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# 1,6-Dihydro-3(2*H*)-pyridinones. IX.[1] A Regioselective Synthesis of Ethyl 3-Methoxycarbonylmethyl-4-oxopiperidine-1-carboxylate from Ethyl 3-Hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate

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The title compound (**6**) was prepared from ethyl 3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**2**) *via* a regioselective hydroxylation at the C-4 position of the olefin (**7**) by utilizing an iodolactonization reaction.

**Keywords**——iodolactonization; tetrahydropyridine; 4-oxopiperidine; α-iodoketone; regioselective hydroxylation

In the preceding paper,[1,2] we demonstrated that alkyl 3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**1**) derived from the alcohol (**2**) gave the alcohols (**3** and **4**) in a ratio of *ca.* 6:4 by a stepwise hydration *via* the epoxide (**5**). The fact that the 4-hydroxy compound (**3b**) has been shown to be a powerful intermediate for some alkaloid syntheses[1,2] prompted us to investigate more regioselective introduction of the hydroxyl group at the C-4 position of olefin compounds such as **1** and its derivatives. In this paper we describe a synthesis of the title compound (**6**) through a regiospecific hydroxylation at the C-4 position of the unsaturated carboxylic acid (**7**) *via* iodolactonization.

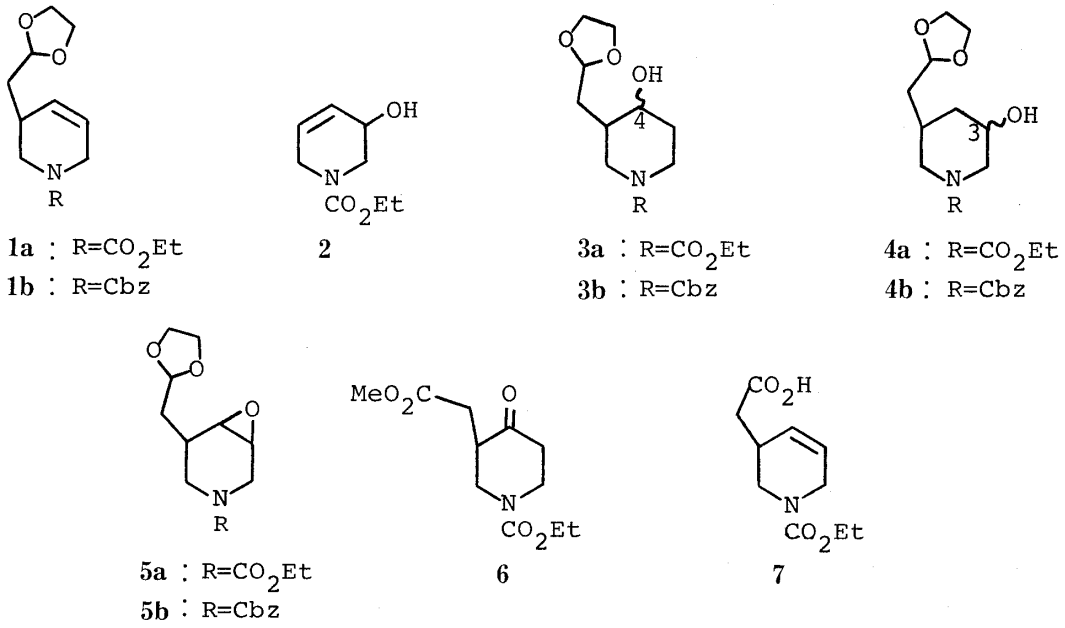


Chart 1

The unsaturated acid (**7**), easily prepared from the allylic alcohol (**2**)[3] *via* the known aldehyde (**8**),[4] was reacted with potassium iodide and iodine in aqueous alkaline solution[5] to

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provide the iodolactone (**9**) as a sole product in 74% yield. The regioisomeric structure (**10**) for this product was ruled out by its infrared (IR) spectrum, which showed a carbonyl band at 1785 $cm^{-1}$ characteristic of a five-membered lactone ring. Unfortunately, several attempts to remove the iodine atom in **9**, *e.g.* reduction with tri-*n*-butyltin hydride[6] or with zinc–sodium iodide,[7] and catalytic hydrogenolysis,[8] were fruitless. Furthermore, the unsaturated lactone (**11**), derived from **9** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in boiling benzene, was subjected to hydrogenation over a palladium, platinum, or rhodium catalyst, resulting in hydrogenolysis of the $C_4$–O bond prior to or concomitantly with the desired hydrogenation of the C–C double bond. Therefore, the iodolactone (**9**) was initially transformed into the hydroxy ester (**12**) in 60% yield by solvolysis with methanol and then **12** was oxidized with the Jones reagent[9] to the corresponding ketone (**13**). When the α-iodoketone (**13**) was treated with zinc and acetic acid in boiling 1,2-dimethoxyethane (DME), the iodine atom was easily removed and the keto ester (**6**) was isolated in 87% yield as a sole product. The structure of **6** was confirmed by an alternative synthesis of **6** from a known compound (**14**).[1] Namely, **14** was treated with 1% hydrochloric acid in acetone to give the keto aldehyde (**15**), which was oxidized with silver (I) oxide to the carboxylic acid (**16**). Esterificatior of **16** with diazomethane furnished the same keto ester (**6**).

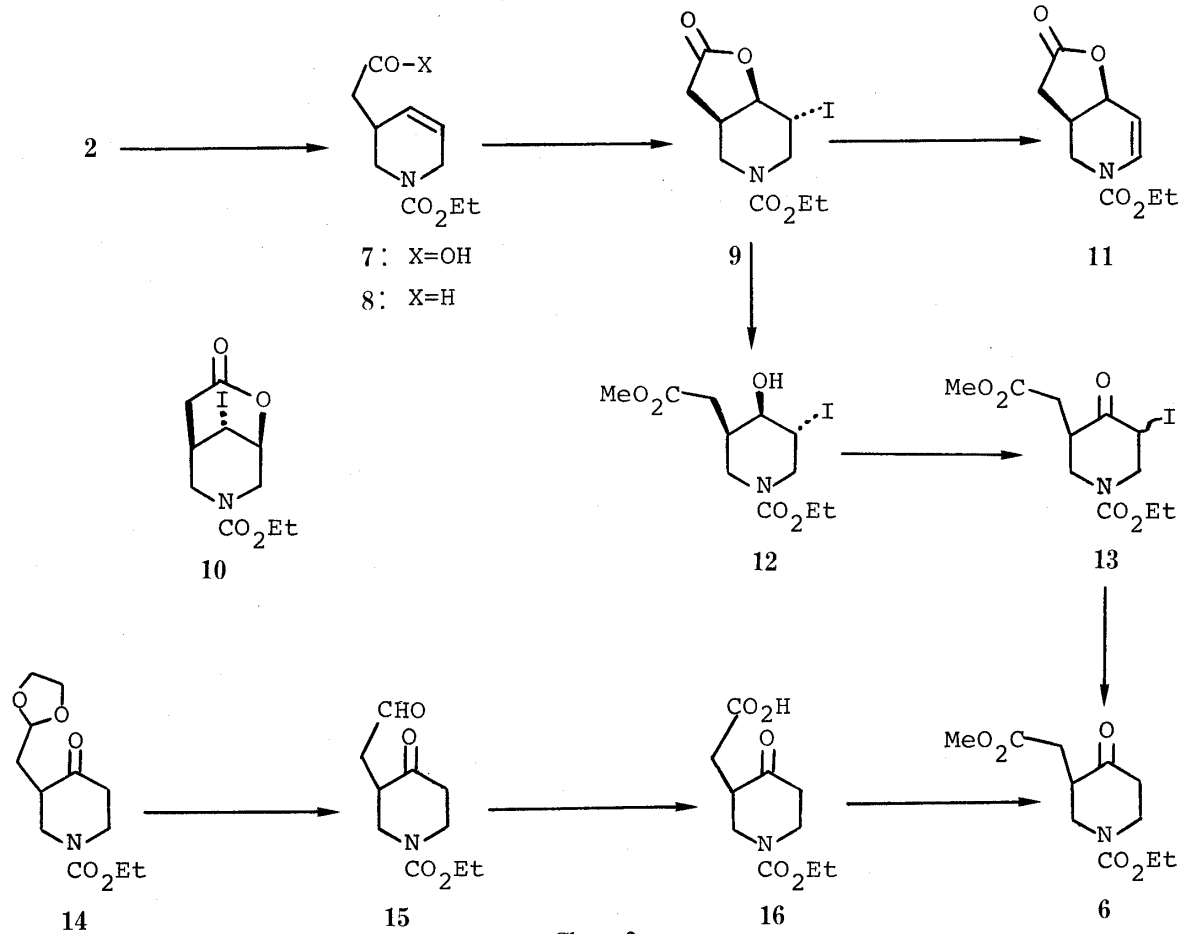


Chart 2

Thus, a regiospecific hydroxylation of the olefin (**7**) was achieved by using the iodolactonization method. The overall yield of **6** was 14% from the starting material (**2**).

## Experimental

IR spectra were measured with a JASCO A-102 spectrometer. Proton nuclear magnetic resonance ($^1$H-NMR)

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spectra were recorded with a JEOL PMX-60 or FX-100 spectrometer in $CDCl_3$ using $Me_4Si$ as an internal standard. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 75 eV). Organic solutions were dried over anhydrous $Na_2SO_4$ and concentrated in a rotary evaporator under reduced pressure. Column chromatography was carried out with Silica gel 60 (Merck) or Alumina 90 (Merck).

**1-Ethoxycarbonyl-1,2,3,6-tetrahydropyridine-3-acetic Acid (7)**——According to the previously reported procedure,[4] the allylic alcohol (**2**; 2.93 g) was allowed to react with ethyl vinyl ether in the presence of $Hg(OAc)_2$ to provide a crude aldehyde (**8**; 2.5 g). A solution of $AgNO_3$ (3.3 g) in distilled water (20 ml) and a solution of KOH (3.3 g) in distilled water (20 ml) were gradually added to a stirred solution of the above aldehyde in EtOH (50 ml) under ice cooling over 10 min. After stirring for another 10 min under cooling, the formed precipitate was filtered off and the filtrate was washed with $CHCl_3$ (30 ml) to remove neutral impurities. The aqueous layer was acidified with conc. HCl and then extracted with $CHCl_3$ (30 ml × 5). Concentration of the dried extract gave 1.5 g (41% from **2**) of the carboxylic acid (**7**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3600—2400 (COOH), 1700 (COO), 1680 (NCOO), 1650 (C=C). $^1$H-NMR $\delta$: 1.25 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 2.37 (2H, d, $J$=6 Hz, $C_3$–$CH_2$), 3.48 (2H, dd, $J$=4.5 and 3.5 Hz, $C_6$–H), 3.86 (2H, br, $C_2$–H), 4.12 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 5.68 (2H, br, $C_4$– and $C_5$–H), 8.88 (1H, s, COOH). MS $m/e$ (%): 213 (21, $M^+$), 102 (100). High resolution MS. Calcd for $C_{10}H_{15}NO_4$: 213.0999. Found: 213.0951.

***rel*-(3*R*, 4*R*, 5*R*)-1-Ethoxycarbonyl-4-hydroxy-5-iodopiperidine-3-acetic Acid γ-Lactone (9)**——A solution of KI (9.4 g) and $I_2$ (2.4 g) in distilled water (10 ml) was added to a solution of the carboxylic acid (**7**; 1.45 g) in 0.5 N $NaHCO_3$ (20 ml) and the resulting mixture was allowed to stand at room temperature for 2 d. The mixture was acidified with 1 N HCl and extracted with $CHCl_3$ (20 ml × 3). The extract was washed with a 1:1 mixture of sat. $NaHCO_3$ and $Na_2S_2O_3$, and then brine. Concentration of the dried extract left an oil, which was chromatographed on alumina in $CHCl_3$ to afford 1.7 g (74%) of the iodolactone (**9**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$ 1785 (lactone), 1685 (NCOO). $^1$H-NMR $\delta$: 1.27 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 4.11 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.68 (1H, t, $J$=4 Hz, $C_4$–H). MS $m/e$ (%): 339 (0.99, $M^+$), 212 (100). High resolution MS. Calcd for $C_{10}H_{14}INO_4$: 338.9967. Found: 338.9967.

***rel*-(3*R*, 4*R*)-1-Ethoxycarbonyl-4-hydroxy-1,2,3,4-tetrahydropyridine-3-acetic Acid γ-Lactone (11)**——A mixture of **9** (510 mg), DBU (240 mg), and dry $C_6H_6$ (15 ml) was heated with stirring at 70—80 °C for 2 h and then diluted with $C_6H_6$ (30 ml). The resulting mixture was washed with 2% HCl and brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 286 mg (90%) of the olefin (**11**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1775 (lactone), 1705 (NCOO), 1645 (C=C). $^1$H-NMR $\delta$: 1.28 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 4.16 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.81 (1H, t, $J$=4 Hz, $C_4$–H), 5.02 (1H, dd, $J$=8 and 4 Hz, $C_5$–H), 7.00 (1H, d, $J$=8 Hz, $C_6$–H). MS $m/e$ (%): 211 (9.9, $M^+$), 94 (100). High resolution MS. Calcd for $C_{10}H_{13}NO_4$: 211.0843. Found: 211.0829.

**Ethyl *rel*-(3*R*, 4*R*, 5*R*)-4-Hydroxy-5-iodo-3-methoxycarbonylmethylpiperidine-1-carboxylate (12)**——A mixture of the lactone (**9**; 436 mg), *p*-TsOH·$H_2O$ (12 mg), and abs. MeOH (10 ml) was refluxed for 3 h. The reaction mixture was made basic with sat. $NaHCO_3$ then concentrated. The residue was taken up in $CHCl_3$ (30 ml) and the $CHCl_3$ layer was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 289 mg (60%) of the ester (**12**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3420 (OH), 1725 (COO), 1680 (NCOO). $^1$H-NMR $\delta$: 1.23 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 3.61 (3H, s, $OCH_3$), 4.06 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$). MS $m/e$ (%): 371 (0.04, $M^+$), 226 (100). High resolution MS. Calcd for $C_{11}H_{18}INO_5$: 371.0239. Found: 371.0214.

**Ethyl 5-Iodo-3-methoxycarbonylmethyl-4-oxopiperidine-1-carboxylate (13)**——The Jones reagent (8 N; 0.25 ml) was added dropwise to a stirred solution of the alcohol (**12**; 97 mg) in purified acetone (2 ml) under ice cooling over 5 min and the mixture was further stirred for 1 h under cooling. After addition of 2—3 drops of MeOH, the reaction mixture was diluted with water (5 ml) and extracted with $CHCl_3$ (10 ml × 3). The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 83 mg (87%) of the ketone (**13**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730 (COO), 1700 sh (CO), 1690 (NCOO). $^1$H-NMR $\delta$: 1.30 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 3.63 (3H, s, $OCH_3$), 4.17 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$). MS $m/e$ (%): 369 (0.03, $M^+$), 242 (100). High resolution MS. Calcd for $C_{11}H_{16}NO_5$ ($M^+-I$): 242.1027. Found: 242.1007.

**Ethyl 4-Oxo-3-(2-oxoethyl)piperidine-1-carboxylate (15)**——A mixture of the acetal (**14**; 145 mg),[1] 1% HCl (3 ml), and acetone (5 ml) was refluxed for 30 min and then the organic solvent was evaporated off. The residue was diluted with water and extracted with $CHCl_3$ (10 ml × 3). The extract was washed with brine, dried, and concentrated to leave 121 mg of crude **15**, which was used in the next step without purification. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2730 (CHO), 1720 sh, 1700 sh (CO), 1680 (NCOO). $^1$H-NMR $\delta$: 1.27 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 4.13 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 9.61 (1H, s, CHO). High resolution MS. Calcd for $C_{10}H_{15}NO_4$: 213.1000. Found: 213.1044.

**1-Ethoxycarbonyl-4-oxopiperidine-3-acetic Acid (16)**——A solution of $AgNO_3$ (164 mg) in distilled water (2 ml) was added to a solution of the aldehyde (**15**; 115 mg) in EtOH (3 ml) and then a solution of KOH (0.20 g) in distilled water (2 ml) was added dropwise to the stirred mixture under ice cooling over 2—3 min. The whole mixture was further stirred under cooling for 20 min and the precipitate was filtered off. The filtrate was washed with $CHCl_3$ and the aqueous layer was acidified with conc. HCl. The resulting aqueous layer was extracted with $CHCl_3$ (10 ml × 3) and the extract was dried. Evaporation of the solvent gave 86 mg (71%) of the carboxylic acid (**16**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3550—2400 (COOH), 1720 sh, 1700 (CO, COO), 1680 (NCOO). $^1$H-NMR $\delta$: 1.27 (3H, t, $J$=7 Hz,

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$OCH_2C\underline{H}_3$), 4.12 (2H, q, $J$= 7 Hz, $OC\underline{H}_2CH_3$), 7.10 (1H, br s, COOH). MS $m/e$ (%): 229 (5.9, $M^+$), 200 (27), 170 (100). High resolution MS. Calcd for $C_{10}H_{15}NO_5$: 229.0948. Found: 229.0948.

**Ethyl 3-Methoxycarbonylmethyl-4-oxopiperidine-1-carboxylate (6)**——a) From **13**: Acetic acid (2 drops) and zinc (63 mg) were added to a solution of **13** (71 mg) in DME (5 ml) and the whole mixture was heated with stirring at 80 °C for 2 h. The inorganic substances were removed by filtration and the filtrate was concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 40 mg (87%) of the keto ester (**6**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730 sh (COO), 1720 (CO), 1680 (NCOO). $^1$H-NMR $\delta$: 1.27 (3H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 3.63 (3H, s, $OCH_3$), 4.12 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$). MS $m/e$ (%): 243 (4.5, $M^+$), 214 (21), 212 (18), 170 (100). High resolution MS. Calcd for $C_{11}H_{17}NO_5$: 243.1105. Found: 243.1105.

b) From **16**: A $CH_2N_2$–ether solution (0.2 M; 5 ml) was added to a solution of the carboxylic acid (**16**; 77 mg) in MeOH (5 ml) and the mixture was stirred under ice cooling for 20 min. The solvent was evaporated off to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 65 mg (79%) of the ester (**6**).

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