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Studies on the Syntheses of Heterocyclic Compounds. CDLII.[1] An Alternative Total Synthesis of Corydalactam

Tetsuji Kametani and Masataka Ihara

Pharmaceutical Institute, Tohoku University[2]

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Condenzation of 1-*p*-toluenesulfonylaziridine (V) with ethyl acetoacetate, followed by a ketalization of the resulting pyrrolidone (X), gave the ketal (XI), which was cleaved with sodium in liquid ammonia to give 3-acetyl-2-pyrrolidone ethylene ketal (II). Since this compound (II) had already been led to corydalactam (I), an alternative synthesis of corydalactam has been accomplished.

Corydalactam (I), isolated from *Corydalis pallida* var. *tenuis* (Yatabe),[3] had already been synthesized by Cummings and his co-workers,[4] and by us.[5] We had synthesized corydalactam in three steps, II→III→IV→I, from 3-acetyl-2-pyrrolidone ethylene ketal (II) prepared by two different methods. In this case, the ethylene ketal (II) was synthesized more easily by the utilization of an activated aziridine, and it was further found that potassium bisulfate is useful for dehydration of the carbinol (IV). Herein we wish to report these results.

Kojima and Kawakita[6] reported that the reaction of 1-*p*-toluenesulfonylaziridine (V) with ethyl malonate in the presence of sodium ethoxide gave 3-ethoxycarbonyl-1-*p*-toluenesulfonylpyrrolidone (VI). When the activated aziridine (V) was refluxed with ethyl acetoacetate (VII) in the presence of sodium ethoxide in ethanol, an unknown compound which had no acetyl group was obtained. Reaction of V with VII in the presence of sodium ethoxide at room temperature gave ethyl α-acetyl-N-*p*-toluenesulfonyl-γ-aminobutyrate (VIII), the structure of which was supported by infrared (IR) and nuclear magnetic resonance (NMR) spectra. Heating of the ester (VIII) at 200° afforded 3-ethoxycarbonyl-4,5-dihydro-2-methyl-1-*p*-toluenesulfonylpyrrole (IX), whose IR spectrum showed a conjugated ester at 1670 and 1628 cm^{-1}; NMR spectrum revealed an ethyl ester at 1.23 and 4.10 ppm; and mass spectrum a molecular ion peak at *m/e* 309. On the other hand, heating of V with VII in the presence of sodium hydride in benzene gave 3-acetyl-1-*p*-toluenesulfonyl-2-pyrrolidone (X) in fairly good yield. On the basis of spectral data the structure of X was confirmed. Ketalization of the pyrrolidone (X) with ethylene glycol in the presence of *p*-toluenesulfonic acid gave a ketal (XI). Treatment of the ketal (XI) with metallic sodium in liquid ammonia according to Milne and Peng's method[7] gave 3-acetyl-2-pyrrolidone ethylene ketal (II), the IR and NMR spectra of which were superimposable on those of the authentic sample.[5]

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7) H.B. Milne and C.H. Peng, *J. Am. Chem. Soc.*, **79**, 309 (1957).

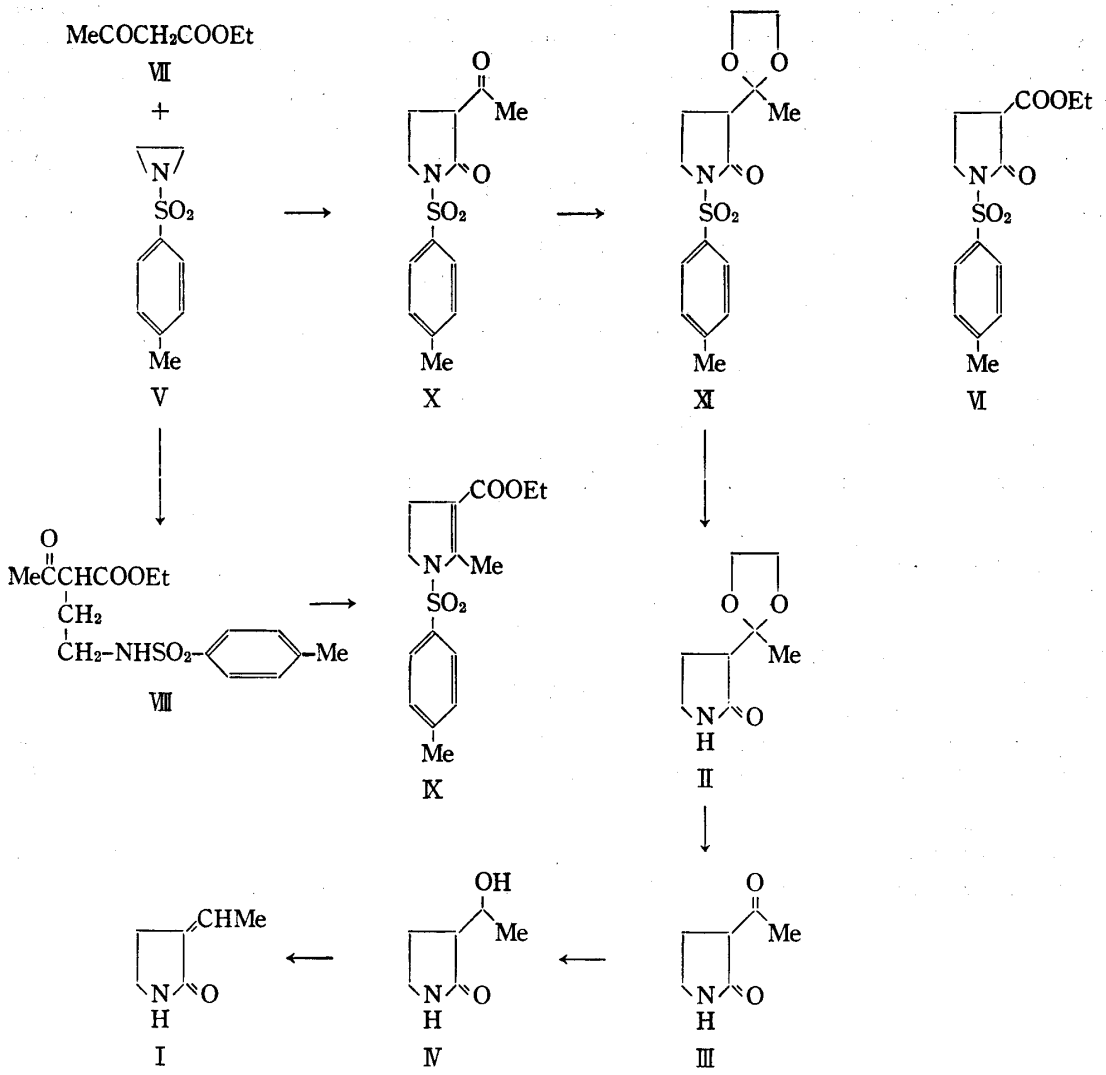

Chart 1

Experimental[8]

3-Ethoxycarbonyl-4,5-dihydro-2-methyl-1-*p*-toluenesulfonylpyrrole (IX)——To a solution of 3.28 g of ethyl acetoacetate (VII) and 0.58 g of Na in 40 ml of ab. EtOH was added, little by little, 5 g of *p*-toluenesulfonylaziridine at 0° with stirring. A mixture was stirred at room temperature for 24 hr, acidified with AcOH, evaporated, and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give a syrup, which was chromatographed on silica gel. Evaporation of chloroform eluate gave 5.2 g (63%) of ethyl α-acetyl-N-*p*-toluenesulfonyl-γ-aminobutyrate (VIII) as a colorless syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 and 1710 (C=O), 1332 and 1156 (SO_2); NMR δ(in $CDCl_3$): 1.24 (3H, t, J=7 Hz, OCH_2CH_3), 2.23 (3H, s, $C_6H_4CH_3$), 2.40 (3H, s, $COCH_3$), 3.65 (1H, t, J=7 Hz, α-H), 4.12 (2H, q, J=7 Hz, OCH_2CH_3), 5.15 (1H, broad t, J=6.5 Hz, NH), 7.20 and 7.64 (each 2H, each d, each J=8 Hz, ArH). Without further purification, 4 g of this material (VIII) was heated at 200° for 30 min to give a powder, which was recrystallized from MeOH to afford 3.55 g (95%) of IX as colorless prisms, mp IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 and 1628 (C=C-CO), 1357 and 1159 (SO_2); NMR δ (in $CDCl_3$) 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 2.43 and 2.46 (each 3H, each s, $C_6H_4CH_3$ and/or 2-CH_3), 4.10 (2H, q, J=7 Hz, OCH_2CH_3), 7.25 and 7.65 (each 2H, each d, each J=8 Hz, ArH); Mass Spectrum (*m/e*): 309 (M^+), 280 (M^+-Et), 264 (M^+-OEt). *Anal.* Calcd. for $C_{15}H_{19}O_4NS$: C, 58.30; H, 6.20; N, 4.53. Found: C, 58.33; H, 6.16; N, 5.11.

8) Infrared spectra were measured on a type EPI-3 recording spectrometer and nuclear magnetic resonance spectra were taken with a Hitachi R-20 for solution in deuteriochloroform with tetramethylsilane as internal standard. Mass spectrum was measured with a Hitachi RMU-7 spectrometer. Melting points were uncorrected.

3-Acetyl-1-*p*-toluenesulfonyl-2-pyrrolidone (X)——To a suspension of 11 g of 50% NaH in 500 ml of benzene was added dropwise with stirring 31 g of ethyl acetoacetate (VIII). After 10 min, to the resulting solution was added 48 g of 1-*p*-toluenesulfonylaziridine (V) in 200 ml of benzene with stirring at room temperature, and the mixture was then refluxed with stirring for 30 hr. After cooling, the reaction mixture was decomposed with H_2O, and acidified with AcOH. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give a syrup, which was recrystallized from MeOH to afford 48 g (71%) of X as chlorless scales, mp 65—67°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (sh) and 1713 (C=O), 1361 and 1158 (SO_2); NMR δ (in $CDCl_3$): 2.28 (3H, s, $COCH_3$), 2.43 (3H, s, $C_6H_4CH_3$), 7.27 and 7.82 (each 2H, each d, each J=8 Hz, ArH). *Anal.* Calcd. for $C_{13}H_{15}O_4NS$: C, 55.50; H, 5.38; N, 4.99. Found: C, 55.32; H, 5.27; N, 5.11.

3-Acetyl-1-*p*-toluenesulfonyl-2-pyrrolidone Ethylene Ketal (XI)——A mixture of 45 g of 3-acetyl-1-*p*-toluenesulfonyl-2-pyrrolidone (X), 23 g of ethylene glycol, 0.9 g of *p*-TsOH and 300 ml of benzene was refluxed in a system containing a water separator for 4 hr. The reaction mixture was cooled, made alkaline with $NaHCO_3$ aq. solution, and shaken. The organic layer was washed with sat. NaCl solution, dried over Na_2SO_4 and evaporated to give a syrup, which was recrystallized from MeOH to give 44 g (85%) of XI as colorless prisms, mp 145—146°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (C=O), 1362 and 1158 (SO_2): NMR δ(in $CDCl_3$): 1.22 (3H, s, CH_3), 2.40 (3H, s, $C_6H_4CH_3$), 3.81 (4H, s, OCH_2CH_2O), 7.20 and 7.81 (each 2H, each s, each J=8 Hz, ArH). *Anal.* Calcd. for $C_{15}H_{19}O_5NS$: C, 55.55; H, 5.60; N, 4.32. Found: C, 55.88; H, 5.49; N, 4.34.

3-Acetyl-2-pyrrolidone Ethylene Ketal (II)——To a mixture of 40 g of the above ethylene ketal (XI), 70 ml of THF and 2 l of liq. NH_3 were added slowly small pieces of metallic Na with stirring until a blue color persisted for 2 or 3 min. After evaporation of NH_3, sat. NH_4Cl solution was added to the residue. Extraction with $CHCl_3$ was washed with sat. NaCl solution, dried over Na_2SO_4 and evaporated to give a powder, which was recrystallized from MeOH–ether to afford 15 g (72%) of II as colorless leaflets, mp 125—126° (lit.,[5] mp 125—126°).

Corydalactam (I)——A mixture of 2.5 g of an epimeric mixture of 3-(1-hydroxyethyl)-2-pyrrolidone (IV) and 2.5 g of fused $KHSO_4$ was heated at 200° for 30 min. After cooling, the mixture was extracted with $CHCl_3$, washed with sat. NaCl solution, dried over Na_2SO_4, and evaporated to afford a syrup. Recrystallization from AcOEt gave 1.6 g (75%) of corydalactam (I) as colorless needles, mp 172—174° (lit.[3] 172—174°).

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