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Synthesis of 1- and 3-Oxo-dihydro-2H-pyrrolo[3,4-*b*]quinoline and Their Reaction with Phosphorus Pentasulfide

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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 I[2] *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.

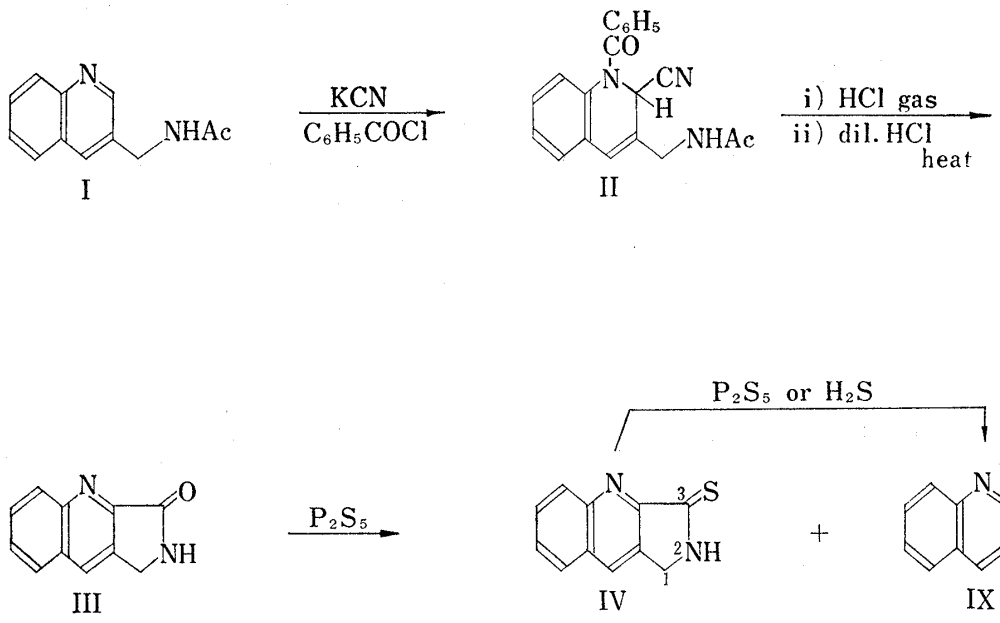

Chart 1

Namely, oximation of V[3] 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.*
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3) Cf. B. Bobranski and E. Sucharda, *C.A.*, **24**, 1381 (1930).

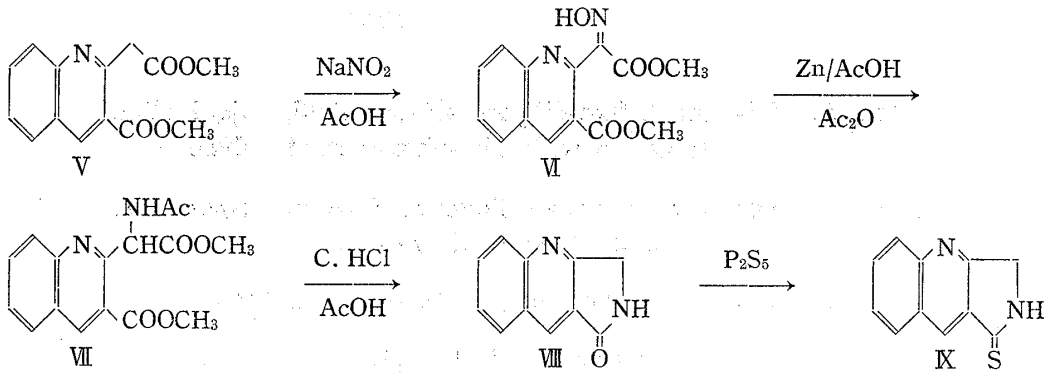

Chart 2

(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 C_3 in IV did not shift directly to C_1 in IX, but rather another molecule of phosphorus or hydrogen sulfide attacked at C_1 in IV, followed by elimination of the S-atom at C_3 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.

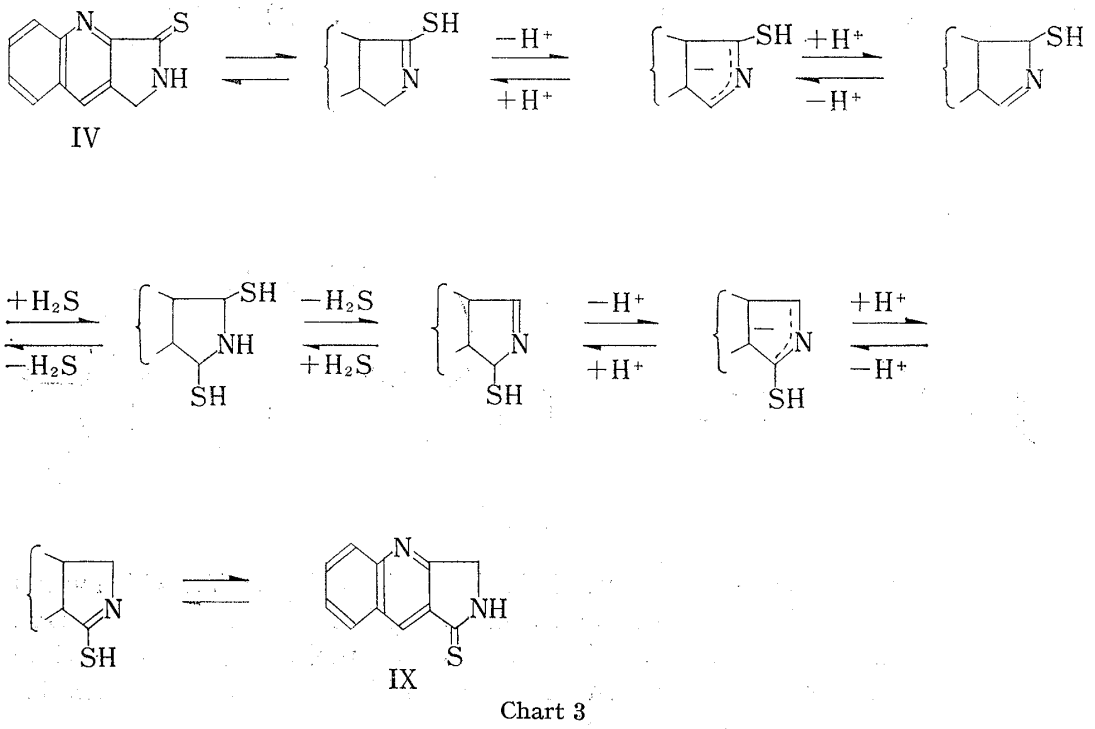

Chart 3

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 H_2O, 40 g of C_6H_5COCl was added portionsweise 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 H_2O, and dissolved in $CHCl_3$. The $CHCl_3$-solution was washed with H_2O and dried. After concentration the residue was recrystallized from MeOH to give 22.1 g of II, (76%), mp 184—186°. *Anal.* Calcd. for $C_{20}H_{16}O_3N_2$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1690—1680 ($NCOC_6H_5$, $NHCOCH_3$). NMR ($CDCl_3$) δ: 2.05 (3H, s, $NCOCH_3$), 4.2 (2H, d, J=5 cps, $-CH_2-$), 6.15 (1H, s, H$\gg$C-CN), 7.35 (5H, s, C_6H_5).

Lactam Formation from II to III——To a solution of 3.36 g of II in 70 ml of $CHCl_3$ and 30 ml abs. dioxane, HCl-gas was introduced under ice-cooling and stirring till the biginning of turbidity appeared. After being kept at 0° overnight the crystals which had separated were filtered off and washed successively with $CHCl_3$ and ether. The resulting yellow crystals (4.3 g) were dissolved in 50 ml of H_2O and the solution was heated at 120° for 20 min. Benzaldehyde produced was removed by steam-destillation 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 H_2O. The crystals were suspended in 10% aq. Na_2CO_3, and the solution was extracted 5 times with $CHCl_3$-MeOH (5:1). The organic layer was washed with H_2O, 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. Na_2CO_3 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 $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.80; H, 4.47; N, 15.17. IR ν_{max}^{Nujol} cm^{-1}: 3207, 3096 (NH), 1695 (NCO). NMR (d_7-DMF) δ: 4.69 (2H, broad-s, $-CH_2-NH$).

Thiolactam Formation from III to IV——A mixture of 100 mg of III (0.55 mmole) and 360 mg of P_2S_5 (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 $CHCl_3$-MeOH (3:1). The organic-layer was washed with H_2O, 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 $CHCl_3$: CH_3COCH_3=5:1) to give a further 6 mg of IV (total yield 79%) (*Rf*: 0.26), 5 mg of IX (5%) (*Rf*: 0.17) and 8 mg of starting material (*Rf* 0.05). GLC Shimadzu GC-1C (FID) 1% OV_1 on gas chrom Q 100—120° mesh 75×4 mm ϕ glass-column. col-temp. 227° inj-temp. 300° det-temp. 250° carrier gas N_2 1.05 kg/cm² *Rt.* 3 min for IV 1.3 min for IX. *Anal.* Calcd. for $C_{11}H_8N_2S$: 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 ν_{max}^{Nujol} cm^{-1}: 3110 (NH), 1540, 1530 (C=S). NMR (d_7-DMF) δ: 5.08 (2H, broad-s, $-CH_2N$), 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 P_2S_5 (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 $C_{11}H_8N_2S$: 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 ν_{max}^{Nujol} cm^{-1}: 3123 (NH), 1528 (C=S). NMR (d_7-DMF) δ: 4.91 (2H, s, $-CH_2N$), 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 $NaNO_2$ (3.86 ×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 H_2O, dried, and recrystallized from CH_2Cl_2-MeOH to give 942 mg of VI, mp 185—187° (85%). *Anal.* Calcd. for $C_{14}H_{15}O_5N_2$: 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 ν_{max}^{Nujol} cm^{-1}: 2800—2400 (OH), 1754, 1724 ($COOCH_3$). NMR (d_6-DMSO) δ: 3.77 (3H, s, $COOCH_3$), 3.85 (3H, s, $COOCH_3$).

Reduction of VI to VII——To a stirred solution of 2.78 g of VI in 140 ml AcOH and 10 ml Ac_2O, 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 $CHCl_3$. The combined filtrate was concentrated at reduced pressure and the residue was recrystallized from $CHCl_3$-MeOH to give 2.29 g of VII, mp 193—194°. The mother-liquor was purified by column-chromatography (10 g Al_2O_3 Merck standardized). Benzene-elution gave a further 0.16 g of VII (total yield 80%). *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$: 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 ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1769, 1743, 1723 ($COOCH_3$), 1678 (NHAc). NMR ($CDCl_3$) δ: 2.12 (3H, s, N-Ac), 3.68 (3H, s, $COOCH_3$), 4.02 (3H, s, $COOCH_3$), 6.96 (1H, d, Ac-N-C$\underline{H}$, 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% K_2CO_3 and the crystals which separated were filtered off and washed. The combined filtrate was extracted with $CHCl_3$-MeOH (3:1), and the organic layer washed with H_2O, dried, and evaporated. The residue and the collected crystals were recrystallized from $CHCl_3$-MeOH to give 932 mg of VIII, mp 271—275° (decomp.). An analitically pure sample melts (decomp.) at 275—277°. *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.44; H, 4.57; N, 15.24. IR ν_{max}^{Nujol} cm^{-1}: 3185, 3190 (NH), 1723, 1705 (N-C=O). NMR (d_6-DMSO) δ: 4.67 (2H, s, CH_2).

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 Steroid[1] 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. 3β,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 trioxide[9] was chosen for the oxidation of 11,12-ketol group in 3β,12β,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.

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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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