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**Synthesis of 1- and 3-Oxo-dihydro-2H-pyrrolo[3,4-*b*]quinoline
and Their Reaction with Phosphorus Pentasulfide**TSUTOMU SUGASAWA, TATSURO TOYOTA, KAZUYUKI SASAKURA,
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One phase of a research programme toward a quinoline alkaloid required the preparation of 3-thio-dihydro-2H-pyrrolo[3,4-*b*]quinoline (IV). This was obtained from the corresponding 3-oxo compound (III) by treatment with phosphorus pentasulfide in 1% aqueous pyridine at 85°. Compound (III) was readily derived from I²⁾ via the Reissert-compound (II) followed by acid-hydrolysis (Chart 1). The yield of IV was 73%, but a preparative thin-layer chromatographic purification of the mother liquor showed the formation of an isomeric thiolactam (IX) (5%), besides further IV (6%) and starting material (8%). IX was readily obtained from V through a 4-step synthesis (Chart 2), which served as an unambiguous structural proof for IX.

Namely, oximation of V³⁾ with sodium nitrite in acetic acid gave VI, which was directly reduced with zinc-powder in acetic acid and acetic anhydride to furnish VII. Hydrolysis of VII with conc. hydrochloric acid in acetic acid caused a simultaneous decarboxylation and lactam formation to afford VIII. Treatment of VIII with phosphorus pentasulfide in 1% aqueous pyridine at 100° gave IX in 90% yield.

When III was treated with phosphorus pentasulfide in 1% aqueous pyridine at 120° and worked up in the same way, IX was obtained as the major product (73%) beside IV

1) Location: Fukushima-ku, Osaka.

2) T. Kametani and K. Kigasawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 566 (1966).3) Cf. B. Bobranski and E. Sucharda, *C.A.*, **24**, 1381 (1930).

Chart 2

(12%). In this experiment at higher temperature it was clearly observed by thin-layer chromatography (TLC) that IX was formed from initially formed IV during the course of reaction. In fact, when IV was again treated with phosphorus pentasulfide at 85° or when hydrogen sulfide was bubbled at 120° in 1% aqueous pyridine slow transformation of IV to IX was observed by TLC and gas-liquid chromatography (GLC). However the boil of IV in 1% aqueous pyridine without phosphorus pentasulfide or hydrogen sulfide did not give any formation of IX. These observations signify that IX is more stable than IV and that the S-atom at C₃ in IV did not shift directly to C₁ in IX, but rather another molecule of phosphorus or hydrogen sulfide attacked at C₁ in IV, followed by elimination of the S-atom at C₃ to give IX. The reaction-path can be rationalized by assuming an equilibrium including the combination of base catalyzed deprotonation and protonation with addition and elimination of hydrogen sulfide as shown in Chart 3.

Chart 3

Experimental

General Methods—All melting points were determined on Yanagimoto Micromelting Apparatus and uncorrected. Infrared (IR) spectra were recorded by using a Koken DS-201B spectrophotometer and nuclear magnetic resonance (NMR) spectra were taken on a Varian A-60 spectrometer, TMS serving as internal standard. The mass spectra were taken on a Hitachi RMU-6 mass spectrometer.

Reissert Reaction of I—To a stirred suspension of 17.6 g of I (mp 103–105°) (0.088 mole) and 34 g of KCN (0.525 mole) in 160 ml of H₂O, 40 g of C₆H₅COCl was added portionswise over 20 min under ice-cooling and the mixture stirred for a further 2 hr at room temperature. The crystals, which separated were filtered off, washed with H₂O, and dissolved in CHCl₃. The CHCl₃-solution was washed with H₂O and dried. After concentration the residue was recrystallized from MeOH to give 22.1 g of II, (76%), mp 184–186°. *Anal.* Calcd. for C₂₀H₁₆O₅N₂: C, 72.28; H, 4.85; O, 14.44; N, 8.43. Found: C, 72.12; H, 5.00; O, 14.65; N, 8.50. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3470 (NH), 1690–1680 (NCOC₆H₅, NHCOCH₃). NMR (CDCl₃) δ : 2.05 (3H, s, NCOCH₃), 4.2 (2H, d, $J=5$ cps, -CH₂-), 6.15 (1H, s, H $\geq$ C-CN), 7.35 (5H, s, C₆H₅).

Lactam Formation from II to III—To a solution of 3.36 g of II in 70 ml of CHCl₃ and 30 ml abs. dioxane, HCl-gas was introduced under ice-cooling and stirring till the beginning of turbidity appeared. After being kept at 0° overnight the crystals which had separated were filtered off and washed successively with CHCl₃ and ether. The resulting yellow crystals (4.3 g) were dissolved in 50 ml of H₂O and the solution was heated at 120° for 20 min. Benzaldehyde produced was removed by steam-distillation and the non-volatile portion was concentrated to about 100 ml, then refluxed with 2 ml of 2N HCl for 20 hr. The crystals which separated on cooling were collected and washed with H₂O. The crystals were suspended in 10% aq. Na₂CO₃, and the solution was extracted 5 times with CHCl₃-MeOH (5:1). The organic layer was washed with H₂O, dried, and concentrated to give 1.03 g of III. The mother-liquor from the filtration of the refluxed reaction mixture was also treated with 10% aq. Na₂CO₃ and worked up in the same way as above to give a further 0.21 g of III (total yield 66%), mp 277–280° (decomp.). *Anal.* Calcd. for C₁₁H₈ON₂: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.80; H, 4.47; N, 15.17. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3207, 3096 (NH), 1695 (NCO). NMR (d_7 -DMF) δ : 4.69 (2H, broad-s, -CH₂-NH).

Thiolactam Formation from III to IV—A mixture of 100 mg of III (0.55 mmole) and 360 mg of P₂S₅ (1.62 mmole) in 1% aq. pyridine was warmed at 85° (bath-temperature) for 1 1/4 hr under stirring. After being cooled the reaction-mixture was poured in ice-water and extracted with CHCl₃-MeOH (3:1). The organic-layer was washed with H₂O, dried, and concentrated to give 80 mg of IV, mp 220–225° (decomp.). The mother-liquor was purified by preparative TLC (Silica gel GF, solvent-system CHCl₃: CH₃COCH₃=5:1) to give a further 6 mg of IV (total yield 79%) (R_f : 0.26), 5 mg of IX (5%) (R_f : 0.17) and 8 mg of starting material (R_f : 0.05). GLC Shimadzu GC-1C (FID) 1% OV₁ on gas chrom Q 100–120° mesh 75 $\times$ 4 mm ϕ glass-column. col-temp. 227° inj-temp. 300° det-temp. 250° carrier gas N₂ 1.05 kg/cm² R_t : 3 min for IV 1.3 min for IX. *Anal.* Calcd. for C₁₁H₈N₂S: C, 66.06; H, 4.03; N, 14.01; S, 16.03. Found: C, 66.23; H, 3.88; N, 14.27; S, 16.12. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3110 (NH), 1540, 1530 (C=S). NMR (d_7 -DMF) δ : 5.08 (2H, broad-s, -CH₂N), 11.3 (1H, broad, NH), Mass Spectrum m/e : 200 (M⁺).

Thiolactam Formation of III to IX—A mixture of 100 mg of III (0.55 mmole) and 240 mg of P₂S₅ (1.1 mmole) in 4 ml of 1% aq. pyridine was warmed at 120° (bath-temperature) for 2 hr under stirring. Analogous work-up followed with purification in TLC as above gave 80 mg of IX, mp 245–249° (decomp.) (total yield 73%) and 13 mg of IV (12%). *Anal.* Calcd. for C₁₁H₈N₂S: C, 66.06; H, 4.03; N, 14.01; S, 16.03. Found: C, 65.87; H, 3.90; N, 14.05; S, 16.10. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3123 (NH), 1528 (C=S). NMR (d_7 -DMF) δ : 4.91 (2H, s, -CH₂N), 11.1 (1H, broad, NH), Mass Spectrum m/e : 200 (M⁺).

Oximation of V to VI—To 1 g of V (mp 89–91°) (3.86 mmole) in 7 ml AcOH, 294 mg NaNO₂ (3.86 $\times$ 1.1 mmole) in 5 ml AcOH was added dropwise at room temperature under stirring. After stirring for a further 30 min the crystals which had separated were filtered off, washed with H₂O, dried, and recrystallized from CH₂Cl₂-MeOH to give 942 mg of VI, mp 185–187° (85%). *Anal.* Calcd. for C₁₄H₁₅O₅N₂: C, 58.33; H, 4.20; O, 27.75; N, 9.72. Found: C, 58.45; H, 4.25; O, 27.02; N, 9.50. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 2800–2400 (OH), 1754, 1724 (COOCH₃). NMR (d_6 -DMSO) δ : 3.77 (3H, s, COOCH₃), 3.85 (3H, s, COOCH₃).

Reduction of VI to VII—To a stirred solution of 2.78 g of VI in 140 ml AcOH and 10 ml Ac₂O, 3.3 g of zinc-powder was added at 30–45° (internal-temperature) and the mixture was stirred for 30 min. The precipitate was filtered off and washed with CHCl₃. The combined filtrate was concentrated at reduced pressure and the residue was recrystallized from CHCl₃-MeOH to give 2.29 g of VII, mp 193–194°. The mother-liquor was purified by column-chromatography (10 g Al₂O₃ Merck standardized). Benzene-elution gave a further 0.16 g of VII (total yield 80%). *Anal.* Calcd. for C₁₆H₁₆O₅N₂: C, 60.75; H, 5.10; O, 25.29; N, 8.86. Found: C, 59.95; H, 4.93; O, 25.13; N, 8.71. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3380 (NH), 1769, 1743, 1723 (COOCH₃), 1678 (NHAc). NMR (CDCl₃) δ : 2.12 (3H, s, N-Ac), 3.68 (3H, s, COOCH₃), 4.02 (3H, s, COOCH₃), 6.96 (1H, d, Ac-N-CH, $J=8.1$ cps).

Lactam Formation of VII to VIII—A solution of 2.25 g of VII in 12 ml AcOH and 3 ml conc. HCl was refluxed for 2.5 hr. After concentration of the solution at reduced pressure, the residue was treated with 10% K₂CO₃ and the crystals which separated were filtered off and washed. The combined filtrate was extracted with CHCl₃-MeOH (3:1), and the organic layer washed with H₂O, dried, and evaporated. The residue and the collected crystals were recrystallized from CHCl₃-MeOH to give 932 mg of VIII, mp 271–275° (decomp.). An analytically pure sample melts (decomp.) at 275–277°. *Anal.* Calcd. for C₁₁H₈ON₂: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.44; H, 4.57; N, 15.24. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3185, 3190 (NH), 1723, 1705 (N-C=O). NMR (d_6 -DMSO) δ : 4.67 (2H, s, CH₂).

Thiolactam Formation of VIII to IX—A mixture of 200 mg of VIII (1.1 mmole) and 360 mg of P_2S_5 (1.62 mmole) in 8 ml of 1% aq. pyridine was warmed at 100° (bath-temperature) under stirring for 1 hr, then after addition of a further 200 mg of P_2S_5 (0.9 mmole) for another 2 hr. After being cooled, the reaction-mixture was poured in ice-water and extracted with $CHCl_3$ -MeOH (3:1). The organic-layer was washed, dried, and evaporated. The residue was dissolved in CH_3COCH_3 , decolorized with active-charcoal, and concentrated to give 206 mg of IX (94%).

Conversion of IV to IX—a) A mixture of 50 mg of IV and 55 mg of P_2S_5 in 2 ml of 1% aq. pyridine was warmed at 85° for 1.5 hr under stirring. After cooling the mixture, the precipitate was filtered off and the filtrate was extracted with $CHCl_3$ -MeOH (3:1). The organic-layer was washed, dried, and concentrated at reduced pressure. The residue was purified by preparative TLC, (Silica gel GF, solvent-system $CHCl_3$ - CH_3COCH_3 (5:1)) to give 14 mg of IV and 10 mg of IX.

b) Hydrogen sulfide was passed into a solution of 30 mg of IV in 1% aq. pyridine heated at 120° for 1 hr under stirring. Solvent was evaporated at reduced pressure and the residue was purified in the same manner as in a) to give 14 mg of IV and 7 mg of IX.

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Synthesis of a Heterocyclic Ring Steroid¹⁾ Rearrangements of C-nor-steroid

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The preparation of steroids containing nitrogen in the ring system has been reported by several workers, but reports concerning the synthesis of 12-aza-^{3,4)} and 11-aza-steroid^{5,6)} are limited.

Hecogenin (I) is a readily available substance for the preparation of steroids modified in ring C and such a modification could be the introduction of nitrogen into C-12 or C-11 position in ring C. Hecogenin (I) had been converted into the C-nor-steroid^{7,8)} and Beckmann rearrangement of the oxime of the C-nor-steroid produced rearrangement products. $3\beta,20$ -Diacetoxy- 5α -pregnan-12-one (IX) was selected as the starting material for C-nor-steroid in consideration of the modification of azasteroids.

Bismuth trioxide⁹⁾ was chosen for the oxidation of 11,12-ketol group in $3\beta,12\beta,20$ -trihydroxy- 5α -pregnan-11-one (X) and by its use, a mixture of compounds with C-3 or C-20 hydroxyl groups acetylated were obtained. Since the following step includes alkaline treatment of the mixture, the next reaction was carried out without separation of the acetates.

- 1) A part of this work was presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
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