SYNTHESIS OF 5-HYDROXY-3-METHYL-3-PYRROLIN-2-ONE [(±)-JATROPHAM, AN ANTITUMOR ALKALOID] AND ITS 4-METHYL ISOMER

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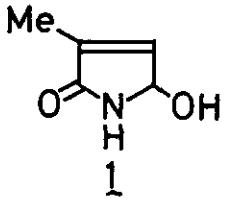
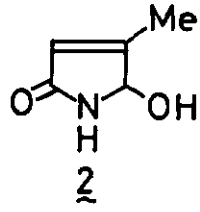
Abstract --- 5-Hydroxy-3-methyl-3-pyrrolin-2-one (1), which is known as jatropham; an antitumor alkaloid, is conveniently synthesized from succinimide. One step synthesis of 5-hydroxy-4-methyl-3-pyrrolin-2-one (2) by the regioselective reduction of methylmaleimide with $NaBH_4/H^+$ is also described.

In the course of study on the chemistry of 2-pyrrolidinones[1], we have been interested in the structure of jatropham, an antitumor alkaloid isolated from Jatropha macrorhiza [Euphorbiaceae], which was presented as 5-hydroxy-4-methyl-3-pyrrolin-2-one (2) by Cole et al.[2] in 1973 and recently revised to its isomer, 5-hydroxy-3-methyl-3-pyrrolin-2-one (1) by Furukawa et al.[3]. In this recent journal[4], Furukawa et al. reported the synthesis of 1 and 2 utilizing an autoxidation of 2-furylcarbamates. In this paper we wish to describe our alternative synthesis of 1 and 2, that is, a convenient route to (±)-jatropham (1) from succinimide (3) and one step synthesis of 2 by a regioselective reduction of methylmaleimide (16).



1

As appropriate modifications of succinimides seemed to be most suitable to prepare 1 and 2, the synthesis of derivatives functionalized at 2-position of succinimide (3) was examined. Lithiation of 1-trimethylsilylsuccinimide (4) and O-ethylsuccinimide (6), which are protected on the NH group and the one carbonyl group of 3, respectively, and easily prepared by the reaction of Ag salt of 3 with trimethylsilyl chloride[5] and ethyl iodide[6], respectively, was attempted but unsuccessful. The reaction of 5-ethoxy-



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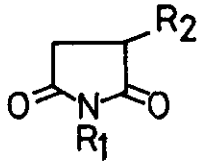
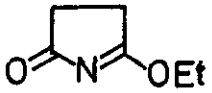
2-pyrrolidinone (7), prepared from 3 by the Speckamp's method[7], with 2.2 equiv of lithium diisopropylamide (LDA) in THF at -78° followed by the reaction of 1.2 equiv of benzophenone afforded no adduct but a reduced product, benzhydrol in 69 % yield. In the meantime it was found that 5-ethoxy-1-trimethylsilyl-2-pyrrolidinone (8), prepared quantitatively by refluxing 7 in hexamethyldisilazane, is a suitable reactant to the lithiation with LDA in THF[8]. The reaction of 8 with *LDA (2.2 eq) in THF followed by selenylation with diphenyl diselenide* (1 eq), successive methylation with methyl iodide (2 eq), and the usual work-up afforded an isomeric mixture of selenide (9) in 94% yield and by-product (10) in 3.7% yield. The conversion of 9 (mixture) to 3-methyl-3-pyrrolin-2-one (13) proceeded on treating selenide (9) with an excess of 30% aqueous hydrogen peroxide (88% yield) or m-chloroperbenzoic acid (68% yield) in THF. α-Methylene compound (14), a double bond isomer of 13, was not detected at all in this reaction[9]. The hydrolysis of 13 to (±)-jatropham (1) was examined under several conditions. Better result was achieved by warming 13 in aqueous acetic acid (1:1) solution at



3: $R_1=R_2=H$
4: $R_1=SiMe_3, R_2=H$
5: $R_1=H, R_2=Me$



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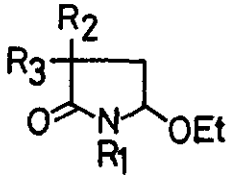
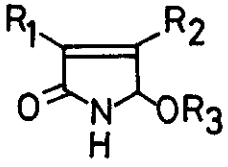
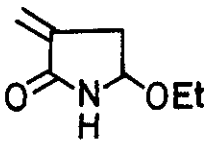


7: $R_1=R_2=R_3=H$
8: $R_1=SiMe_3, R_2=R_3=H$
9: $R_1=H, R_2=Me, R_3=PhSe$
10: $R_1=H, R_2=R_3=Me$



11: $R_1=R_2=R_3=H$
12: $R_1=R_2=H, R_3=Et$
13: $R_1=Me, R_2=H, R_3=Et$
17: $R_1=H, R_2=Me, R_3=Et$



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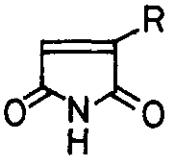

15: R = H
16: R = Me

60°. In this way (±)-jatropham (1) was formed quantitatively as a sole product[10]. For the synthesis of 5-hydroxy-3-pyrrolin-2-ones (2 and 11), the $NaBH_4/H^+$ reduction of maleimides (15 and 16) was examined, since Speckamp reported that the $NaBH_4/H^+$ reduction of succinimides in EtOH affords 5-hydroxy-2-pyrrolidinones *via* "Base work-up" and 5-ethoxy-2-pyrrolidinones *via* "acid work-up", respectively, in high yields[7]. In the case of maleimides, the reaction was rather troublesome due to the instability of products. The reduction of 15, as a model experiment, with $NaBH_4$ (1 eq) in EtOH at -30 - -40° for 1 hr and the base work-up (pH 7) gave a mixture of 11 and 3 (the ratio 1:3)[11] in quantitative yield. The latter (3) would be easily formed from the former (11) by the migration of double bond and the subsequent keto-enol tautomerism during the work-up. This assumption was supported by the formation of 3 on treating 11 with the catalytic amount of acid (HCl) in EtOH[12]. Although we failed to get a sole product (11) from 15, fortunately the objective product (2) was exclusively obtained from 16 in quantitative yield by the $NaBH_4/H^+$ reduction (see experimental). In this case only the trace of (±)-jatropham (1) and methylsuccinimide (5) was observed in the NMR spectrum of the crude product. This means that the reduction of 16 with $NaBH_4$ is regioselective and under this reduction condition (pH 7), 2 is more stable than 11 because of the existence of methyl group at the double bond. This regioselectivity would be rationalized on the basis of a different electronic character and a different steric circumstance of the two carbonyl groups. This result is in accord with the general tendency of the reduction of imides having two different carbonyl groups[13]. On the other hand, the acid work-up (pH 3) in the reduction of 16 with $NaBH_4$ afforded a mixture of 5-ethoxy-4-methyl-3-pyrrolin-2-one (17) and methylsuccinimide (5)[14] (the ratio 3:4) in 64% yield. The former (17) was converted to 2 by the procedure described for the synthesis of 1 from 13.

(±)-Jatropham (1) and its 4-methyl isomer (2) were identical with the corresponding authentic samples by comparison of their IR, UV, MS, ^{1}H-NMR, and ^{13}C-NMR spectra.

In conclusion, the present procedures provide valuable alternative synthetic methods of (±)-jatropham (1) and its isomer (2) since almost optimum reaction conditions have been established.

EXPERIMENTAL

5-Ethoxy-1-trimethylsilyl-2-pyrrolidinone (8) ---- A mixture of 5-ethoxy-2-pyrrolidinone (7, 6.0 g)[7] and hexamethyldisilazane (HMDS) (12 ml) was refluxed for 5 hr. After an excess of HMDS was evaporated under reduced pressure, the residual oil was distilled to afford 8 as a colorless oil, bp 73-74° (2 mmHg), in 76-79% yield. IR (neat) cm^{-1}: 1685 (C=O), 840 (Me_3Si). ^{1}H-NMR ($CDCl_3$) δ: 0.30 (9H, s), 1.20 (3H, t), 1.8-2.6 (4H, m), 3.43 (2H, m), 4.96 (1H, m).

5-Ethoxy-3-methyl-3-phenylseleno-2-pyrrolidinone (9) ---- To a solution of diisopropylamine (2.58 ml, 18 mmol) in THF (13 ml) was added at -78° a hexane solution of n-BuLi (13.2 mmol). The mixture was stirred at -78° for 20 min. A solution of 8 (1.2 g, 6 mmol) in THF (3.5 ml) was added dropwise over a 15 min period. After the mixture was stirred at -78° for 1 hr, diphenyl diselenide (1.87 g, 6 mmol) dissolved in THF (3.5 ml) was then added dropwise over a 10 min period and the reaction mixture was stirred for an additional 1 hr at -78°. CH_3I (1.70 g, 12 mmol) in THF (2 ml) was added over a 10 min period. After stirring at -78° for 1 hr and warming to room temp over 1 hr, the reaction mixture was poured into H_2O and extracted with ether. The ethereal extract was washed with 5% NaOH and H_2O, dried over $MgSO_4$, and evaporated to give a brown oil (3.05 g), which was chromatographed on silica gel with elution of $CHCl_3$ to afford 1.67 g (94%) of 9 and 35 mg (3.7%) of 10. When 9 was submitted to the high resolution chromatography on iatrobeads with elution of $CHCl_3$, two isomers were separated in the ratio of 4 (from former fraction) to 1 (from latter fraction). The former : colorless prisms from isopropyl ether, mp 101-103°, IR (KBr) cm^{-1}: 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (3H, s), 4.44 (1H, m, C_5-H). MS m/e: 299(M^+). Anal. Calcd for $C_{13}H_{17}NO_2Se$: C, 52.35; H, 5.75; N, 4.70. Found: C, 52.43; H, 5.69; N, 4.69. The latter : colorless needles from isopropyl ether, mp 90-91°. IR (KBr) cm^{-1}: 1695. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, s), 4.88 (1H, m, C_5-H). MS m/e: 299(M^+). Anal. Calcd for $C_{13}H_{17}NO_2Se$: C, 52.35; H, 5.75; N, 4.70. Found: C, 52.25; H, 5.72, N, 4.66. 10: colorless needles from isopropyl ether, mp 75-78°. IR (KBr) cm^{-1}: 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, s), 1.30 (3H, s), 4.86 (1H, m). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.92. Found: C, 61.00; H, 9.57; N, 9.17.

5-Ethoxy-3-methyl-3-pyrrolin-2-one (13) ---- 30% H_2O_2 (2.27 g, 20 mmol) was added to a solution of 9 (mixture, 1.32 g, 6.7 mmol) in THF (15 ml) under ice cooling. The solution was stirred at 0° for 1 hr and evaporated to give a red oil, which

was repeatedly chromatographed on alumina with elution of benzene-acetone (10:1) to afford 548 mg (88%) of 13: colorless needles from isopropyl ether, mp 49-50°. IR (KBr) cm^{-1}: 1710, 1660. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, d, J=1 Hz), 5.33 (1H, m, C_5-H), 6.50 (1H, m, olefin H). MS m/e: 141(M^+). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.90; H, 7.89; N, 9.97.

5-Hydroxy-3-methyl-3-pyrrolin-2-one: Jatropham (1) ---- A solution of 13 (200 mg) in 50% AcOH (2 ml) was warmed at 60° for 2 hr. When the solvent was evaporated, 1 was obtained quantitatively as crystals. 1: colorless needles from $CHCl_3$, mp 120-121° (lit.[4] 115-118°). IR (KBr) cm^{-1}: 3250, 1690, 1650. UV (EtOH) nm: 230. MS m/e: 113(M^+). ^{1}H-NMR (d_6-acetone) δ: 1.76 (3H, s), 4.86 (1H, d, J=9 Hz, OH), 5.40 (1H, br, C_5-H), 6.58 (1H, m, loefin H), 7.43 (1H, br, NH). ^{13}C-NMR (CD_3OD) δ: 10.44 (Me, q), 79.80 (C_5, d), 136.70 (C_3, s), 142.88 (C_4, d), 175.28 (C_2, s). Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.04; H, 6.23; N, 12.45.

5-Hydroxy-4-methyl-3-pyrrolin-2-one (2) ---- $NaBH_4$ (38 mg, 1 mmol) was added at -30° to a solution of methylmaleimide (16, 111 mg, 1 mmol) in abs. EtOH (20 ml). After the reaction mixture was stirred at -30 - -40° for 50 min, the excess $NaBH_4$ was destroyed at — 40° by adding dropwise 10% aqueous AcOH till pH 7 over a 45 min period. The solvent was evaporated under reduced pressure at room temp and the residue was extracted with acetone. After filtration, evaporation of the extract afforded 113 mg (100%) of almost pure 2: colorless leaf-like crystals from acetone, mp 163-164° (lit.[4] 154-157°). IR (KBr) cm^{-1}: 1700, 1630. MS m/e: 113(M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 5.40 (1H, s, C_5-H), 5.75 (1H, m, loefin H). ^{13}C-NMR (CD_3OD) δ: 13.43 (Me, q), 83.43 (C_5, d), 122.35 (C_3,d), 163.29 (C_4, s), 175.34 (C_2, s). Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.29; N, 12.38. Found: C, 53.23; H, 6.35; N, 12.44. When dil HCl-EtOH was added to the reaction mixture till pH 3, the mixture of 5[14] and 17 (the ratio 4:3) with a small amount of 2 was obtained. 17 was separated from a $CHCl_3$ solution of this mixture by washing with a small amount of H_2O for the removal of 5. 17: colorless oil, bp 112-114° (2 mmHg). IR (neat) cm^{-1}: 1700, 1100. MS m/e: 141(M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s), 5.30 (1H, s, C_5-H), 5.83 (1H, br d, olefin H). 17 was converted to 2 by the procedure described for the synthesis of 1 from 13.

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