92 (1H, dd, J=8 Hz, J=2.5 Hz, C_9–H), 8.28 (1H, d, J=8 Hz, C_{10}–H), 8.79 (1H, s, C_2–H). Beilstein test: positive.

4-β-Hydroxyethylamino-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (VIIb)——A mixture of 0.40 g of VIb and 1.5 g of ethanolamine was heated at 140—150° for 3 hr and then volatile liquid was evaporated *in vacuo*. The residue was suspended with H_2O and the suspension was made alkaline with 2N NaOH. The resulting precipitate was collected, and recrystallized two times from dil. EtOH followed by benzene–EtOH to give 0.26 g (59.8%) of VIIb as colorless needles, mp 179—180°. *Anal.* Calcd. for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.38; H, 6.34; N, 15.37. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3340 (O–H), 3150 (N–H).

7-Methoxy-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolinium Bromide (VIIIb)——A mixture of 294 mg of VIIb, 4 ml of PBr_3 and 5 ml of dry benzene was refluxed for 2 hr and then volatile liquid was evaporated *in vacuo*. The residue was dissolved in H_2O, treated with charcoal and filtered. The filtrate was evaporated to dryness, and it was recrystallized from dil. EtOH to give 267 mg (73.7%) of VIIIb as colorless needles, mp 274.5—275.5°. *Anal.* Calcd. for $C_{15}H_{16}ON_3Br$: C, 53.86; H, 4.79; N, 12.56. Found: C, 53.40; H, 4.79; N, 12.43. Mass Spectrum: *m/e* (M^+)=253.

7-Methoxy-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (IVb)——When aq. solution of 35 mg of VIIIb was made alkaline with K_2CO_3, yellow crystals were precipitated. The crystals were collected and recrystallized from benzene–cyclohexane to give 20 mg (74.5%) of IVb as yellow needles, mp 170.5—171.5°, identical with the material from the method of the previous paper[3] (mixed mp, IR, NMR, and TLC).

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