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Studies on the Syntheses of Heterocyclic Compounds. DCXXVI.[1] A Modified Synthesis of Pentazocine

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Pentazocine (**1**) was synthesized from L-tyrosine (**2**). N-Benzylation of methyl ester (**3**), obtained from L-tyrosine, followed by Schotten-Baumann reaction of the amine (**4**), gave the amide (**5**). Dieckmann reaction of **5** gave the racemic β-ketoester (**6**), whose methylation followed by decarboxylation afforded the ketoamide (**8**). Grignard reaction gave the carbinol (**9**), which was cyclized with hydrobromic acid to afford the amide (**10**) in good yield. Reduction of **10** with sodium bis-(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride gave the amine (**11**), which had already been converted into pentazocine.

Since pentazocine (**1**) firstly synthesized by Archer, *et al.*[3] has a non-narcotic analgesic activity, the modified syntheses have been investigated by many researchers.[4–8] Herein we wish to report a modified synthesis of pentazocine by using L-tyrosine as a starting material, which is easily available.

The hydrochloride of methyl *p*-methoxy-L-phenylalanate (**3**), which was prepared from tyrosine (**2**) in 3 steps according to Baker's method,[9] was basified to afford the free base of **3**, which was used immediately in the following reaction.

The Schiff base, which was obtained by condensation of the above free base (**3**) with benzaldehyde in methanol, was reduced with sodium borohydride at 0—5° to give N-benzyl derivative (**4**) in 87% yield, which was confirmed as its hydrochloride, mp 156.5—158°, $[\alpha]_D^{20}$ +39.3° (MeOH). Condensation of the free base of **4** with methyl 3-chloroformylpropionate[10] in the presence of potassium carbonate[11] gave the amide (**5**), $[\alpha]_D^{20}$ −74.4° (MeOH), in 98% yield.

Dieckmann reaction of this amide (**5**) with excess of sodium hydride in dry dioxane[11] at 100—110° for 5.5 hr gave the ketoester (**6**) in 83% yield. The structure of this was confirmed by infrared (IR), nuclear magnetic resonance (NMR), mass spectra and microanalysis

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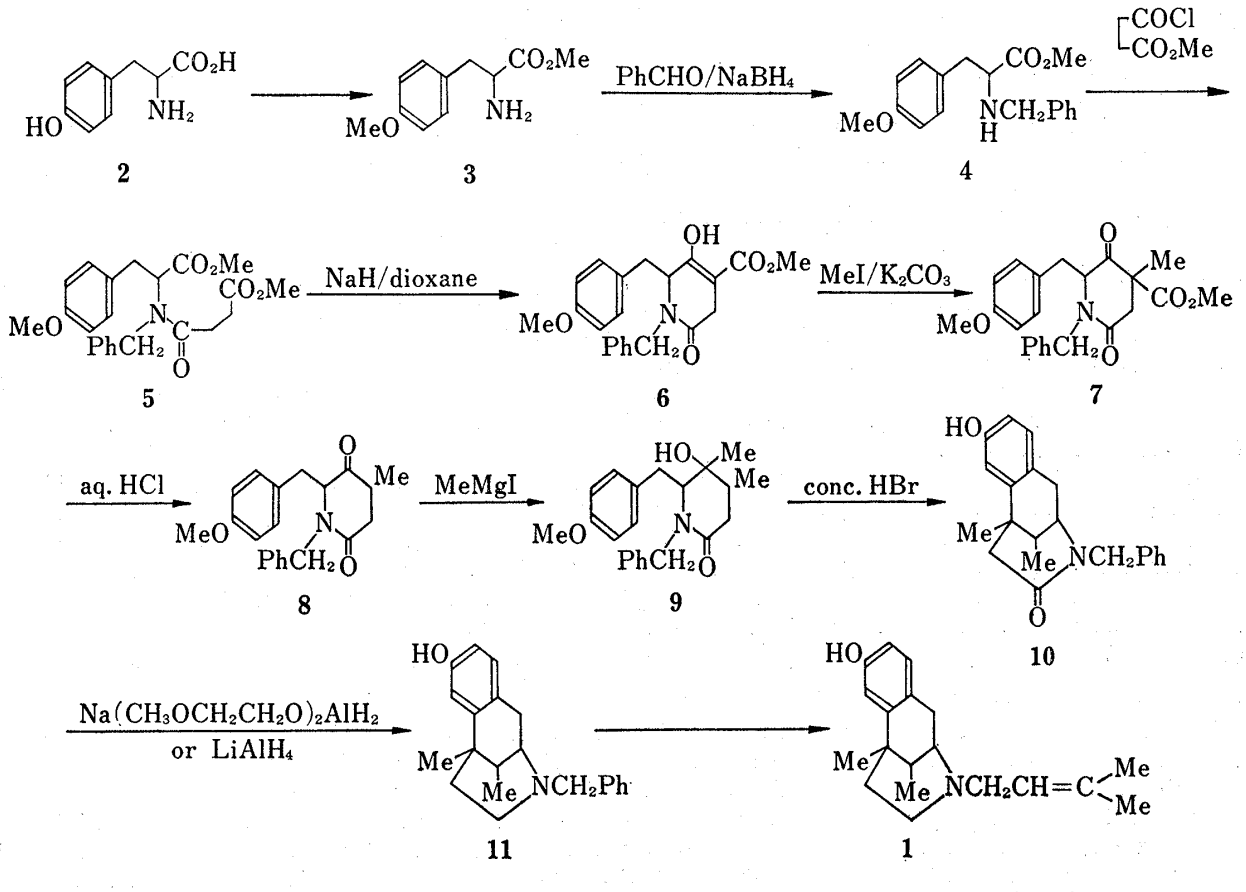
and also supported by positive ferric chloride test. In this case racemization of **6** occurred, the fact of which was supported by optical rotatory dispersion (ORD) measurements of this product and the following derivatives. Furthermore, this reaction was investigated by using the other organic solvents such as toluene in the presence of sodium hydride, but the yield of **6** was not improved.

Treatment of **6** with methyl iodide in acetone in the presence of potassium carbonate[11] gave methylated derivative (**7**) in 89% yield. The IR ($CHCl_3$) spectrum showed three carbonyl absorptions at 1740, 1720 and 1657 cm^{-1} and the NMR ($CDCl_3$) spectrum revealed a methyl group at 1.29 as singlet together with two O-methyl groups at 3.72 and 3.80 and methylene protons of N-benzyl group at 3.51 and 5.56 ppm as doublet with $J=14$ Hz, respectively. This reaction proceeded when the basic catalyst such as sodium hydride was used, but potassium carbonate was found to be superior to another catalyst. When the above compound (**7**) was heated with conc. hydrochloric acid–methanol (1 : 1) for 2 hr, decarboxylation occurred to give the ketopiperidone derivative (**8**), mp 142—143°, in 91% yield. In the IR ($CHCl_3$) spectrum of **8**, absorptions due to two carbonyl groups were observed at 1720 and 1640 cm^{-1} and the NMR ($CDCl_3$) spectrum exhibited a methyl group at 0.93 as doublet with $J=7$ Hz, one O-methyl group at 3.80 and methylene protons of N-benzyl group at 3.52 and 5.60 ppm as doublet with $J=15$ Hz, respectively.

Grignard reaction of (**8**) with methylmagnesium iodide in dry ether and tetrahydrofuran (THF) afforded the carbinol (**9**) in 74.5% yield whose IR ($CHCl_3$) spectrum revealed one hydroxy group at 3610 (non-conjugated OH) and 3410 (conjugated OH) and an amide group at 1630 cm^{-1}. Furthermore the NMR ($CDCl_3$) spectrum suggested the appearance of a methyl group at 0.95 as singlet as well as the presence of a methyl group at 1.04 ppm as doublet with



J=6 Hz. When **9** was heated with conc. hydrobromic acid in acetic acid for 38 hr, dehydration, followed by ring closure and O-demethylation, occurred to give the amide (**10**) in 77% yield. During this reaction the double bond formed by dehydration would be rearranged in order to conjugate with the ketone group, by the result of which a nucleophilic attack would be easily occurred and the yield of cyclized product was improved.

Although there would be two stereoisomers in case of this compound, only one compound, namely *cis*-derivative was obtained, whose fact was persumed by the difference between the chemical shifts due to two methyl groups in its NMR spectrum,[12] showing a methyl group of C-11 position at 0.93 as doublet with J=7.5 Hz and a methyl group of C-6 position at 1.25 ppm as singlet. This fact was also supported by the IR and NMR spectral comparisons of an authentic sample[4] with the amine (**11**), which was obtained by reduction of **10** as described later. Furthermore, the hydrochloride of **11** was also found to be identical with the authentic sample by mixing melting point test and its IR spectral (KBr) comparison.

Reduction of **10** with sodium bis-(2-methoxyethoxy)aluminum hydride in xylene and lithium aluminum hydride in dioxane was carried out under reflux to afford our desired amine (**11**) in 70% and 54% yield, respectively, which had already been converted to pentazocine (**1**) by us.[4]

Thus a modified synthesis has been accomplished. All the reaction mentioned above proceeded almost stereoselectively, but in the case of the decarboxylation and Grignard reaction a small amount of the products, which would be considered as diastereoisomers and not easily separable as pure quality, formed. The details on the stereochemistry of the compounds (**7**), (**8**), and (**9**) will be the subject of a subsequent investigation. However it seems that the cyclization of the carbinol (**9**) with hydrobromic acid does not suffer from the stereochemical problem. This procedure would provide the general synthesis of pentzocine type derivatives.

Experimental[13]

Methyl 2-(N-Benzylamino)-3-(4-methoxyphenyl)propionate (**4**)——After the hydrochloride of the amino-ester (**3**)[9] had been basified with 10% NH_4OH and extracted with ether, the ethereal extract was dried over Na_2SO_4 and evaporated to afford the free base (**3**), which was used in the following reaction immediately.

To a solution of **3** (11.5 g) in MeOH (50 ml) benzaldehyde (6.82 g) was added and the mixture was stirred at room temperature for 2 hr and then $NaBH_4$ (1.45 g) was added to the above cooled solution at 0—5° in small portions under stirring. After stirring for 1 hr, a small amount of AcOH was added and the solvent was evaporated. A solution of the resulting residue in benzene was washed with 10% $NaHCO_3$ aq. solution and water, dried over Na_2SO_4, and evaporated to give an oil, which was purified by chromatography on silica gel using benzene to afford (**4**) (14.5 g) (87%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). NMR ($CDCl_3$) ppm: 2.86 (2H, d, J=7 Hz, 3-CH_2), 3.57 (3H, s, OMe), 3.78 (5H, s, OMe and NC$\underline{H}_2C_6H_5$), 6.72 and 7.03 (4H, two d, J=8.2 Hz, 2, 3, 5, and 6-H), 7.18 (5H, s, $C_6\underline{H}_5$).

Recrystallization of the hydrochloride from MeOH–ether afforded colorless crystals, mp 156.5—158°, $[\alpha]_D^{20}$ +39.3 (c=0.24 in MeOH). *Anal.* Calcd. for $C_{18}H_{21}O_3N\cdot HCl$: C, 64.37; H, 6.60; N, 4.17. Found: C, 64.25; H, 7.04; N, 4.23.

Methyl 2-(N-Benzyl-β-methoxycarbonylpropionylamino)-3-(4-methoxyphenyl)propionate (**5**)——To a mixture of the above compound (**4**) (762 mg; 2.54 mmole), benzene (5 ml) and 15% K_2CO_3 aq. solution (3 ml; 3.26 mmole) a solution of methyl 3-chloroformylpropionate[10] (482 mg; 3.2 mmole) in dry benzene (5 ml) was added drop by drop at 6—10° under stirring during 30 min and the resulting mixture was then kept at room temperature. To the above mixture 30% K_2CO_3 aq. solution (0.2 ml; 0.44 mmole) was again added and the stirring was continued for 3.5 hr. Furthermore, a mixture of 30% K_2CO_3 aq. solution (0.29 ml; 0.64 mmole) and methyl 3-chloroformylpropionate (90 mg; 0.6 mmole) was added to the above reaction

12) S.E. Fullerton, E.L. May, and E.D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

13) All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MP-S2). IR spectra were measured with a Hitachi 215 grating spectrophotometer, NMR spectra with Hitachi H-60, JEOL-JNM-PMX-60, and JEOL-JNM-PS-100 spectrometers with Me_4Si as an internal standard, mass spectra with a Hitachi RMU-7 spectrometer, ultraviolet (UV) spectra with a Hitachi 124 spectrometer, optical rotations with a JASCO-PIP-SL automatic polarimeter, and ORD spectra with a JASCO/UV-5 spectropolarimeter.

mixture and stirring was continued at room temperature for 1 hr. The benzene layer was separated, washed with 10% HCl, saturated $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to give an oil (1.03 g, 98%), $[\alpha]_D^{20}$ −74.4° (c=0.52 in MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1718 (CO_2Me), 1638 (CON<). NMR (CCl_4) ppm: 2.50 (4H, s, $NCOC\underline{H}_2C\underline{H}_2CO_2Me$), 3.09 (2H, d, J=7 Hz, 3-$C\underline{H}_2$), 3.51, 3.60 and 3.72 (9H, three s, 3×OMe), 6,77 and 6.95 (4H, two s, 2, 3, 5, 6-H), 7.13 (5H, s, $C_6\underline{H}_5$).

1-Benzyl-4-methoxycarbonyl-6-(4-methoxybenzyl)piperidine-2,5-dione (6)——To a solution of the above amide (**5**) (9.92 g, 0.024 mole) in dry dioxane (40 ml) a suspension of 50% NaH (2.88 g, 0.06 mole) in dry dioxane (30 ml) was added under stirring in a current of nitrogen and the resulting mixture was heated at 100—110° in an oil-bath for 5.5 hr under stirring. After evaporation of the solvent, the resulting residue was mixed with water, neutralized with NH_4Cl, and extracted with benzene. The extract was dried over Na_2SO_4 and evaporated to afford a solid, which was, after washing with hexane, recrystallized from benzene–hexane to yield **6** (7.5 g; 83%) as colorless needles, mp 106.5—107°, $[\alpha]_D^{20}$ 0° (in MeOH), which showed a positive ferric chloride test. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675, 1638 (C=O). NMR ($CDCl_3$) ppm: 3.71 and 3.76 (6H, two s, 2×OMe), 3.85 and 5.55 (2H, two d, J=15 Hz, $NC\underline{H}_2C_6H_5$), 6.74 and 6.94 (4H, two d, J=9 Hz, 2,3,5,6-H), 7.26 (5H, s, $C_6\underline{H}_5$). Mass Spectrum m/e: 381 (M^+), 352, 260. *Anal.* Calcd. for $C_{22}H_{23}O_5N \cdot 1/3C_6H_{14}$: C, 70.28; H, 6.80; N, 3.42. Found: C, 69.92; H, 6.32; N, 3.71.

1-Benzyl-4-methoxycarbonyl-6-(4-methoxybenzyl)-4-methylpiperidine-2,5-dione (7)——To a solution of β-ketoester (**6**) (191 mg, 0.5 mmole) in dry acetone (5 ml) a mixture of MeI (710 mg; 5 mmole) and K_2CO_3 (138 mg; 1 mmole) were added and the resulting mixture was heated under reflux for 2.5 hr. After the reaction, an inorganic substance was filtered off and the filtrate was condensed to dryness to give a solid, which was extracted with benzene. The extract was washed with saturated NaCl aq. solution, dried over Na_2SO_4 and evaporated to afford a solid, whose recrystallization from benzene gave colorless needles (176 mg; 89%), mp 144.5—145.5°, $[\alpha]_D^{20}$ 0° (in MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1720, 1657 (C=O). NMR ($CDCl_3$) ppm: 1.29 (3H, s, C_4–Me); 2.42 (2H, s, 3-$C\underline{H}_2$), 3.16 (2H, d, J=6 Hz, C_6–$C\underline{H}_2$Ar), 3.51 and 5.56 (2H, two d, J=14Hz, $NC\underline{H}_2C_6H_5$), 3.72 and 3.80 (6H, two s, 2×OMe), 6.84 and 7.02 (4H, two d, J=8 Hz, 2,3,5,6-H), 7.26 (5H, s, $C_6\underline{H}_5$). Mass Spectrum m/e: 395 (M^+), 364, 274. *Anal.* Calcd. for $C_{23}H_{25}O_5N$: C, 69.85; H, 6.37; N, 3.54. Found: C, 70.11; H, 6.41; N, 3.41.

1-Benzyl-6-(4-methoxybenzyl)-4-methylpiperidine-2,5-dione (8)——A mixture of the above ester (**7**) (91 mg; 0.23 mmole), conc. HCl aq. solution (2.5 ml) and MeOH (2.5 ml) was heated under reflux for 2 hr. After a complete evolution of carbon dioxide, the reaction mixture was extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a solid, whose recrystallization from benzene afforded colorless crystals (70 mg; 91%), mp 142—143°, $[\alpha]_D^{20}$ 0° (in MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1640 (C=O). NMR ($CDCl_3$) ppm: 0.93 (3H, d, J=7 Hz, C_4–Me), 3.52 and 5.60 (2H, two d, J=15 Hz, $NC\underline{H}_2C_6H_5$), 3.80 (3H, s, OMe), 6.85 (4H, broad s, 2,3,5,6-H), 7.26 (5H, s, $C_6\underline{H}_5$). Mass Spectrum m/e: 337 (M^+), 216. *Anal.* Calcd. for $C_{21}H_{23}O_3N$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.32; H, 6.99; N, 4.02.

1-Benzyl-5-hydroxy-6-(4-methoxybenzyl)-4,5-dimethylpiperidine-2-one (9)——To a Grignard reagent, which was prepared from Mg turning (7.15 g; 0.294 mole) and MeI (41.7 g: 0.294 mole) in dry ether (50 ml), a solution of the above keto amide (**8**) (9.9 g; 0.0294 mole) in dry ether (20 ml) and dry THF (30 ml) was added drop by drop under stirring. After stirring for 5 hr, the resulting mixture was acidified with 10% HCl aq. solution under cooling and then extracted with ether in the presence of NaCl. The extract was dried over Na_2SO_4 and evaporated to give a residue, which was chromatographed on silica gel using $CHCl_3$ to afford the starting material (2.5 g) and the carbinol (7.38 g; 74.5%). Recrystallization of the latter from benzene gave **9** as colorless crystals, mp 119.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610, 3410 (OH), 1630 (C=O). NMR ($CDCl_3$) ppm: 0.95 (3H, s, C_5–Me), 1.04 (3H, d, J=6 Hz, C_4–Me), 2.40—3.66 (7H, m), 3.78 (3H, s, OMe), 5.30 (1H, d, J=15 Hz, $NC\underline{H}_2C_6H_5$), 6.71—7.27 (9H, m, ArH). Mass Spectrum m/e: 353 (M^+), 332. *Anal.* Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.58; H, 7.73; N, 3.96.

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocine-4-one (10)——A mixture of the above carbinol (**9**) (3.15 g; 8.92 mmole), AcOH (8 ml) and 47% HBr aq. solution (40 ml) was heated under reflux at 140—160° for 38 hr and, after cooling, water was added to the above reaction mixture, which was extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and distilled to give a syrup, which was purified by chromatography on silica gel, followed by recrystallization from $CHCl_3$–hexane to give a colorless powder (2.21 g; 77%), mp 118—120°, $[\alpha]_D^{20}$ 0° (in MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 (C=O). NMR ($CDCl_3$) ppm: 0.93 (3H, d, J=7 Hz, C_{11}–Me), 1.25 (3H, s, C_6–Me), 2.50 (2H, s, 5-CH_2), 4.03 and 5.37 (2H, two d, J=15 Hz, $NC\underline{H}_2C_6H_5$), 6.50—7.01 (3H, m, 7,8,10-H), 7.27 (5H, s, $C_6\underline{H}_5$). Mass Spectrum m/e: 321 (M^+). *Anal.* Calcd. for $C_{21}H_{23}O_2N$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.48; H, 7.32; N, 4.03.

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocine (11)——(a) A solution of the above amide (**10**) (300 mg) in dry xylene (5 ml) was added to a solution of 70% sodium bis(2-methoxyethoxy)aluminum hydride (2.7 g) in dry xylene (3 ml) and the resulting mixture was heated under reflux and stirring in an oil-bath for 5 hr under a current of nitrogen. After the reaction mixture had been acidified with 10% HCl, the organic layer separated was extracted with water. Both aqueous layers were combined and neutralized with 10% NH_4OH. The free base was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to give a caramel-like substance, which was identical with the authentic sample (**11**).

NMR ($CDCl_3$) ppm: 0.78 (3H, d, $J=7.5$ Hz, C_{11}–Me), 1.26 (3H, s, C_6–Me), 3.69 (2H, s, $NC\underline{H}_2C_6H_5$), 5.08 (1H, broad s, OH), 6.47—7.02 (3H, m, 7,8,10-H), 7.28 (5H, s, $C_6\underline{H}_5$). Recrystallization of the hydrochloride of **11** from iso-PrOH afforded colorless crystals (225 mg; 70%), mp 268—270° (decomp.), which was confirmed by mixed melting point test and IR spectral comparison (KBr) with the authentic sample.

(b) A mixture of the above amide (**10**) (16 mg) in dry dioxane (2 ml) was added drop by drop to a mixture of $LiAlH_4$ (4.5 mg) and dry dioxane (2 ml) under stirring and the resulting mixture was heated under reflux for 5 hr. After addition of water, an insoluble material was removed by filtration and the solvent was distilled off from the filtrate to give a syrup, which was extracted with $CHCl_3$. The extract was washed with saturated NH_4Cl solution and water, dried over Na_2SO_4 and evaporated to give a syrup, which was purified by chromatography on silica gel to afford **11** (8.3 mg; 54%). The IR and NMR spectra and thin-layer chromatography were identical with those of the above authentic sample.

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