

SYNTHESIS OF THE NATURALLY OCCURRING 6-(3-METHYLBUTA-1,3-DIENYL)INDOLE VIA
ADVANCED FISCHER INDOLIZATION OF A 2-METHOXYPHENYLHYDRAZONE DERIVATIVE¹⁾

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Recently, it was reported isolation of the first isoprenylindole, 6-(3-methylbuta-1,3-dienyl)indole (1), from the seed of *Monodora tenuifolia*.²⁾ Now, we would like to show the synthesis of the product *via* the advanced Fischer indolization of a 2-methoxyphenylhydrazone derivative.

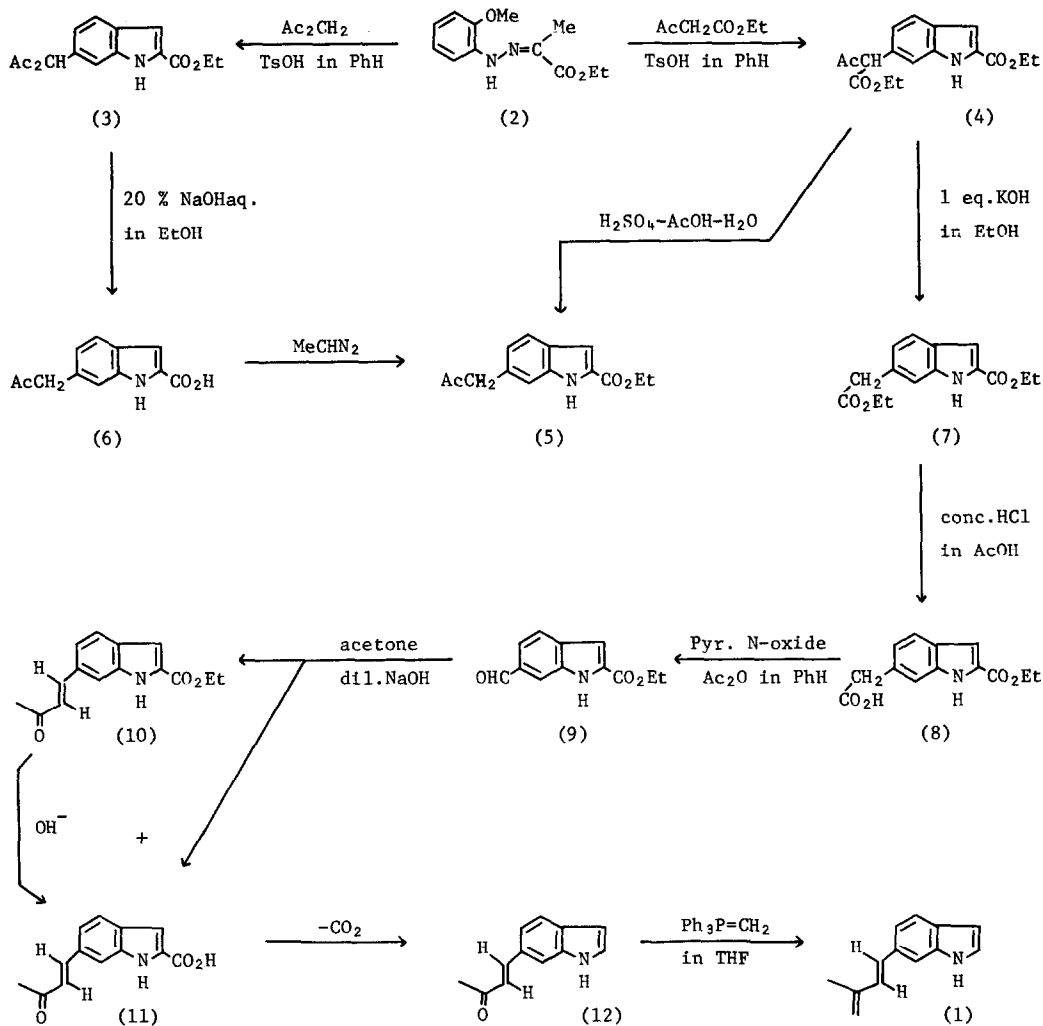
In the previous paper,³⁾ we showed that the Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (2) with anhydrous TsOH in abs. benzene in the presence of an excess amount of acetylacetone resulted in the formation of ethyl 6-(1-acetyl-2-oxopropyl)indole-2-carboxylate (3) as a main product. This experiment provided a short convenient method for syntheses of 6-substituted indole derivatives.

The key intermediate in our synthetic approach may be a derivative of indole-6-aldehyde, which was prepared as follows. Treatment of ethyl pyruvate 2-methoxyphenylhydrazone (2) (1 eq.) with anhydrous TsOH in abs. benzene in the presence of ethyl acetoacetate (15 eq.) followed by column chromatography on silicic acid gave ethyl α -acetyl-2-ethoxycarbonylindole-6-acetate (4), mp 116-118°, in 56.1 % yield. The structure of the product (4) was established by the chemical fact that treatment of 4 in mixed sulfuric and acetic acids gave ethyl 6-(2-oxopropyl)indole-2-carboxylate (5), mp 78.5-80.5°, in 52.5 % yield, which was identified by comparison with a sample prepared by esterification of the 6-(2-oxopropyl)indole-2-carboxylic acid³⁾ (6).

Treatment of 4 with potassium hydroxide (1 eq.) in ethanol afforded ethyl 2-ethoxycarbonylindole-6-acetate (7), mp 93-94°, [C₁₅H₁₇O₄N* (M⁺: m/e 275); IR (Nujol) cm⁻¹: 3308(NH), 1734, 1688 (C=O); NMR (CDCl₃) δ : 1.24 and 1.40(3H, t., J=7.0 Hz, CH₂CH₃) x 2, 3.69(2H, s., PhCH₂CO), 5.85 and 5.62(2H, q., J=7.0 Hz, OCH₂CH₃) x 2], in 69.2 % yield.

* All compounds given for formulae gave satisfactory elementary analyses.

Partial hydrolysis of the dicarboxylate (7) with conc. HCl in acetic acid produced 2-ethoxy-carbonylindole-6-acetic acid (8), mp 178.5-179.5°, [C₁₃H₁₃O₄N (M⁺: m/e 247); IR (Nujol) cm⁻¹: 3240(NH), 1712, 1669(C=O); NMR (DMSO-d₆) δ: 1.36(3H, t., J=7.5 Hz, CH₂CH₃), 3.60(2H, s., CH₂CO₂H), 4.32(2H, q., J=7.5 Hz, OCH₂CH₃), 6.93(1H, q., J=8.0 Hz and 1.8 Hz, C₅-H), 7.03(1H, d., J=2.5 Hz, C₃-H), 7.32(1H, diffused s., C₇-H), 7.51(1H, d., J=8.0 Hz, C₄-H), 11.65(1H, br. s., NH)], in 74.6 % yield.



In 1965, Cohen and Rüchardt⁴⁾ independently reported oxidation of derivatives of phenylacetic acid with pyridine N-oxide to give benzaldehyde derivatives. Then the above indole-6-acetic acid (8) was treated by this procedure to give ethyl 6-formylindole-2-carboxylate (9), mp 180-181.5°, [$C_{12}H_{11}O_3N$ (M^+ : m/e 217); IR (Nujol) cm^{-1} : 3321(NH), 1694, 1683(C=O); NMR (DMSO- d_6) δ : 1.39(3H, t., J=7.3 Hz, CH_2CH_3), 4.38(2H, q., J=7.3 Hz, OCH_2CH_3), 7.18(1H, d., J=2.3 Hz, C_3 -H), 7.55(1H, q., J=8.0 Hz and 2.0 Hz, C_5 -H), 7.78(1H, d., J=8.0 Hz, C_4 -H), 8.01(1H, diffused s., C_7 -H), 10.02(1H, s., CHO), 12.32(1H, br. s., NH)], in 48.0 % yield.

Aldol condensation of 9 with acetone by dil. NaOH aq. gave a mixture of ethyl 6-(3-oxo-1-butenyl)indole-2-carboxylate (10), mp 148-149°, [$C_{15}H_{15}O_3N$ (M^+ : m/e 257); IR (Nujol) cm^{-1} : 3308(NH), 1690, 1669(C=O); NMR ($CDCl_3$) δ : 1.43(3H, t., J=7.2 Hz, CH_2CH_3), 2.38(3H, s., $COCH_3$), 4.43(2H, q., J=7.2 Hz, OCH_2CH_3), 6.75(1H, d., J=16.0 Hz, $CH=CHCO$), 7.18(1H, diffused s., C_3 -H), 7.33(1H, q., J=8.0 Hz and 2.0 Hz, C_5 -H), 7.58(1H, diffused s., C_7 -H), 7.61(1H, d., J=16.0 Hz, $PhCH=CHCO$), 7.65(1H, d., J=8.0 Hz, C_4 -H), 9.49(1H, br. s., NH)] and its free acid (11), mp 283-285°(dec.), [$C_{13}H_{11}O_3N$ (M^+ : m/e 229): IR (Nujol) cm^{-1} : 3310(NH), 1688(C=O); NMR (DMSO- d_6) δ : 2.34(3H, s., $COCH_3$), 6.70(1H, d., J=16.0 Hz, $CH=CHCO$), 7.05(1H, d., J=2.0 Hz, C_3 -H), 7.38(1H, diffused d., J=8.5 Hz, C_5 -H), 7.64(1H, d., J=8.5 Hz, C_4 -H), 7.68(1H, diffused s., C_7 -H), 7.67(1H, d., J=16.0 Hz, $PhCH=CHCO$), 11.88(1H, br. s., NH)], in 24.6 % and 64.7 % yields respectively.

Hydrolysis of the ester (10) gave the free acid (11) quantitatively.

Decarboxylation of 11 with copper chromite in quinoline afforded 4-(6-indolyl)-3-butene-2-one (12), mp 135-137°, [$C_{12}H_{11}ON$ (M^+ : m/e 185); IR (Nujol) cm^{-1} : 3325(NH), 1675(C=O); NMR ($CDCl_3$) δ : 2.37(3H, s., $COCH_3$), 6.54(1H, m., C_2 or C_3 -H, changed to doublet by addition of D_2O), 6.73(1H, d., J=16.0 Hz, $CH=CHCO$), 7.28(1H, m., C_2 or C_3 -H), 7.30(1H, q., J=8.2 Hz and 2.0 Hz, C_5 -H), 7.57(1H, diffused s., C_7 -H), 7.61(1H, d., J=8.2 Hz, C_4 -H), 7.63(1H, d., J=16.0 Hz, $PhCH=CHCO$), 8.71(1H, br. s., NH)], in 60.7 % yield.

Wittig reaction of the above ketoindole (12) with methylenetriphenylphosphorane gave colorless leaflets, mp 126-130°, [$C_{13}H_{13}N$ (M^+ : m/e 183)], in 76.9 % yield, which was identified by direct comparison with an authentic sample of naturally occurring 6-(3-methylbuta-1,3-dienyl)-indole, mp 124-127°.

Taylor *et al*²⁾ did not mention about the geometry of the double bond of this natural product in their report of the structural establishment. We could establish the geometry of the double bond in this paper by the NMR decoupling technique. Decoupling experiments of 10, 11 and 12 allowed us to discriminate the signals due to the olefinic protons of them from those due to

the aromatic protons. All signals due to the olefinic protons appear as doublets whose coupling constants are 16.0 Hz. Such a large value of the coupling constants indicates the *trans* configuration of the double bond. Therefore, the geometrical configuration of the isoprenyl side chain of the natural product is assigned to be *trans*, because the relationship of the double bond should be maintained during Wittig reaction. In other words, the natural product can be safely designated as 6-(*trans*-3-methylbuta-1,3-dienyl)indole.

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References

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