Polycyclic *N*-Hetero Compounds. XXXVI. Syntheses and Antidepressive Evaluation of 11,13,15,17-Tetraazasteroids and Their 17-Oxides

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Syntheses of 11,13,15,17-tetraazasteroids, their B-homologues, and 17-oxide derivatives are described. Antidepressive evaluation of these compounds and their precursors were screened by inhibitory action of reserpine-induced hypothermia.

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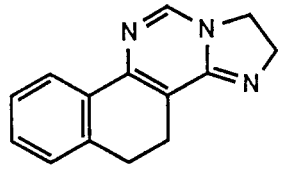
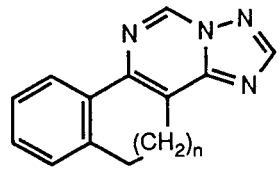
In the previous paper, we reported the synthesis of 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (**I**) [1], corresponding to 11,13,15-triazasteroidal compound, and its antidepressive activity in mice [2]. During the course of studies in this series, syntheses of 11,13,15,17-tetraazasteroids and their homologues **II** were planned as a modification of **I** concerning the structure-activity relationship

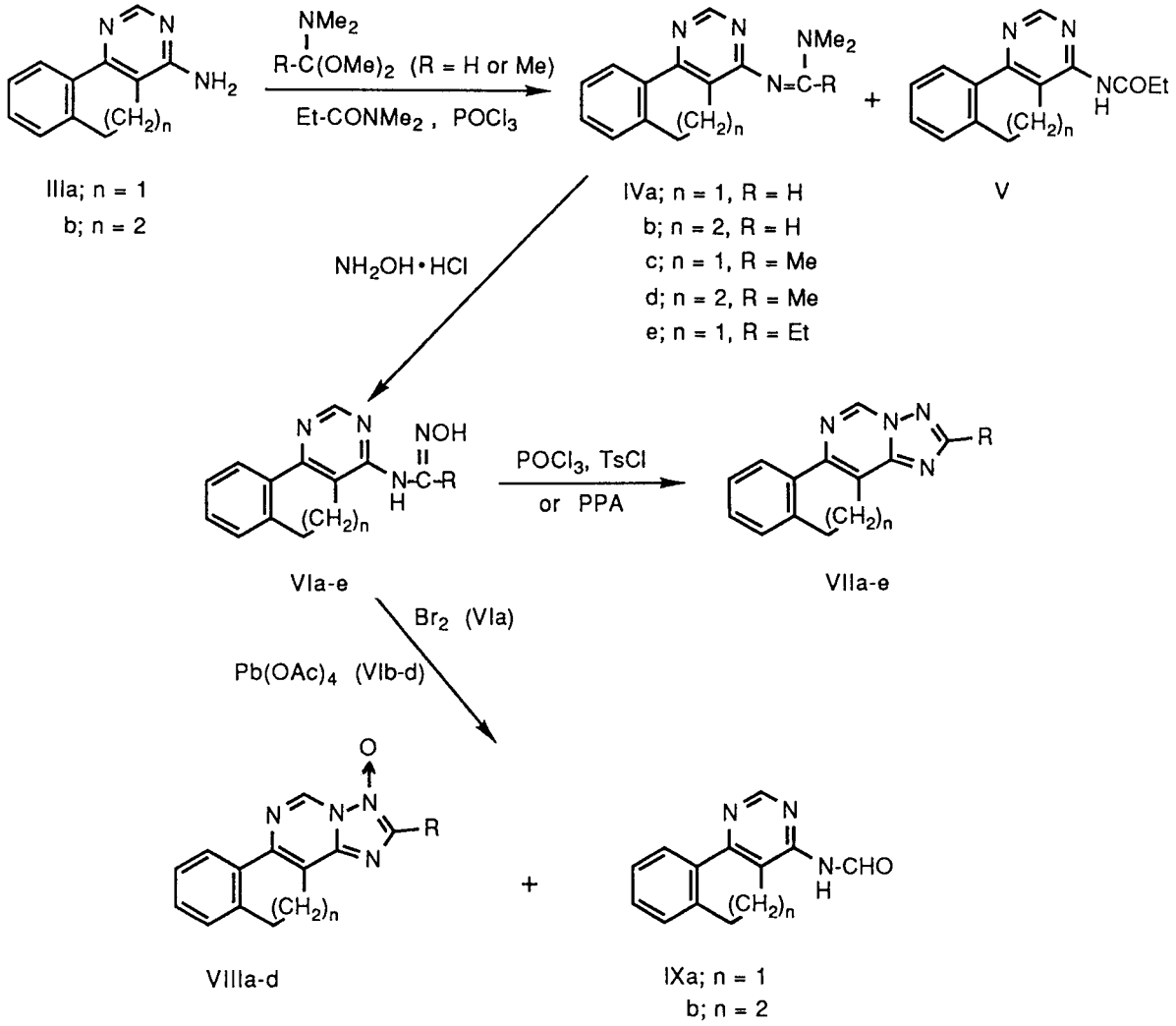


I



II: n = 1 or 2

Scheme 1



between the azasteroidal analogues and antidepressive activity. This paper deals with the syntheses and antidepressive evaluation of tetraazasteroids, their B-homologues, 17-oxides, and their precursors.

Partial synthesis of triazolopyrimidine moiety, *s*-triazolo[1,5-*a*]pyrimidine, in compound **II** was already reported by Jenko *et al.* [3] and similar cyclization was reviewed by Tišler [4]. As shown in Scheme 1, 4-amino-5,6-dihydrobenzo[*h*]quinazoline (**IIIa**) [1a] and its homologue **IIIb** [5] were respectively used as starting materials. Heterylamidines **IVa-d** were synthesized by heating **III** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) or *N*,*N*-dimethylacetamide dimethyl acetal (DMADMA) in toluene. Compound **IVe** was obtained by the Vilsmeier reaction for **IIIa** using *N*,*N*-dimethylpropionamide and phosphoryl chloride. In this case, *N*-heterylpropionamide **V** was yielded as a by-product. Reaction of the amidines **IV** with 1.2 equivalents of hydroxylamine hydrochloride in methanol gave the expected heterylamide oximes **VIa-e** in good yield. Cyclization of **VI** to 11,13,15,17-tetraazasteroid **VII** was performed by using phosphoryl chloride, tosyl chloride, or polyphosphoric acid and proceeded in relatively good yield.

The 17-oxide of tetraazasteroids **VIIIb-d** were synthesized from corresponding heterylamide oxime **VIb-d** according to the method of Gilchrist *et al.* [6] by using lead tetraacetate. In the case of **VIb**, *N*-heterylformamide **IXb** was yielded together with **VIIIb**. Cyclization of **VIa** to **VIIIa** with the same reagent did not proceed and this reaction afforded *N*-heterylformamide derivative **IXa**. Babič *et al.* [7] used bromine in acetic acid for a similar cyclization. Thus, the reaction of **VIa** with bromine was carried out according to Babič's method. Although the expected tetraazasteroid 17-oxide **VIIIa** could be obtained, compound **IXa** was still a major product. A similar observation was reported by Boyer and Frints [8]. They isolated benzamide from *N*-phenylbenzamide oxime by oxidation with lead tetraacetate or *N*-bromosuccinimide. Formation of **IX** in our reaction seems to be similar to their results.

Evaluation of the antidepressive activity of the thus obtained 11,13,15,17-tetraazasteroids **VII**, their 17-oxides **VIII**, and tricyclic compounds **IV-VI** and **IX** was screened by the method of Askew [9] which including inhibitory activity against reserpine-induced hypothermia in mice and those data were compared with those of control (saline) and imipramine. When the body temperature of mice administered with a test compound was significantly different from that of mice administered with saline at $p < 0.05$ on the statistical analysis using Student's *t*-test, the test compound was estimated as a potent one. Compounds **VId**, **VIIa**, and **VIIb** exhibited potent anti-reserpine activity among compounds **IV-IX**, and effects of these potent ones on reserpine-induced hypothermia are shown in Table I.

Only **VIIa** showed higher potent activity than imipramine at 1 hour after administration, but the other compounds exhibited weaker activities. It has already been reported that tetracyclic compound **I** exhibited potent anti-reserpine activity [2], and its homologue, benzocycloheptimidazopyrimidine, did not possess such activity [5]. In this paper, tetracyclic compound **VIa** also exhibited a more potent activity than its homologue **VIIb**. Thus, it seems that ring-expansion of cyclohexadiene to cycloheptadiene in the tetracyclic compound reduces the activity.

In tetracyclic triazolopyrimidine derivatives, it is interesting that only non-substituted compounds **VIIa,b** exhibited potent activity. On the other hand, only **VId** had potent activity in the tricyclic compounds, benzoquinazolines and benzocycloheptapyrimidines.

EXPERIMENTAL

All 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 EI-ms spectra were taken on a Shimadzu LKB-9000 Instrument. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were recorded on a Hitachi R-22 FTS

Table I

Effect of Compounds VId, VIIa and VIIb on Reserpine-Induced Hypothermia in Mice

Compound	Body temperature (°C), mean value ± SE				
	Before administration	Time after administration			
		30 minutes	1 hour	2 hours	4 hours
saline	22.7 ±0.7	23.0 ±0.5	23.6 ±0.6	25.0 ±0.9	27.5 ±0.8
imipramine	22.8 ±0.7	24.0 ±1.2	26.2 ±1.3	30.7 ±1.7 [b]	32.2 ±0.6 [a]
VId	22.9 ±0.4	24.0 ±0.7	25.1 ±0.6	27.9 ±0.7 [b]	31.1 ±1.1 [b]
VIIa	22.8 ±0.6	24.1 ±1.1	28.2 ±1.2 [a]	29.4 ±1.1 [b]	29.1 ±1.2
VIIb	22.9 ±0.8	24.6 ±1.0	25.9 ±0.7 [b]	27.1 ±1.6	28.4 ±1.4

Five male ICR-JCL mice weighing 23 to 33 g were used in all experiments and test compounds (10 mg/kg, *i.p.*) were injected at 18 hours after reserpine (2 mg/kg, *i.p.*) was administered to mice. [a] Significantly different from the control (saline) at $p < 0.01$. [b] Significantly different from the control (saline) at $p < 0.05$.

FT-NMR spectrometer (90-MHz) or Varian VXR-200 Instrument (200-MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard, and the signals are designated as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The uv spectra were taken on a Hitachi ESP-2 spectrophotometer.

IUPAC numbering is used in the Experimental.

N,*N*-Dimethyl-*N'*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)formamidine (**IVa**).

A solution of 789 mg (4.0 mmoles) of **IIIa** amd 0.6 ml (4.8 mmoles) of DMFDMA in 4 ml of dry toluene was refluxed for 3 hours. After evaporation of the solvent, the hot cyclohexane soluble fraction of the residue was recrystallized from *n*-hexane to give 787 mg (78%) of **IVa** as pale yellow plates, mp 109-111°; ms: m/z 252 (M^+, 100%); ir (potassium bromide): cm^{-1} 1620 (C=N); pmr (deuteriochloroform): 2.98 (4H, m, 5,6-H), 3.17 (6H, s, $N(CH_3)_2$), 7.32 (3H, m, 7,8,9-H), 8.27 (1H, m, 10-H), 8.65 (1H, s, 2-H), 8.73 [1H, s, C*H*$N(CH_3)_2$]; uv: λ max (log ϵ) nm 257 (4.26), 297 (3.76), 335 (4.19).

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.44; H, 6.32; N, 21.99.

N,*N*-Dimethyl-*N'*-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]-pyrimidin-4-yl)formamidine (**IVb**).

A solution of 2.11 g (10 mmoles) of **IIIb** and 1.5 ml (12 mmoles) of DMFDMA in 10 ml of dry toluene was refluxed for 2 hours. After evaporation of the solvent, the residue was recrystallized from ethanol to give 2.59 g (98%) of **IVb** as colorless needles, mp 82-83°; ms: m/z 266 (M^+, 49%); ir (potassium bromide): cm^{-1} 1623 (C=N); pmr (deuteriochloroform): 2.27 (2H, m, 6-H), 2.57 (2H, t, J = 6 Hz, 7-H), 2.72 (2H, t, J = 7 Hz, 5-H), 3.26 (6H, s, $N(CH_3)_2$), 7.34 (3H, m, 8,9,10-H), 7.73 (1H, m, 11-H), 8.65 and 8.76 (each 1H, each s, 2-H and C*H*$N(CH_3)_2$); uv: λ max (log ϵ) nm 253 (4.09), 268 (shoulder, 3.94), 298 (shoulder, 3.81), 310 (shoulder, 4.05), 322 (4.15).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.16; H, 6.78; N, 20.76.

N,*N*-Dimethyl-*N'*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)acetamidine (**IVc**).

A solution of 1.18 g (6 mmoles) of **IIIa** and 1.8 ml (7.2 mmoles) of DMADMA in 6 ml of dry toluene was refluxed for 10 hours. After evaporation of the solvent, the residue resisted the crystallization and 1.21 g (76%) of **IVc** was obtained as brownish viscous oil which showed single spot on tlc; ms: m/z 266 (M^+, 100%); ir (chloroform): cm^{-1} 1620 (C=N); pmr (deuteriochloroform): 2.07 (3H, s, $N=CCH_3$), 2.87 (4H, br s, 5,6-H), 3.14 (6H, s, $N(CH_3)_2$), 7.32 (3H, m, 7,8,9-H), 8.30 (1H, m, 10-H), 8.78 (1H, s, 2-H); uv: λ max (log ϵ) nm 233 (4.10), 255 (4.02), 262 (shoulder, 4.01), 286 (3.93), 3.06 (3.90), 312 (shoulder, 3.90), 330 (3.56).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.50; H, 6.70; N, 20.81.

N,*N*-Dimethyl-*N'*-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]-pyrimidin-4-yl)acetamidine (**IVd**).

A solution of 1.27 g (6 mmoles) of **IIIb** and 1.8 ml (7.2 mmoles) of DMADMA in 6 ml of dry toluene was refluxed for 4.5 hours. Similar treatment of the the reaction mixture described in the synthesis of **IVc** gave 1.43 g (85%) of **IVd** as brownish viscous oil; ms: m/z 280 (M^+, 55%); ir (chloroform): cm^{-1} 1600 (C=N); pmr (deuteriochloroform): 2.10 (3H, s, $N=CCH_3$), 2.19 and 2.50 (2H and 4H, each m, 5,6,7-H), 3.12 (6H, s, $N(CH_3)_2$), 7.31 (3H, m, 8,9,10-H), 7.75 (1H, m, 11-H), 8.81 (1H, s, 2-H); uv: λ max (log ϵ) nm 251 (4.45), 280 (shoulder, 4.31), 306 (4.30).

Anal. Calcd. for $C_{17}H_{20}N_4$: C, 72.82; H, 7.19; N, 19.99. Found: C, 73.01; H, 7.05; N, 20.14.

N,*N*-Dimethyl-*N'*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)propionamidine (**IVe**) and 4-Propionamido-5,6-dihydrobenzo[*h*]quinazoline (**V**).

To a solution of 1.21 g (12 mmoles) of *N*,*N*-dimethylpropionamide in 8 ml of dry chloroform was added 1.21 ml (13 mmoles) of phosphoryl chloride dropwise under ice-cooling. After the end of the addition, the mixture was stirred at 5-10° for 1 hour. To a resulting Vilsmeier reagent was added 1.97 g (10 mmoles) of **IIIa** in 50 ml of dry chloroform dropwise for 0.5 hour. Then, 4.2 ml (30 mmoles) of triethylamine was added to the solution to promote the proceeding of the reaction. The mixture was heated at 65-70° for 5 hours. The resulting mixture was poured into 50 ml of ice water, made alkaline with sodium hydrogen carbonate, and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The resulting residue was chromatographed on silica gel. The eluate of chloroform-ethyl acetate (4:1, v/v) was recrystallized from benzene-cyclohexane to give 107 mg (4.2%) of **V** as colorless needles, mp 143-145°; ms: m/z 253 (M^+, 41%); ir (potassium bromide): cm^{-1} 3400, 3240 (broad, N-H), 1672 (C=O); pmr (deuteriochloroform): 1.26 (3H, t, J = 7 Hz, CH_3), 2.67 (2H, q, J = 7 Hz, CH_2CH_3), 2.87 (4H, br s, 5,6-H), 7.34 (3H, m, 7,8,9-H), 8.30 (1H, m, 10-H), 8.55 (1H, br s, exchangeable with deuterium oxide, NH), 8.86 (1H, s, 2-H); uv: λ max (log ϵ) nm 228 (shoulder, 4.39), 263 (4.12), 286 (4.31), 301 (4.26), 309 (shoulder, 4.24).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97; N, 16.59. Found: C, 71.15; H, 6.03; N, 16.49.

Further eluate of ethyl acetate-acetone (9:1, v/v) gave 439 mg (16%) of **IVe** as a brownish viscous oil; ms: m/z 280 (M^+, 100%); ir (chloroform): cm^{-1} 1600 (C=N); pmr (deuteriochloroform): 1.06 (3H, t, J = 7 Hz, CH_2CH_3), 2.51 (2H, q, J = 7 Hz, CH_2CH_3), 2.86 (4H, br s, 5,6-H), 3.10 (6H, s, $N(CH_3)_2$), 7.30 (3H, m, 7,8,9-H), 8.27 (1H, m, 10-H), 8.76 (1H, s, 2-H); uv: λ max (log ϵ) nm 257 (4.40), 316 (4.24).

Anal. Calcd. for $C_{17}H_{20}N_4$: C, 72.82; H, 7.19; N, 19.99. Found: C, 72.71; H, 7.21; N, 19.79.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)formamide Oxime (**VIa**).

To a solution of 756 mg (3.0 mmoles) of **IVa** in 25 ml of dry methanol was added 250 mg (3.6 mmoles) of hydroxylamine hydrochloride. The solution was stirred at room temperature for 2 hours. The precipitated crystals were collected, washed with water, and recrystallized from ethanol to give 511 mg (71%) of **VIa** as colorless plates, mp 203-204°; ms: m/z 240 (M^+, 45%); ir (potassium bromide): cm^{-1} 3400, 3060 (N-H, O-H), 1660 (C=N); pmr (DMSO-d_6): 2.90 (4H, m, 5,6-H), 7.35 (3H, m, 7,8,9-H), 8.02 (1H, br d, J = 8 Hz, changed to singlet after addition of deuterium oxide, C*H*NOH), 8.18 (1H, m, 10-H), 8.37 (1H, br, exchangeable with deuterium oxide, NH), 8.66 (1H, s, 2-H), 10.61 (1H, br, exchangeable with deuterium oxide, OH); uv: λ max (log ϵ) nm 246 (4.04), 294 (3.69), 313 (384).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.07; H, 5.00; N, 23.40.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-formamide Oxime (**VIb**).

The title compound was yielded in 90% in a manner similar to that described in the synthesis of **VIa**, mp 230-232° (colorless needles from methanol); ms: m/z 254 (M^+, 68%); ir (potassium bromide): cm^{-1} 3340, 3100 (N-H, O-H), 1650 (C=N); pmr (DMSO-d_6): 2.10-2.70 (6H, m, 5,6,7-H), 7.36 (3H, m, 8,9,10-H), 7.63 (1H, m, 11-H), 8.04 (1H, d, J = 9 Hz, changed to singlet after addition of deuterium oxide, C*H*NOH), 8.54 (1H, br d, J = 9 Hz, exchangeable with deuterium oxide, NH), 8.69 (1H, s, 2-H), 10.56 (1H, br, exchangeable with deuterium oxide, OH); uv: λ max (log ε) nm 248 (4.27), 287 (3.94), 299 (4.06).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 66.07; H, 5.64; N, 21.78.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)acetamide Oxime (**VIc**).

The title compound was yielded in 66% in a manner similar to that described in the synthesis of **VIa**, mp 238-240° (colorless powder from ethanol); ms: m/z 254 (M^+, 38%); ir (potassium bromide): cm^{-1} 3370 (broad, N-H, O-H), 1630 (C=N); pmr (DMSO-d_6): 2.35 (3H, s, CH_3), 2.84 (4H, m, 5,6-H), 7.36 (3H, m, 7,8,9-H), 8.16 (1H, m, 10-H), 8.21 (1H, br, exchangeable with deuterium oxide, NH), 8.64 (1H, s, 2-H), 10.46 (1H, br, exchangeable with deuterium oxide, OH); uv: λ max (log ε) nm 252 (4.33), 297 (3.96), 313 (4.09).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 65.88; H, 5.56; N, 21.91.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-acetamide Oxime (**VId**).

The title compound was yielded in 68% in a manner similar to that described in the synthesis of **VIa**, mp 214-217° (colorless powder from methanol); ms: m/z 268 (M^+, 93%); ir (potassium bromide): cm^{-1} 3380, 3120 (N-H, O-H), 1630 (C=N); pmr (DMSO-d_6): 2.37 and 2.53 (2H and 4H, each m, 5, 6, 7-H), 7.40 (3H, m, 8, 9,10-H), 7.67 (1H, m, 11-H), 8.36 (1H, br, exchangeable with deuterium oxide, NH), 8.71 (1H, s, 2-H), 10.48 (1H, br, exchangeable with deuterium oxide, OH); uv: λ max (log ε) nm 252 (4.27), 297 (4.00), 312 (shoulder, 3.88).

Anal. Calcd. for $C_{15}H_{16}N_4O$: C, 67.14; H, 6.01; N, 20.88. Found: C, 67.29; H, 5.91; N, 20.62.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)propionamide Oxime (**VIe**).

The title compound was yielded in 62% in a manner similar to that described in the synthesis of **VIa**, mp 200-203° (pale yellow plates from ethanol); ms: m/z 268 (M^+, 16%); ir (potassium bromide): cm^{-1} 3100 (broad, N-H, O-H), 1600 (C=N); pmr (DMSO-d_6): 1.10 (3H, t, J = 7 Hz, CH_3), 2.86 (2H, q, J = 7 Hz, CH_2CH_3), 2.86 (4H, m, 5,6-H), 7.30 (3H, m, 7,8,9-H), 8.16 (1H, m, 10-H), 8.18 (1H, br, exchangeable with deuterium oxide, NH), 8.63 (1H, s, 2-H), 10.48 (1H, br, exchangeable with deuterium oxide, OH); uv: λ max (log ε) nm 252 (4.35), 294 (3.99), 313 (4.12).

Anal. Calcd. for $C_{15}H_{16}N_4O$: C, 67.14; H, 6.01; N, 20.88. Found: C, 66.95; H, 6.12; N, 20.75.

4,5-Dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline (**VIIa**).

A solution of 101 mg (0.42 mmole) of **VIa** and 95 mg (0.50 mmole) of tosyl chloride on 10 ml of dioxane was heated at 70° for 23 hours. After evaporation of the solvent, the residue was suspended in water and made alkaline with sodium hydrogen carbonate. The resulting mixture was extracted with chloroform. The organic layer was washed, dried, and evaporated. The residue was chromatographed on silica gel. The eluate of chloroform was recrystallized from ethanol to give 19 mg (20%) of **VIIa** as colorless needles, mp 145-147°; ms: m/z 222 (M^+, 100%); ir (potassium bromide): cm^{-1} 1610 (C=N); pmr (deuteriochloroform): 3.22 (4H, m, 4,5-H), 7.36 (3H, m, 6,7,8-H), 8.33 (1H, m, 9-H), 8.41 (1H, s, 2-H), 9.35 (1H, s, 11-H); uv: λ max (log ε) nm 234 (4.08), 250 (shoulder, 3.74), 293 (3.99), 306 (4.02), 319 (3.92).

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.50; H, 4.40; N, 25.31.

5,6-Dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine (**VIIb**).

A mixture of 508 mg (2.0 mmoles) of **Vb**, 10 g of polyphosphoric acid, and 1.0 g of phosphorus pentoxide was heated at 120° for 3 hours. After cooling the reaction mixture, water was added to the mixture until a white solid precipitated, and the resulting suspension was allowed to stand overnight. The deposited crystals were collected, washed with water, and recrystallized from ethanol to give 316 mg (67%) of **VIIb** as colorless needles, mp 102-103°; ms: m/z 236 (M^+, 100%); ir (potassium bromide): cm^{-1} 1610 (C=N); pmr (deuteriochloroform): 2.61 (4H, m, 5,6-H), 2.99 (2H, t, J = 7 Hz, 4-H), 7.42 (3H, m, 7,8,9-H), 7.78 (1H, m, 10-H), 8.45 (1H, s, 2-H), 9.44 (1H, s, 12-H); uv: λ max (log ε) nm 243 (3.97), 267 (shoulder, 4.06), 282 (4.17), 300 (shoulder, 3.94).

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.26; H, 5.11; N, 23.73.

2-Methyl-4,5-dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline (**VIIc**).

To a boiling solution of 665 mg (2.6 mmoles) of **VIc** in 25 ml of dry chloroform was added 1.8 ml (20 mmoles) of phosphoryl chloride in 5 ml of dry chloroform dropwise, and the resulting solution was refluxed for 0.5 hour. After evaporation of the solvent, water was added to the residue. The precipitated solid was collected, washed with water, and recrystallized from ethanol to give 442 mg (71%) of **VIIc** as colorless plates, mp 148-150°; ms: m/z 236 (M^+, 100%); ir (potassium bromide): cm^{-1} 1615 (C=N); pmr (deuteriochloroform): 2.64 (3H, s, CH_3), 3.17 (4H, m, 4, 5-H), 7.33 (3H, m, 6,7,8-H), 8.28 (1H, m, 9-H), 9.20 (1H, s, 11-H); uv: λ max (log ε) nm 238 (4.52), 294 (4.40), 307 (4.46), 320 (4.37).

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.41; H, 5.03; N, 23.75.

2-Methyl-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (**VIId**).

To a boiling solution of 918 mg (3.4 mmoles) of **VId** in 35 ml of dry chloroform was added 2.4 ml (25.6 mmoles) of phosphoryl chloride in 5 ml of dry chloroform dropwise, and the solution was refluxed for 0.5 hour. The resulting solution was poured into water, made alkaline with sodium hydrogen carbonate, and extracted with chloroform. The organic layer was washed with water, dried, and evaporated. The residue was recrystallized from ethanol to give 522 mg (61%) of **VIId** as colorless needles, mp 165-168°; ms: m/z 250 (M^+, 100%); ir (potassium bromide): cm^{-1} 1605 (C=N); pmr (deuteriochloroform): 2.56 and 2.86 (4H and 2H, each m, 4,5,6-H), 2.66 (3H, s, CH_3), 7.31 (3H, m, 7, 8,9-H), 7.73 (1H, m, 10-H), 9.28 (1H, s, 12-H); uv: λ max (log ε) nm 231 (4.28), 240 (shoulder, 4.21), 284 (4.24), 303 (shoulder, 4.02).

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.97; H, 5.64; N, 22.39. Found: C, 72.11; H, 5.50; N, 22.52.

2-Ethyl-4,5-dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline (**VIIe**).

The title compound was yielded in 67% in a manner similar to that described in the synthesis of **VIIc**, mp 120-122° (colorless needles from ethanol); ms: m/z 250 (M^+, 100%); ir (potassium bromide): cm^{-1} 1620 (C=N); pmr (deuteriochloroform): 1.45 (3H, t, J = 7 Hz, CH_3), 2.99 (2H, q, J = 7 Hz, CH_2CH_3), 3.22 (4H, m, 4, 5-H), 7.32 (3H, m, 6,7,8-H), 8.27 (1H, m, 9-H), 9.22 (1H, s, 11-H); uv: λ max (log ε) nm 238 (4.30), 294 (4.17), 306 (4.22), 320 (4.13).

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.97; H, 5.64; N, 22.39. Found: C, 71.82; H, 5.54; N, 22.45.

4,5-Dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline 1-Oxide (**VIIIa**) and 4-Formylamino-5,6-dihydrobenzo[*h*]quinazoline (**IXa**).

To a suspension of 678 mg (2.8 mmoles) of **VIa** in 17 ml of acetic acid were added 338 mg (4.2 mmoles) of sodium acetate and excess bromine in 17 ml of acetic acid dropwise under stirring at room temperature. After a few minutes, the reaction mixture was poured into ice water. The resulting solution was neutralized with sodium carbonate and extracted with chloroform. The organic layer was washed, dried, and evaporated. The residue was chromatographed on silica gel. The eluate of chloroform was recrystallized from benzene to give 379 mg (60%) of **IXa** as pale yellow prisms, mp 247-249°; ms: m/z 225 (M^+, 100%); ir (potassium bromide): cm^{-1} 3210 (N-H), 1690 (C=O); pmr (DMSO-d_6): 2.90 (4H, br s, 5,6-H), 7.41 (3H, m, 7,8,9-H), 8.25 (1H, m, 10-H), 8.81 (1H, s, 2-H), 9.49 (1H, d, J = 9 Hz, changed to singlet after addition of deuterium oxide, CHO), 10.69 (1H, br d, J = 9 Hz, exchangeable with deuterium oxide, NH); uv: λ max (log ε) nm 230 (4.41), 267 (3.97), 280 (shoulder, 4.01), 289 (4.14), 304 (4.15), 315 (4.12).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.23; H, 4.85; N, 18.64.

The further eluate of chloroform-ethyl acetate (9:1, v/v) was recrystallized from benzene to give 70 mg (10%) of **VIIIa** as pale orange needles, mp 194-196°; ms: m/z 238 (M^+, 54%); ir (potassium bromide): cm^{-1} 1598 (C=N), 1201 (N-O); pmr (deuteriochloroform): 3.18 (4H, m, 4,5-H), 7.35 (3H, m, 6,7,8-H), 8.16 (1H, s, 2-H), 8.29 (1H, m, 9-H), 9.34 (1H, s, 11-H); uv: λ max (log ε) nm 223 (4.49), 239 (shoulder, 4.36), 301 (shoulder, 4.19), 328 (4.47).

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.38; H, 4.01; N, 23.26.

5,6-Dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine 1-Oxide (**VIIIb**) and 4-Formylamino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IXb**).

To a solution of 201 mg (0.79 mmole) of **VIb** in 100 ml of dichloromethane was added 350 mg (0.79 mmole) of lead tetraacetate at -15° under nitrogen stream. After stirring at room temperature for 1 hour, the mixture was poured into ice water, made alkaline with sodium hydrogen carbonate, and extracted with dichloromethane. The organic layer was washed, dried, and evaporated. The residue was chromatographed on silica gel. The eluate of chloroform was recrystallized from benzene to give 31 mg (16%) of **IXb** as colorless prisms, mp 198-200°; ms: m/z 239 (M^+, 67%); ir (potassium bromide): cm^{-1} 3200 (N-H), 1685 (C=O); pmr (deuteriochloroform): 2.52 (6H, m, 5,6,7-H), 7.36 (3H, m, 8,9, 10-H), 7.75 (1H, m, 11-H), 8.84 (1H, s, 2-H), 9.29 (1H, br d, J = 9 Hz, exchangeable with deuterium oxide, NH), 9.68 (1H, d, J = 9 Hz, changed to singlet after addition of deuterium oxide, CHO); uv: λ max (log ε) nm 229 (shoulder, 4.34), 232 (4.35), 257 (3.90), 286 (4.15).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.12; H, 5.43; N, 17.39.

The further eluate of chloroform-ethyl acetate (9:1, v/v) was recrystallized from benzene to give 22 mg (11%) of **VIIIb** as pale yellow plates, mp 191-193°; ms: m/z 252 (M^+, 63%); ir (potassium bromide): cm^{-1} 1586 (C=N), 1250 (N-O); pmr (deuteriochloroform): 2.57 and 2.92 (4H and 2H, each m, 4,5,6-H), 7.38 (3H, m, 7,8,9-H), 7.78 (1H, m, 10-H), 8.17 (1H, s, 2-H), 9.40 (1H, s, 12-H); uv: λ max (log ε) nm 224 (4.52), 257 (shoulder, 3.91), 311 (4.43).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.70; H, 4.62; N, 21.92.

2-Methyl-4,5-dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline 1-Oxide (**VIIIc**).

The title compound was yielded in 44% in a manner similar to that described in the synthesis of **VIIIb** except for the purification. In this case, **VIIIc** was obtained by recrystallization of the residue from benzene-cyclohexane without process of chromatography, mp 225-227° (pale green prisms); ms: m/z 252 (M^+, 8%); ir (potassium bromide): cm^{-1} 1595 (C=N), 1200 (N-O); pmr (deuteriochloroform): 2.69 (3H, s, CH_3), 3.16 (4H, m, 4,5-H), 7.35 (3H, m, 6,7,8-H), 8.29 (1H, m, 9-H), 9.27 (1H, s, 11-H); uv: λ max (log ε) nm 223 (4.46), 237 (shoulder, 4.39), 260 (shoulder, 3.98), 299 (shoulder, 4.09), 328 (4.38).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.75; H, 4.69; N, 22.03.

2-Methyl-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 1-Oxide (**VIIId**).

The title compound was yielded in 36% in a manner similar to that described in the synthesis of **VIIIc**, mp 228-230° (pale brown prisms from benzene-cyclohexane); ms: m/z 266 (M^+, 48%); ir (potassium bromide): cm^{-1} 1600 (C=N), 1200 (N-O); pmr (deuteriochloroform): 2.57 and 2.86 (4H and 2H, each m, 4,5,6-H), 2.71 (3H, s, CH_3), 7.35 (3H, m, 7,8,9-H), 7.76 (1H, m, 10-H), 9.36 (1H, s, 12-H); uv: λ max (log ε) nm 224 (4.39), 233 (shoulder, 4.33), 249 (shoulder, 4.27), 259 (shoulder, 3.83), 310 (4.27).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.99; H, 5.24; N, 20.75.

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