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Synthesis in the Diazasteroid Group. XIX.[1] Synthesis of the 9,13-Diazasteroid System

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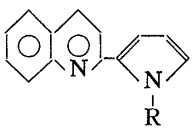
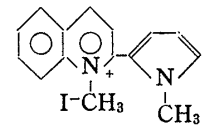
Quinoline *N*-oxide was treated with 1*H*-pyrrole in the presence of acetic anhydride to give 2-(2[1*H*]pyrrolyl)quinoline (Ib) in 37.4% yield. In the reaction of Ib and 2-chloroethyl tosylate (V) in acetone catalyzed by potassium hydroxide, 2-(1-(2-tosyloxyethyl)-2[1*H*]-pyrrolyl]quinoline (Ic) was obtained. Ic was unstable and cyclized gradually to a quaternary tosylate (VIa), which was reduced with sodium borohydride in methanol to 9,13-diazagona-1,3,5(10),14,16-pentaene (VII), which was identified as its picrolonate.

Keywords——diazasteroid; 9,13-diazasteroid; quinolyl pyrrole; quinoline *N*-oxide; pyrrole *N*-alkylation; condensation reaction; cyclization reaction

In our laboratory, various diazasteroids have been synthesized from a biological point of view.[1] In this paper, we will describe the synthesis of the 9,13-diazasteroid system, which has never previously been synthesized, starting with quinoline *N*-oxide (QNO) and 1*H*-pyrrole. The reaction of aromatic N-oxides with active methylene compounds in the presence of acylating reagents have been widely studied,[2] but almost no work with heterocyclic compounds appears in the literature.[3] To examine the possibility of synthesizing the 9,13-diazasteroid system, QNO was treated with 1-methyl-1*H*-pyrrole at 70°C overnight in the presence of acetic anhydride to give 2-(1-methyl-2[1*H*]pyrrolyl)quinoline (Ia) in 17.7% yield. In the nuclear magnetic resonance (NMR) spectrum, Ia showed two peaks at δ 6.11 (corresponding to one proton) and 6.70 ppm (two protons) assigned to the C_4-proton and $C_{3,5}$-protons of the pyrrole ring, respectively. 1-Methyl-1*H*-pyrrole exhibits two peaks at δ 6.00 and 6.40 ppm due to the $C_{3,4}$- and $C_{2,5}$-protons, respectively. The characteristic chemical shifts of the pyrrole ring protons in Ia can be explained in terms of the electron-withdrawing effect of quinoline ring. 1-Methyl-2[1*H*]-pyrrolecarbonitrile also exhibits similar behaviour in the NMR spectrum.[4] When benzoyl chloride was used as an acylating reagent instead of acetic anhydride,[3] Ia could not be isolated in a pure state owing to contamination with 2-benzoylquinoline. Ia was also obtained in 19.4% yield from the reaction of QNO and 2-lithio-1-methyl-1*H*-pyrrole



Ia: R=CH_3
Ib: R=H
Ic: R=CH_2-CH_2-OTs



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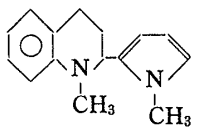

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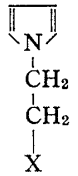
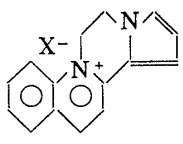


IV

IVa: X=OAc
IVb: X=Cl

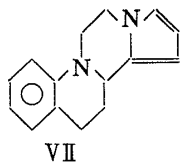
Cl-CH_2-CH_2-OTs

V



VI

VIa: X=OTs
VIb: X=I
VIc: X=Cl
VId: X=ClO_4



VII

Chart 1

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in ethyl ether and tetramethyl ethylenediamine (TMEDA). When QNO was treated with 1*H*-pyrrole in acetic anhydride, an exothermic reaction occurred and 2-(2-[1*H*]-pyrrolyl)-quinoline (Ib) was obtained in 37.4% yield. Ib also exhibited the chemical shifts of pyrrole ring protons like Ia in the NMR spectrum.

As a model experiment for synthesis of the 9,13-diazasteroid system, the reduction of 1-methyl-2-(1-methyl-2[1*H*]-pyrrolyl)quinolinium iodide (II) prepared from Ia was carried out. II was treated with sodium borohydride in ethanol to give the corresponding tetrahydro derivative, 1-methyl-2-(1-methyl-2[1*H*]-pyrrolyl)-1,2,3,4-tetrahydroquinoline (III) in good yield. Therefore, if the two carbon chain extension from the nitrogen atom of the pyrrole ring, and quaternization of the nitrogen atom of the quinoline ring with the chain are possible in Ib, the 9.13-diazasteroid system should be easily constructed. For this purpose, the condensation reaction of 1-(2-acetoxyethyl)-1*H*-pyrrole (IVa) and QNO was examined first. However, the trials using acetic anhydride or *n*-butyl lithium were unsuccessful, possibly due to the poor nucleophilicity of IVa compared with 1*H*-pyrrole or 1-methyl-1*H*-pyrrole. Thus the authors had to examine *N*-2-functionalized-ethylation of the pyrrole ring in Ib.

Jones *et al.*[5] reported a preparation of 1-(3-chloropropyl)-1*H*-pyrrole using sodium hydride and 3-chloropropyl tosylate in dimethoxyethane (DME). Our attempt to obtain 1-(2-chloroethyl)-1*H*-pyrrole (IVb) from 1*H*-pyrrole and 2-chloroethyl tosylate (V) using this method was unsuccessful. An attempt to extend a two-carbon unit from the nitrogen of the pyrrole ring in Ib under the same conditions was also unsuccessful. Then, Kikugawa[6] reported *N*-alkylation of imidazole using powdered potassium hydroxide in accetone. Using this method, we could convert Ib to Ia with methyl iodide in 71% yield. In a similar manner, Ib could be transformed to 2-[1-(2-tosyloxyethyl)-2[1*H*]-pyrrolyl]quinoline (Ic) with V. Ic was soluble in benzene and changed gradually to a quaternary salt, VIa, which was scarecely soluble in chloroform and was not developed by chloroform in thin layer chromatography (TLC); however, the spot located at the origin exhibited strong fluorescence under Manaslu light (366 nm). When Ic was developed with chloroform in TLC, a spot (*Rf* 0.8) also fluoresced under UV light. The fluorescence was suggested to be attributable to the cyclization of Ic.

The conversion of Ic to VIa was detected by TLC and in the NMR spectrum. In the NMR spectrum of the crude VIa measured in deuteriochloroform, a pair of multiplets centered at δ 4.0 and 4.9 ppm changed gradually to a pair centered at δ 4.68 and 5.18 ppm due to two methylene protons. VIa could not be recrystallized and therefore it was converted to the iodide (VIb) with sodium iodide. The microanalysis supported this structure. To examine biological activity, VIb was converted to the corresponding chloride (VIc) with silver chloride. Both VIb and VIc were hygroscopic, but the corresponding perchlorate (VId) was not.

Next, VIa was reduced with sodium borohydride in methanol to give tetrahydro derivative, 9,13-diazagona-1,3,5(10),14,16-pentaene (VII), which was unfortunately unstable and did not exhibit a definite Bohlmann band in the IR spectrum. The NMR spectrum showed signals at δ 5.85, 6.00, and 6.40 ppm due to β-, β-, and α-proton of the pyrrole ring, respectively. The high field shift of the signal due to the $\alpha(C_2)$-proton was attributed to the cleavage of a conjugation with the quinoline ring. The structure of this unstable tetrahydro derivative, VII, was proved as its picrolonate. The mass spectrum of the picrolonate exhibited two characteristic strong peaks at *m/e* 224 and 223 corresponding to M^+ and M^+-1, respectively, and the signals due to picrolonic acid (mol. wt.: 264) were negligible. The elemental analysis was consistent with the expected formula of this compound.

Biological screening tests for VIc are being carried out.

Experimental

All the melting points were determined on a Yanagimoto micro-melting point apparatus (a hot stage type) and are uncorretced. Silica gel (Wako C-200) and pre-coated TLC plates (Merck silica gel $60F_{254}$)

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were used for column chromatography and TLC, respectively. Gas liquid chromatography (GLC) was carried out with 5% SE-30 (stainless steel column, 3 mm × 2 m) as the liquid phase at an N_2 flow rate of 40 ml/min on a Shimadzu GC-6AM machine (FID detector). IR spectra were determined by using a JASCO IRA-1 diffraction grating spectrophotometer; absorption data are given in cm^{-1}. NMR spectra were recorded on a JEOL C-60H spectrometer with 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 a JEOL TMS-01SG (70 eV, direct inlet system) spectrometer. UV spectra were obtained in ethanol with a Hitachi 200-10 spectrophotometer, and absorption maxima are given in nm. All solvents were removed by evaporation under reduced pressure.

2-(1-Methyl-2[1*H*]-pyrrolyl)quinoline (Ia)——1) 1-Methyl-1*H*-pyrrole (2.2 g, 23 mmol) was added to a mixture of freshly distilled quinoline *N*-oxide (QNO, 3 g, 21 mmol) and Ac_2O (2.6 g, 25 mmol) at room temperature during 5 min. The solution was warmed at 70°C for 14h and checked periodically by GLC. The resulting mixture was poured into 10% NaOH-ice water and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The residue obtained after removal of the solvent was purified by column chromatography. Ia was eluted with benzene and recrystallized from aq. EtOH. mp 58—60°C. GLC (200°C): 12.6 min, (250°C): 10.2 min. The yield was 0.76 g (17.7%). MS, *m/e* (%): 208 (M^+, 57), 207 M^+-1, 100). IR (Nujol): $\nu_{C=C}$ 1605, δ_{CH} 720, 755, 825. UV, λ_{max}: 350, 215. NMR (CCl_4): 4.20 (3H, s, >N–CH_3), 6.11 (1H, t, $J=3.0$, C_4–H), 6.70 (2H, d, $J=3.0$, C_3– and C_5–H), 7.2—8.1 (6H, m, quinolyl H). *Anal.* Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.74; H, 5.72; N, 13.19.

2) In the above experiment, benzoyl chloride (2.8 g, 20 mmol) was used instead of Ac_2O. The reaction was carried out at room temperature for 3 h. The residue was purified twice by column chromatography but Ia was not isolated in a crystalline state. The physical data of the crude product (0.46 g) were as follows: NMR (CCl_4): 4.13 (3H, s), 6.1 (1H, t, $J=3.0$), 6.6 (2H, nearly s), 6.9—8.2 (*ca.* 10H, m). MS: strong peaks were consistent with the structure of Ia. In the column chromatography, phenyl 2-quinolyl ketone (0.24 g) was eluted with benzene–AcOEt (9: 1). mp 119—120°C (recrystallized from aq. EtOH, Lit.[7] mp 111—112°C). IR (Nujol): $\nu_{C=O}$ 1690, δ_{CH} 700. NMR (CCl_4): 7.2—7.8 (6H, m), 8.0—8.4 (5H, m).

3)[8] *n*-BuLi (1.6 N in *n*-hexane, 100 ml, 160 mmol) was added dropwise to an ethereal solution of 1-methyl-1*H*-pyrrole (8.1 g, 84 mmol) and TMEDA (14.0 g, 121 mmol) with stirring at room temperature under an Ar atmosphere. The color of the solution changed from pale yellow to brown *via* purple. After the mixture had been refluxed for 2 h, QNO (11.6 g, 80 mmol) in Et_2O was added dropwise with ice-cooling. The ethereal mixture was stirred at room temperature for 1 h then washed with brine. The mixture was dried and concentrated, then the yellow solid was filtered off, and the filtrate was purified by column chromatography. The yield of a Ia was 3.2 g (19.4%).

2-(2[1*H*]-Pyrrolyl)quinoline (Ib)——1*H*-Pyrrole (5 g, 75 mmol) was added to a mixture of freshly distilled QNO (8 g, 55 mmol) and Ac_2O (7 g, 69 mmol) at room temperature. The temperature rose to 30°C. The mixture was warmed at 40°C with stirring for 4 h, then poured into ice-water. The aq. solution was extracted with $CHCl_3$ and the organic layer was washed with brine. The residue obtained after concentration of the dried solution was purified by column chromatography. Ib was eluted with benzene and obtained as an orange crystalline substance, which was recrystallized from aq. EtOH to give pure Ib. mp 133—135°C. The yield was 4.0 g (37.4%). IR (Nujol): $\nu_{C=C}$ 1600, δ_{CH} 830, 805, 725. NMR (CCl_4): 6.17 (1H, q, $J=3$, C_4–H), 6.70 (2H, t, $J=3$, C_3– and C_5–H), 6.8—8.2 (6H, m, quinolyl H), 10.38 (1H, br s, >NH). *Anal.* Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.45; H, 5.30; N, 14.27.

1-Methyl-2(1-methyl-2[1*H*]-pyrrolyl)quinolinium Iodide (II)——The crude Ia (1.94 g) in an excess of CH_3I was heated at 70°C in a sealed tube for 12 h to give brown crystals, which were recrystallized from EtOH. 0.95 g. mp 160—161°C. NMR ($CDCl_3$–TFA=1: 1): 3.85 (3H, s, pyrrolyl CH_3), 4.65 (3H, s, quinolyl CH_3), 6.55, 6.90, and 7.20 (each 1H, br s, pyrrolyl H), 7.8—8.6 (5H, m, quinolyl H), 8.93 (1H, d, $J=9$, quinolyl C_4–H). *Anal.* Calcd for $C_{15}H_{15}IN_2$: C, 51.45; H, 4.32; N, 8.00. Found: C, 51.30; H, 4.48; N, 7.49.

1-Methyl-2-(1-methyl-2[1*H*]-pyrrolyl)-1,2,3,4-tetrahydroquinoline (III)——Excess $NaBH_4$ was added portionwise to an ethanolic solution of II (0.95 g, 4.3 mmol). The color of the reaction medium changed from red-brown to pale yellow. The mixture was stirred at room temperature for 1 h, then water was added to obtain a precipitate, which was recrystallized from MeOH. The yield was 0.44 g (72.3%). mp 82—83°C. NMR ($CDCl_3$): 2.0 (2H, m, quinolyl C_4–H), 2.5—2.9 (5H, m, quinolyl CH_3 and C_3–H), 3.45 (3H, s, pyrrolyl CH_3), 4.4 (1H, t, $J=5$, quinolyl C_2–H), 5.7—6.0 (2H, m, pyrrolyl H), 6.3—7.2 (1H, m, pyrrolyl H), 6.3—6.8 and 6.8—7.2 (each 2H, symmetrical m, quinolyl H) *Anal* Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.26; H, 7.77; N, 12.21.

From Ib to Ia——Powdered KOH (0.91 g, 16.3 mmol) was added to a solution of Ib (0.63 g, 3.3 mmol) in Me_2CO. After a few minutes, CH_3I (0.51 g, 3.6 mmol) was added with vigorous stirring. An exothermic reaction occurred. After 10 min, the Me_2CO solution was transferred to a separating funnel containing benzene. The benzene layer was washed with brine and dried. The crystalline compound obtained after removal of the solvent was recrystallized from aq. EtOH. mp 58—60°C. NMR: identical with that of Ia. The yield of Ia was 0.48 g (71.0%).

Reaction of Ib with V——A DME mixture of Ib (1.2 g, 6 mmol) and NaH (0.16 g of 60% dispersed in oil, 6 mmol) was refluxed for 1 h. V (1.6 g, 6 mmol) was added to the above warmed mixture and the solution

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was refluxed for 2.5 h. The residue obtained after removal of solvent was dissolved in 5% HCl and sat. NaI solution was added to the acidic solution to give a precipitate, which was recrystallized from EtOH. mp 180—183°C. MS: identical with Ib. The Beilstein test was positive, so this product was suggested to be Ib-hydroiodide. NMR ($CDCl_3$–TFA): 6.5 (1H, t like), 7.4 (2H, t like), 7.5—8.3 (5H, m), 8.5 (1H, d, $J=9$).

2-[1-(2-Tosyloxyethyl)-2[1*H*]-pyrrolyl]quinoline (Ic) and Quaternary Salts (VIa, b, c, and d)——In a manner similar to that used for the preparation of Ia from Ib, Ic was obtained from Ib (0.3 g, 1.5 mmol), KOH (0.4 g, 7.7 mmol), and V (0.44 g, 1.7 mmol). TLC ($CHCl_3$): *Rf* 0.8 (weak fluorescence under UV light). NMR of the crude Ic: 2.40 (3H, s, $-CH_3$), 4.00 (2H, t like, $O-CH_2$), 4.90 (2H, t like, $>N-CH_2$). Ic changed to the corresponding quaternary salt (VIa) on standing overnight at room temperature. Crude VIa: mp 100—102°C. IR (Nujol): ν 1600, 1560, 1540. UV: λ 417, 288, 218. NMR ($CDCl_3$): 2.24 (3H, s, $-CH_3$), 4.68 (2H, t like, $>N-CH_2$), 5.18 (2H, t like, $>\overset{|}{N^+}-CH_2$). ($CDCl_3$–TFA): 2.33 (3H, s, $-CH_3$), 4.70 (2H, t like, $>N-CH_2$), 5.10 (2H, t like, $>\overset{|}{N^+}-CH_2$), 6.50 (1H, m), 7.23 (2H, m), 7.6—8.4 (5H, m), 8.45 (1H, d, $J=10$).

The aq. alkaline solution was extracted with $CHCl_3$. The residue obtained after concentration of the $CHCl_3$ solution was fractionated by column chromatography to obtain Ib (0.17 g) from a $CHCl_3$ fraction. Sat. NaI solution was added to the crude VIa in 5% HCl to give VIb, 0.18 g. The conversion yield from Ib was quantitative. VIb: mp 282—284°C (dec.), hygroscopic material. IR (Nujol): ν 1600, 1560, 1540. UV: λ_{max} 417, 290, 218. NMR ($CDCl_3$–TFA=1:1): 4.76 (2H, m), 5.16 (2H, m), 6.70 (1H, m), 8.93 (1H, d, $J=10$). MS *m/e*: 221 (M^+, base peak). *Anal.* Calcd for $C_{15}H_{13}IN_2+4/5H_2O$: C, 49.69; H, 4.06; N, 7.73. Fonnd: C, 49.75; H, 3.72; N, 7.75. VIb was mixed well with an excess of AgCl in a mortar and the mixture was extracted several times with EtOH. From the concentrated solution, VIc was precipitated. mp 278—280°C (dec.), hygroscopic material. A methanolic solution of VIa was treated with 60% $HClO_4$ to give a perchlorate, VId. mp 162—164°C. UV λ_{max} (ε): 417 (26400), 290 (16200), 218 (20500). *Anal.* Calcd for $C_{15}H_{13}ClN_2O_4$: C, 56.18; H, 4.09; N, 8.73. Found: C, 56.31; H, 4.14; N, 8.54.

9,13-Diazagona-1,3,5(10),14,16-pentaene (VII)——Excess $NaBH_4$ was added to a methanolic solution of VIa (0.3 g). After being stirred for 2 h at room temperature, the reaction mixture was extracted with benzene. The residue obtained from the benzene layer was unstable. From gross column chromatography, crude VII was obtained as a viscous oil (0.1 g). IR (film): ν 1590, 1570. (CCl_4): ν 1590, 1580. no Bohlmann band. NMR (CCl_4): 2.0—2.5 (2H, m, C_7–H), 2.8 (2H, m, C_6–H), 3.2—3.6 (1H, t like, C_8–H), 3.8 (2H, m, C_{11}–H), 4.1—4.6 (2H, m), 5.85 (1H, d like, C_{15}–H), 6.00 (1H, t, $J=2$, C_{16}–H), 6.40 (1H, nearly s, C_{17}–H).

Picrolonate of VII: mp 160—162°C (recrystallized from EtOH). IR (Nujol): ν 1600, 1580. MS *m/e* (%): 224 (M^+, 58), 223 (M^+-1, 100). *Anal.* Calcd for $C_{25}H_{24}N_6O_5$: C, 61.46; H, 4.95; N, 17.21. Found: C, 61.43; H, 4.98; N, 17.17.

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References and Notes

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