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8,13-Diazagona-1,3,5(10)-triene-12-ones, Synthesis and Stereochemistry

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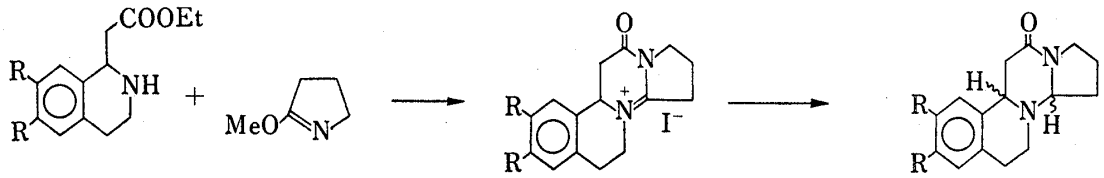
Preparation and separation of two isomeric 8,13-diazagona-1,3,5(10)-triene-12-ones are described. The stereochemistry of both isomers is also discussed.

Keywords——diazasteroid; stereochemistry; N-heterocycles; 8,13-diazagonatriene-12-one; 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline; 2-acetyl-1,2-dihydroisoquinoline acetic acid (isoquinoline)

Previously one of the present authors (T. Y.) reported the synthesis of 2,3-dimethoxy-8,13-diazagona-1,3,5(10)-triene-12-one (**7**)[2)] by the reaction of methyl butyrolactim (**3**) with 1-ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**), followed by reduction of tetracyclic immonium intermediate (**5**). Although the compound **7** was suspected to be a mixture of configurational isomers from the observed broad range of melting point, all attempts for the separation were not successful. In this note we describe the synthesis of 8,13-diazagona-1,3,5(10)-triene-12-one (**6**), desmethoxy compound of **7**, and isolation of two configurational isomers and their stereochemical relationship.



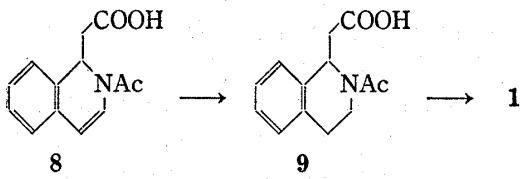
1 : R=H, **2** : R=OMe; **3**; **4** : R=H, **5** : R=OMe; **6** : R=H, **7** : R=OMe

Chart 1

In the present experiment, the same annelation reaction was employed again, but A,B-ring block (**1**)[3)] was prepared using 2-acetyl-1,2-dihydroisoquinoline acetic acid (**8**)[4)] as a starting material. The catalytic hydrogenation followed by acid hydrolysis and esterification gave **1** in a fair yield (Chart 2).

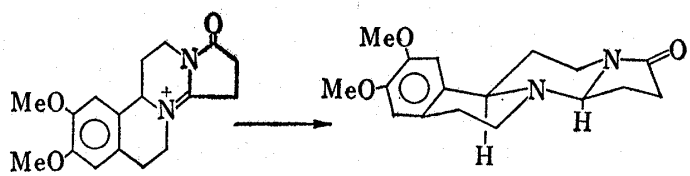
The reaction of **1** with **3** at 90° and subsequent treatment of the condensation product with sodium iodide afforded crude **4** which unlike with dimethoxy derivative (**5**) could not be crystallized. Therefore, the immonium iodide **4** without purification was reduced with sodium borohydride to give an amorphous solid in about 85% yield. Careful thin-layer chromatographic analysis revealed that this reduction product is a mixture of two components. Separa-

1) Location: *Sugitani, Toyama 930-01, Japan.*
2) K. Matoba, K. Isomura, M. Nagata, T. Yamazaki, and R.N. Castle, *J. Heterocyclic Chem.*, **9**, 1359 (1972).
3) Ordinary preparation method of **1** is based on the condensation of phenethyl chloride and ethyl cyanoacetate and subsequent hydrogenation. *a*) A.I. Meyers, G.G. Munoz, W. Sobotka, and K. Baburace, *Tetrahedron Lett.*, **1965**, 255; *b*) W. Sobotka, W.N. Beverung, G.G. Munoz, J.C. Sircar, and A.I. Meyers, *J. Org. Chem.*, **30**, 3667 (1965).
4) *a*) H. Yamanaka, T. Shiraishi, and T. Sakamoto, *Heterocycles*, 3, 1075 (1975); *b*) T. Shiraishi and H. Yamanaka, *Heterocycles*, **6**, 535 (1977).



8 9

Chart 2



10 11

Chart 3

tion was effected by silica gel column chromatography using ethyl acetate–chloroform as an eluting agent to give major product (**6a**, mp 197°) in 35% yield and minor product (**6b**, mp 117—121°) in 10% yield. Since the elemental analyses and mass spectral data of both compounds were consistent with the diazasteroid structure (**6**), these must be configurational isomers at C_9 and C_{14} (*syn* or *anti*).[5] The characteristic differences in spectral data were such that the major product **6a** showed clear Bohlmann band for *trans* quinolizidine at 2780 and 2750 cm^{-1} and no discernible signal of 9-H below 4.2 ppm whereas the minor product **6b** did not show Bohlmann band but exhibited a broad signal at 4.5—4.2 ppm indicating the 9-H to be gauche to the adjacent nitrogen lone pair (*cis*-quinolizidine structure).[6]

For the assignment of these isomers, it was helpful to refer to the report of Burkhalter, *et al.*[7] describing the synthesis and the stereochemistry of 17-keto-8,13-diazasteroid (**11**). By the reduction of the immonium precursor (**10**) with sodium borohydride, they obtained a single product which by X ray crystallographic analysis was determined to be 9,14-*syn* isomer with *trans*-quinolizidine structure. The fact means that in this particular reduction the attack of the hydride reagent occurred preferentially from the *syn* side to 9-H leading to the

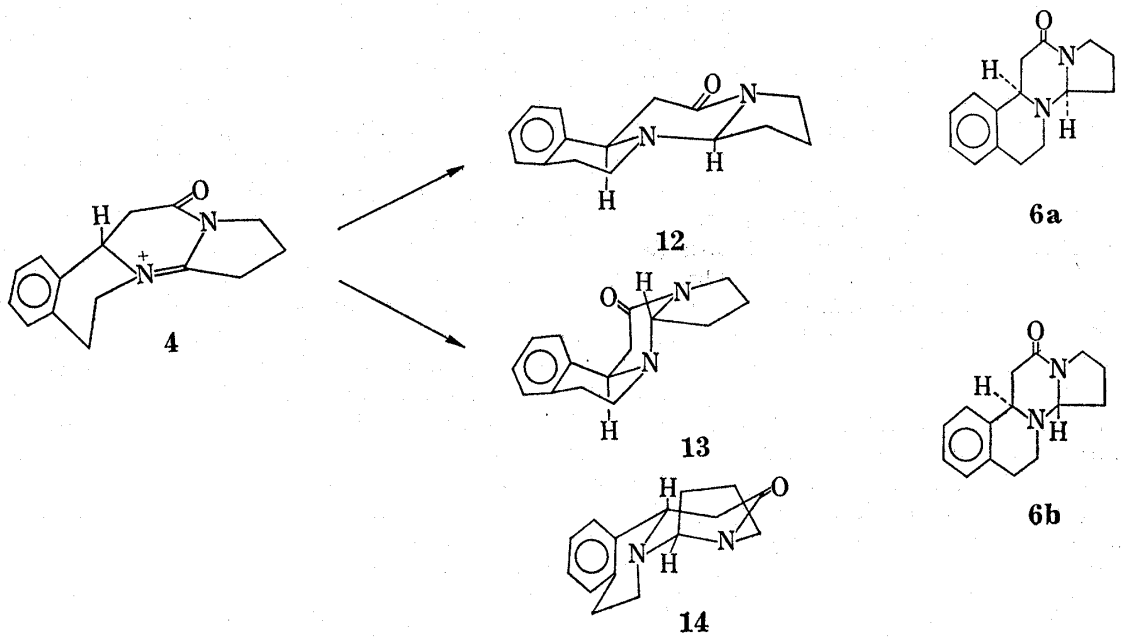


Chart 4

5) Isomeric relationship was also supported by the following experiment: The mercuric acetate oxidation of each isomer followed by sodium borohydride reduction gave a mixture of **6a** and **6b** (2—3 : 1).

6) For the basis of this argument, see; *a*) T.A. Crabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); *b*) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

7) *a*) J.H. Burkhalter and H.N. Abramson, *Chem. Commun.*, **1966**, 805; *b*) J.H. Burkhalter, H.N. Abramson, J.G. MacConnell, R.J. Thill, A.J. Olson, J.C. Hanson, and C.E. Nordman, *Chem. Commun.*, **1968**, 1274.

most stable product. The same steric course should be expected for the case of **4**, since the structure **4** and **10** are closely related in their functionality and conformation.

Based on the above mechanistic prediction and spectroscopic evidence (*vide ante*) the major product was assigned to *syn* isomer with *trans*-quinolizidine ring fusion (**12**), and accordingly the minor product to *anti* isomer. For the *anti* isomer, two distinct conformations (**13** and **14**) incorporating *cis*-quinolizidine are possible. Of the two, the preferred one should be **13**, since with this conformation there is only one axial bond on ring C and no severe distortion of B, C rings is required for coplanarity of the lactam group.

Experimental

Melting points were determined on a hot stage using a Yanagimoto micro melting point apparatus and uncorrected. IR absorption spectra were obtained with a JASCO model IR S spectrometer, NMR spectra were obtained by JEOL model PMX 60 and Varian EM-390 with TMS as an internal standard. Mass spectra were obtained with JEOL Model 01SG-2. Methyl butyrolactim **3** was prepared by the Petersen method modified by T. Onaka.[8]

2-Acetyl-1,2-dihydroisoquinoline Acetic Acid (8)——A mixture of 10 g of isoquinoline and 100 g of acetic anhydride was refluxed for 40 hr. After cooling, to the reaction mixture, was added dil. $NaHCO_3$ solution and the mixture was acidified to pH 2—3 with dil. HCl. The brown precipitate was collected. The crystallization from acetone–hexane gave 6.5 g of colorless plates, mp 164—166° (lit.[4a] 161—162°). *Anal.* Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.04. Found: C, 67.45; H, 5.73; N, 6.31. IR ν_{max}^{KBr} cm^{-1}: 3200—2320, 1720, 1593, 1560, 775, 750.

2-Acetyl-1,2,3,4-tetrahydroisoquinoline Acetic Acid (9)——Three grams of **8** in 50 ml of dist. EtOH were hydrogenated over 1.2 g of 5% Pd/C at atmospheric pressure. Hydrogen uptake ceased after 1 eq. of H_2 (12 hr) and the solvent was removed after the filtration of the catalyst. The residue was crystallized from acetone to give colorless plates 2.2 g, mp 165—167° (lit.[4b] 165—166°). *Anal.* Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.78; H, 6.31; N, 6.12. IR ν_{max}^{KBr} cm^{-1}: 1720, 1600, 770.

1-Ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline (1)——Ten grams of **9** were dissolved in a mixture of 210 ml of conc. HCl, 90 ml of H_2O, and 150 ml of EtOH and refluxed for 67 hr. The solvent was evaporated *in vacuo* to give 9.1 g of the crude hydrolysis product. After drying in a desiccator over P_2O_5 the product was dissolved in 200 ml of dry EtOH and dry HCl gas was saturated. After 69 hr the solvent was evaporated *in vacuo* and the residue was made alkaline with dil. $NaHCO_3$ and was extracted with AcOEt three times. The AcOEt solution was dried over $MgSO_4$ and the solvent was evaporated. The oily product was distilled under the reduced pressure to give 6.0 g of **1** (64%). bp 123—129° (1 mmHg). IR ν_{max}^{film} cm^{-1}: 3350, 1735, 770. NMR ($CDCl_3$) δ: 1.25 (3H, triplet, J=7 Hz, $-CH_2\underline{CH_3}$), 2.27 (1H, broad singlet), 2.7—3.5 (6H, multiplet), 4.17 (2H, quartet, J=7 Hz, $-\underline{CH_2}CH_3$), 4.45 (1H, multiplet), 7.1 (4H, singlet).

8,13-Diazagona-1,3,5(10)-triene-12-ones (6)——A mixture of 2.9 g of **1** and 2.5 g of butyrolactim (**3**) was heated in a sealed tube at 90° for 3 hr. A slight excess of dil. HCl (12 ml) was added to the reaction mixture and kept at room temperature for 30 min. To the clear brownish solution was added saturated NaI. No precipitate was formed. The solvent was evaporated *in vacuo* and the residue was suspended in 50 ml of MeOH. To the ice-cooled suspension 1.5 g of $NaBH_4$ was added portionwise with vigorous stirring for 2 hr. The reaction mixture was treated with dil. AcOH and then was made alkaline with dil. $NaHCO_3$ and extracted with AcOEt three times. The AcOEt layer was dried over $MgSO_4$ and the solvent was evaporated to give pale yellow crystalline mass (2.8 g). Crystallization from acetone gave 920 mg of colorless needles, **6a**. The residue (two spots on TLC: Merck Silica gel plate 5715, AcOEt as a developing agent) was separated by column chromatography using 45 g of silica gel and AcOEt–$CHCl_3$ (1: 1). After 200 mg of **6a** was eluted, the minor product **6b** was obtained as a resinous material (300 mg, one spot on TLC), which was crystallized from acetone–hexane to give 27 mg of colorless plates.

6a mp 197° MS *m/e*: 242 (M^+), 214, 172, 132, 83. *Anal.* Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.58; H, 7.57; N, 11.56. IR ν_{max}^{KBr} cm^{-1}: 2970, 2920, 2880, 2780, 2750, 1640, 740. NMR ($CDCl_3$) δ: 1.6—4.05 (complex signals), 7.15 (4H, aromatic protons).

6b mp 117—121°. MS *m/e*: 242 (M^+), 214, 172, 132, 83. *Anal.* Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.61; H, 7.18; N, 11.40. IR ν_{max}^{KBr} cm^{-1}: 2920, 2880, 2840, 1620, 760, 740. NMR ($CDCl_3$) δ: 1.5—4.0 (complex signals), 4.2—4.5 (multiplet), 2.85 (4H, aromatic protons).

Mercuric Acetate Oxidation of 6a and 6b followed by $NaBH_4$ Reduction——Thirty six mg of **6a** or **6b** was added to a mixture of $Hg(OAc)_2$ (200 mg), 5% AcOH (4 ml), and EtOH (3 ml) and the mixture was stirred for 4 hr at r.t. and then heated at 100° for 40 min (no starting material on TLC). To the cooled reaction mixture was added 400 mg of $NaBH_4$ and stirred for 1 hr at r.t. The reaction mixture was treated with

8) T. Onaka, *Tetrahedron Lett.*, **1971**, 4387.

30% AcOH and then made alkaline with dil. $NaHCO_3$ and extracted with $CHCl_3$. The solvent was evaporated to give the crude product 26 mg for **6a**, 27 mg for **6b** respectively. The NMR spectra of the crude products were almost identical, although both products exhibited clear two spots on TLC. The column chromatography using 5 g of silica gel and $CHCl_3$–AcOEt as an eluting system gave 14 mg of **6a** and 7 mg of **6b** in the case of the crude product from **6a**. With **6b** 12 mg of **6a** and 4 mg of **6b** were obtained.

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Pharmacological Properties of Galenic Preparations. II.[1] Intestinal Absorption Inhibitor of Alkaloid in the *Scopolia* Extract

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Screening of the inhibitor to the absorption of alkaloid in the *Scopolia* extract was taken up and following results were obtained.

The alkaloid absorption through the intestine in the administration of *Scopolia* extract is affected by scopoletin, tannin-like substance(s) and others, but is not affected by the acidic component(s).

Keywords——*Scopolia* extract; intestinal absorption; alkaloid; isolated mouse intestine; tannin; scopoletin; hyoscyamine

In a previous paper,[1] we have suggested that a part of the pharmacological properties of the *Scopolia* extract should be attributed to the decreased absorption of *l*-hyoscyamine through intestine. This study is concerned with the screening of the inhibitor to the absorption of alkaloid in the *Scopolia* extract.

Experimental

Chart 1 shows the process of fractionation of the extract.

The alkaloid were eventually transferred to Fr. 6 and 7. The absorption rate of alkaloids through the isolated small intestine of mouse was measured according to the method described elsewhere.[1] Each material that contained alkaloids 8.0×10^{-4} g/ml as hyoscyamine by dilution with water was ajusted to become isotonic with sodium chloride. Fraction 3, 5 and 8 were tested after adding the same amount of hyoscyamine. The amount of administration was always fixed at 0.3 ml of material.

Results and Discussion

The quantity of alkaloids which permeated through the isolated intestine is shown for each fraction in Table I and plotted against time in Figs. 1, 2, 3, and 4.

1) Part I: Y. Kano and M. Konoshima, *Yakugaku Zasshi*, **94**, 898 (1974).
2) Location: *a*) *Katuraoka-cho, Otaru*; *b*) *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*