

Synthesis of Diazasteroids II (1). Synthesis of 8,11-Diaza-2,3-dimethoxygon-1,3,5(10),9(11)-tetraene

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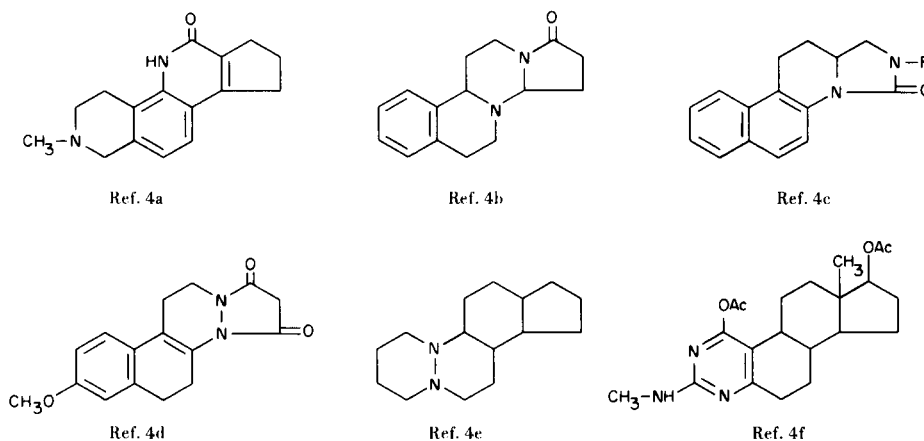
Homoveratrylamine was condensed with 1-cyanocyclopentene to afford the corresponding 2-cyano-*N*-(3,4-dimethoxyphenethyl)cyclopentylamine (III), which was ethoxycarbonylated with ethyl chlorocarbonate to give the *trans*-urethan (IVt) (major product) and the *cis*-urethan (IVc) which could be separated through a silica gel column. The *cis*-urethan was converted to the *trans*-urethan by the action of a catalytic amount of sodium ethoxide. Based upon general considerations of nucleophilic addition such as the Michael type reaction, the physical data obtained, and the difference in ease of cyclization of the 2-aminomethyl-*N*-ethoxycarbonyl-*N*-homoveratrylcyclopentylamines (Vt and Vc) to the corresponding cyclic ureas (VI and VIc), it was concluded that the major product was the *trans* and the minor the *cis* isomer.

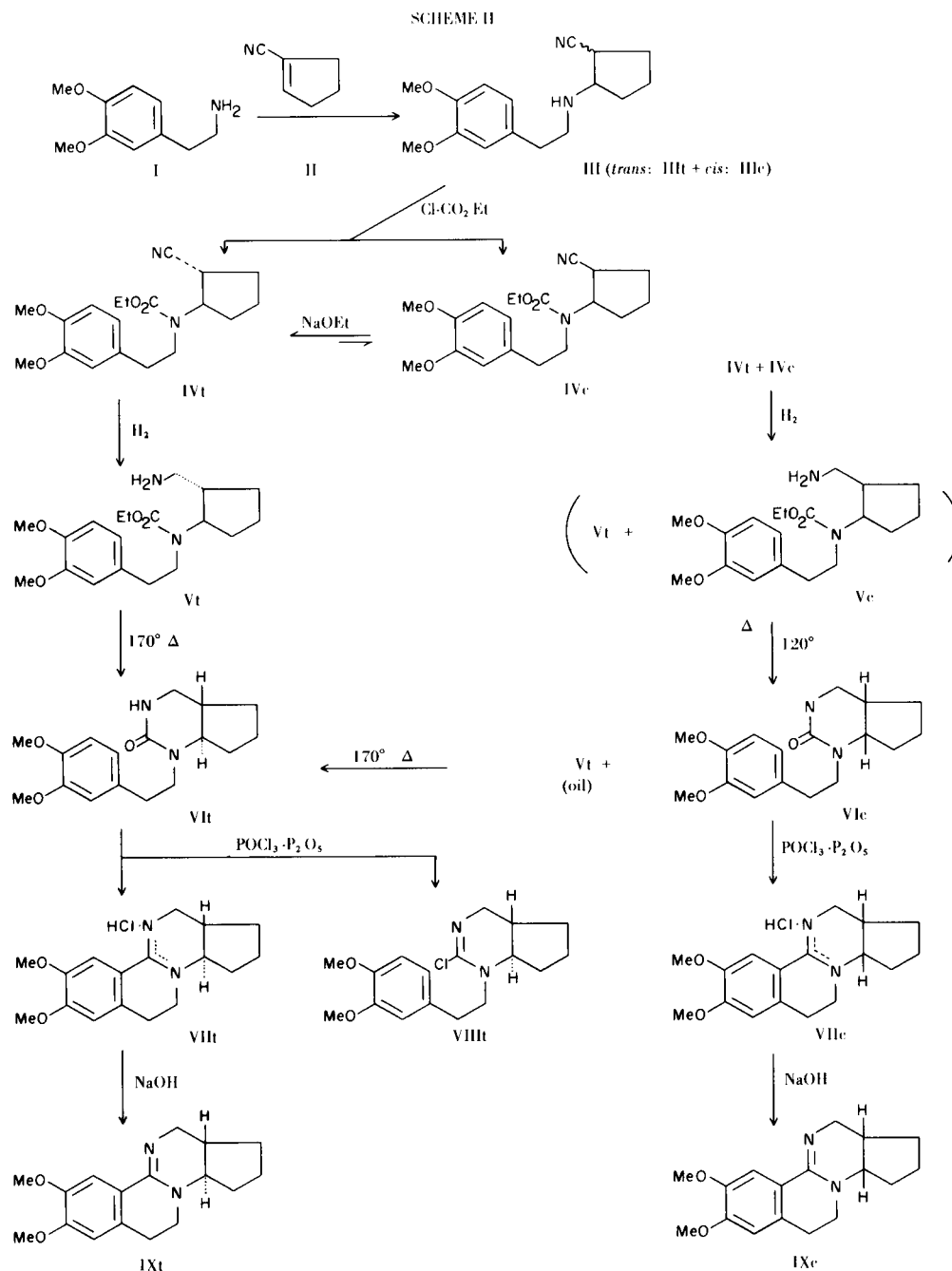
The cyclized compounds, VI and VIc, were subsequently submitted to the Bischler-Napieralski reaction furnishing the corresponding isoquinoline derivatives respectively. Thus the authors established a skeletal synthesis of the title compound, a 8,11-diazasteroid, and its stereochemical configuration at the C/D ring juncture was elucidated.

Recently, considerable attention has been paid to steroidal alkaloids found in nature, and various azasteroids have been synthesized by several research groups (3). In connection with these studies, various diazasteroids in which two ring carbon atoms have been substituted by nitrogen atoms in constructing the steroidal skeleton have also been synthesized as shown by Scheme I (4).

In addition, Yamazaki, *et al.* have synthesized azaquinolizidine (5), azabenz[*a*]quinolizidine (6), and azabenz[*c*]quinolizidine (7) and made efforts towards elucidation of the correlations between their chemical structures and physiological actions. Beginning with these studies, this research was extended to studies on the skeletal synthesis of a series of diazasteroids, in which the 8,13- (1), 8,14-

SCHEME I





(8), and 8,16- (9) diazasteroid skeletons have been synthesized.

Now we describe a synthesis of the 8,11-diazasteroid skeleton as shown by Scheme II.

Yamazaki had already synthesized the 1-azabenz[*a*]-quinolizidine skeleton (6), and the synthesis of the title compound was carried out successfully in a manner analogous to that of 1-azabenz[*a*]quinolizidine. Homoveratrylamine (I) was condensed with 1-cyanocyclopentene

(II) to afford an oily adduct (III) in 44% yield. The spectral data (ir and nmr) and the elemental analysis supported the structure 2-cyano-*N*-(3,4-dimethoxyphenyl)cyclopentylamine (III). Although the adduct could consist of two diastereoisomers (*trans* isomer III_t, and *cis* isomer III_c), tlc and glc gave only one spot and only one peak, respectively, and in addition, neither the hydrochlorides nor the picrates could be resolved into two isomers. The oily adduct was then converted into the corresponding urethan (IV) in quantitative yield.

Compound IV gave two peaks of ratio, 5:1 on glc, while giving a single spot on tlc. The isolation and the purification of both the major and the minor products were satisfactorily effected with silica gel column chromatography. It was deduced from the spectral data (ir and nmr) and elemental analyses that the two components were identical in their planar structures, but were conformationally isomeric. However, determination of *cis-trans* isomerism by nmr was impossible because of difficulty in assignment of the methylene protons of the five membered ring of each urethan. Based upon the general consideration, however, that the thermodynamically stable *trans* isomer should be the major product in the Michael condensation, the following experiment was performed. The minor product (IVc) upon treatment with sodium ethoxide in absolute ethanol was converted into the major product (IVt) in 95% yield.

The Michael condensation, when carried out in the presence of a catalytic amount of sodium ethoxide, furnished the urethan (IVt) in a 95% ratio after ethoxycarbonylation of the product (III), though the total yield of the adducts was 30-35%, poorer than that in the condensation without sodium ethoxide. On the basis of these facts and the report given by Truce (10) that the *trans* adduct was the sole product in the condensation of 1-*p*-tolylsulfonylcyclopentene with *p*-toluenethiol, it was deduced that the major product (IVt) was the *trans* isomer and the minor product the *cis* isomer. Compound IVt, after purification as described in the experimental, was subsequently subjected to hydrogenation over Raney nickel at 100° under high pressure in the presence of triethylamine in dioxane to furnish a colorless oil in 74% yield. The spectral data (ir and nmr) of the product supported the hydrogenation product as being *trans*-2-aminomethyl-*N*-ethoxycarbonyl-*N*-(3,4-dimethoxyphenethyl)cyclopentylamine (Vt).

Compound Vt, when heated at 170° in ethylene glycol for 35 hours gave a colorless crystalline solid, m.p. 168-169°, in 20% yield. An ir lactam band at 1635 cm⁻¹, the disappearance of the ethoxy signal in the nmr and the elemental analysis suggested that Vt had been cyclized to *trans*-octahydro-1-(3,4-dimethoxyphenethyl)-5*H*-cyclopenta[d]pyrimidin-2-one (VIIt).

Furthermore, Dreiding models of Vt and Vc and several reports (11) suggested that Vc might be cyclized to the corresponding urea (VIc) in preference to VIIt.

Compound IV (5:1 mixture of IVt and IVc) was therefore hydrogenated as indicated for IVt. The product was heated in ethylene glycol this time under milder conditions than those for the aforementioned experiment. After heating at 120° (bath temperature) in ethylene glycol for 30 minutes, the reaction mixture afforded a new peak probably due to the cyclic urea (VIc) on glc, and

the reaction was continued for another 15 hours at 120° (bath temperature).

The reaction product was then purified on a silica gel column to furnish a colorless solid, m.p. 102-103° in a yield of 11% and a dark brown oil probably unchanged *trans*-2-aminomethyl compound, Vt. The former resembled VIIt in the ir and nmr spectra, but admixture with VIIt showed a considerable depression in the melting point. Elemental analysis was, however, consistent with VIIt. From these results it was concluded that the former was *cis*-octahydro-1-(3,4-dimethoxyphenethyl)-5*H*-cyclopenta[d]pyrimidin-2-one (VIc). The latter dark brown oil was heated at 170° in ethylene glycol for 35 hours to furnish a crystalline solid identical with VIIt, which was confirmed by spectral data (ir and nmr), elemental analysis and admixture with an authentic sample obtained from IVt via Vt. Thus the difference in ease of cyclization is in good agreement with Dreiding model considerations. Provided that the cyclic urea moiety of VIIt and VIc maintains the planarity like urea itself due to resonance energy, some of the seven protons on the five membered ring of VIc are expected to be located above the plane of the urea moiety, resulting in a diamagnetic upfield shift (8.35 τ) in the nmr spectrum compared with the shift of VIIt (8.1 τ). All of these suggested that VIc was the *cis* isomer and VIIt the *trans* isomer.

Compounds VIIt and VIc were then subjected to the Bischler-Napieralski reaction, respectively, under drastic conditions using phosphoryl chloride and phosphorus pentoxide as the condensing agents (6,12,13), to afford the corresponding isoquinoline derivatives, VIIIt and VIIc, although in poor yields, after treatment of the reaction mixture as described in the experimental. However, another product (VIIIIt), m.p. 111-113°, was obtained from VIIt in a yield of 63%, whereas no isomer of VIIIIt was obtained from VIc. This product was insoluble in water, exhibited a positive Beilstein test, showed three aromatic protons signals in the nmr, and its elemental analysis coincided with VII, all of which supported the structure of the noncyclized chloro compound VIIIIt.

Compounds VIIIt and VIIc were definitely the corresponding water soluble isoquinoline hydrochlorides, which was verified by spectral data (ir, uv, and nmr) and elemental analyses, and showed an appreciable depression in the melting point on admixture.

The free bases, IXIt and IXc, were obtained in the usual manner and their physical data are given in the experimental.

Thus the synthesis of 2,3-dimethoxy-8,11-diazagona-1,3,5(10),9(11)trienes has been accomplished. The *c*-series has been established to be *C/D cis* and the *t*-series has been shown to be *C/D trans*.

EXPERIMENTAL

Ir spectral data were obtained using a Hitachi Grating Infrared spectrophotometer 215, and uv spectral data using a Hitachi 124 spectrophotometer. Glc measurements were carried out using a Shimadzu GC-4A instrument (SE-30 as column material, hydrogen as the carrier gas). Nmr spectral data were obtained from JEOL C-60H and C-100H (TMS as internal standard). The wave length (λ) of the uv spectra is reported nm. Mass spectral data were obtained from a Hitachi RMU-7L. All melting points are uncorrected.

2-Cyano-*N*-(3,4-dimethoxyphenethyl)cyclopentylamine (III).

A mixture of homoveratrylamine (I), (30 g., 0.166 mole) and 1-cyanocyclopentene (II), (18.5 g., 0.199 mole) was heated at 120-130° (bath temperature) for 45 hours with stirring until the spot of I on tlc disappeared. The reaction mixture, after acidification with 10% hydrochloric acid was extracted with benzene to remove neutral substances and then the water layer was basified with sodium carbonate solution and extracted with benzene. The benzene extract, after drying over potassium carbonate and removal of the solvent, gave a dark brown oil, which when purified through a silica gel column using benzene as an eluent, afforded a yellow oil, (18.9 g.), 44%; ν (film) cm^{-1} : 3335 (NH), 2250 ($\text{C}\equiv\text{N}$); nmr (chloroform) τ : 3.28 (s, 3H, aromatic H), 6.23, 6.27 (s, 6H, 2 CH_3O), 6.50-7.40 (b.m., 6H, $\text{ArCH}_2\text{CH}_2\text{NCH}$, CHCN), 7.80-8.80 (b.m., 6H $\text{CH}_2\text{CH}_2\text{CH}_2$ of cyclopentane ring), 8.05 (b.s., 1H, $>\text{NH}$, disappearing on deuterium oxide treatment).

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.13; H, 8.17; N, 10.20.

trans and *cis*-2-Cyano-*N*-ethoxycarbonyl-*N*-(3,4-dimethoxyphenethyl)cyclopentylamine (IVt and IVc).

Compound III (18 g.) in benzene (100 ml.) was suspended in sodium carbonate solution (15 g. in 100 ml. of water) and the suspension was treated with ethyl chlorocarbonate (9.2 g., 0.085 mole) at 40° for 1.5 hours with stirring. The supernatant layer, which gave a negative Beilstein test, was dried over sodium sulfate to afford a brown oil after the removal of the solvent. The brown oil was eluted with chloroform from a silica gel column to give a pale yellow oil (22.2 g., 98%). The oil, while giving a single spot on tlc, gave two peaks (area ratio 5:1) on glc, and was again chromatographed using benzene as an eluent. The first eluate obtained from IV (2 g.) was IVt, (1.2 g.) and the next eluate IVc (240 mg.).

Compound IVt, ν (film) cm^{-1} : 2250 ($\text{C}\equiv\text{N}$), 1690 (CO); nmr (chloroform) τ : 3.36 (s, 3H, aromatic H), 5.97 (q, 2H, $\text{CH}_3\text{CH}_2\text{OCO}$), 6.28, 6.33 (s, 6H, 2 CH_3O), 5.70-7.60 (b.m., 6H, $\text{ArCH}_2\text{CH}_2\text{NCH}$, CHCN), 7.70-8.50 (b.m., 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$ of cyclopentane ring), 8.32 (t, 3H, $\text{CH}_3\text{CH}_2\text{OCO}$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.84; H, 7.47; N, 7.80.

Compound IVc, ν (film) cm^{-1} : 2250 (CN), 1690 (CO); nmr (carbon tetrachloride) τ : 3.36 (s, 3H, aromatic H), 5.84 (q, 2H, $\text{CH}_3\text{CH}_2\text{OCO}$), 6.24, 6.27 (s, 6H, 2 CH_3O), 5.60-7.60 (b.m., 6H, CHCN , $\text{ArCH}_2\text{CH}_2\text{NCH}$), 7.60-8.50 (b.m., 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$ of cyclopentane ring), 8.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{OCO}$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 66.13; H, 7.82; N, 7.80.

Epimerisation of IVc to IVt and the Purification of IVt.

Compound IVc (100 mg. in absolute ethanol (3 ml.)) was treated with sodium ethoxide (50 mg.) at 35° for 30 minutes. After the removal of the solvent, the reaction mixture was diluted with water (2 ml.) and extracted with benzene and the benzene extract, after drying over sodium sulfate, gave a pale yellow oil (100 mg.) after the removal of the solvent. The oil consisted of 95% of IVt, which was verified by glc. After purification through silica gel, a pale yellow oil (74 mg.) was obtained. The oil was confirmed to be IVt by ir and glc.

In addition, IV (a mixture of IVt and IVc of ratio 5:1) (20 g.) in ethanol (250 ml.) was treated with sodium ethoxide (0.5 g.) at 35° for 1.5 hours. The reaction mixture, which was worked up as mentioned above, gave an oil, which was purified through a silica gel column to give IVt (17 g.) and a mixture of IVt and IVc (2.2 g.). Thus the purification of IVt was accomplished successfully by applying the epimerisation of IVc to IVt.

trans-2-Aminomethyl-*N*-ethoxycarbonyl-*N*-(3,4-dimethoxyphenethyl)cyclopentylamine (Vt).

Compound IVt (15 g., 0.043 mole) in dioxane (100 ml.) was hydrogenated over Raney nickel at 100° under 100 atmospheres in the presence of triethylamine (5 ml.). The reaction was complete after 1.5 hours. Worked up as usual after cooling, the reaction product was purified through a silica gel column using chloroform-ethanol (1:1) as an eluent, leaving a colorless oil (11.26 g., 74%); ν (film) cm^{-1} : 3300-3400 (NH_2), 1690 (CO); nmr (deuteriochloroform) τ : 3.24 (s, 3H, aromatic H), 5.70 (q, 2H, $\text{CH}_3\text{CH}_2\text{OCO}$), 6.15, 6.18 (s, 6H, 2 CH_3O), 6.50-7.50 (b.m., 7H, $\text{ArCH}_2\text{CH}_2\text{NCH}$, CH_2NH_2), 7.80-8.53 (b.s., 7H, $\text{CHCH}_2\text{CH}_2\text{CH}_2$ of cyclopentane ring), 8.58 (b.s., 2H, NH_2 , disappearing on the deuterium oxide treatment) 8.70 (t, 3H, $\text{CH}_3\text{CH}_2\text{OCO}$).

trans-Octahydro-1-(3,4-dimethoxyphenethyl)-5*H*-cyclopenta[d]-pyrimid-2-one (VIIt).

Compound Vt, (11 g., 0.033 mole) in ethylene glycol, (150 ml.) was heated at 170° (bath temperature) for 35 hours, after which 100 ml. of saturated sodium chloride solution was added to the reaction mixture in the cold. The mixture was extracted with chloroform and the extract was dried over calcium sulfate. When worked up as usual, the extract afforded a dark brown oil, which was eluted with chloroform from a silica gel column to give colorless crystals (1.91 g., 20%), m.p. 168-169° (from benzene-petroleum ether (1:1)); ν (film) cm^{-1} : 3460 (NH), 1637 (CO); nmr (deuteriochloroform) τ : 3.15 (s, 3H, aromatic H), 6.07, 6.10 (s, 6H, 2 CH_3O), 6.15-7.50 (b.m., 7H, $\text{NHCH}_2\text{ArCH}_2\text{CH}_2\text{NCH}$), 7.50-9.00 (b.m., 7H, $\text{CHCH}_2\text{CH}_2\text{CH}_2$ of cyclopentane ring).

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.83; H, 7.09; N, 9.09.

cis-Octahydro-1-(3,4-dimethoxyphenethyl)-5*H*-cyclopenta[d]pyrimid-2-one (VIc).

Compound IV (a mixture of IVt and IVc in the ratio, 5:1 on glc) (20 g., 0.058 mole) in dioxan (150 ml.) was hydrogenated over Raney nickel (15 g.) in the presence of triethylamine (8 ml.) at 100° under 120 atmospheres. Uptake of hydrogen ceased after 1.5 hours. When worked up as usual, the reaction mixture furnished a colorless oil (19.5 g.). The oil, without purification, was heated in ethylene glycol (200 ml.) at 120° (bath temperature) for 15 hours, and after cooling, a saturated sodium chloride solution was added. The solution was extracted with chloroform and the extract worked up as usual, furnished a dark brown oil, which was eluted with chloroform from a silica gel column to

afford colorless crystals (1.95 g., 11%) and a brown oil. The colorless crystals were recrystallized from benzene-petroleum ether (1:1), giving IVc, m.p. 102-103° and showed a considerable depression in the melting point on the admixture with VIc. The latter oil was heated at 170° in ethylene glycol for 35 hours and was worked up in the usual manner giving colorless crystals (2 g., 11.5%), m.p. 168-169° (from benzene-petroleum ether 1:1), which was identical with the compound obtained above from VIc, showing no depression in the melting point on the admixture with VIc; ir (VIc) ν (film) cm^{-1} : 3460 (NH), 1637 (CO); nmr (deuteriochloroform) τ : 3.22 (s, 3H, aromatic H), 4.72 (b.m., 1H, NH disappearing on deuterium oxide treatment) 6.12, 6.15 (s, 6H, 2CH₃O), 6.25-7.35, (b.m., 7H, ArCH₂CH₂NCH, CH₂NH), 7.35-8.70 (b.m., 7H, CH₂CH₂CH₂CH of cyclopentane ring).

Anal. Calcd. for C₁₇H₂₄N₂O₃: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.89; H, 8.20; N, 9.13.

trans-2,3-Dimethoxy-8,11-diazagona-1,3,5(10),9(11)tetraene Hydrochloride (VIIIc) and 1,4,4a,5,6,7-Hexahydro-1-(3,4-dimethoxyphenethyl)-2-chloro-5H-cyclopenta[d]pyrimidine (VIIIc).

To a suspension of VIIc (2 g., 0.0066 mole) in phosphorus trichloride (5 ml.) was added phosphorus pentoxide (2 g.) and the mixture was heated at 130° (bath temperature) for 5 hours, with vigorous stirring. The resultant orange-yellow mixture, after trituration with petroleum ether in the cold to remove unreacted phosphoryl chloride as much as possible, afforded a yellow semi-solid mass, which was decomposed with 10 ml. of ice water and 10% hydrochloric acid (2 ml.) to give a solution which was extracted with benzene to remove the starting material VIIc. The water layer was made slightly basic with 50% potassium hydroxide and extracted with chloroform. The chloroform extract, dried over calcium sulfate was worked up in the usual fashion to give a solid mass which was crystallized to colorless plates, VIIIc (m.p. 257-258°), (148 mg., 7%) on the addition of acetone. The mother liquor, treated with benzene-petroleum ether (1:1), afforded the chloro compound VIIIc (1.34 g., 63%); ir (VIIIc) ν (chloroform) cm^{-1} : 3360 (NH broad), 1620 (C=N or C=C), 1600 (C=C); nmr (deuteriomethanol) 100 Hz τ : 2.51, 3.06 (s, 2H, aromatic H), 6.09 (s, 6H, 2CH₃O), 5.70-7.20 (m., 7H, ArCH₂CH₂NCH, NHCH₂), 7.35-8.80 (b.m., 7H, CH₂CH₂CH₂CH of cyclopentane ring); uv λ max (ethanol): 233, 277, 316 (log ϵ : 4.19, 3.85, 3.76); mass: m/e 286 (M-36)⁺; Beilstein test positive; soluble in water.

Anal. Calcd. for C₁₇H₂₂N₂O₂·HCl: C, 63.21; H, 7.18; N, 8.67. Found: C, 63.00; H, 7.09; N, 8.50.

Compound VIIIc, ir (chloroform) cm^{-1} : 1617 (C=N); nmr (deuteriochloroform) τ : 3.25 (s, 3H, aromatic H) 6.17 (s, 6H, 2CH₃O), 5.90-7.50 (b.m., 7H, ArCH₂CH₂NCH, NCH₂), 7.65-9.05 (b.m., 7H, CH₂CH₂CH₂CH of cyclopentane ring); mass m/e 286 (M-36)⁺; Beilstein test positive; insoluble in water.

Anal. Calcd. for C₁₇H₂₃ClN₂O₂: C, 63.21; H, 7.18; N, 8.67. Found: C, 62.72; H, 7.16; N, 8.41.

In this ring closure, when 3 times as much phosphorus pentoxide as that used in the above experiment was employed and the other conditions were unchanged, VIIc (210 mg., 10%) was obtained. Furthermore, the starting material (45 mg.) was recovered and not a trace of VIIIc was detected.

cis-2,3-Dimethoxy-8,11-diazagona-1,3,5(10),9(11)tetraene Hydrochloride (VIIIt).

To a suspension of VIc (1.5 g., 0.0049 mole) in phosphorus trichloride (4 ml.) was added phosphorus pentoxide (4.5 g.) and the mixture was treated in the same manner as that in the case of VIc to afford colorless plates, m.p. 235° (143 mg., 9%); ir ν (chloroform) cm^{-1} : 1635 (C=N or C=C), 1608 (C=C); nmr (deuteriomethanol) 100 Hz τ : 2.44, 3.26 (s, 2H, aromatic H) 6.15 (s, 6H, 2CH₃O), 6.30-7.50 (b.m., 7H, ArCH₂CH₂NCH, NCH₂), 7.60-8.90 (b.m., 7H, CH₂CH₂CH₂CH of cyclopentane ring); uv λ max (ethanol): 231, 277, 312 (log ϵ : 4.44, 4.10, 4.01); mass: m/e 286 (M-36)⁺; Beilstein test positive; soluble in water.

Anal. Calcd. for C₁₇H₂₂N₂O₂·HCl: C, 63.21; H, 7.18; N, 8.67. Found: C, 63.09; H, 6.96; N, 8.53.

trans-2,3-Dimethoxy-8,11-diazagona-1,3,5(10),9(11)tetraene (IXt).

The free base of VIIc was obtained in the usual manner as colorless crystals, m.p. 166-168° (85%); ir ν (chloroform) cm^{-1} : 1600 (C=N); nmr (deuteriomethanol) 100 Hz τ : 2.55, 2.99 (s, 2H, aromatic H), 6.06 (s, 6H, 2CH₃O), 6.10-7.10 (b.m., 7H, =NCH₂, ArCH₂CH₂NCH), 7.30-8.40 (b.m., 7H, CH₂CH₂CH₂CH of cyclopentane ring); uv λ max (ethanol): 230, 275, 313 (log ϵ : 4.39, 4.05, 3.96); mass: m/e 286, M⁺; Beilstein test negative.

Anal. Calcd. for C₁₇H₂₂N₂O₂: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.18; H, 7.93; N, 9.63.

cis-2,3-Dimethoxy-8,11-diazagona-1,3,5(10),9(11)tetraene (IXc).

The free base of VIIc was obtained in the usual manner as colorless crystals, m.p. 145-147° (77%); ir ν (chloroform) cm^{-1} : 1600 (C=N); uv λ max (ethanol): 232, 276, 314 (log ϵ : 4.36, 3.99, 3.91); mass: m/e 286, M⁺.

Anal. Calcd. for C₁₇H₂₂N₂O₂: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.10; H, 7.58; N, 9.70.

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REFERENCES

- (1) Part 1, K. Matoba, K. Isomura, M. Nagata, T. Yamazaki, and R. N. Castle, *J. Heterocyclic Chem.*, **9**, 1359 (1972).
- (2a) Gofuku, Toyama, Japan; (b) Department of Chemistry, Brigham Young University, Provo, Utah 84601.
- (3) E. R. H. Jones, *J. Chem. Soc.*, 5907 (1964); S. V. Kessar, A. K. Sobti, and G. S. Johi, *ibid.*, 259, 262 (1971); S. Ohki and M. Akiba, *Chem. Pharm. Bull. (Tokyo)*, **16**, 1889 (1968); *idem.*, *ibid.*, **18**, 2195 (1970).
- (4a) F. D. Popp, W. R. Schleigh, P. M. Proehlic, R. J. Dubois, and A. C. Casey, *J. Org. Chem.*, **33**, 833 (1968); (b) G. Redeuilk and C. Viel, *Bull. Soc. Chim. France*, 3115 (1969); J. H. Burckhalter, H. N. Abramson, J. G. MacConnell, R. J. Thill, A. J. Olson, J. C. Hanson, and C. E. Nordman, *Chem. Commun.*, 1274 (1968); (c) L. E. Katz and F. D. Popp, *J. Heterocyclic Chem.*, **5**, 249 (1968); (d) V. K. Pandit, K. D. Jonge, and H. O. Huisman, *Rec. Trav. Chim.*, **88**, 149 (1969); (e) M. F. Brana, M. Lora-Tamayo, P. Navorro, and T. L. Soto, *Tetrahedron Letters*, 1523

(1969); (f) D. M. Piatak and E. Caspi, *J. Med. Chem.*, **13**, 335 (1970).

(5) T. Yamazaki, M. Nagata, H. Sugano, and N. Inoue, *Yakugaku Zasshi*, **87**, 663 (1967); *idem.*, *ibid.*, **87**, 668 (1967); *idem.*, *ibid.*, **88**, 212, 216 (1968).

(6) T. Yamazaki, *ibid.*, **79**, 1003, 1008 (1959).

(7) M. Nagata, *ibid.*, **80**, 1414 (1960); M. Nagata and T. Yamazaki, *ibid.*, **83**, 679, 683 (1963); *idem.*, *ibid.*, **86**, 608, 613 (1966).

(8) T. Yamazaki, M. Nagata, and H. Takesawa, The 90th

Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July, 1970.

(9) Unpublished.

(10) W. E. Truce and A. J. Levy, *J. Org. Chem.*, **28**, 679 (1963).

(11) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, M. W. Osborne, and R. I. Meltzer, *J. Med. Chem.*, **7**, 232 (1964); *idem.*, *J. Org. Chem.*, **31**, 1489 (1966).

(12) L. M. Mohunta, J. N. Ray, *J. Chem. Soc.*, 1263 (1934).

(13) T. Yamazaki and M. Nagata, *Yakugaku Zasshi*, **82**, 352 (1962).