Polycyclic N-Hetero Compounds. XXXII [1]. Synthesis and Antidepressive Evaluation of B-Homo-11,13,15-triazasteroids and Their Precursors

Takashi Hirota*, Kenji Sasaki, Katsuhiro Ieno, Yuhki Sekiya, and Taiji Nakayama

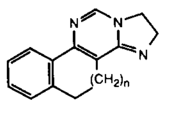
Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan

Received August 21, 1989

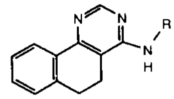
Synthesis of 4-(2-hydroxyethylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine derivatives **V** and their cyclized products, B-homo-11,13,15-triazasteroidal compounds **VI** and **VII**, are described. These products were screened to evaluate the antidepressive activity .

J. Heterocyclic Chem., **27**, 759 (1990).

In the previous paper, we reported that 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (**Ia**), corresponding to a 11,13,15-triazasteroidal compound, exhibited the antidepressive activity in mice [2], and some 4-substituted 5,6-dihydrobenzo[*h*]quinazolines **II** showed the same activity [3].



Ia; n = 1
b; n = 2

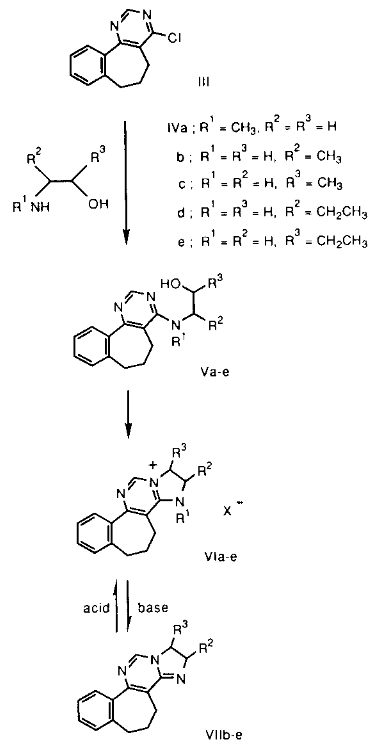


IIa; R = CH_2CH_2OH
b; R = $CH_2CH_2OCH_3$
c; R = $CH_2CH(OH)CH_2OH$

Synthesis and antidepressive evaluation of a B-homo-11,13,15-triazasteroidal compound **Ib** and its precursors were also performed during the course of this study [4]. For the further investigation of the structure-activity relationship of azasteroids, the chemical modification of **Ib** was performed. This paper deals with the synthesis and antidepressive evaluation of B-homo-11,13,15-triazasteroids bearing an alkyl group in D-ring and their precursors.

As shown in Scheme 1, 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**III**) [4] was used as a starting material. Reaction of **III** with ethanolamine derivatives **IV** afforded the corresponding 4-(2-hydroxyethylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine derivatives **V** in good yield, respectively. Reaction times, yields, melting points, and elemental analyses of **V** are listed in Table I.

Cyclization of **Va** with phosphorus tribromide gave 3-methyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta-[1,2-*e*]imidazo[1,2-*c*]pyrimidinium bromide. This compound was so hygroscopic that it was difficult to crystallize. Therefore, it was converted to the perchlorate **VIa**, which was obtained as colorless plates. A similar reaction of **Vb** with phosphoryl chloride gave 2-methyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]-pyrimidinium chloride (**VIb**) which was obtained as colorless granules. Treatment of **VIb** with sodium hydrogen



Scheme 1

carbonate to obtain the corresponding free base **VIIb**, however, gave a mixture consisting of two components, which always showed the same behaviour each another on thin-layer chromatography (tlc) in spite of using some solvent systems. The ^{1}H-nmr measurement of the free base showed that this mixture was consisted with **VIIb** and 1-methyl isomer **VIIc**, of which the molar ratio was approximately 7:3 from the comparison of the peak height of each methyl signal in the spectrum. We assumed that the formation of **VIIc** on the above reaction was owing to the Dimroth-type rearrangement of **VIIb**. It is well-known that *N*-alkylated iminopyrimidines undergo the Dimroth-type rearrangement to the corresponding alkylaminopyrimidines [5]. The imidazo[1,2-*c*]pyrimidine derivatives

Table I

Reaction Times, Yields, Melting Points, and Elemental Analyses of Compounds V

Compound No.	Reaction time (hours)	Yield (%)	Mp, °C (Recrystallization solvent)	Formula	Elemental analysis Calcd./(Found) C	H	N
Va	3.0	90	81-83.5 [a] (ethyl acetate-*n*-hexane)	$C_{16}H_{19}N_3O$	71.34 (71.18)	7.11 (6.97)	15.60 (15.73)
Vb	2.5	87	153-155 [b] (ethyl acetate)	$C_{16}H_{19}N_3O$	71.34 (71.19)	7.11 (7.17)	15.60 (15.38)
Vc	5.0	97	185-187 [b] (benzene)	$C_{16}H_{19}N_3O$	71.34 (71.11)	7.11 (7.16)	15.60 (15.77)
Vd	4.0	86	158-160 [c] (ethanol)	$C_{17}H_{21}H_3O$	72.05 (71.77)	7.47 (7.63)	14.83 (14.63)
Ve	1.0	95	175-176 [b] (ethanol)	$C_{17}H_{21}N_3O$	72.05 (72.12)	7.47 (7.52)	14.83 (14.96)

[a] Colorless prisms. [b] Colorless needles. [c] Colorless granules.

Table II

Reaction Conditions and Yields on Cyclization of Compounds V

Starting material	Reaction conditions: Halogenation reagent (Molar ratio to V)	Solvent [a]	Time (hours)	Products as isolated salt (yield, %)
Va	PBr_3 (10 molar equiv.)	toluene	8.0	**VIa** (86)
Vb	$POCl_3$ (5 molar equiv.)	chloroform	4.5	**VIb** (58)
Vc	$POCl_3$ (10 molar equiv.)	toluene	8.0	**VIc** (83)
Vd	$POCl_3$ (10 molar equiv.)	toluene	9.0	**VId** (82)
Ve	$POCl_3$ (10 molar equiv.)	toluene	9.0	**VIe** (78)

[a] Dry and alcohol-free solvent was used.

bearing a oxo group in the imidazole ring undergo a similar rearrangement [6]. Guerret *et al.* have reported that 2-or 3-methylimidazo[1,2-*c*]pyrimidines undero the Dimroth-type rearrangement under basic aqueous condition to a mixture of the 2-and 3-methyl derivatives, respectively, both which are equilibrated under conditions used [7]. But, similar rearrangements for annelated iminopyrimidines, corresponding to 2,3-dihydroimidazo[1,2-*c*]pyrimidines, have not been reported.

Cyclization of **Vc-e** with phosphoryl chloride followed by sodium hydrogen carbonate afforded the corresponding 1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidines **VIIc-e** as the free bases in good yield. A very small amount of **VIIb** was detected on cyclization of **Vc** by a capillary gas chromatography and slight **VIIe** was also done on that of **Vd**. But, in these cases, the possibility could not be denied that **VIIb** or **VIIe** was a

Table III

Melting Points, Appearances, and Elemental Analyses of Compounds VI

Compound No.	Mp, °C (Recrystallization solvent)	Appearance	Formula	Elemental analysis Calcd./(Found) C	H	N
VIa	231-232.5 (water)	colorless plates	$C_{16}H_{18}N_3{\cdot}ClO_4$	54.63 (54.39)	5.16 (5.19)	11.94 (11.82)
VIb	294-295 dec (ethanol-diethyl ether)	colorless granules	$C_{16}H_{17}N_3{\cdot}HCl$	66.77 (66.53)	6.30 (6.29)	14.60 (14.47)
VIc	152-153 (ethanol-diethyl ether)	colorless plates	$C_{16}H_{17}N_3{\cdot}C_4H_4O_4$	65.38 (65.27)	5.76 (5.54)	11.44 (11.28)
VId	138-139 (ethanol-diethyl ether)	colorless prisms	$C_{17}H_{19}H_3{\cdot}C_4H_4O_4$	66.12 (65.93)	6.08 (6.06)	11.02 (10.95)
VIe	214.5-216 (ethanol)	colorless plates	$C_{17}H_{19}N_3{\cdot}HClO_4$	55.85 (55.73)	5.51 (5.57)	11.49 (11.25)

Table IV

Effects of Compounds **Vb**, **Vc** and **Ve** on Reserpine-Induced Hypothermia in Mice

Compound	Body temperature (°C), mean value ± SD				
	Before administration	Time after administration 30 minutes	1 hour	2 hours	4hours
saline	24.0 ± 0.33	24.9 ± 0.45	25.8 ± 1.59	27.3 ± 0.78	29.5 ± 0.67
Imipramine	24.2 ± 1.23	29.4 ± 2.01 [a]	31.6 ± 0.67 [a]	33.4 ± 1.01 [a]	34.4 ± 0.56 [a]
Vb	24.2 ± 0.34	25.7 ± 0.22 [a]	28.5 ± 0.45 [a]	29.6 ± 1.45 [b]	30.2 ± 0.22
Vc	23.8 ± 0.67	26.0 ± 1.01	27.0 ± 0.34	29.4 ± 0.11 [a]	30.1 ± 0.89
Ve	24.2 ± 0.34	25.4 ± 0.67	26.7 ± 2.12	29.3 ± 2.01	32.1 ± 1.79 [b]

Five male ICR-JCL mice weighing 22 to 27 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 $p < 0.05$.

thermal product by gas chromatography and not a rearrangement product by alkali. The formation of **VIId** was not detected on cyclization of **Ve**. As these cyclized products **VIIc-e** resisted crystallization, purification was performed by derivatization to the corresponding crystalline pyrimidinium salts **VIc-e** followed by recrystallization from an appropriate solvent.

Cyclization conditions of compounds **V** and some data of the cyclized products **VI** are listed in Tables II and III.

Antidepressive activity of the above crystalline B-homo-11,13,15-triazasteroids **VI** and their precursors **V** were screened by evaluating the inhibitory action of reserpine-induced hypothermia in mice [8]. Compounds **Vb**, **Vc**, and **Ve** exhibited effective action. These data are shown in Table IV.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. The ir spectra were obtained with a JASCO IRA-102 spectrometer as potassium bromide desk and the frequencies were expressed in cm^{-1}. The ^{1}H-nmr spectra were measured with a Hitachi R-22 FTS instrument (90 MHz). The chemical shift (δ) were measured relative to tetramethylsilane as an internal standard. The ms spectra were obtained by using a direct inlet probe with a Shimadzu LKB-9000 instrument at 70 eV. The tlc was performed in silica gel (Wakogel B-5FM, 0.25 mm thickness) using some solvent systems. Capillary gas chromatography was carried out on a Shimadzu GC-4CM with a flame ionization detector, using a 25 m fused silica capillary column (HiCap-CBP 1, corresponding to methylsilicon, OV-1; 0.53 mm ID; 1.0 μm film thickness). Helium was used as a carrier gas at a flow rate of 0.9 ml/minute. The injector and the detector temperature was constantly set at 220°. The microanalyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. IUPAC numbering is used in the experimental.

General Procedure for Preparation of **Va-e**.

A mixture of **III** (3 mmoles) and **IV** (15 mmoles) was allowed to stand on boiling water bath for 1-5 hours with tlc monitoring. After cooling, a small amount of water was added to the reaction mixture. In the cases of **IVd** and **IVe**, the precipitated crystals were collected on a filter, washed with a small amount of water, and recrystallized to give **Vd** and **Ve**, respectively. In other cases, each aqueous mixture was extracted with chloroform, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from appropriate solvent to give corresponding 4-alkylamino derivatives **Va-c**.

4-(*N*-Methyl-2-hydroxyethylamino)-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine (**Va**).

This compound had ir: 3280 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.44 and 2.69 (6H, each m, H-5, 6, and 7), 3.23 (3H, s, CH_3), 3.71 and 3.91 (each 2H, m, NCH_2CH_2), 5.3 (1H, br, exchangeable with deuterium oxide, OH), 7.35 (3H, m, H-8, 9, and 10), 7.80 (1H, m, H-11), 8.58 (1H, s, H-2); ms: m/z 269 (M^+, 5%), 239 (M^+ -CHOH, 100%).

4-(2-Hydroxy-1-methylethylamino)-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine (**Vb**).

This compound had ir: 3340, 3220 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.32 (3H, d, J = 7 Hz, CH_3), 2.27 and 2.57 (6H, each m, H-5, 6, and 7), 3.72 (2H, m, CH_2OH), 4.35 (1H, m, *CH*NH), 4.0 and 4.9 (each 1H, br, exchangeable with deuterium oxide, NH and OH), 7.33 (3H, m, H-8, 9, and 10), 7.70 (1H, m, H-11), 8.66 (1H, s, H-2); ms: m/z 269 (M^+, 5%), 238 (M^+ -CH_2OH, 100%).

4-(2-Hydroxypropylamino)-6,7-dihydro-5*H*-benzo[3,4]cyclohepta-[1,2-*d*]pyrimidine (**Vc**).

This compound had ir: 3330, 3230 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.23 (3H, d, J = 6 Hz, CH_3), 2.28 and 2.57 (6H, each m, H-5, 6, and 7), 3.2-3.9 [2H, m, changed to two double doublet signals at 3.38 ppm (J = 13.5 Hz, 7.0 Hz) and 3.62 ppm (J = 13.5 Hz, 10.5 Hz) after addition of deuterium oxide, CH_2NH], 4.00 (1H, m, C*H*OH), 4.1 and 5.4 (each 1H, br, exchangeable with deuterium oxide, NH and OH), 7.29 (3H, m, H-8, 9, and 10), 7.77 (1H, m, H-11), 8.60 (1H, s, H-2); ms: m/z 269 (M^+, 5%), 224 (M^+ -CH_3CHOH, 100%).

4-[(1-Hydroxymethyl)propylamino]-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine (**Vd**).

This compound had ir: 3340, 3200 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.02 (3H, t, J = 7 Hz, CH_3), 1.66 (2H, m, CH_2CH_3), 2.30 and 2.57 (6H, each m, H-5, 6, and 7), 3.76 (2H, m, CH_2OH), 4.10 (1H, m, *CH*NH), 4.98 (2H, br, exchangeable with deuterium oxide, NH and OH), 7.33 (3H, m, H-8, 9, and 10), 7.70 (1H, m, H -11), 8.56 (1H, s, H-2); ms: m/z 283 (M^+, 9%), 252 (M^+ -CH_2OH, 100%).

4-(2-Hydroxybutylamino)-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine (**Ve**).

This compound had ir: 3325, 3130 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.00 (3H, t, J = 6.5 Hz, CH_3), 1.53 (2H, m, CH_2CH_3), 2.30 and 2.55 (6H, each m, H-5, 6, and 7), 3.3-3.9 [3H, m, changed to two double doublet signals at 3.42 ppm (J = 13.5 Hz, 7.5 Hz, one of $NHCH_2$) and 3.58 ppm (J = 13.5 Hz, 12.0 Hz, one of $NHCH_2$) and one multiplet signal at 3.66 ppm ($NHCH_2CH$) after addition of deuterium oxide], 4.06 and 5.39 (each 1H, br, exchangeable with deuterium oxide, NH and OH), 7.30 (3H, m, H-8, 9, and 10), 7.69 (1H, m, H-11), 8.57 (1H, s, H-2); ms: m/z 283 (M^+, 3%), 224 (M^+ -C_2H_5CHOH, 100%).

General Procedure for Cyclization of **V**.

The halogenating reagent was added to each solution of **V** in an appropriate solvent under ice-cooling (Table II). The mixture was refluxed for an appropriate period with tlc monitoring and evaporated *in vacuo*. Crystallization of the residue was only successful for **VIb**. In the case of cyclization of **Va**, aqueous sodium perchlorate was added to the aqueous solution of the residue and then the mixture was allowed to stand on boiling water for a few minutes. After cooling of the mixture, the precipitated solid were collected on a filter, washed with a small amount of water, dried *in vacuo*, and recrystallized to give corresponding perchlorate **VIa**. In the case of **VIb**, an aliquot of **VIb**, which was obtained by recrystallization, was treated with aqueous sodium hydrogen carbonate under ice-cooling to be converted to the free base. The mixture was extracted with chloroform, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give an oily residue. This residue resisted crystallization and always behaved as a single spot on tlc in spite of using some solvent systems. But the ^{1}H-nmr spectrum of the residue showed that it was a mixture of **VIIb** (70%) and **VIIc** (30%). In the cases of cyclizations of **Vc-e**, each residue was made alkaline with aqueous sodium hydrogen carbonate under ice-cooling. They were individually extracted with chloroform, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give an oily residue. All of them resisted crystallization, but each of them always behaved as a single spot on tlc in spite of using some solvent systems. Their ^{1}H-nmr spectra showed that they contained some slight impurities, individually. For the purpose of purification, an aliquot of each of them was transformed into the appropriate crystalline salt **VIc**, **VId**, or **VIe** by the usual method.

3-Methyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidinium Perchlorate (**VIa**).

This compound had ir: 2910, 2850, 1620, 1555 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.41 and 2.62 (6H, each m, H-4, 5, and 6), 3.37 (3H, s, CH_3), 4.06 and 4.64 (each 2H, br t, J = 9.5 Hz, H-1 and 2), 7.48 (3H, m, H-7, 8, and 9), 7.70 (1H, m, H-10), 8.87 (1H, s, H-12); ms: (parent peak was not observed) m/z 252 (M -ClO_4, 100%).

2-Methyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidinium Chloride (**VIb**).

This compound had ir: 3400, 2750, 1600, 1535 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 1.42 (3H, d, J = 5.0 Hz, CH_3), 2.33 and 2.58 (6H, each m, H-4, 5, and 6), 4.36 and 4.85 (each 1H, br t, J = 9.0 Hz, H-1), 4.45 (1H, m, H-2), 7.47 (3H, m, H-7, 8, and 9), 7.64 (1H, m, H-10), 8.88 (1H, s, H-12), 10.9 (1H, br s, exchangeable with deuterium oxide, NH); ms: (parent peak was not observed) m/z 251 (M -HCl, 30%), 236 (M -HCl-CH_3, 100%).

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

This compound had ^{1}H-nmr (deuteriochloroform): 1.38 (3H, d, J = 6.0 Hz, CH_3), 2.33 and 2.66 (6H, each m, H-4, 5, and 6), 3.67 (1H, m, H-2), 4.20 (1H, br t, J = 10.5 Hz, H-1), 4.29 (1H, dd, J = 10.5 Hz, 6.0 Hz, H-1), 7.33 (3H, m, H-7, 8, and 9), 7.63 (1H, m, H-10), 7.79 (1H, s, H-12).

1-Methyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidinium Maleate (**VIc**).

This compound had ir: 3400, 3250-2200, 1635, 1565 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 1.70 (3H, d, J = 6.5 Hz, CH_3), 2.34 and 2.56 (6H, each m, H-4, 5, and 6), 3.3 (1H, br s, exchangeable with deuterium oxide, NH), 3.67 (1H, dd, J = 11.0 Hz, 8.0 Hz, H-2), 4.22 (1H, t, J = 11.0 Hz, H-2), 5.10 (1H, m, H-1), 6.03 (2H, s, olefinic protons of maleic acid), 7.47 (3H, m, H-7, 8, and 9), 7.65 (1H, m, H-10), 9.01 (1H, s, H-12); ms: (parent peak was not observed) m/z 251 (M -$C_4H_4O_4$, 60%), 250 (M -$C_4H_4O_4$- H, 100%).

1-Methyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidine (**VIIc**).

This compound had ^{1}H-nmr (deuteriochloroform): 1.51 (3H, d, J = 6.0 Hz, CH_3), 2.35 and 2.62 (6H, each m, H-4, 5, and 6), 3.61 (1H, dd, J = 13.5 Hz, 6.5 Hz, H-2), 4.21 (1H, dd, J = 13.5 Hz, 10.5 Hz, H-2), 4.41 (1H, m, H-1), 7.28 (3H, m, H-7, 8, and 9), 7.62 (1H, m, H-10), 7.79 (1H, s, H-12). Determination of this compound by the capillary gas chromatography showed that it contained less than 1% of **VIIb**.

2-Ethyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidinium Maleate (**VId**).

This compound had ir: 3420, 3250-2100, 1630, 1555 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 0.99 (3H, t, J = 6.5 Hz, CH_3), 1.75 (2H, m, CH_2CH_3), 2.36 and 2.60 (6H, each m, H-4, 5, and 6), 3.3 (1H, br s, exchangeable with deuterium oxide, NH), 4.40 [2H, multiplet signal (H-2) overlapped with double doublet signal (J = 13.5 Hz, 6.5 Hz, H-1)], 4.84 (1H, t, J = 13.5 Hz, H-1), 6.02 (2H, s, olefinic protons of maleic acid), 7.48 (3H, m, H-7, 8, and 9), 7.68 (1H, m, H-10), 8.87 (1H, s, H-12); ms: (parent peak was not observed) m/z 265 (M -$C_4H_4O_4$, 15%), 236 (M -$C_4H_4O_4$ -C_2H_5, 100%).

2-Ethyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidine (**VIId**).

This compound had ^{1}H-nmr (deuteriochloroform): 0.98 (3H, t, J = 7.5 Hz, CH_3), 1.65 (2H, m, CH_2CH_3), 2.35 and 2.61 (6H, each m, H-4, 5, and 6), 3.73 (1H, m, H-2), 4.19 (2H, m, H-1), 7.30 (3H, m, H-7, 8, and 9), 7.59 (1H, m, H-10), 7.81 (1H, s, H-12). Determination of this compound by the capillary gas chromatography showed that it contained less than 1% of **VIIe**.

1-Ethyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidinium Perchlorate (**VIe**).

This compound had ir: 3220, 2700, 1630, 1555 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 0.97 (3H, t, J = 7.0 Hz, CH_3), 2.07 (2H, m, CH_2CH_3), 2.34 and 2.60 (6H, each m, H-4, 5, and 6), 3.80 (1H, dd, J = 10.5 Hz, 7.0 Hz, H-2), 4.19 (1H, t, J = 10.5 Hz, H-2), 5.00 (1H, m, H-1), 7.47 (3H, m, H-7, 8, and 9), 7.67 (1H, m, H-10), 8.98 (1H, s, H -12), 10.24 (1H, br s, exchangeable with deuterium oxide, NH); ms: (parent peak was not observed) m/z 265 (M $-HClO_4$, 99%), 236 (M $-HClO_4$ $-C_2H_5$, 100%).

1-Ethyl-1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo-[1,2-*c*]pyrimidine (**VIIe**).

This compound had ^{1}H-nmr (deuteriochloroform): 1.00 (3H, t, J = 7.0 Hz, CH_3), 1.83 (2H, m, CH_2CH_3), 2.36 and 2.63 (6H, each m, H-4, 5, and 6), 3.73 (1H, m, H-2), 4.11 (1H, t, J = 10.0 Hz, H-2), 4.24 (1H, m, H-1), 7.29 (3H, m, H-7, 8, and 9), 7.63 (1H, m, H-10), 7.79 (1H, s, H-12).

Acknowledgements.

The authors are grateful to Mr. A. Iwadoh for mass spectral measurements. This work was supported in part by a Grant-in-Aid for General Scientific Research (No. 01571152) from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

REFERENCES AND NOTES

[1] Part **XXXI**: T. Hirota, K. Sasaki, H. Ohtomo, A. Uehara, and T. Nakayama, *Heterocycles*, **31**, 153 (1990).

[2] T. Hirota, K. Kawanishi, K. Sasaki, T. Namba, A. Iwadoh, and S. Hayakawa, *J. Heterocyclic Chem.*, **23**, 685 (1986).

[3] T. Hirota, K. Kawanishi, K. Sasaki, and T. Namba, *Chem. Pharm. Bull.*, **34**, 3011 (1986).

[4] T. Hirota, K. Ieno, and K. Sasaki, *J. Heterocyclic Chem.*, **23**, 1685 (1986).

[5] D. J. Brown, The Pyrimidines, Supplement I, John Wiley and Sonc, Inc., New York, 1970, p 290.

[6] T. Ueda and J. J. Fox, *J. Org. Chem.*, **29**, 1762 (1964).

[7] P. Guerret, R. Jacquier, and G. Maury, *J. Heterocyclic Chem.*, **8**, 643 (1971).

[8] B. M. Askew, *Life Sci.*, **2**, 725 (1963).