SYNTHESIS OF 4-SUBSTITUTED INDOLE DERIVATIVES[1]

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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.

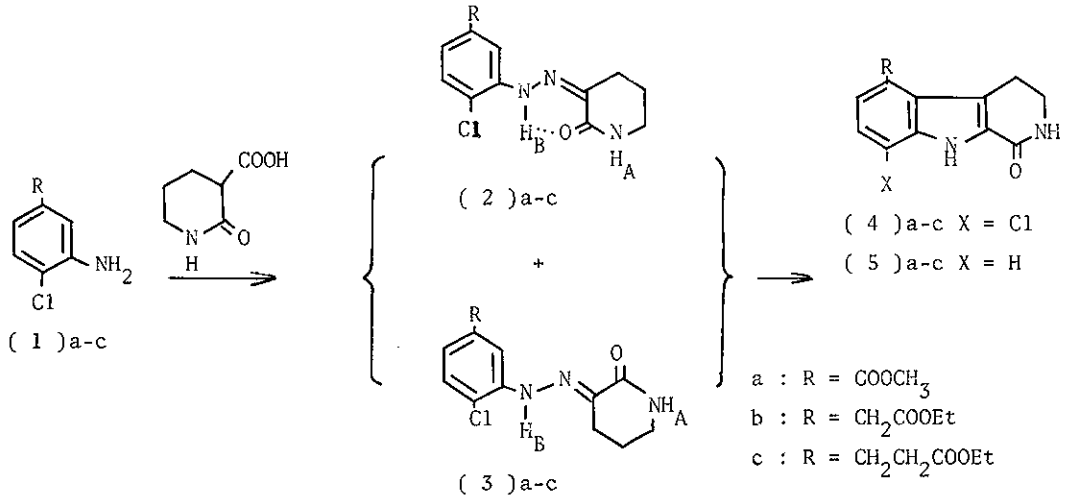
The Fischer indolization of 3-substituted phenylhydrazone gives a mixture of 4- and 6-substituted indoles.[5] 4-Substituted indoles may be selectively obtained from the phenylhydrazones (such as 2, 3, 7, and 8) having chlorine atom on the one ortho position.[6] However, it was reported by Ishii et al.[7] 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-piperidone[9] 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 ($BF_3 \cdot Et_2O$, AcOH, 100°, 6 hr) of the hydrazone (2 or 3) gave 1,2,3,4-tetrahydro-β-carbolines (4): 4a, mp 255-257°, 74 %; 4b, mp 205-207°, 67 %; 4c, mp 175-176°, 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-carbolines (5): 5a, mp 262-264°, 65 %; 5b, mp 164-166°, 69 %; 5c, mp 181-182°, 61 %. 5 is a useful intermediate in order to induce to 4-substituted tryptamines[9] and 5-substituted β-carbolines.

The Japp-Klingemann reaction[11] of diazonium ion derived from amino acid (1d) with ethyl methylacetoacetate gave an azoester (6), uv (EtOH) λmax 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°, 25 %; 10, mp 199-200°, 14 %; 11, mp 132-133°, 8 %.


(1)a-c
(2)a-c
(3)a-c
(4)a-c X = Cl
(5)a-c X = H
a : R = COOCH3
b : R = CH2COOEt
c : R = CH2CH2COOEt

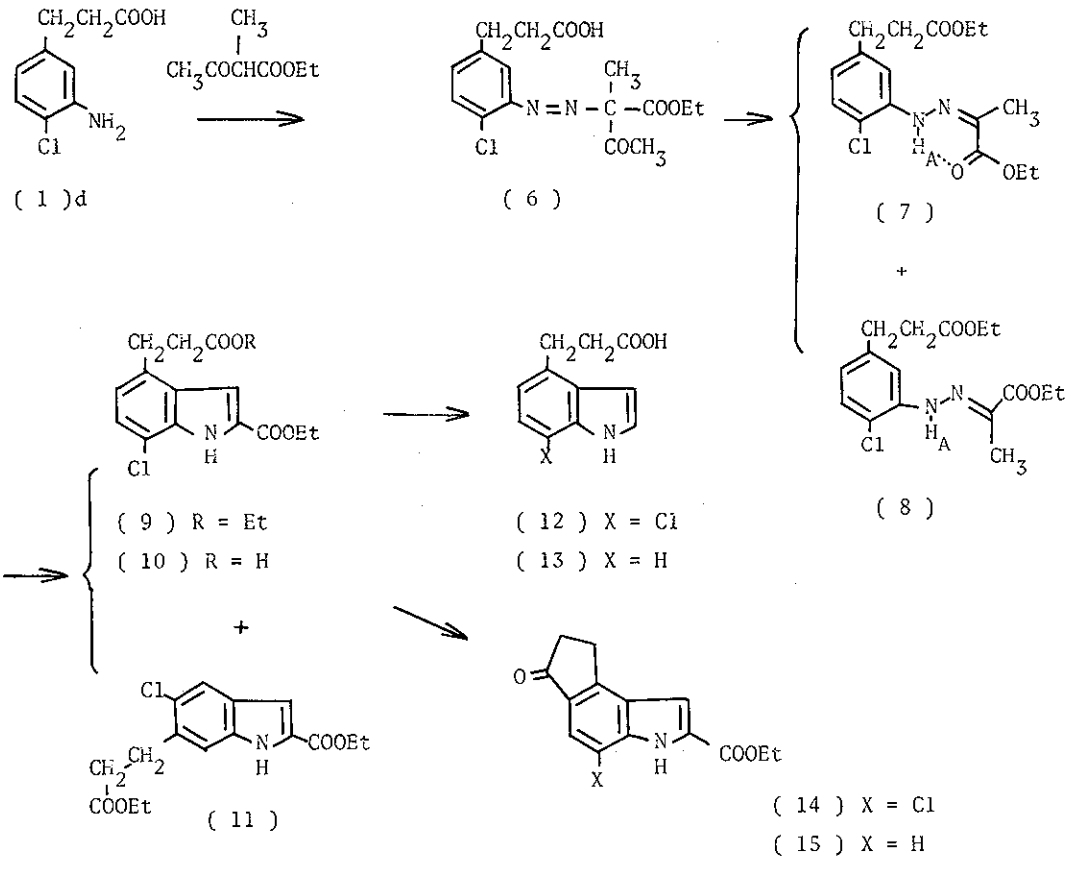

(1)d
(6)
(7)
(8)
(9) R = Et
(10) R = H
(11)
(12) X = Cl
(13) X = H
(14) X = Cl
(15) X = H

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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