Studies on the Syntheses of Heterocyclic Compounds. Part DLXXXI (1). Syntheses of 3-Carboxy-1,2,3,4-tetrahydroisoquinoline Derivatives by Phenolic Cyclization

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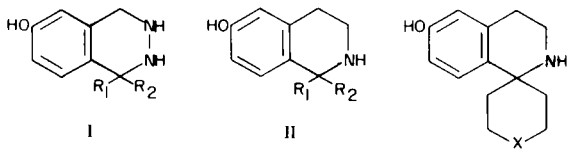
3-Carboxy-1,1-dimethylisoquinoline and 3-carboxy-1-spirocycloalkano- and 1-spiroheterocycloalkanoisoquinoline derivatives were synthesized by phenolic cyclization reaction using *m*-tyrosine and several carbonyl compounds.

In the previous paper (3), we synthesized 1-substituted 1,2,3,4-tetrahydrophthalazine derivatives (I) by a phenolic cyclization of 3-hydroxybenzylhydrazine with carbonyl compounds. So far, many 1,1-disubstituted (II) or 1-spiroisoquinoline derivatives (III) including natural products have been synthesized by phenolic cyclization using 3-hydroxyphenethylamines and carbonyl compounds without acidic catalyst (4-13).

SCHEME I



I II III

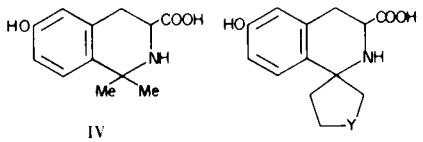
Ia : $R_1 = R_2 = Me$
Ib : $R_1 = Me$, $R_2 = Et$
Ic : $R_1 = R_2 = Et$
Id : $R_1, R_2 = [CH_2]_5$
Ie : $R_1, R_2 = [CH_2]_2\text{-}N(CH_3)\text{-}[CH_2]_2$

IIa : $R_1 = R_2 = Me$
IIb : $R_1 = Me$, $R_2 = Et$
IIc : $R_1 = Ph$, $R_2 = H$
IId : $R_1 = Ph$, $R_2 = Me$

IIIa : X = CH_2
IIIb : X = NMe
IIIc : X = NCH_2Ph
IIId : X = S

Phenolic cyclization using *m*-tyrosine and some carbonyl compounds gave the expected 3-carboxy-1,1-dimethylisoquinoline, 3-carboxy-1-spirocycloalkano-, and 3-carboxy-1-spiroheterocycloalkanoisoquinoline derivatives. Heating *m*-tyrosine, prepared from 3-hydroxybenzaldehyde according to a known procedure (14), with acetone, cyclopentanone, cyclohexanone or *N*-methylpiperidone for 10 hours in the presence of hydrochloric acid gave the corresponding isoquinoline derivatives. The reaction in neutral condition was not tried because of the poor solubility of *m*-tyrosine. When the reaction was carried out in hot ammoniacal solution for 3 hours, the same isoquinoline derivatives were obtained. The successful reaction under basic condition would support the reaction to proceed through phenolic cyclization. The structures of the products were determined on the basis of spectral data. For example, the uv absorption of the product IV was observed at 279 nm with red shift comparing with that of the starting *m*-tyrosine at 275 nm. *m*-Cresol and 2,3-dimethylphenol showed the uv absorption at 276.5 nm, whereas that of 3,4-dimethylphenol was observed at 281 nm. Therefore the possibility of the cyclization at *ortho* position against the hydroxy group was excluded. In the ir spectrum, no absorption due to C=N bond was observed. The nmr spectrum of IV in deuterium oxide showed three aromatic protons, one proton of C-8 position at −2.63 ppm as a doublet (J = 10.5 Hz), one of C-5 position at −2.24 ppm as a doublet (J = 2.2 Hz) and one of C-7 position at −2.03 ppm as a quartet (J = 10.5 and 2.2 Hz). The resonance of the methine proton at C-3 position appeared at 0.40 ppm as quartet (J = 12.3 and 9 Hz) and two methyl signals at C-1 position were observed at 3.14 and 3.33 ppm.

SCHEME II



IV

V : Y = CH_2 , VII : Y = $-NCH_3\text{-}CH_2-$

VI : Y = $(CH_2)_2$

EXPERIMENTAL

3-Carboxy-1,2,3,4-tetrahydro-6-hydroxy-1,1-dimethylisoquinoline (IV).

To a mixture of 50 ml. of acetone and 3 ml. of 10% hydrochloric acid, 3 g. of *m*-tyrosine was added and the mixture was refluxed

Fig.1 NMR Spectrum of Compound IV in D_2O

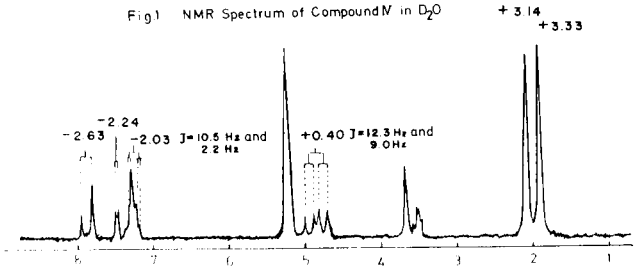
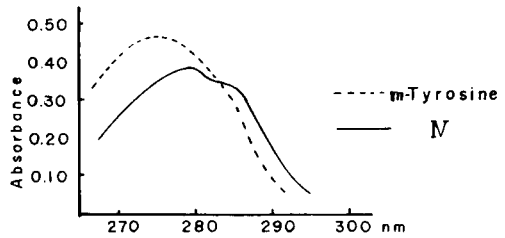


Fig. 2 UV Spectra of m-Tyrosine and Compound IV



for 5 hours. After evaporation of the solvent, the resulting solid was recrystallized from ethanol to afford 3.1 g. (72.9%) of the hydrochloride of IV as colorless needles, m.p. 258° dec.; uv λ max (ethanol, log ε) nm: 279 (3.30); ir ν max (potassium bromide) cm^{-1}: 1725 (C=O); nmr δ (deuterium oxide): -2.63(1H, d, J = 10.5 Hz, Ar*H*), -2.24 (1H, d, J = 2.2 Hz, Ar*H*), -2.03 (1H, dd, J = 10.5 and 2.2 Hz, Ar*H*), 0.40 (1H, dd, J = 12.3 and 9.0 Hz, C*H*), 3.14 and 3.32 (6H, each s, CH_3).

Anal. Calcd. for $C_{12}H_{15}NO_3$.HCl: C, 55.92; H, 6.26. Found: C, 55,92; H, 6.39.

3-Carboxy-1,2,3,4-tetrahydro-6-hydroxy-1-spirocyclopentanoisoquinoline (V).

To a mixture of 3 g. of cyclopentanone and 1 ml. of 10% hydrochloric acid, 1 g. of *m*-tyrosine was added and the mixture was heated for 10 hours on a water bath. After evaporation of the excess of cyclopentanone and hydrochloric acid, the residue was recrystallized from ethanol and ether to afford 650 mg. (40.0%) of the hydrochloride of V as colorless needles, m.p. 255° dec.; uv λ max (ethanol, log ε) nm: 280 (3.33); ir ν max (potassium bromide) cm^{-1}: 1760 (C=O); nmr δ (deuterium oxide): -2.58(1H, d, J = 9.3 Hz, Ar*H*), -2.26 (1H, d, J = 2.5 Hz, Ar*H*), -1.95 (1H, dd, J = 9.3 and 2.4 Hz, Ar*H*), 0.49 (1H, dd, J = 10.5 and 7.5 Hz, C*H*).

Anal. Calcd. for $C_{14}H_{17}NO_3$.HCl: C, 59.25; H, 6.39; N, 4.94. Found: C, 59.11; H, 6.25; N, 4.84.

3-Carboxy-1,2,3,4-tetrahydro-6-hydroxy-1-spirocyclohexanoisoquinoline (VI).

(a) To a mixture of 3 g. of cyclohexanone, 1 ml. of 10% hydrochloric acid, 1 g. of *m*-tyrosine was added and the mixture was heated for 10 hours on a water bath. After evaporation of the excess of cyclohexanone and hydrochloric acid, the residue was recrystallized from isopropanol and ether to afford 680 mg. (41.7%) of the hydrochloride of VI as colorless needles, m.p. 224° dec.; uv λ max (ethanol, log ε) nm: 279 (3.40); ir ν max (potassium bromide) cm^{-1}: 1730 (C=O); nmr δ (deuterium oxide): -2;72 (1H, d, J = 9.0 Hz, Ar*H*), -2.28 (1H, d, J = 2.7 Hz, Ar*H*), -2.15 ~ -2.0 (1H, broad, Ar*H*), 0.35 (1H, dd, J = 7.5 and 11.4 Hz, ≥C*H*).

Anal. Calcd. for $C_{15}H_{19}NO_3$.HCl: C, 60.50; H, 6.77; N, 4.70. Found: C, 60.86 H, 6.93 N, 4.32.

(b) To a solution of 200 mg. of *m*-tyrosine in 1 ml. of 28% ammonia, 1 ml. of cyclohexanone was added and the mixture was heated for 14 hours at 70°. After evaporation of the excess of cyclohexanone and ammonia, the residue was triturated with ether and then converted into the hydrochloride as usual. Recrystallization from ethanol and ether gave 220 mg. (67.4%) of the same hydrochloride of VI as above.

3-Carboxy-1,2,3,4-tetrahydro-6-hydroxy-1-spiro(*N*-methyl-4-piperidino)isoquinoline (VII).

To a mixture of 1 g. of *N*-methyl-4-piperidone and 0.5 ml. of 10% hydrochloric acid, 200 mg. of *m*-tyrosine was added and the mixture was heated for 5 hours on a water bath. After cooling, 20 ml. of ethanol was added and the crystals were collected by filtration. Recrystallization from ethanol and water gave 300 mg. (78.0%) of the dihydrochloride of VII as colorless needles, m.p. 257° dec.; uv λ max (water, log ε) nm: 277 (3.16); ir ν max (potassium bromide) cm^{-1}: 1760 (C=O); nmr δ (deuterium oxide): -2.70 (1H, d, J = 9 Hz, Ar*H*), -2.26 (1H, d, J = 2.0 Hz, Ar*H*), -1.97 ~ -2.15 (1H, broad, Ar*H*), 1.90 (3H, s, N-Me).

Anal. Calcd. for $C_{15}H_{20}N_2O_3$.2HCl: C, 60.50; H, 6.77; N, 4.70. Found: C, 60.71; H, 6.53; N, 4.76.

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