[Chem. Pharm. Bull. 22(7)1451—1454(1974)]

UDC 547.92.057 : 547.859.057

Polycyclic N-Hetero Compounds. II.[1] Synthesis of 11,13,15-Triazasteroidal Skeleton

Takaji Koyama, Takashi Hirota, Tadaaki Yoshida,
Hideki Hara, and Shinji Ohmori[2]

Faculty of Pharmaceutical Sciences, Medical School, Okayama University[2]

(Received September 10, 1973)

Heating of 2-cyano-1-tetralones (I) with formamide and phosphoryl chloride afforded 4-amino-5,6-dihydrobenzo[*h*]quinazolines (II). 4-(2-Hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazolines (III) were obtained from II with ethylene chlorohydrin, and gave 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolines (V), *i.e.*, 11,13,15-triazasteroid compounds, on treatment with sodium carbonate after refluxing with phosphorus tribromide.

As reported in the previous paper,[3] α-acyl-α-arylacetonitriles afforded 3-substituted 4-isoquinolinecarbonitriles or 6-substituted 4-amino-5-arylpyrimidines when heated with formamide and phosphoryl chloride. As shown in Chart 1, this reaction was applied to 2-cyano-1-tetralones (I) to synthesize 11,13, 15-triazasteroidal compounds.

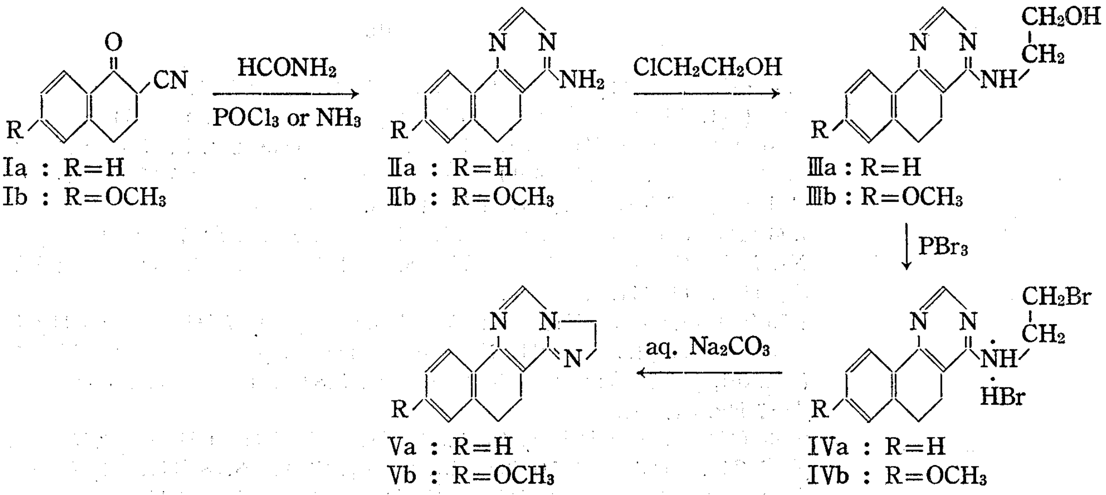

Chart 1

The first starting material, 2-cyano-1-tetralone (Ia), was prepared from 1-tetralone according to Johnson, *et al.*[4] On heating Ia with excess formamide and phosphoryl chloride, 4-amino-5,6-dihydrobenzo[*h*]quinazoline (IIa) was formed. The infrared (IR) spectrum of IIa showed disappearance of C=O and C≡N bands, and appearance of bands at 3340, 3140, and 1665 cm^{-1} due to N–H. The nuclear magnetic resonance (NMR) spectral data of IIa

---

[1] Part I: Synthesis of 1,3,10-Triazaphenanthrenes: T. Koyama, T. Hirota, M. Yamato, and N. Ohta, *Yakugaku Zasshi*, **93**, 330 (1973).

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

[3] T. Koyama, T. Hirota, I. Itoh, M. Toda, and M. Yamato, *Yakugaku Zasshi*, **89**, 1492 (1969); T. Koyama, T. Hirota, M. Toda, K. Iwai, M. Minami, and M. Yamato, *Yakugaku Zasshi*, **89**, 1334 (1969); T. Koyama, M. Toda, T. Hirota, M. Hashimoto, and M. Yamato, *Yakugaku Zasshi*, **89**, 1688 (1969); T. Koyama, M. Toda, T. Hirota, and M. Yamato, *Yakugaku Zasshi*, **90**, 8 (1970); T. Koyama, T. Hirota, T. Matsumura, and M. Yamato, *Yakugaku Zasshi*, **92**, 1233 (1972).

[4] W.S. Johnson and W.E. Shelberg, *J. Am. Chem. Soc.*, **67**, 1745 (1945).

are shown in Table I. These data supported the structure of IIa. The lower field shift of C_{10}–H should result from the anisotropic effect of the pyrimidine ring. On the other hand, IIa was produced from Ia when it was heated at 180° with excess formamide in the presence of dry ammonia stream.[5] The yield by this method was better than the former.

As an analogous reaction, Sengupta, *et al.*[6] obtained 2,4-diamino-5,6-dihydrobenzo[*h*]-quinazoline on heating 1-tetralone with dicyandiamide in Triton-B, and Taylor, *et al.*[7] obtained 1-amino-8-methoxybenzo[*f*]quinazoline from 2-amino-1-cyano-6-methoxynaphthalene either heating with formamide or with ethyl orthoformate, and treatment of the resulting 1-cyano-2-ethoxymethyleneamino-6-methoxynaphthalene with ethanolic ammonia.

The reaction of IIa with ethylene chlorohydrin resulted in the formation of 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (IIIa). In order to brominate the hydroxyl group, IIIa was refluxed with phosphorus tribromide and subsequently recrystallized from dil. ethanol to 4-(2-bromoethylamino)-5,6-dihydrobenzo[*h*]quinazoline hydrobromide (IVa). In the IR spectrum of IVa, broad absorption of $=N^{+}H_2$ appeared at 3100—2000 cm^{-1}. The NMR spectral data are shown in Table I.

Va was obtained by treatment of IVa with aq. sodium carbonate. The IR spectrum of Va has no $=N^{+}H_2$ band, its NMR spectral data are shown in Table I, and its mass spectrum gave *m/e* of the parent peak at 223.1090 ($C_{14}H_{11}N_3$: Calcd. 223.1108). These data support the structure of Va. As similar reactions, Ramage, *et al.*[8] and Martin, *et al.*[9] obtained 2,3-

TABLE I. NMR Spectra of the Products II to V[a)]

Compd. No.	Solv.	NMR (δ-value)
IIa	$CDCl_3$	2.83 (4H, m, CH_2CH_2), 5.22 (2H, b, NH_2), 7.30 (3H, m, C_7, C_8, C_9–H), 8.23 (1H, dd, $J=8$ Hz, $J=2.5$ Hz, C_{10}–H), 8.58 (1H, s, C_2–H).
IIb	$CDCl_3$	2.80 (4H, m, CH_2CH_2), 3.85 (3H, s, OCH_3), 4.89 (2H, b, NH_2), 6.78 (1H, d, $J=2.5$ Hz, C_7–H), 6.90 (1H, dd, $J=7.5$ Hz, $J=2.5$ Hz, C_9–H), 8.23 (1H, d, $J=7.5$ Hz, C_{10}–H), 8.54 (1H, s, C_2–H).
IIIa	CF_3COOH	3.06 (4H, m, C–CH_2CH_2–C), 4.42, 4.78 (each 2H, t, $J=7$ Hz, O–CH_2CH_2–N), 7.55 (3H, m, C_7, C_8, C_9–H), 8.10 (1H, dd, $J=7.5$ Hz, $J=2.5$ Hz, C_{10}–H), 9.02 (1H, s, C_2–H).
IIIb	$CDCl_3$	2.75 (4H, m, C–CH_2CH_2–C), 3.85 (3H, s, OCH_3), 4.07 (4H, m, O–CH_2CH_2–N), 3.0—4.5 (2H, b, OH, NH), 6.78 (1H, d, $J=2.5$ Hz, C_7–H), 6.89 (1H, dd, $J=7.5$ Hz, $J=2.5$ Hz, C_9–H), 7.84 (1H, s, C_2–H), 8.04 (1H, d, $J=7$ Hz, C_{10}–H).
IVa	Me_2SO-d_6	2.93 (4H, m, C–CH_2CH_2–C), 3.88 (2H, t, $J=7$ Hz, CH_2Br), 4.75 (2H, t, $J=7$ Hz, CH_2N^+), 7.50 (3H, m, C_7, C_8, C_9–H), 8.18 (1H, dd, $J=8$ Hz, $J=2.5$ Hz, C_{10}–H), 8.85 (1H, s, C_2–H), 8.96 (>1H, b, NH).
IVb	Me_2SO–d_6	2.88 (4H, m, C–CH_2CH_2–C), 3.85 (3H, s, OCH_3), 3.89 (2H, t, $J=7$ Hz, CH_2Br), 4.72 (2H, t, $J=7$ Hz, CH_2N^+), 7.01 (2H, m, C_7, C_9–H), 8.13 (1H, d, $J=8$ Hz, C_{10}–H), 8.78 (1H, s, C_2–H), 8.97 (>1H, b, NH).
Va	$CDCl_3$	2.78 (4H, m, C–CH_2CH_2–C), 4.09 (4H, s, N–CH_2CH_2–N), 7.23(3H, m, C_6, C_7, C_8–H), 7.85 (1H, s, C_{11}–H), 8.01 (1H, dd, $J=7.5$ Hz, $J=2.5$ Hz, C_9–H).
Vb	$CDCl_3$	2.80 (4H, m, C–CH_2CH_2–C), 3.85 (3H, s, OCH_3), 4.10 (4H, s, N–CH_2CH_2–N), 6.80 (1H, d, $J=2.5$ Hz, C_6–H), 6.85 (1H, dd, $J=7.5$ Hz, $J=2.5$ Hz, C_8–H), 7.89 (1H, s, C_{11}–H), 8.01 (1H, d, $J=7.5$ Hz, C_9–H).

a) Hitachi R-22 spectrometer (90 MHz) was used, with tetramethylsilane as internal standard. s(singlet), d(doublet), t(triplet), m(multiplet), b(broad), dd(double doublet)

---

5) W.H. Davies and H.A. Piggott, *J. Chem. Soc.*, **1945**, 347.

6) S.K. Sengupta, S. Chatterjee, H.K. Protopapa, and E.J. Modest, *J. Org. Chem.*, 37, 1323 (1972).

7) E.C. Taylor, A. McKillop, Y. Shov, and G.H. Hawks, *Tetrahedron*, 23, 2081 (1967).

8) G.R. Ramage and G. Trappe, *J. Chem. Soc.*, **1952**, 4410; J. Clark and G.R. Ramage, *J. Chem. Soc.*, **1958**, 2821.

9) R.H. Martin and J. Mathieu, *Tetrahedron*, **1**, 75 (1957).

dihydroimidazo[1,2-*c*]pyrimidines from various 4-(2-chloroethylamino)pyrimidines by heating with water or ethanol and subsequently treating with alcoholic ammonia or sodium bicarbonate.

The second starting material, 2-cyano-6-methoxy-1-tetralone (Ib) was prepared from 6-methoxy-1-tetralone by a procedure similar to that for Ia.[10] When Ib was heated with excess formamide in the presence of dry ammonia stream, 4-amino-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (IIb) was formed. Its IR and NMR spectra were similar to that of IIa.

The reaction of ethylene chlorohydrin on IIb gave an ethanolamine derivative (IIIb), which was heated with phosphorus tribromide and subsequently recrystallized from dil. ethanol to 4-(2-bromoethylamino)-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline hydrobromide (IVb). The IR spectrum IVb showed a broad absorption for $=N^+H_2$ at 3100—2000 cm^{-1} and NMR spectral data also supported the structure of IVb.

Treatment of IVb with aq. sodium carbonate gave 7-methoxy-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (Vb), *i.e.*, 3-methoxy-11,13,15-triazasteroid compound. Its IR, NMR, mass spectra supported the structure of Vb.

Experimental

4-Amino-5,6-dihydrobenzo[*h*]quinazoline (IIa)——(a) To a solution of 2-cyano-1-tetralone (Ia) (10 g) in $HCONH_2$ (150 ml), $POCl_3$ (27 g) was added dropwise under cooling, and the mixture was heated at 120—130° for 4 hr with stirring. The reaction mixture was poured carefully into ice water, basified with aq. Na_2CO_3 and extracted with $(C_2H_5)_2O$. The $(C_2H_5)_2O$ layer was washed with H_2O, dried over Na_2SO_4, and $(C_2H_5)_2O$ was evaporated. The residue (yellowish red powder) was recrystallized from benzene to 3.1 g (24.7%) of IIa as pale yellow needles, mp 161—162°. *Anal.* Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31. Found: C, 73.29; H, 5.57; N, 20.93. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3340, 3140, 1665 (N–H).

(b) $HCONH_2$ (150 ml) solution of Ia (43 g) was heated at 180° for 15 hr in dry NH_3 stream, and during the reaction H_2O formed was distilled off. The reaction mixture was diluted with H_2O, extracted with $(C_2H_5)_2O$, $(C_2H_5)_2O$ layer was washed with H_2O, dried over Na_2SO_4, and $(C_2H_5)_2O$ was evaporated. The residue was recrystallized from benzene to 27 g (52.5%) of IIa, identical with the material prepared by method (a) (mixed mp determination, IR, and NMR).

4-(2-Hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazoline (IIIa)——A solution of 5 g of IIa dissolved in 10 ml of ethylene chlorohydrin at room temperature was heated at 125—135° for 5 hr. The precipitated crystals were collected by filtration and washed with EtOH–benzene (1: 1). The crystals were suspended in aq. NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and $CHCl_3$ was evaporated. The yellowish residue was recrystallized from EtOH–benzene (1: 2) to 2.4 g (40.1%) of IIIa as pale yellow needles, mp 189—190°. *Anal.* Calcd. for $C_{14}H_{15}ON_3$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.90; H, 6.23; N, 17.46. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3300 (O–H), 3100 (N–H).

4-(2-Bromoethylamino)-5,6-dihydrobenzo[*h*]quinazoline Hydrobromide (IVa)——A mixture of 1 g of IIIa and 15 ml of PBr_3 was refluxed for 2 hr and the excess PBr_3 was evaporated under a reduced pressure. The residue was recrystallized from dil. EtOH to 1.3 g (80%) of IVa as colorless needles, mp 295—300° (decomp.) after sublimation at *ca.* 230—235°. *Anal.* Calcd. for $C_{14}H_{15}N_3Br_2$: C, 43.67; H, 3.93; N, 10.90. Found: C, 43.62; H, 3.94; N, 10.77. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3100—2000 ($=N^+H_2$). Beilstein test: positive.

1,2,4,5-Tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (Va)——A warm aq. solution of Va (1 g) was basified with Na_2CO_3, by which the solution turned yellow, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The residual crystals were recrystallized from benzene–cyclohexane to 0.66 g (76%) of Va as yellow needles, mp 127—128°. *Anal.* Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.02; H, 5.81; N, 18.69. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1637 (C=N). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 233 (4.33), 258 (4.40), 285 (4.19), 328 (3.97), 340 (3.98). Mass Spectrum: *m/e* (M^+) = 223.1090 (Calcd. for $C_{14}H_{13}N_3$: 223.1108).

4-Amino-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (IIb)——A solution of 2-cyano-6-methoxy-1-tetralone (Ib) (20.4 g) in $HCONH_2$ (150 ml) was heated at 180° for 18 hr in dry NH_3 stream, the H_2O formed during the reaction was distilled off. The reaction mixture was diluted with H_2O, extracted with $CHCl_3$, the $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to 10.5 g (44.0%) of IIb as pale yellow needles, mp 215.5—216.5°. *Anal.* Calcd. for $C_{13}H_{13}ON_3$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.94; H, 5.77; N, 18.36. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3320, 3120, 1648 (N–H).

4-(2-Hydroxyethylamino)-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline (IIIb)——A solution of 2.3 g of IIb dissolved in 5.4 ml each of ethylene chlorohydrin and toluene at room temperature was refluxed for 5 hr.

---

[10] D.K. Banerjee, S. Chatterjee, C.N. Pillai, and N.V. Bhatt, *J. Am. Chem. Soc.*, 78, 3769 (1956).

The precipitated crystals were collected by filtration and washed with EtOH–benzene (1 : 1). After treatment as in the case of IIIa, recrystallization from EtOH–benzene (1: 2) gave 0.8 g (34.1%) of IIIb as pale yellow needles, mp 179—179.5°. *Anal.* Calcd. for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.30; H, 6.29; N, 15.41. IR ν_{max}^{KBr} cm^{-1}: 3320 (O–H), 3110 (N–H).

4-(2-Bromoethylamino)-8-methoxy-5,6-dihydrobenzo[*h*]quinazoline Hydrobromide (IVb)——A solution of 0.9 g of IIIb and 15 ml of PBr_3 was refluxed for 1 hr and the excess PBr_3 was distilled off under a reduced pressure. The residue was recrystallized from dil. EtOH to 0.62 g (51%) of IVb as colorless needles, mp 260—263° (decomp.). *Anal.* Calcd. for $C_{15}H_{17}ON_3Br_2$: C, 43.39; H, 4.12; N, 10.12. Found: C, 43.10; H, 4.22; N, 9.69. IR ν_{max}^{KBr} cm^{-1}: 3100—2000 ($=N^+H_2$). Beilstein test: positive.

7-Methoxy-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (Vb)——A warm aq. solution of IVb (0.32 g) was basified with Na_2CO_3, by which the solution turned yellow, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The yellow residue was recrystallized from benzene–cyclohexane to 0.14 g (81%) of Vb as yellow needles, mp 170.5—171.5°. *Anal.* Calcd. for $C_{15}H_{15}ON_3$: C, 71.12; H, 5.97; N, 16.59. Found: C, 71.26; H, 5.88; N, 16.41. IR ν_{max}^{Nujol} cm^{-1}: 1635 (C=N). Mass Spectrum: *m/e* (M^+) 253.1191 (Calcd. for $C_{15}H_{15}ON_3$: 253.1215). UV λ_{max}^{EtOH} nm (log ε): 233 (4.38), 260 (4.15), 311 (3.83), 346 (4.24), 360 (shoulder).

Acknowledgement The authors are very grateful to Mr. A. Iwadoh for microanalytical data and measurement of NMR spectra.