Synthesis in the Diazasteroid Group. III (1). Syntheses of the 8,16- and 8,17-Diazasteroid Systems

Takao Yamazaki, Katsuhide Matoba, Kazumasa Isomura, Masanori Nagata

Faculty of Pharmaceutical Sciences, University of Toyama, Gofuku, Toyama, Japan

and

Raymond N. Castle

Department of Chemistry, Brigham Young University, Provo, Utah 84602

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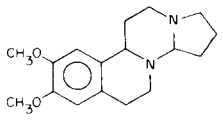
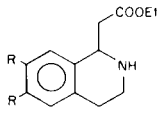
By using 3-pyrrolidone derivatives as a source of the D ring, the following five diazasteroids were synthesized: 8,16-diaza-2,3-dimethoxy-15,15,16-trimethylgona-1,3,5(10),13-tetraen-12-one (VII), 8,16-diaza-2,3-dimethoxy-16-acetylgona-1,3,5(10),13-tetraen-12-one (X), 8,17-diaza-2,3-dimethoxy-17-acetylgona-1,3,5(10),13-tetraen-12-one (XI), 8,16-diaza-16-acetylgona-1,3,5(10),13-tetraen-12-one (XII), and 8,17-diaza-17-acetylgona-1,3,5(10),13-tetraen-12-one (XIII).

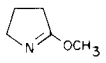
Previously, a new synthesis of 8,13-diaza-2,3-dimethoxygona-1,3,5(10)-triene (I) starting from 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) and methyl butyrolactim (III), an α-pyrrolidone derivative, was reported (2).



I



II: R OMe
IV: R H



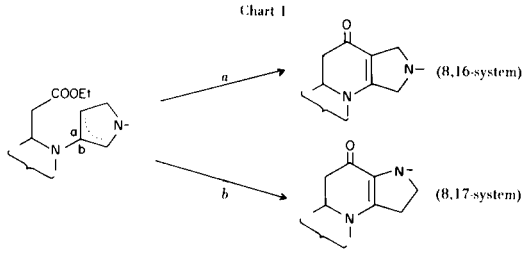
III

In this paper the condensation reaction of β-pyrrolidone derivatives with II or 1-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (IV) yielding enamines is reported.

Stork, *et al.*, (3) have reported on enamines, in which one involved the formation of an enamino ester from a carbonyl compound and a β-aminoester followed by cyclization in ethylene glycol (4) to the six membered vinylogous amide. Applying this reaction, Meyers, *et al.*, synthesized an azasteroid system from II and a five membered ketone (5). In addition, they found the one step cyclization to occur in an appreciable yield in toluene by using trifluoracetic acid as a catalyst.

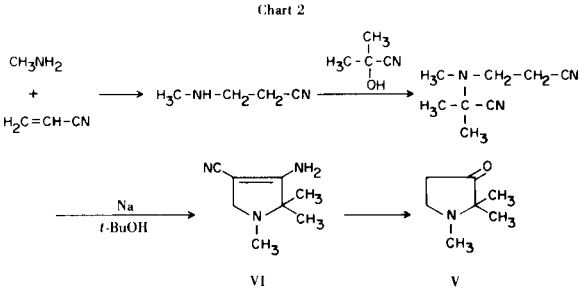
When β-pyrrolidone was used as a source of the D ring of the steroid system, two pathways (path *a* and path *b* in Chart 1), depending upon the orientation of the intermediate enamine, are possible.

Chart 1



Therefore, 1,2,3-trimethyl-3-pyrrolidone (V) was selected as the β-pyrrolidone derivative since it can undergo enamine formation in only one direction. Compound V was prepared as shown in Chart 2.

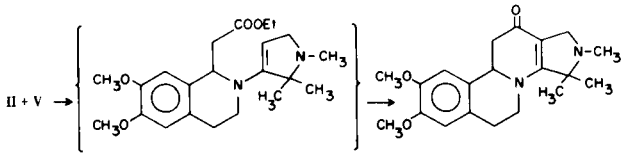
Chart 2



Although it has been reported that hydrolysis of the Thorpe-Ziegler condensation product VI to V is difficult and gives a poor yield (6), this hydrolysis was performed in 71% yield by the addition of VI portionwise to the concentrated hydrochloric acid followed by stirring over-

night with gentle warming. Compound V was relatively stable in contrast with general *N*-alkyl-β-pyrrolidones.

Compound V obtained in this way was treated with II for 2 days in toluene in the presence of a catalytic amount of trifluoroacetic acid, while continually removing water and ethanol with molecular sieves. The reaction product was then purified on an alumina column to furnish a solid, m.p. 205-207° dec. The ir spectrum of the product exhibited vinylogous amide bands at 1625 and 1560 cm^{-1}. The uv spectrum showed two absorption maxima at 292 and 330 nm associated with the veratryl group and the vinylogous amide group, respectively, and in the nmr spectrum, signals assigned to *gem*-dimethyl, *N*-methyl, *O*-methyl and aromatic protons were observed. These data suggested the product to be the condensation product, 8,16-diaza-2,3-dimethoxy-15,15,16-trimethylgona-1,3,5(10),13-tetraen-12-one (VII).



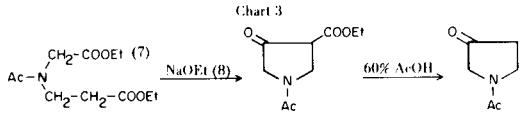
VII

The mass spectrum of VII-perchlorate showed a parent peak at m/e 342 corresponding to $C_{20}H_{26}N_2O_3$.

The yield of VII was about 15%, and much starting material, II, was recovered, but the enamino ester type compound considered as an intermediate in this reaction could not be detected. This poor yield may be due to steric hindrance in the formation of the enamine.

However, it provided evidence that the β-pyrrolidone derivative could be a source of the D ring of the steroid system. Therefore, 1-acetyl-3-pyrrolidone (VIII) was next examined. Compound VIII was prepared as shown in Chart 3.

Chart 3



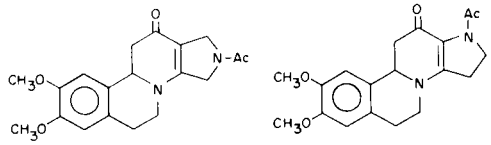
IX VIII

Hydrolysis of the ketoester IX was performed in the best yield by refluxing in 60% acetic acid. Compound VIII gave one spot on tlc and one peak on glc, but the nmr spectrum showed a doublet assigned to the methyl protons of the *N*-acetyl group. However, when measured at an elevated temperature, this doublet coalesced into a singlet. This phenomenon was ascribed to restricted rotation (9).

Compound VIII was treated with II under the same conditions as V, but only one product was eluted by benzene and could be isolated. This product A is considered to be a condensed product, judged from ir, uv, nmr and elementary analysis; the yield of A was 41%.

Compound VIII was treated with II under milder conditions. The reaction mixture was refluxed for 2 hours removing water, and then for 2 additional hours removing water and ethanol with molecular sieves. The reaction mixture obtained under such conditions showed two spots on tlc. The upper spot was identical with that of A. The product associated with the lower spot was purified on a silica gel column. This product B was also a condensation product based upon elementary analysis and physical data. Yields of A and B were 36.6 and 5.5%, respectively.

Products A and B were shown to be 8,16-diaza-2,3-dimethoxy-16-acetylgona,1,3,5(10),13-tetraen-12-one (X) and 8,17-diaza-2,3-dimethoxy-17-acetylgona-1,3,5(10),13-tetraen-12-one (XI) respectively, from the data shown below:



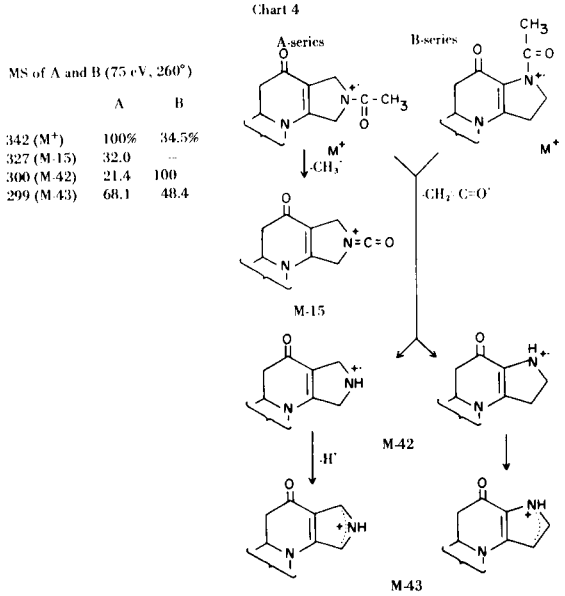
X (A) XI (B)

1) In the uv spectrum, A had two absorption maxima at 294 and 324 nm, which were nearly identical with that of VII. On the other hand, B had an absorption maximum at 350 nm.

2) In the nmr spectrum of A, two singlet-like peaks at 5.43 and 5.54 τ assigned to 17 and 15 methylene protons, respectively, were found.

3) In the mass spectrum, fragment patterns for both compounds were reasonable as shown in Chart 4.

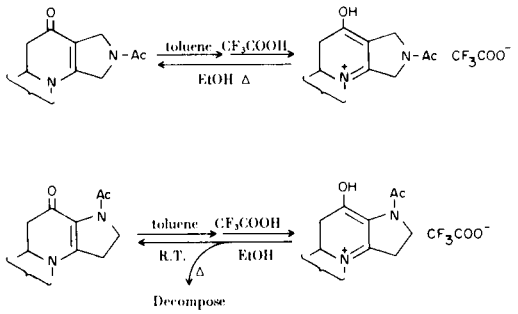
Chart 4



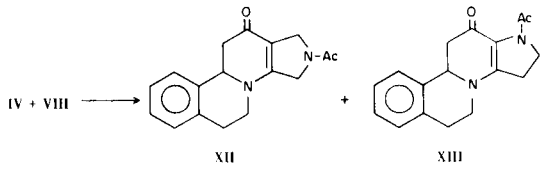
That is, in B, M-42 was stable owing to an allylic cation radical, and in A, M-43 was a relatively stable ion on the same grounds.

The dependency of the reaction products upon conditions was studied, and the details are described in the Experimental (10) and the salient features are outlined in Chart 5 below.

Chart 5



8,16-Diaza-16-acetylgona-1,3,5(10),13-tetraen-12-one (XII) and 8,17-diaza-17-acetylgona-1,3,5(10),13-tetraen-12-one (XIII) were synthesized from IV and VIII in a manner analogous to X and XI. The physical data and chemical behavior of XII and XIII were similar to those of IX and X, respectively. Under milder conditions, yields of XII and XIII were 34% and 19%, respectively.



EXPERIMENTAL

Melting points were determined on a hot stage by using a Yanagimoto micro melting apparatus and are uncorrected. Ir absorption spectra were obtained by using a Hitachi Grating Infrared 215 spectrometer. Uv absorption spectra were obtained in ethanol by using Hitachi Model EPS-2T spectrometer and nmr spectra by JEOL Model C-60H spectrometer at 60 MHz with TMS as an internal standard. The chemical shifts are given in τ units. Mass spectra were obtained by using JMS-01SG. The Rf values were determined by tlc on plates coated with neutral alumina. The developing solvent was 1:1 acetone-chloroform. Spots were made visible by spraying ceric sulfate solution in 10% sulfuric acid followed by heating. All the solvents were evaporated under reduced pressure.

1,2,2-Trimethyl-3-pyrrolidone (V).

3-Amino-4-cyano-1,2,2-trimethyl-3-pyrroline (VI) (15 g., 0.1 mole) prepared by Cavalla's method (6) was added portionwise to ice-cooled concentrated hydrochloric acid (49 ml.). This mixture was stirred overnight and warmed gradually to the boiling point during 5 hours and then refluxed for 1 hour. This was then cooled to room temperature followed by basification with 10*N* sodium hydroxide solution and extraction with chloroform. After drying, the solvent was evaporated and distilled, V (8 g., yield 71%), b.p.$_{22}$ 64-66° (Lit. (11) b.p.$_{10}$ 50°); ir (film): ν 1755 cm^{-1}.

8,16-Diaza-2,3-dimethoxy-15,15,16-trimethylgona-1,3,5(10),13-tetraen-12-one (VII).

The mixture of 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) (12) (5.6 g., 20 mmoles), V (5.1 g., 40 mmoles) and trifluoroacetic acid (1.6 ml., 22 mmoles) in toluene (30 ml.) was refluxed for 2 days removing water and ethanol by means of a Dean-Stark apparatus packed with molecular sieves 3A and 4A. The reaction solution was cooled to room temperature followed by washing with sodium bicarbonate solution and drying over magnesium sulfate. The solvent was evaporated and the resultant residue was fractionated through neutral alumina. The crystals obtained by elution with benzene were identified with starting material II (0.9 g.,) and then by elution with chloroform-ether, crude VII was isolated, which was recrystallized from acetone. The yield was about 15%; VII, m.p. 205-207° dec.; ir (nujol): ν 1625, 1560 cm^{-1}; uv: λ max 292, 330 nm; nmr (deuteriochloroform-trifluoroacetic acid): 3.33 (1H, s, aromatic H), 3.37 (1H, s, aromatic H), 6.12 (3H, s, OCH_3), 6.15 (3H, s, OCH_3), 7.12 (3H, s, N-CH_3), 8.20 (6H, s, geminal dimethyl).

VII Perchlorate.

Compound VII was dissolved in ethanol and 60% perchloric acid was added to give crude VII perchlorate, which was recrystallized from ethanol; m.p. 180-183°; ir (nujol): ν 2740, 1630, 1570 cm^{-1}; uv: λ max 293, 328 nm; mass spectrum: m/e 342 (50%, M-$HClO_4$).

Anal. Calcd. for $C_{20}H_{26}N_2O_3 \cdot 6/5HClO_4$: C, 51.93; H, 5.94; N, 6.05. Found: C, 51.78; H, 6.00; N, 6.07.

1-Acetyl-3-pyrrolidone (VIII).

Crude ketoester IX (49 g.,) dissolved in 60% acetic acid (200 ml.) was refluxed for 8 hours followed by concentration. The resultant residue was neutralized with sodium bicarbonate solution and then extracted with chloroform. The organic layer was dried and distilled *in vacuo*; VIII: b.p.$_3$ 159-163° (Lit. (13) b.p.$_{0.55}$ 120-123°); yield, 16.8 g., (54%); ir (film): ν 1760, 1650 cm^{-1}; nmr (deuteriochloroform): (measured at 25°) 7.30 (2/2H, t, J = 7.5 Hz), 7.40 (2/2H, t, J = 7.5 Hz), 7.88 (3/2H, s), 7.93 (3/2H, s), (measured at 100°) 7.38 (2H, t, J = 7.5 Hz, CH_2-CH_2-CO), 7.95 (3H, s, CO-CH_3).

8,16-Diaza-2,3-dimethoxy-16-acethylgona-1,3,5(10),13-tetraen-12-one (X).

(a) Under Sever Conditions.

Compound II (15 g., 54 mmoles), compound VIII (15 g., 118 mmoles) and trifluoroacetic acid (1 ml.) were dissolved in toluene (60 ml.). This solution was treated and worked up as described for the synthesis of VII. The resultant residue was fractionated through a silica gel column (Wakogel C-200). The crystals obtained by elution with chloroform were recrystallized from water; IX: long needles m.p. 288-290° dec.; 7.5 g., (yield, 41%); ir (nujol): ν 1655, 1630, 1590 cm^{-1}; uv: λ max 294 nm (ϵ, 5,900), 324 nm (ϵ, 12,000); mass spectrum: shown in Chart 4; nmr (deuteriochloroform): 3.35 (2H, d, J = 1.5 Hz, aromatic H), 5.20 (1H, d.d, J = 5, 15 Hz, 9-CH), 5.43 (2H, s, 17-CH_2), 5.54 (2H, s, 15-CH_2), 6.15, 6.17 (each 3H, s, OCH_3), 7.91 (3H, s, CO-CH_3).

Anal. Calcd. for $C_{19}H_{22}N_2O_4 \cdot H_2O$ (dried over phosphorus pentoxide for 58 hours at 80°): C, 63.32; H, 6.71; N, 7.77. Found: C, 63.47; H. 6.59; N, 7.47.

(b) Under Mild Conditions.

Compound II (24.5 g., 87 mmoles), compound VIII (14.5 g., 114 mmoles) and trifluoroacetic acid (1.5 ml.) were refluxed for 2

hours removing water by means of a Dean-Stark apparatus and then refluxed for an additional 2 hours removing water and ethanol with the same apparatus packed with molecular sieves 3A and 4A. The reaction mixture was allowed to stand overnight. A precipitate was obtained which was not filterable. The mixture was washed with sodium bicarbonate solution followed by extraction from aqueous solution with chloroform. The combined organic layers were dried and concentrated. The resultant residue was dissolved in benzene and upon standing gave crystals of X (6 g.,).

8,17-Diaza-2,3-dimethoxy-17-acetylgona-1,3,5(10),13-tetraen-12-one (XI).

The mother liquor obtained under (b) conditions mentioned above showed two spots on tlc: Rf 0.24 (X), Rf 0.15 (XI). Both compounds were fractionated through a silica gel column. With chloroform-ethanol (4:1), X (4.7 g.,) was first eluted and XI was then eluted. Compound XI was recrystallized from chloroform-ethanol to give prisms, m.p. 232-233°; ir (nujol): ν 1640, 1623, 1600, 1580 cm^{-1}; uv: λ max 350 nm (ϵ, 11,300); mass spectrum: shown in Chart 4; nmr (deuteriochloroform): 3.34 (2H, d, J = 2.5 Hz, aromatic H), 5.25 (1H, d.d, J = 5, 15 Hz, 9-CH), 6.15 (6H, s, OCH_3), 7.78 (3H, s, N-CH_3).

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.62; H, 6.66; N, 7.92.

Reaction of X with Trifluoroacetic Acid.

Compound X was refluxed in toluene for 1 hour followed by the addition of an equimolar amount of trifluoroacetic acid to give a homogeneous solution of *O*-protonated salt (10). The salt, X trifluoroacetate, showed a spot, Rf 0.12, on tlc. After the mixture was refluxed for 2 hours an equimolar amount of ethanol was added and this mixture was refluxed for 2 hours during which time X precipitated (no change).

Reaction of XI and Trifluoroacetic Acid.

Compound XI was treated with trifluoroacetic acid as described above for X. The XI trifluoroacetate salt gave Rf 0.10 (long spot). When an equimolar amount of ethanol was added to it, XI precipitated. On the other hand, when it was refluxed for 2 hours after the addition of ethanol, a brown-black oil separated which contained scarcely any starting material.

8,16-Diaza-16-acetylgona-1,3,5(10),13-tetraen-12-one (XII) and 8,17-Diaza-17-acetylgona-1,3,5(10),13-tetraen-12-one (XIII).

1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (5) (IV) (20 g., 84 mmoles), VIII (12.8 g., 100 mmoles) and trifluoroacetic acid (3 ml.) were treated under the same conditions as those in the preparation of X and XI. The reddish-black solution obtained was washed with saturated sodium bicarbonate solution and water. After drying, the solvent was removed to give an oil, which showed three spots on tlc; Rf 0.7 (IV), Rf 0.3 (XII), Rf 0.2 (XIII). The solution was fractionated through a silica gel column. After IV was recovered by elution with chloroform, the crystals obtained by elution with chloroform-ethanol (9:1) were recrystallized from ethanol to give white prisms (XII), 34%, m.p. 213-215°; ir (nujol): ν 1638, 1585, 1570 cm^{-1}; uv: λ max 324 nm (ϵ, 12,200), nmr (deuteriochloroform): 7.95 (3H, s, N-CH_3), 5.55 (2H, s, 15-CH_2), 5.47 (2H, s, 17-CH_2), 5.15 (1H, d.d, J = 5, 15 Hz 9-CH), 2.81 (4H, s, aromatic H).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.22; H, 6.43; N, 9.64.

With the same solvent, XIII was eluted and recrystallized from acetone to give prisms 19%, m.p. 210-212°; ir (nujol): ν 1705, 1600, 1550 cm^{-1}; uv: λ max 245 nm (ϵ, 10,700), 346 nm (ϵ, 11,800); nmr (deuteriochloroform): 7.77 (3H, s, N-CH_3), 5.20 (1H, d.d, J = 5, 15 Hz, 9-CH), 2.79 (4H, s, aromatic H).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.57; H, 6.72; N, 9.76.

Acknowledgement.

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