REACTIONS AND SYNTHESES WITH ORGANOMETALLIC COMPOUNDS. IX. THE TOTAL SYNTHESIS OF ISO-6-HYDROXY-2'-(2-METHYLPROPYL)-3,3'-SPIRO-TETRAHYDROPYRROLIDINO-OXINDOLE VIA ARYLNICKEL COMPLEX

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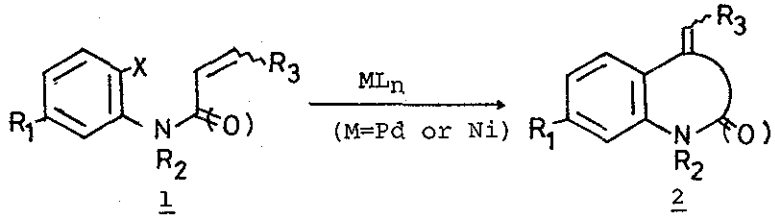
This paper is dedicated to Professor R.B.Woodward on the occasion of his 60th birthday

The total synthesis of the epimeric isomer of the natural alkaloid(4b) was achieved by use of the oxindole synthesis via arylnickel complex which was prepared from $Ni(PPh_3)_n$ and an aryl halide having the internal double bond.

It has been already reported that the aryl halide(1) could react with the internal double bond by use of the low valent metal complex(ML_n, M=Pd or Ni) to afford the heterocyclic compound (2).[1] This reaction was particularly useful for the synthesis of heterocyclic compounds having substituents on the aromatic ring, since the cyclization should occur *regiospecifically* at the initial position of the halogen atom of an aromatic ring. Thus, 6-methoxy-oxindole derivative(3) could be synthesized in a fairly good yield.[1]

Now, we would like to describe the total synthesis of the epimeric isomer of the natural alkaloid, 6-hydroxy-2'-(2-methylpropyl)-3,3'-spiro-tetrahydropyrrolidino-oxindole(4a) which was isolated from the root of the bark of *Eleagunus commutata* by James and the whole structure was established by an X-ray analysis.[2]

Chart 1.



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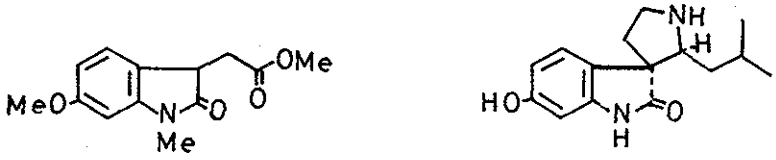


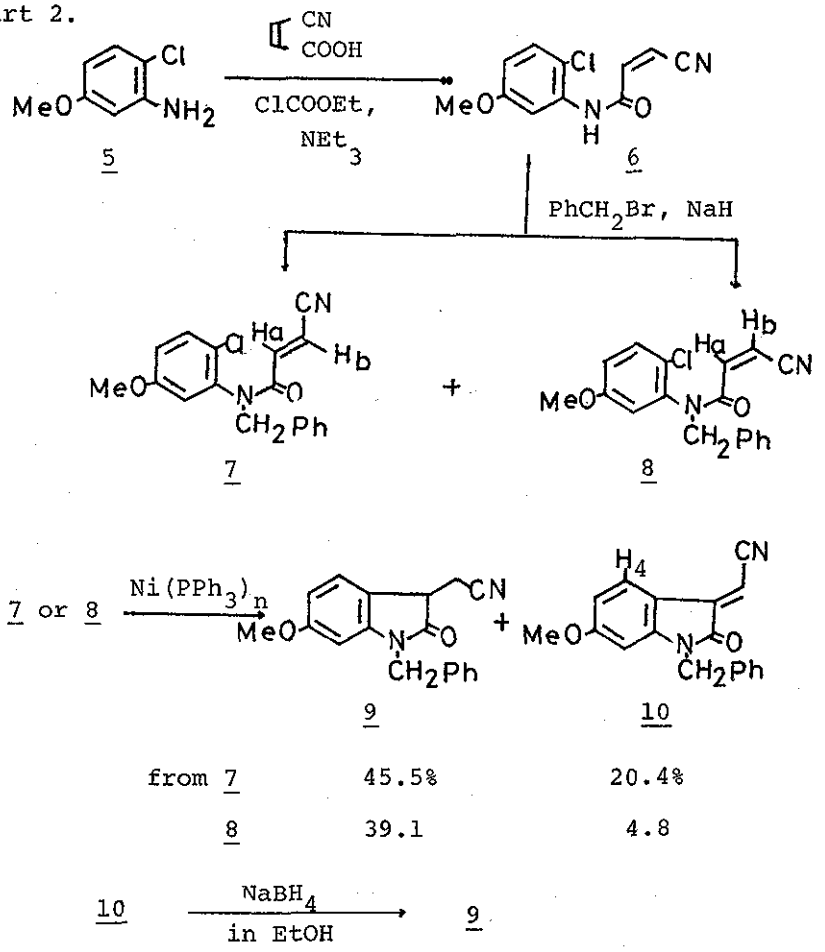
3 4a

Condensation of 2-chloro-5-methoxyaniline(5) and β-cyanoacrylic acid in the presence of ClCOOEt and NEt_3 afforded 6 in 51.5% yield along with the starting material(22%). Treatment of 6 with $PhCH_2Br$ and NaH gave 7(E-isomer)[colorless plates(from ether-hexane); mp 179-180°C; m/e 326, 328(M^+) and 291(M^+-Cl); ν_{max}(nujol) 2210(CN), 1660(CO)cm^{-1}; δ($CDCl_3$) 3.65(3H, s, CH_3O), 4.30(1H, d, J=14cps, PhCH), 4.58(1H, d, J=14cps, PhCH), 6.58(2H, s, CH=CH-CN), 6.70-7.55(8H, m, aromatic protons), 64.1% yield] and 8(Z-isomer)[colorless needles(from ether-hexane); mp 95.8-96.5°C; m/e 326, 328(M^+) and 291(M^+-Cl); ν_{max}(nujol) 2220(CN), 1650(CO)cm^{-1} δ($CDCl_3$) 3.61(3H, s, CH_3O), 4.31(1H, d, J=14cps, PhCH), 5.59(1H,

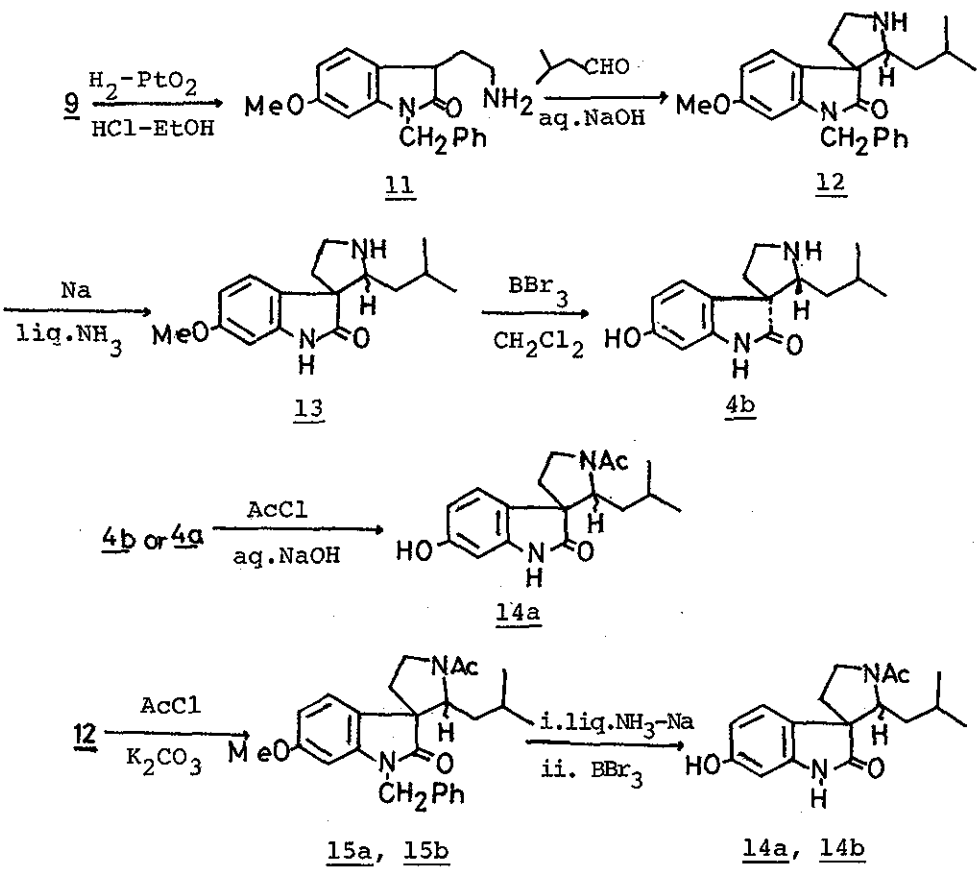
d, J=14cps, PhCH), 5.53(1H, d, J=11cps, CH=CHCN), 6.43(1H, d, J=11cps, CH=CHCN), 6.7-7.5(8H, m, aromatic protons), 12.2% yield], respectively.[3]

The compound(7) was warmed with $Ni(PPh_3)_n$, which was prepared from $NiCl_2(PPh_3)_2$ and Zn in the presence of PPh_3[4], in dimethylformamide at 60°C for 20 h to give an expected oxindole derivative(9) [colorless needles(from hexane-acetone); mp 127-128°C; m/e 292(M^+); ν_{max}(nujol) 2230(CN) and 1710(CO)cm^{-1}; $\delta(CDCl_3)$ 2.92(2H, m, CH_2CN), 3.74-3.85(1H, m, C(3)-H), 3.75(3H, s, CH_3O), 4.92(2H, s, $PhCH_2$), 6.40(1H, d, J=3cps,

Chart 2.



C(7)-H), 6.62(1H, q, J=3 and 8cps, C(5)-H), 7.47(1H, d, J=8cps, C(4)-H), and 7.35(5H, s, aromatic protons), 45.5% yield] and the unsaturated oxindole(10) [red crystals(from ethanol); mp 163-164°C; m/e 290 (M^+); ν_{max}(nujol) 2205(CN), and 1720(CO)cm^{-1}; $\delta(CDCl_3)$ 3.81(3H, s, CH_3O), 4.92(2H, s, $PhCH_2$), 6.22(1H, s, =CH-CN), 6.33(1H, d, J= 3cps), C(7)-H), 6.58(1H, q, J=3 and 9cps, C(5)-H), 7.35(5H, aromatic protons), and 8.07(1H, d, J=9cps, C(4)-H),[5] 20.4% yield]. The reduction with $NaBH_4$ in ethanol easily converted 10 into 9 in 70% yield. Similarly,the compound(8) was warmed with $Ni(PPh_3)_4$ which was prepared from $Ni(acac)_2$ and $AlEt_3$ in the presence of PPh_3[6] in dimethylformamide at 60°C for 20 h to give also 9(39.1%) and 10(4.8%). The reduction of 9 with Adams' catalyst in ethanol containing dilute hydrochloric acid afforded the 1-benzyl-2-hydroxy-6-methoxytryptamine hydrochloride(11) in 89% yield [colorless needles(from ethanol); mp 212-213°C; m/e 296(M^+-HCl), 279 and 266; ν_{max}(nujol) 1705(CO)cm^{-1}]. Condensation of 11 with isoamylaldehyde in the presence of aqueous NaOH in ethanol gave 12(96.5%), which was followed by debenzylation with liq.NH_3 and Na[7] to produce colorless oil of 13 in 71.2% yield [m/e 274(M^+), and 259; ν_{max}(nujol) 3320, 3200(NH), and 1700(CO)cm^{-1}]. Finally, the compound(13) was treated with BBr_3 in CH_2Cl_2 at room temperature for 18 h to give 4b as colorless needles[41% yield, mp 255-256.5°C (from acetone); m/e 260(M^+); UV(EtOH) λ_{max}265, 289, 297nm]. The spectral data(nmr, uv, and mass) and the behaviors of this compound(4b) on tlc developed with several solvent systems were fully identical with those of the natural product(4a), which was kindly sent by Prof. M.N.G.James, but the carbonyl absorption of ir



spectrum of the synthetic product(4b) [ν_{max}(KBr) 1680cm^{-1}] was not agreed with those of the natural product(4a) [ν_{max}(KBr) 1710cm^{-1}]. When the natural(4a) and synthetic product(4b) were treated with AcCl in an aqueous NaOH, respectively, the same compound(14a) was obtained in either case. Moreover, the compound(12) was treated with AcCl and K_2CO_3 in acetone to give two isomeric products which could be easily seperated by chromatography on silica gel. Each isomer was treated with liq.NH_3 and Na to eliminate the

benzyl group[7] and then with BBr_3 for cleavage of the methoxy group to afford 14a and 14b respectively. This product(14a) was identical with the acetyl derivative obtained from either 4a or 4b. These results suggest that one of the compounds(4a and 4b) must have been epimerized to the other under the basic condition. Therefore, our synthetic product(4b) should be an isomeric derivative of the natural alkaloid(4a) or a mixture of 4a and 4b, since the studies on the isomerization of oxindole alkaloids under acidic or basic conditions have been already reported[8] to support the present results.

Thus, there have been accomplished the total synthesis of the epimeric isomer of the natural alkaloid by utilization of organometallic complexes.

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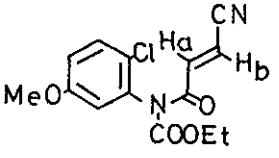
3. The structure of these isomers(7 and 8) were assigned on comparison with the chemical shifts and the coupling constants of H_a and H_b in the nmr spectra of 16(E-isomer)[$\delta(CDCl_3)$ 6.43

(d, 1H, J=16cps), 7.82(d, 1H, J=16cps)] and 17(Z-isomer) [δ($CDCl_3$) 5.83(d, 1H, J=11cps) and 7.55(d, 1H, J=11cps)]. The coupling constant(J=11cps) of H_a and H_b of 8 was corresponding to the above value of 17, for which assignment was made for 8 to be in Z-configuration. Therefore, E-configuration was given to the other isomer(7), although the corresponding signal of this compound appeared at δ 6.58 incidentally as a single peak.



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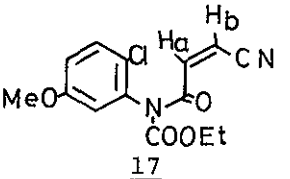

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