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Synthesis in the Diazasteroid Group. XIV.[1] Synthesis of the 13,15-Diazasteroid System

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A 13,15-diazasteroid system was synthesized from 2-(6-methoxynaphthyl)ethyl tosylate (steroidal segment of the A, B rings) and ethylene urea (steroidal segment of the D ring) in 24.3% overall yield. The tosylate formed a 1:1 adduct with ethylene urea in 44% yield, using 2 molar equivalents of ethylene urea in the presence of sodium hydride in benzene. The adduct was cyclized to 13,15-diazasteroid hydrochloride in 69.7% yield by prolonged heating in the presence of phosphorus pentoxide in phosphorus oxychloride. The hydrochloride was neutralized to provide the 13,15-diazasteroid in 79.1% yield by treatment with potassium hydroxide solution. The biological activity of the hydrochloride of the 13,15-diazasteroid is now being examined.

Keywords——diazasteroid; Bischler-Napieralski cyclization; azasteroid; ethylene urea derivatives; naphthyl ethyl derivatives

We have succeeded in synthesizing the 13,15-diazasteroid system (I) starting with ethylene urea and 2-(6-methoxynaphthyl)ethyl tosylate (IIa) as the steroidal segments of the D ring and A, B rings, respectively. In the literature, it was reported that the 13,14-diazasteroid system (III) and 8,13-diazateroid system (IV) have analgesic or inflammatory activity.[3,4]

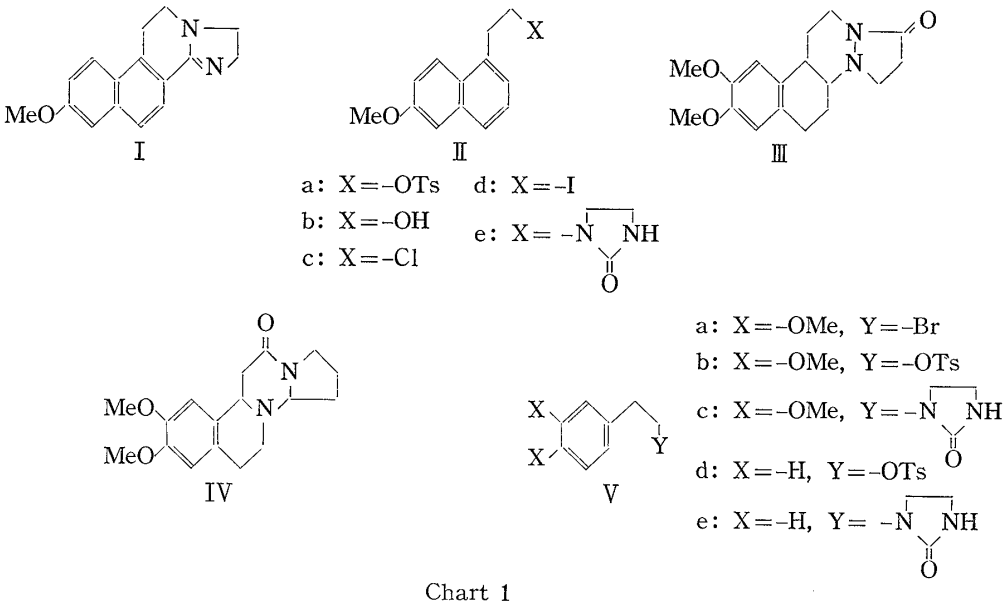

Chart 1

1) Part XIII: H. Takahata, H. Okajima, M. Nagata, and T. Yamazaki, *Chem. Pharm. Bull.*, **28**, 984 (1980); A part of this work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.
2) Location: *Sugitani, Toyama, 930-01, Japan.*
3) U.K. Pandit, K. De Jonge, and H.O. Huisman, *Rec. Trav. Chim. Pays-Bas*, **88**, 149 (1969) [*C.A.*, **70**, 97038*z* (1969)].
4) K. Isomura, T. Yamazaki, M. Nagata, and K. Matoba, Japan Kokai, 75 05400 (1975) [*C.A.*, **83**, P 10596*b* (1975)].

We have already reported the synthesis of a diazasteroid system by the Bischler-Napieralski reaction between a urea derivative and an aromatic ring.[5]

First, we examined the possibility of condensation between ethylene urea and 2-(3,4-dimethoxyphenyl)ethyl bromide (Va) or its tosylate (Vb), which were synthesized through the azlactone method reported by Okamoto.[6] In the case of Va, the expected product, 1-[2-(3,4-dimethoxyphenyl)ethyl]imidazolidin-2-one (Vc), was a minor component (the yield was only 8%), and 3,4-dimethoxy-1-vinyl-benzene (VIIa) was the major product (yield, 46%). On the other hand, its tosylate (Vb) gave Vc and 1,3-bis[2-(3,4-dimethoxyphenyl)ethyl]imidazolidin-2-one (VIa) in yields of 22% and 10%, respectively. In the same manner, 1-(2-phenylethyl)imidazolidin-2-one (Ve) and 1,3-bis(2-phenylethyl)imidazolidin-2-one (VIb) were obtained in yields of 21% and 11%, respectively, by the reaction of 2-phenylethyl tosylate (Vd) and ethylene urea.

Next, the possibility of Bischler-Napieralski ring closure for Vc was examined. Vc was treated with phosphorus pentoxide in phosphorus oxychloride at 120—130° for 5 hr to give a white crystalline compound in 75% yield, which was positive in Beilstein's test. As it was likely that the reaction product was a hydrochloride, it was neutralized with 10% sodium carbonate solution to give 8,9-dimethoxy-2,3,5,6-tetrahydro-imidazo[2,1-*a*]isoquinoline (VIII), whose structure was confirmed by the spectral and analytical data. On the other hand, attempts to cyclize Ve under various conditions were not successful.

As it seemed possible to use ethylene urea as the D ring moiety in the 13,15-diazasteroid skeleton, attempts to synthesize the target compound were carried out. The starting material, 2-(6-methoxynaphthyl)ethyl alcohol (IIb), was synthesized *via* six steps from 1-amino-naphthalene-6-sulfonic acid (1,6-Cleve's acid).[7] IIa was obtained from the reaction of IIb and tosyl chloride in pyridine, accompanied by 2-(6-methoxynaphthyl)ethyl chloride (IIc).[8] The results of the reactions between IIa, d and ethylene urea in the presence of sodium hydride are summarized in Table I.

Table I

Ratio of starting materials			Solvent	Recovery of II (%)	Conversion yield of products (%)		
II	Ethylene urea	NaH			IIe	VIc	VIIc
1 (IIa)	1	1	Benzene	68.2	11.1	22.1	—
1 (IIa)	1	1	Dioxane	—	23.9	40.6	27.1
1 (IIa)	2	1	Benzene	14.8	44.0	—	40.0
1 (IId)	2	1	Benzene	—	—	—	92.0

As shown in Table I, the best result was obtained using 2 molar equivalents of ethylene urea in benzene. On the other hand, the attempts to obtain IIe from the reactions between 2-methoxy-imidazoline (X) and 2-(6-methoxynaphthyl)ethyl derivatives (IIa, c, and d) in toluene were not successful.

The cyclization of IIe required severe conditions (heating for 3 days) in comparison with those used for Vc. The cyclization product was isolated as its iodide (IXa), then IXa was neutralized with aqueous potassium hydroxide to give I in 79.1% yield. I exhibited absorption maxima at 300 and 254 nm in the ultraviolet (UV) spectrum, and the structure was confirmed by elemental analysis. The biological activity of the hydrochloride of I (IXb) is now being examined.

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7) L.A. Paquette and N.A. Nelson, *J. Org. Chem.*, **27**, 1085 (1962).
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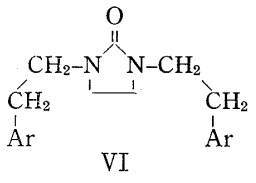
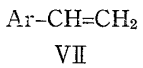
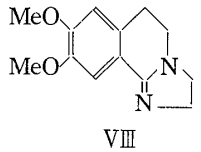


VI

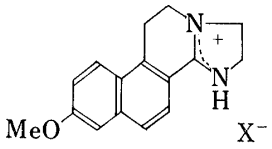
a: Ar=3,4-dimethoxyphenyl
b: Ar=phenyl
c: Ar=6-methoxynaphthyl



VII

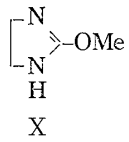


VIII



IX

a: X=I
b: X=Cl



X

Chart 2

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined using a Hitachi 215 grating spectrophotometer with absorptions given in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL C-60H spectrometer using TMS as an internal standard. The chemical shifts and coupling constants (J) are given in δ and Hz, respectively. Mass spectra (MS) were measured with JEOL TMS-01SG (75 eV, direct inlet system) spectrometer. UV spectra were obtained in ethanol using a Hitachi 200-10 spectrophotometer. All solvents were removed by evaporation under reduced pressure.

The Reaction between 2-(3,4-Dimethoxyphenyl)ethyl Bromide (Va) and Ethylene Urea——A suspension of NaH (1.6 g of 50% in oil, 33 mmol) and ethylene urea (2.84 g, 33 mmol) in absolute benzene (100 ml) was refluxed for 4 hr. After cooling the mixture, Va (7.5 g, 33 mmol) in benzene (50 ml) was added dropwise with stirring and the mixture was refluxed for 16 hr. After cooling, excess NaH was decomposed with EtOH and the benzene layer was washed with water and dried over $MgSO_4$. The residue obtained after removal of the solvent was crystallized from n-hexane, and the crystals were recrystallized from benzene–Et_2O to give 1-[2-(3,4-dimethoxyphenyl)ethyl]imidazolidin-2-one (Vc). mp 133—135°. Yield, 0.7 g (8.4%). IR (Nujol); ν_{NH} 3250, $\nu_{C=O}$ 1690. NMR ($CDCl_3$): 6.70 (s, 3H, aromatic H), 5.30 (s, 1H, >NH), 3.83 (s, 6H, 2×–OCH_3), 3.56—3.30 (m, 2H, >N–CH_2–), 3.30 (s, 4H, >N–CH_2–CH_2–N<), 2.93—2.50 (m, 2H, Ar–CH_2–). *Anal.* Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.20; H, 7.51; N, 11.10. 3,4-Dimethoxy-1-vinyl-benzene (VIIa) was obtained from the mother liquor in the crystallization from n-hexane by silica-gel column chromatography (eluting with n-hexane). Yield was 2.5 g (46%). IR (film): $\nu_{C=C}$ 1640. NMR (CCl_4): 6.70—6.10 (m, 4H), 5.40 (d, 1H, J=16), 4.95 (d, 1H, J=10).

The Reaction between 2-(3,4-Dimethoxy-phenyl)ethyl Tosylate (Vb) and Ethylene Urea——Vb (15 g, 44.6 mmol), ethylene urea (3.84 g, 44.6, mmol) and NaH (2.14 g of 50% in oil, 44.6 mmol) were treated under the conditions described for the reaction between Va and ethylene urea. The residue was crystallized from n-hexane to give Vc. The yield of Vc was 2.5 g (22%). The crystalline compound obtained from the mother liquor was recrystallized from benzene–Et_2O to give 1,3-bis[2-(3,4-dimethoxy-phenyl)ethyl]imidazolidin-2-one (VIa) in 10% (1.8 g) yield. VIa: mp 128—130°. IR (Nujol): $\nu_{C=O}$ 1680. NMR ($CDCl_3$): 6.77 (s, 6H, aromatic H), 3.90 (s, 12H, 4×–OCH_3), 3.15 (s, 4H, >N–CH_2–CH_2–N<). *Anal.* Calcd for $C_{23}H_{30}N_2O_5$: C, 66.64; H, 7.30; N, 6.76. Found: C, 66.91; H, 7.46; N, 6.52.

The Reaction between 2-Phenylethyl Tosylate (Vd) and Ethylene Urea——Ethylene urea (4.68 g, 54 mmol), NaH (2.59 g of 50% in oil, 54 mmol), and Vd (15 g, 54 mmol) were treated under the conditions described for the reaction between Vb and ethylene urea. 1-(2-Phenylethyl)imidazolidin-2-one (VIb) were obtained, respectively, as the first and the second crop of crystals on recrystallization of the residue from benzene–Et_2O. Ve: white powder. The yield was 2.2 g (21%). mp 146—149°. IR (Nujol): ν_{NH} 3240, $\nu_{C=O}$ 1690. NMR ($CDCl_3$): 6.20 (s, 5H, aromatic H), 5.70 (s, 1H, >NH, this signal disappeared on the addition of D_2O), 3.66—3.30 (m, 2H, Ar–CH_2–), 3.30 (s, 4H, >N–CH_2–CH_2–N<), 3.00—2.50 (m, 2H, >N–CH_2–). *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.18; H, 7.24; N, 14.50. VIb: white needles. The yield was 0.8 g (11%). mp 108—110°. IR (Nujol): $\nu_{C=O}$ 1685. NMR ($CDCl_3$): 7.23 (s, 10H, aromatic H), 3.55—3.17 (m, 4H), 3.08 (s, 4H), 2.95—2.53 (m, 4H). *Anal.* Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.81; H, 7.50; N, 9.43.

Bischler-Napieralski Cyclization of Vc——A mixture of Vc (0.5 g, 2 mmol), $POCl_3$ (10 ml), and P_2O_5 (0.5 g, 3.5 mmol) was heated at 120—130° for 5 hr. $POCl_3$ was evaporated off under reduced pressure, and

the residue was washed with petroleum ether to remove $POCl_3$. The residue was treated with 10% aqueous HCl to give white crystals, which were recrystallized from water. Hydrochloride of 8,9-dimethoxy-2,3,5,6-tetrahydro-imidazo[2.1-*a*]isoquinoline (VIII). mp 270—272°. The yield was 0.4 g (75%). IR (Nujol): $\nu_{C=N}$ 1630. NMR (CF_3COOH): 7.40 (s, 1H, aromatic H), 7.00 (s, 1H, aromatic H), 4.17 (s, 4H), 4.06 (s, 6H, 2×$-OCH_3$), 3.88—3.02 (m, 4H). The hydrochloride of VIII was neutralized with 10% Na_2CO_3 and the aqueous solution was extracted with benzene. Removal of the benzene after drying gave white crystals. The yield was quantitative. mp 157—160°. IR (Nujol): $\nu_{C=N}$ 1630. NMR ($CDCl_3$): 7.60 (s, 1H, C_{10}–H), 6.60 (s, 1H, C_7–H), 4.15—3.60 (m, 2H), 3.95 (s, 6H, 2×$-OCH_3$), 3.58—2.77 (m, 6H). UV λ_{max} nm (ε): 264 (11, 350), 223 (23, 260). MS *m/e*: 232 (M^+, 90%), 231 (M-1, base peak). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 7.23; N, 12.34.

The Reaction of 2-(6-Methoxy-1-naphthyl)ethyl Alcohol (IIb) and Tosyl Chloride——TsCl (10.34 g, 54 mmol) was added in three portions under cooling (<10°) to a pyridine solution of IIb (10 g, 49 mmol). The mixture was stirred for 3 hr below 20°, and then kept at room temperature for 48 hr. After adding conc. HCl (44.5 ml) and ice water (150 ml), the mixture was extracted with Et_2O. The organic layer was washed with water and dried over $MgSO_4$. The residue obtained after removal of the Et_2O was crystallized from *n*-hexane and recrystallized from Et_2O to give 2-(6-methoxy-1-naphthyl)ethyl tosylate (IIa). IIa: mp 58—60° (lit.[7] mp 59—60°). The mother liquor was purified by silica gel column chromatography. From the early part of the fraction eluted with benzene, 2-(6-methoxy-1-naphthyl)ethyl chloride (IIc) was obtained, and was subsequently microdistilled. The yield was 2.0 g (18.4%). IIc: bp 130° (0.1 mmHg). NMR (CCl_4): 7.97—6.87 (m, 6H, aromatic H), 3.93—3.03 (m, 4H), 3.88 (s, 3H, $-OCH_3$), MS *m/e*: 222 ($M+2$, *ca.* 30%), 220 (M^+, *ca.* 100%), 171 ($M-CH_2Cl$, *ca.* 100%). From the later part of the fraction eluted with benzene, IIa was obtained. The yield of IIa was 7.6 g (44.0%).

The Reaction between IIa and Ethylene Urea——Ethylene urea (0.92 g, 10.7 mmol), NaH (0.52 g of 50% in oil, 10.7 mmol), and IIa (3.8 g, 10.7 mmol) were treated in anhydrous dioxane under conditions similar to those described for the reaction between Vb and ethylene urea. The residue was fractionated by silica gel column chromatography. From the fractions eluted with benzene, Et_2O, and $CHCl_3$–EtOH (9: 1), 6-methoxy-1-vinyl-naphthalene (VIIc) (0.57 g, 27.1%), 1,3-bis[2-(6-methoxy-1-naphthyl)ethyl]imidazolidin-2-one (VIc, 1.97 g, 40.6%), and 1-[2-(6-methoxy-1-naphthyl)ethyl]imidazolidin-2-one (IIe, 0.69 g, 23.9%) were obtained, respectively. IIe: mp 140—141° (recrystallized from benzene). IR (Nujol): ν_{NH} 3250, $\nu_{C=O}$ 1685. NMR ($CDCl_3$): 8.30—7.10 (m, 6H), 5.83 (br.s, 1H, >NH), 3.92 (s, 3H, $-OCH_3$), 3.90—3.00 (m, 4H), 3.28 (s, 4H). *Anal. Calcd* for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.37; H, 6.51; N, 10.09. VIc: mp 114° recrystallized from benzene–Et_2O). IR (Nujol): $\nu_{C=O}$ 1685. NMR ($CDCl_3$): 8.20—7.00 (m, 12H, aromatic H), 3.92 (s, 6H, 2×$-OCH_3$), 3.70—3.35 (m, 4H), 3.35—3.00 (m, 4H), 3.08 (s, 4H). *Anal.* Calcd for $C_{29}H_{30}N_2O_3$: C, 76.62; H, 6.65; N, 6.16. Found: C, 76.69; H, 6.41; N, 5.90. VIIc: mp 41—43° (lit.[9] mp 41—42°). IR (Nujol): $\nu_{C=C}$ 1630. NMR ($CDCl_3$): 5.72 (d.d, 1H, $J=17, 2$), 5.38 (d.d, 1H, $J=11, 2$).

Bischler-Napieralski Cyclization of IIe——A mixture of IIe (1.1 g, 3.9 mmol), P_2O_5 (*ca.* 2 g) and $POCl_3$ (30 ml) was refluxed for 72 hr with stirring then excess $POCl_3$ was removed by washing with *n*-hexane and the residue was poured onto ice. The aqueous layer was acidified with 10% HCl. After filtration, an excess of saturated NaI solution was added to give the 13,15-diazasteroid hydroiodide (IXa, 1.04 g, 69.7%). mp 294—295°, yellow needles (recrystallized from water). IR (Nujol): $\nu_{C=N}$ 1620. MS *m/e*: 252 (M^+, 87%), 251 ($M-1$, base peak). *Anal.* Calcd for $C_{16}H_{17}IN_2O$: C, 50.54; H, 4.51; N, 7.37. Found: C, 50.41; H, 4.37; N, 7.61.

An aqueous suspension of IXa (0.93 g, 2.5 mmol) was stirred in the presence of KOH (0.2 g, 3.5 mmol) at room temperature for 2 hr. The solid was filtered off and recrystallized from benzene to give the 13,15-diazasteroid (I). mp 150—151° (0.49 g, 79.1%). IR (Nujol): $\nu_{C=N}$ 1620, $\nu_{C=C}$ 1600, 1570. NMR ($CDCl_3$)[10] 2.86—3.15 (m, 6H), 3.66—4.00 (m, 2H), 3.86 (s, 3H, $-OCH_3$), 7.10 (nearly s, 1H, C_4–H), 7.16 (d.d, 1H, $J=10, 2.5$, C_2–H), 7.63 (d, 1H, $J=9$, C_6–H), 7.85 (d.d, 1H, $J=10, 1$, C_1–H), 8.13 (d, 1H, $J=9$, C_7–H). UV ν_{max} nm (ε): 300 (12,600), 254 (50,730). MS *m/e*: 252 (M^+, 80%), 251 ($M-1$, base peak). *Anal.* Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.18; H, 6.25; N, 11.12.

A saturated ethanolic HCl solution was added to an ethanolic solution of I (0.72 g, 2.8 mmol) to give I-hydrochloride (IXb) quantitatively. mp 290—292° (recrystallized from EtOH). *Anal.* Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.38; H, 6.10; N, 9.65.

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9) A. Cohen and F.C. Warren, *J. Chem. Soc.*, **1937**, 1319.
10) This spectrum was recorded on a Varian EM-390 spectrometer.