Synthesis in the Diazasteroid Group. I. A New Synthesis of 8,13-Diaza-2,3-dimethoxygona-1,3,5(10)triene and Its Mercuric Acetate Oxidation (1)

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Received September 18, 1972

From the condensation reaction of methyl butyrolactim (I) with 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II), 8,13-diaza-2,3-dimethoxygona-1,3,5(10)trien-12-one (VI) and 8,13-diaza-2,3-dimethoxygona-1,3,5(10)triene (VII) were obtained in good yield. The oxidation of VI and VII with mercuric acetate was examined.

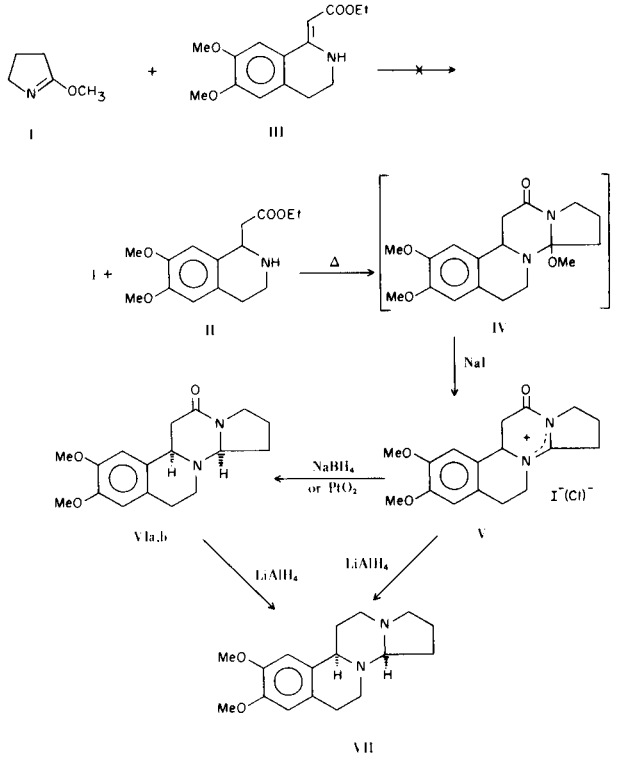
The synthesis of the 8,13-diazasteroid system using succinimide derivatives as the source of the five membered D-ring containing the nitrogen atom has already been reported by Burckhalter (2) and Taylor (3).

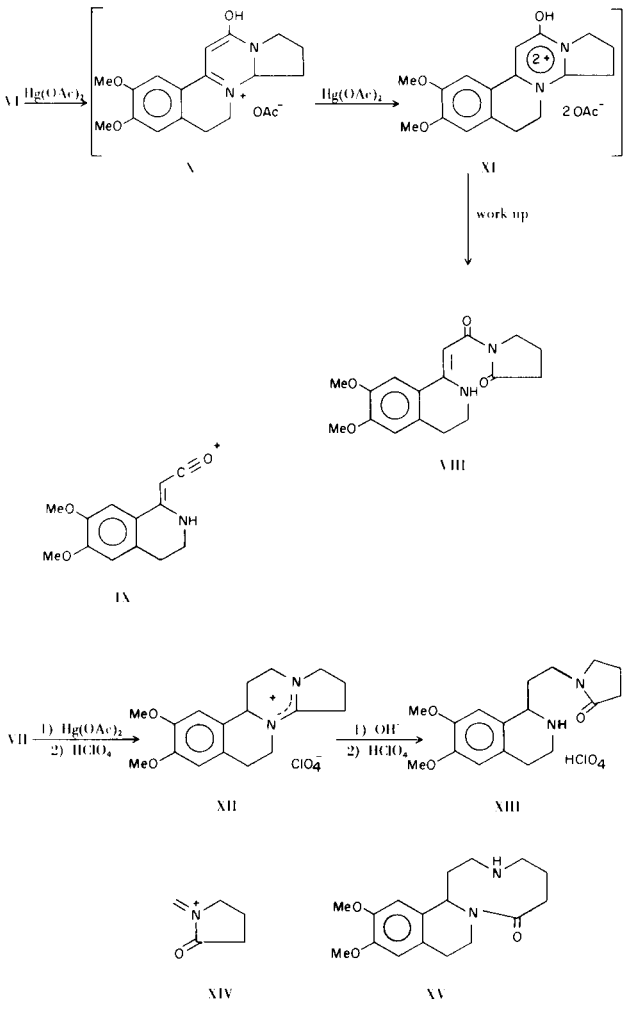
Onaka (4) synthesized several pyrrolidinoquinazolone alkaloids by a cyclization reaction using methyl butyrolactim (I) obtained from the methylation of pyrrolidone. Some examples (5) of the condensation with enamino acids or esters in which the amines are primary amines have been reported.

In this work we report an alterate synthesis of the 8,13-diazasteroid system by the condensation reaction of I with the secondary amine, 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) and the oxidation of this diazasteroid with mercuric acetate.

The reaction of I with the enamino ester, 1-ethoxycarbonylmethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (III) was first attempted. Molar equivalents of I and III were allowed to reflux in benzene. Unfortunately, only the starting material III was recovered. This result may be associated with the decrease in nucleophilicity at the nitrogen atom caused by conjugation with the ester group.

However, when II was condensed with I under the same conditions, a brown solid product was obtained. The yield of this product was highest when carried out at 90° in a sealed tube without any solvent. This product was too unstable to be recrystallized, but in its crude state, the nmr spectrum showed a singlet signal at 6.15 τ associated with the three methoxy groups and the ir spectrum exhibited a carbonyl band at 1650 cm^{-1} which was different from that of the iodide V mentioned below. These physical data and its mechanism of formation suggested the structure of the 14-methoxy derivative IV. Without further purification, IV was dissolved in dilute hydrochloric acid solution and converted to V by addition of a saturated sodium iodide solution. Compound V was stable and melted at 273-274°. Elemental analysis and a





mass spectrum supported this structure. The ir spectrum exhibited strong bands at 1740, 1675 cm^{-1} and the uv spectrum showed only the absorption band due to the veratryl group.

The reduction of V with sodium borohydride gave 8,13-diaza-2,3-dimethoxygona-1,3,5(10)trien-12-one (VI). The melting range of VI (219-240°) and the manner of melting indicated that VI was a mixture of at least two components. However, VI showed only one spot on tlc under various conditions, but reduction of the melting point range was unsuccessful either by repeated recrystallization or by column chromatography. Catalytic reduction of V chloride with Adam's catalyst also gave VI with the same melting point range. Elemental analysis and the mass spectrum supported this structure, and the ir spectrum exhibited a lactam band at 1635 cm^{-1}. The perchlorate and hydrochloride of VI also showed a similar melting point range.

Lithium aluminum hydride (LAH) reduction of VI in tetrahydrofuran at room temperature gave 8,13-diaza-2,3-dimethoxygona-1,3,5(10)triene (VII), which melted at 126-127° and was nearly identical with that reported by Burckhalter (m.p. 124°) (2). Compound VII was also obtained in good yield directly from V under the same conditions. The structure of VII was proven by its elemental analysis, mass spectrum, and other physical data. The overall yield of VII from II was 70.5% (*via* iodide V) and 62.7% (*via* iodide V and amide VI). Therefore, methyl butyrolactim (I) has been shown to be useful in the synthesis of the 8,13-diazasteroid system.

Compound VI was readily oxidized with four equivalents of mercuric acetate accompanied by precipitation of mercurous acetate, but with one equivalent of the reagent, metallic mercury was deposited and in both cases wool-like needles were obtained which melted at 185-186°. The ir spectrum of the product exhibited imide carbonyl bands at 1700 cm^{-1} and several strong bands (6) between 1620 and 1570 cm^{-1}. The uv spectrum showed an absorption maximum at 360 nm due to a β-amino-β-phenyl-α,β-unsaturated ketone (6) and in the nmr spectrum a signal at 3.42 τ (singlet) characteristic of the vinylic proton of a vinyl amide was observed. Moreover, the mass spectrum showed a parent peak at m/e 316 corresponding to $C_{17}H_{20}N_2O_4$ and a fragment ion peak m/e 232 corresponding to $C_{13}H_{14}NO_3$ (IX) which supported the fact that the oxidation product was the "ring cleaved imide" VIII.

The following mechanism for the dehydrogenation of VI to VIII is proposed: Compound VIII may be formed by the continuous two step dehydrogenation as depicted by X and XI. In this case, the intermediate X may be further susceptible to the oxidizing agent and be dehydrogenated to XI which is stabilized by full conjugation.

In the same way, VII was oxidized, followed by treatment with aqueous alkali to give the free base which was converted into the perchlorate (m.p. 204-205.5°). The perchlorate exhibited a lactam carbonyl band at 1665 cm^{-1} in the ir spectrum and only the veratryl band in the uv spectrum. Elemental analysis and the mass spectrum of the perchlorate confirmed that the product was the "ring cleaved lactam" XIII. Formation of a possible alternative isomer, the nine membered aminolactam XV, was excluded by the presence of the fragment ion, m/e 98 corresponding to C_5H_8NO (XIV). When the reaction mixture was treated with perchloric acid prior to the addition of aqueous alkali, a normal perchlorate XII, which melted at 199.5-201° and exhibited the immonium band at 1660 cm^{-1} was obtained. Treatment of XII with alkali gave XIII. Thus, in the case of VII, the preceding dehydrogenation at the 14-position prohibited subsequent dehydrogenation at the 9-position because of the higher reactivity of the 14-proton compared with the 9-proton.

Based upon melting point, VII seems to be the same compound as the one whose conformation Burckhalter

determined by X-ray crystallography (2). Bohlmann bands (7) in the ir spectrum, the absence of any signal except that of the methoxy groups in a field lower than 6.65 τ in the nmr (8), the result of reaction with mercuric acetate and the stability shown by a Dreiding model support this assignment. The stereochemistry of VI is more difficult to solve. The melting point range and the manner of melting suggested that VI is a mixture of at least two components, possibly 14-epimers, VIa and VIb, which was based upon the following experimental data: (a) Compound VII was the only product obtained in high yield by the reduction of VI with LAH and the isomerization was assumed at the 14-position in this case; (b) the ir spectrum of VI exhibited Bohlmann bands; (c) in the dehydrogenation of VI with mercuric acetate, VIII was the sole product and is independent of the configuration at the 14-position.

EXPERIMENTAL

Melting points were determined on a hot stage by using a Yanagimoto micro melting apparatus and are uncorrected. Ir absorption spectra were obtained with a JASCO Model IR-S spectrometer in potassium bromide disks. Uv absorption spectra were obtained in ethanol with a Hitachi Model EPS-3T spectrometer and nmr spectra were obtained by JEOL Model C-60H spectrometer at 60 MHz with TMS as an internal standard. The chemical shifts are given as τ values. Mass spectra were obtained with Hitachi Model RMU-6L or RMU-7L. The intensity of fragment peaks are given as relative intensities to the base peak. The R_f values were determined by tlc on plates coated with neutral alumina. Spots were made visible by spraying with the Dragendorff reagent. All the solvents were evaporated under reduced pressure.

Materials.

Methyl butyrolactim (I) was prepared by a modification of the Petersen method (10), loss of product due to the azeotropic phenomenon being prevented by the substitution of ether for ether-benzene as the solvent (11), b.p. 119-120° (reported, b.p. 118-121°). 1-Ethoxycarbonylmethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (II), m.p. 88-89° (reported (12) m.p. 86-87°). 1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (III), m.p. 77-78° (reported (13), m.p. 77-78°).

Iodide (V).

Compound III (5.0 g., 18 mmoles) and I (3.0 g., 30 mmoles), was heated overnight in a sealed tube at 90° to give the 4-methoxy derivative IV as a brown precipitate. Compound IV was dissolved in a small excess of dilute hydrochloric acid and a saturated solution of sodium iodide was added to give crude V, which was washed several times with cold water to give white prisms, m.p. 273-274° dec., 7.0 g. (yield, 91%); ir ν max 1740, 1675, 1610 cm^{-1}; uv λ max 285 nm (ϵ, 5,100); mass spectrum m/e 300 (base peak, M^+-HI).

Anal. Calcd. for $C_{17}H_{21}IN_2O_3$: C, 47.68; H, 4.94; N, 6.54. Found: C, 47.50; H, 4.92; N, 6.54.

8,13-Diaza-2,3-dimethoxygona-1,3,5(10)trien-12-one (VI).

Route a.

Sodium borohydride (0.4 g., 10 mmoles) was added portionwise with ice-cooling and stirring to a methanol suspension of V (2.0 g., 5.4 mmoles). The mixture quickly became homogeneous and then was stirred for one hour at room temperature. The solution was acidified with acetic acid followed by the evaporation of the solvent, basification with saturated sodium bicarbonate solution and extraction with chloroform. After drying, the solvent was evaporated to give crystals, which were recrystallized from ethanol to give VI as white prisms, 1.2 g. (86%), m.p. 219-240° dec.; tlc: solvent (R_f), chloroform (0.41), 5:1 chloroform-acetone (0.80), 5:1 chloroform-ethyl acetate (0.56), 2:1 benzene-acetone (0.53), 1:1 benzene-ethyl acetate (0.33), 5:1 benzene-ethanol (0.69). In every case, only one spot was obtained; ir ν max 2810, 2780, 2730 (Bohlmann bands), 1635 cm^{-1}; uv λ max 284 nm (ϵ, 4,300); nmr (deuteriochloroform): 3.37 (1H, s), 3.40 (1H, s), 6.15 (6H, s).

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.37; H, 7.25; N, 9.07.

Compound VI-Hydrochloride.

This compound had m.p. 214-239° dec.; ir ν max 2450, 2300, 1650 cm^{-1}; mass spectrum m/e 302 (60%, M^+-HCl).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_3$: C, 60.32; H, 6.85; N, 8.28. Found: C, 60.38; H, 6.80; N, 8.35.

Route b.

Iodide V was converted to the corresponding chloride with silver chloride. The chloride, m.p. 246-247° dec. (recrystallized from ethanol), was reduced with Adam's catalyst in acetic acid at atmospheric pressure. After uptake of the calculated amount of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated to give an oily residue which was dissolved in chloroform. The chloroform layer was washed with saturated sodium bicarbonate solution and dried. The solvent was evaporated to give crystals, which were recrystallized from ethanol to give white prisms of VI (63%), m.p. 220-246° dec. The physical data of VI were identical with those of VI obtained by Route a, while the m.p. of 220-246° was a little higher than that obtained from the compound *via* Route a.

8,13-Diaza-2,3-dimethoxygona-1,3,5(10)triene (VII).

Route a.

Compound VI (1.0 g., 3 mmoles) was added portionwise to a THF suspension of LAH (0.5 g., 13 mmoles) with ice-cooling and stirring. After the reaction mixture was stirred for 1 hour at room temperature, 3 g. of ammonium chloride was added and the complex was decomposed with the calculated amount of water. The organic filtrate was dried over magnesium sulfate and then concentrated *in vacuo*. The resultant residue was fractionated through neutral alumina. The crystals obtained by elution with ether were recrystallized from acetone to give white needles (VII), m.p. 126-127° (reported (2), m.p. 123-124°) 0.76 g. (80%); ir ν max 2770, 2740 (Bohlmann bands), 1610 cm^{-1}; mass spectra m/e 288 (92%, M^+); nmr (deuteriochloroform): 3.32 (1H, s), 3.41 (1H, s), 6.19 (6H, s).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 71.06; H, 8.54; N, 9.90.

Route b.

Compound V (2.5 g., 5.9 mmoles) was reduced with LAH (0.9 g., 24 mmoles) in THF as in the case of Route a to give VII, m.p. 124-125.5°. The other physical data were also nearly identical with those of Route a.

Oxidation of VI to Ring Cleaved Imide VIII with Mercuric Acetate.

Compound VI (0.8 g., 2.7 mmoles) was added to a solution of mercuric acetate (3.5 g., 11 mmoles), in 5% acetic acid with stirring. After homogeneity, the reaction mixture was heated in an oil bath at 100° and mercurous acetate immediately separated out from the red solution. The mixture was stirred for 1 hour, cooled to room temperature and filtered. The filtrate was saturated with hydrogen sulfide and the precipitated mercuric sulfide was removed. This filtrate was concentrated under reduced pressure. The residue was made basic with 20% sodium hydroxide solution and extracted with chloroform (only one spot on tlc). After drying, the solvent was evaporated to give crystals which were recrystallized from ethanol to give white needles of VIII, m.p. 185-186° dec., 0.50 g. (60%); ir ν max 3330, 1700, 1620, 1610, 1580, 1570 cm^{-1}; uv λ max 233 nm (ϵ, 21,300), 283 (6,100), 360 (29,000); nmr (DMSO-d_6): 2.84 (1H, s), 3.05 (1H, s), 3.32 (1H, s), 6.15 (3H, s), 6.20 (3H, s); mass spectrum m/e 316 (57%, M^+), 232 (base peak, $C_{13}H_{14}NO_3$, IX).

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.24; H, 6.22; N, 8.76.

In the case of the oxidation with 1 equivalent of mercuric acetate, metallic mercury deposited but the other results were nearly identical with those above.

Ring Cleaved Lactam Perchlorate XIII.

Compound VII (0.7 g., 2.4 mmoles) was added with stirring to a solution of mercuric acetate (3.1 g., 9.7 mmoles) in 5% acetic acid to give a homogeneous solution. Stirring and heating at 90° in an oil bath quickly gave a precipitate of mercurous acetate. After stirring at 90° for an additional hour, the mixture was cooled to room temperature and the precipitate was removed. The filtrate was saturated with hydrogen sulfide and mercuric sulfide was removed. The filtrate was concentrated, made basic with 20% sodium hydroxide, and extracted with chloroform. After the removal of the solvent, the residue (one spot on tlc) was dissolved in ethanol and 60% perchloric acid was added to give crystals of XIII, which were recrystallized from ethanol, m.p. 204-205.5°, 0.6 g. (61%); ir ν max 3130, 1665, 1613 cm^{-1}; uv λ max 232 nm (ϵ, 8,600), 285 nm (4,200); mass spectrum m/e 304 (9%, M^+-$HClO_4$), 206 (62%, $C_{12}H_{16}NO_2$), 192 (base peak, $C_{11}H_{14}NO_2$), 98 (10%, C_5H_8ON, XIV).

Anal. Calcd. for $C_{17}H_{25}ClN_2O_7$: C, 50.47; H, 6.23; N, 6.92. Found: C, 50.27; H, 6.21; N, 6.88.

The Normal Perchlorate XII.

Mercuric acetate (2.2 g., 7 mmoles), and VII (1.0 g., 3.5 mmoles) were dissolved in a small amount of 5% acetic acid, then stirred and heated at 80°. Mercurous acetate quickly precipitated. The reaction was continued for 1 hour, the mixture was cooled to room temperature and mercurous acetate was removed. A 60% perchloric acid solution was added to the filtrate to give crystals of XII, which were recrystallized from ethanol, m.p. 199.5-201°, 1.14 g. (84.6%); ir ν max 1660, 1610 cm^{-1}; uv λ max 225 nm (ϵ, 21,000), 284 (4.300).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_6$: C, 52.80; H, 6.00; N, 7.25. Found: C, 52.63; H, 5.97; N, 7.12.

An aqueous solution of XII was made basic with 20% sodium hydroxide solution and extracted with chloroform. After drying, chloroform was evaporated. A 60% perchloric acid solution was added to this residue in ethanol to give crystals which were recrystallized and found to be identical with XIII based upon physical data.

Acknowledgement.

The authors wish to express their thanks to Dr. T. Onaka, ITSUU Laboratory, for his helpful advice. Thanks are also due to the Measurement Division of University of Toyama for nmr measurements and for elemental microanalyses.

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