Polycyclic *N*-Hetero Compounds. XXVII [1]. Synthesis and Investigation of the Antidepressive Activity of a B-Homo-11,13,15-triazasteroid and its Related Compounds

Takashi Hirota*, Katsuhiro Ieno, and Kenji Sasaki

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

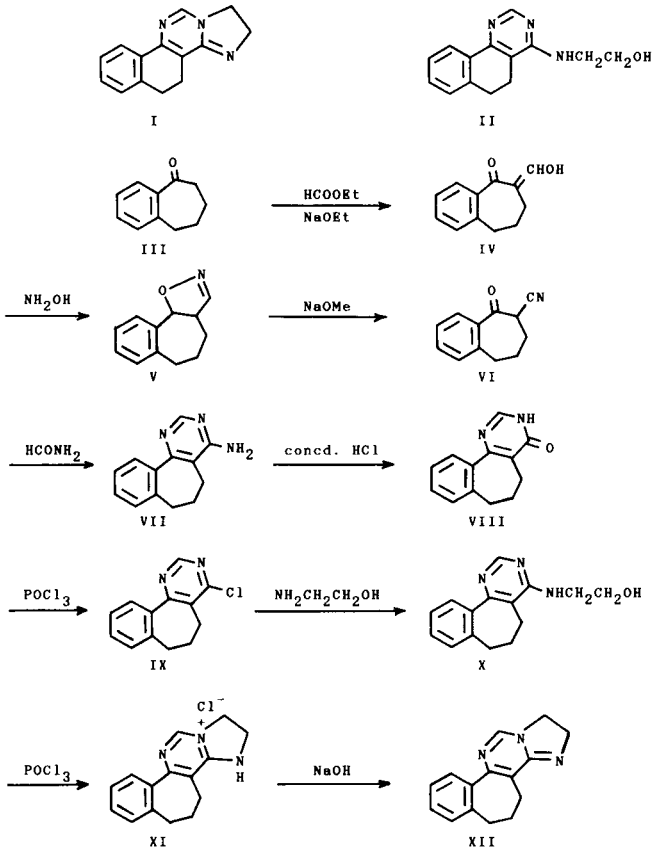
Received April 21, 1986

A synthesis of 1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidine (XII) having a novel ring system is described. Antidepressive activity of XII and its precursors VII-X was screened by inhibitory action of reserpine-induced hypothermia.

J. Heterocyclic Chem., **23**, 1685 (1986).

In an earlier paper, it was reported that 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (I) [2] corresponding to 11,13,15-triazasteroid and its precursor, 4-hydroxyethylamino-5,6-dihydrobenzo[*h*]quinazoline (II) [3], exhibited antidepressive activity in mice. In the course of our study of this series, synthesis of 1,2,5,6-tetrahydro-4*H*-benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidine (XII) corresponding to B-homo-11,13,15-triazasteroid was designed. Furthermore, no reports of the ring system prompted us to synthesize the B-homotriazasteroidal compound XII. This paper deals with the synthesis of XII and investigation of antidepressive activity of XII and its precursors VII-X.

Scheme 1



As shown in Scheme 1, commercially available benzocyclohepten-5-one (III) was used as a starting material. Ketonitrile VI was obtained by the application of Johnson's method [4], which included the synthesis of 2-cyano-1-tetralone from 1-tetralone. Khanna and Anand already reported the synthesis of compounds IV, V, and VI from compound III by a similar method, however, experimental data of them were not described except for compound V [5]. Tarbell *et al.* also obtained compound VI with an alternative synthesis [6]. In our case, although compounds IV and V were not isolated, compound VI could be obtained in better yield than that of Tarbell's method without use of toxic sodium cyanide. Reaction of VI with hot formamide under an ammonia stream afforded 4-amino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]-pyrimidine (VII) in 52% yield. The ir and pmr spectra of VII showed N-H bands at 3400 and 3350 cm^{-1} and the pyrimidine proton at δ 8.61 ppm as a one-proton singlet, respectively. Hydrolysis of VII with refluxing 6*N* hydrochloric acid gave lactam VIII. The ir and pmr spectra showed N-H and C=O bands at 2960 and 1660 cm^{-1} and the pyrimidine proton at δ 8.48 ppm as a one-proton singlet, respectively. Treatment of VIII with phosphoryl chloride gave the 4-chloro derivative IX almost quantitatively. Excess ethanolamine was allowed to react with IX to obtain the 4-hydroxyethylamino derivative X, which was cyclized to B-homotriazasteroidal skeleton XI with phosphoryl chloride. Treatment of XI with sodium hydroxide gave the title compound XII as a free base.

The antidepressive activity of XII and its precursors VII-X was screened by the inhibition against reserpine-induced hypothermia in mice and compared with that of control [7]. Compounds VII, IX, X, and XII did not exhibit an antireserpine action, however, compound VIII showed activity.

Further works of this series 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 ir spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer. The 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 ms spectra were taken with a Shimadzu LKB-9000 instrument at 70eV. The uv absorption spectra were taken on a Hitachi ESP-2 spectrophotometer in ethanol.

IUPAC numbering is used in the experimental.

6-Cyano-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (VI).

A solution of 120 g (649 mmoles) of V in 500 ml of ether was added dropwise to dry powdered sodium methoxide prepared from 28 g (1.2 g-atoms) of sodium and dry methanol under stirring. The mixture was stirred at room temperature for 2 hours. After addition of water, the resulting mixture was acidified with concentrated hydrochloric acid. After separation of the ethereal layer, the aqueous layer was extracted with ether. The combined ethereal layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The resulting oil was dissolved in ether again and the solution was shaken with 1*N* sodium hydroxide to transfer the ketonitrile into the aqueous layer. However, colorless crystals (sodium salt of VI) were precipitated between organic and aqueous layers. The crystals were collected on a filter and washed with ether and a small amount of cold water. The combined filtrate was separated and the aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The extract was worked up as usual to give VI as a brown oil. The crystals (sodium salt of VI) described above were dissolved in water and worked up in a similar manner as described in the treatment of the filtrate. Vacuum distillation of the residue gave 90.2 g of VI as a brown oil (overall yield based on III was 74%), bp 105-108°/0.1 mm Hg (lit [6] 119°/0.3 mm Hg); ir (chloroform): cm^{-1} 2200 (C≡N), 1690 (C=O); pmr (deuteriochloroform): 2.16 (4H, m, H-7 and 8), 3.02 (2H, m, H-9), 3.96 (1H, dd, J = 9 Hz, 5 Hz, H-6), 7.32 (3H, m, H-1, 2, and 3), 7.76 (1H, br d, J = 8 Hz, H-4); cmr (deuteriochloroform): 117.9 (s, C≡N), 196.4 (s, C=O).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.85; H, 5.92; N, 7.49.

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

A solution of 84.5 g (457 mmoles) of VI in 700 ml of formamide was stirred at 170° for 13 hours under an ammonia stream. After evaporation of formamide *in vacuo*, *ca.* 500 ml of water was added to the residue and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from dioxane to give 50.1 g (52%) of VII as colorless needles, mp 202-203°; ms: m/z 211 (M^+, 100%); ir (potassium bromide): cm^{-1} 3400, 3350, 1660 (N-H); pmr (deuteriochloroform): 2.32 and 2.59 (4H and 2H, m and t, J = 6 Hz, H-5, 6, and 7), 5.41 (2H, br s, deuterium oxide exchangeable, NH_2), 7.17-7.53 (3H, m, H-8, 9, and 10), 7.78 (1H, dd, J = 8 Hz, 2 Hz, H-11), 8.61 (1H, s, H-2); uv: ν max (log ϵ) nm 241 (4.38), 288 (3.75).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.62; H, 6.12; N, 19.71.

6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one (VIII).

A solution of 42.1 g (200 mmoles) of VII in 600 ml of 6*N* hydrochloric acid was refluxed for 1 day. The resulting solution was evaporated to dryness and the residue was dissolved in water again. The solution was basified with sodium bicarbonate. The deposited crystals were collected and recrystallized from pyridine to give 30.8 g (73%) of VIII as colorless plates, mp 234-236°; ms: m/z 212 (M^+, 100%); pmr (pyridine-d_5): 2.24 (2H, m, H-6), 2.55 and 2.64 (each 2H, each br t, J = 6 Hz, J = 7 Hz, H-5 and 7), 7.26-7.50 (3H, m, H-8, 9, and 10), 7.98 (1H, m, H-11), 8.48 (1H, s, H-2); uv: ν max (log ϵ) nm 249 (4.23), 287 (3.83).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.69; N, 13.19. Found: C, 73.42; H, 5.58; N, 13.12.

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

A solution of 30.3 g (143 mmoles) of VIII in 160 ml of phosphoryl chloride was refluxed for 4 hours. The solution was evaporated to dryness and *ca.* 100 ml of ice-water was added to the yellowish oily residue. The mixture was basified with sodium bicarbonate and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from petroleum ether to give 30.3 g (92%) of IX as pale yellow prisms, mp 60-62°; ms: m/z 232 (M^+ + 2, 32%), 230 (M^+, 100%); pmr (deuteriochloroform): 2.38 (2H, m, H-6), 2.57 and 2.72 (each 2H, each br t, J = 6 Hz, H-5 and 7), 7.20-7.57 (3H, m, H-8, 9, and 10), 7.73 (1H, m, H-11), 8.94 (1H, s, H-2); uv: ν max (log ϵ) nm 229 (shoulder), 258 (shoulder), 274 (4.05).

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.80; N, 12.14. Found: C, 67.46; H, 4.71; N, 12.23.

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

A mixture of 1.56 g (6.78 mmoles) of IX and 4.13 g (67.7 mmoles) of ethanolamine was heated at 150° for 1 hour. The reaction mixture was evaporated to dryness and the crystalline residue was washed with water to remove ethanolamine hydrochloride. The crystals were recrystallized from diluted ethanol to give 1.67 g (97%) of X as colorless prisms, mp 173-174°; ms: m/z 255 (M^+, 16%), 224 ($M^+ - CH_2OH$, 100%); ir (potassium bromide): cm^{-1} 3340, 3220 (O-H and N-H); pmr (DMSO-d_6): 2.26 and 2.48 (4H and 2H, each m, H-5, 6, and 7), 3.55 (4H, m, NCH_2CH_2O), 4.71 and 7.06 (each 1H, each br, deuterium oxide exchangeable, NH and OH), 7.17-7.50 (3H, m, H-8, 9, and 10), 7.57 (1H, m, H-11), 8.43 (1H, s, H-2); uv: ν max (log ϵ) nm 247 (4.31), 297 (3.60).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.45. Found: C, 70.48; H, 6.80; N, 16.33.

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

A solution of 1.24 g (4.86 mmoles) of X in 8 ml of phosphoryl chloride was refluxed for 1 hour. The reaction mixture was evaporated to dryness and the resulting residue was recrystallized from ethanol-benzene to give 1.09 g (82%) of XI as colorless needles, mp 298-300°; ms: m/z 237 (M − HCl, 100%); ir (potassium bromide): cm^{-1} 3470, 3030 (N-H); pmr (deuterium oxide): 2.39 and 2.63 (4H and 2H, m and t, J = 6 Hz, H-4, 5, and 6), 4.17 and 4.86 (each 2H, each t, J = 9 Hz, H-1 and 2), 7.39-7.75 (3H, m, H-7, 8, and 9), 7.77 (1H, m, H-10), 8.73 (1H, s, H-12); uv: ν max (log ϵ) nm 253 (4.24), 269 (shoulder), 315 (3.52).

Anal. Calcd. for $C_{15}H_{15}N_3 \cdot HCl \cdot 2H_2O$: C, 58.15; H, 6.50; N, 13.56. Found: C, 58.27; H, 6.36; N, 13.55.

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

A solution of 401 mg (1.47 mmoles) of XI in water was basified with 1*N* sodium hydroxide and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to afford a pale yellowish oily product, almost quantitatively. This oil resisted crystallization; ms: m/z 237 (M^+, 100%); pmr (deuteriochloroform): 2.38 and 2.76 (4H and 2H, br s and t, J = 7 Hz, H-4, 5, and 6), 4.13 (4H, br s, H-1 and 2), 7.16-7.43 (3H, m, H-7, 8, and 9), 7.62 (1H, m, H-10), 7.86 (1H, s, H-12).

Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.65; H, 6.65; N, 17.42.

Acknowledgements.

The authors are grateful to Mr. A. Iwadoh for mass spectral measurements and to Mrs. M. Aiki for microanalyses.

REFERENCES AND NOTES

[1] Part XXVI: T. Hirota, M. Fukumoto, and K. Sasaki, *Heterocycles*, **24**, 1997 (1986).

[2a] T. Koyama, T. Hirota, T. Yoshida, H. Hara, and S. Ohmori, *Chem. Pharm. Bull.*, **22**, 1451 (1974); [b] T. Koyama, H. Hara, T. Hirota, S.

Ohmori, and M. Yamato, *ibid.*, **23**, 2015 (1975).

[3a] T. Hirota, K. Kawanishi, K. Sasaki, T. Namba, A. Iwadoh and S. Hayakawa, *J. Heterocyclic Chem.*, **23**, 685 (1986); [b] T. Hirota, K. Kawanishi, K. Sasaki, and T. Namba, *Chem. Pharm. Bull.*, **34**, 3011 (1986).

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

[5] J. M. Khanna and N. Anand, *Indian J. Chem.*, **6**, 6 (1968).

[6] D. S. Tarbell, H. F. Wilson, and E. Ott, *J. Am. Chem. Soc.*, **74**, 6263 (1952).

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