

SYNTHESIS OF 4-SUBSTITUTED INDOLE DERIVATIVES¹Tatsuo Nagasaka, Tohru Yuge, and Sadao Ohki*Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

A general synthetic method of 4-substituted indoles was examined.

The Fischer indolization of phenylhydrazones (2, 3, 7, and 8) having chlorine on ortho position gave 7-chloro-4-substituted indoles (4, 9, and 10), which were converted to 4-substituted indoles (5 and 13) by catalytic hydrogenation.

Cyclization of 3-(2-ethoxycarbonyl-7-chloroindol-4-yl)propionic acid (10) with polyphosphoric acid (PPA) took place at the 5-position of indole ring to give a tricyclic ketone (14).

4-Substituted indole derivatives have been of interest for many years because of the psychotomimetic activity of compounds such as lysergic acid diethylamide (LSD) and psilocybin.² The intramolecular cyclization reaction to 4-position of indole ring has been reported recently.^{1, 3} However introduction of a certain substituent to 4-position by intermolecular reaction seems more difficult.⁴ In this paper we wish to report the useful synthetic method of 4-substituted indole derivatives.

The Fischer indolization of 3-substituted phenylhydrazone gives a mixture of 4- and 6-substituted indoles.⁵ 4-Substituted indoles may be selectively obtained from the phenylhydrazones (such as 2, 3, 7, and 8) having chlorine atom on the one ortho position.⁶ However, it was reported by Ishii et al.⁷ that the Fischer

indolization occurs at both the ortho positions of hydrazones even if substituents protect ortho positions. Therefore we examined the possibility for the synthesis of 4-substituted indoles via these chlorohydrazones.

The reaction of diazonium ions derived from aniline derivatives (1)⁸ with 3-carboxy-2-piperidone⁹ gave a mixture of phenylhydrazones (2 and 3) in a good yield which was easily separated each other by chromatography (silica gel, CHCl_3). The characteristic spectral data listed in Table 1 clearly demonstrate that the structure of 2 and 3 are Z- and E-forms, respectively. The ratio of the formation of 2 and 3 varied with the pH value of the reaction solution. The E-isomer (3) was transformed into the Z-isomer (2) quantitatively by refluxing it in ethanol.¹⁰

The Fischer indolization ($\text{BF}_3 \cdot \text{Et}_2\text{O}$, AcOH , 100° , 6 hr) of the hydrazone (2 or 3) gave 1,2,3,4-tetrahydro- β -carboline (4): 4a, mp $255-257^\circ$, 74 %; 4b, mp $205-207^\circ$, 67 %; 4c, mp $175-176^\circ$, 70 %. However the obvious difference between the yield of 4 from 2 and that from 3 was not observed. Catalytic hydrogenation (5% Pd-C, 60% MeOH) of chloro compounds (4) in the presence of ammonium acetate gave 5-substituted 1-oxo-tetrahydro- β -carboline (5): 5a, mp $262-264^\circ$, 65 %; 5b, mp $164-166^\circ$, 69 %; 5c, mp $181-182^\circ$, 61 %. 5 is a useful intermediate in order to induce to 4-substituted tryptamines⁹ and 5-substituted β -carboline.

The Japp-Klingemann reaction¹¹ of diazonium ion derived from amino acid (1d) with ethyl methylacetoacetate gave an azoester (6), uv (EtOH) λ_{max} 293, 317 nm, which was refluxed in ethanol containing sulfuric acid without purification to furnish hydrazones (7 and 8). Both the hydrazones were separated by chromatography (silica gel, CHCl_3). The yield in this two steps was very high. The Fischer indolization (ZnCl_2 , AcOH , reflux, 14 hr) of the hydrazone (7 or 8) gave 4-substituted indoles (9 and 10) and 6-substituted indole (11), the latter of which was presumably due to the 'abnormal' Fischer indolization pointed out by Ishii et al.⁷ : 9, mp $79-80^\circ$, 25 %; 10, mp $199-200^\circ$, 14 %; 11, mp $132-133^\circ$, 8 %.

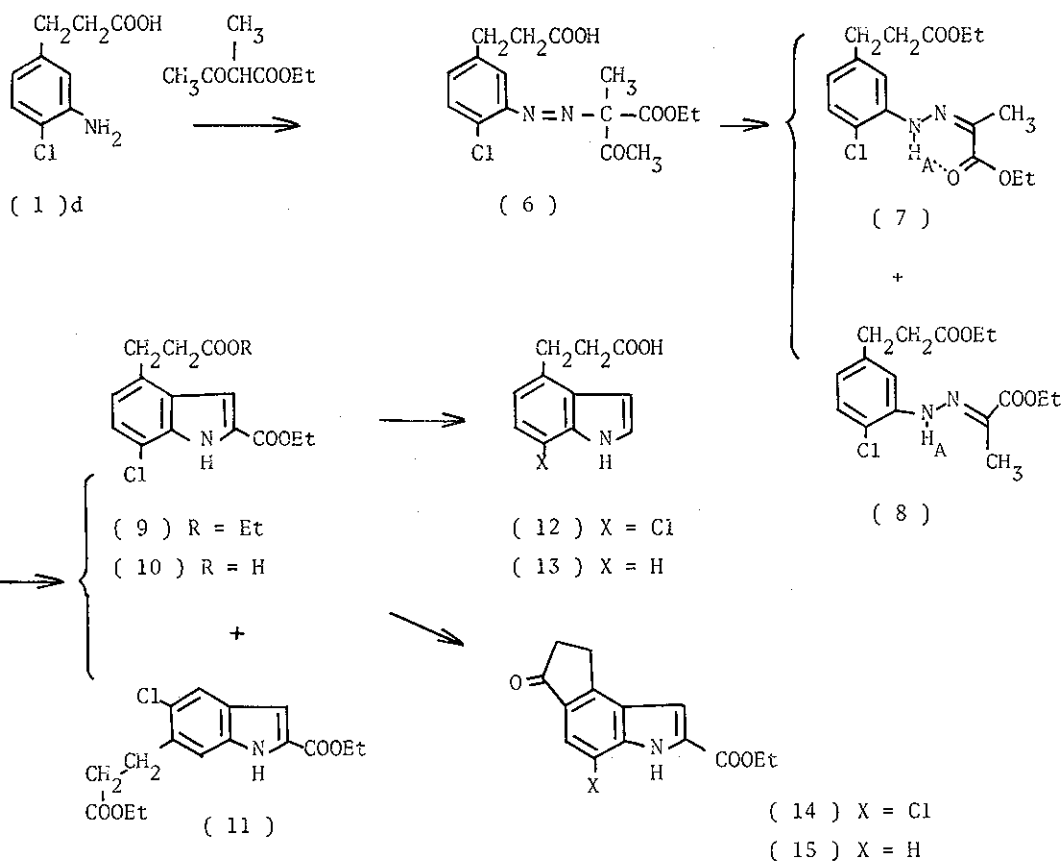
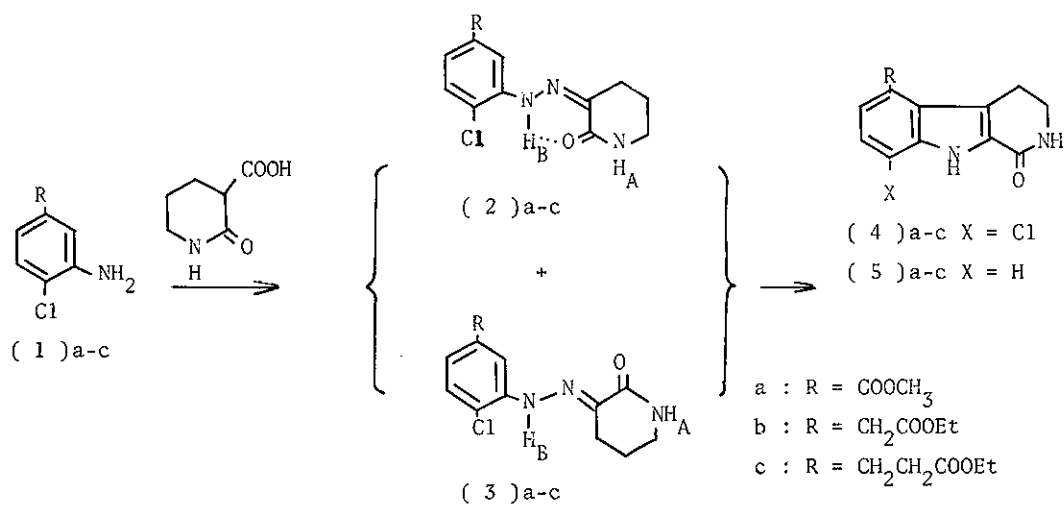


Table 1. Characteristic Spectral Data of Z-isomers (2 and 7) and E-isomers (3 and 8) of Phenylhydrazones

Compound	m p (°C)	IR (CHCl ₃) cm ⁻¹	NMR (CDCl ₃) δ (ppm)	UV (EtOH) λ max nm
2a	230-233	3390, 3150 (NH) 1720, 1645 (C=O)	H _A 6.48 H _B 13.30	233, 334
3a	198-200	3390, 3340 (NH) 1720, 1670 (C=O)	H _A 8.28 H _B 8.15	227, 309
2b	127-128	3400, 3150 (NH) 1730, 1650 (C=O)	H _A 6.63 H _B 13.30	241, 304 348
2c	113-114	3405, 3170 (NH) 1725, 1650 (C=O)	H _A 6.12 H _B 13.24	243, 305 348
3c	113-114	3405, 3345 (NH) 1725, 1670 (C=O)	H _A 8.28 H _B 8.15	234, 296 323
7	56-57	3230 (NH) 1720, 1680 (C=O)	H _A 12.24	215, 240 344
8	69-70	3350 (NH) 1725, 1705 (C=O)	H _A 8.12	213, 295 320

Saponification of ester (9 and 10) and the following decarboxylation (230-240°, 1 hr) in quinoline with copper powder gave an acid (12), mp 146-147° in 81 % yield. Catalytic hydrogenation of the chloro compound (12) described above gave 3-(indol-4-yl)propionic acid (13), mp 159-160°, in 86 % yield. Cyclization of 3-(2-ethoxycarbonyl-7-chloroindol-4-yl)propionic acid (10) with PPA gave a tricyclic ketone (14), mp 232-234°, in 51 % yield. NMR spectrum of 14 revealed that the cyclization of 10 took place at not the 3-position but the 5-position of indole ring. 14 was quantitatively converted to a ketone (15), mp 260-262°, by the same catalytic hydrogenation.

In conclusion the above investigation clarified that the Fischer indolization

of hydrazones masked with halogen on ortho position provides one of useful synthetic methods of 4-substituted indoles.

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8 All the new compounds in this communication gave satisfactory analytical and spectral values: 1b, oil (carboxylic acid, mp 115-116°); 1c, oil (acetate, mp 89-90°); 1d, mp 112-113°.

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