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THE SUBSTITUTION AND MIGRATION OF METHOXYL GROUP IN THE FISCHER INDOLIZATION OF ETHYL PYRUVATE 2-METHOXYPHENYLHYDRAZONE

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In the previous publication[1], we showed that treatment of 2,5-dimethoxyphenylhydrazine or ethyl phenylpyruvate 2,5-dimethoxyphenylhydrazone with ethanolic hydrogen chloride afforded 2,5-dimethoxy-p-phenylenediamine as a main product. In this communication, we wish to represent migration of methoxyl group and substitution of it with some nucleophiles in the Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone. In 1958, Pappalardo et al[2] found that treatment of this phenylhydrazone with ethanolic hydrogen chloride gave an unidentified indolic compound, mp 168°, instead of the expected ethyl 7-methoxyindole-2-carboxylate, which was obtained by cyclization of the same phenylhydrazone in mixed acetic and sulfuric acids. This description prompts us to reinvestigate their experiments as a clue of establishment of mechanism of the Fischer indolization.

Japp-Klingemann reaction of o-anisidine and ethyl α-methylacetoacetate followed by column chromatography on silicic acid gave the syn-hydrazone (1) [mp 90-90.5°, IR(CCl_4) 3271(NH), 1681 (C=O), NMR(CCl_4, τ) -2.08(1H, br. s.,NH)] and the anti-hydrazone (2) [mp 74.5-76°, IR(CCl_4) 3368 (NH), 1703(C=O), NMR(CCl_4, τ) 2.08(1H, br. s., NH)]. Indolization of the syn-hydrazone (1) with 3N-ethanolic hydrogen chloride gave a mixture of three indolic compounds detected by t.l.c.. Chromatography of this mixture on silicic acid, in the order of elution, afforded ethyl 6-chloroindole-2-carboxylate (3) [$C_{11}H_{10}O_2NCl$[*1], mp 180-182°, NMR no OCH_3, Mass spectrum M^++2 at m/e 225 with a 34% intensity of M^+(m/e 223), Beilstein's test positive], the expected ethyl 7-methoxyindole-2-carboxylate (4) [$C_{12}H_{13}O_3N$, mp 117.5-118.5°, NMR(CCl_4, τ) 6.03(3H, s., OCH_3)] and ethyl 6-ethoxyindole-2-carboxylate (5) [$C_{13}H_{15}O_3N$, mp 118-120°, NMR($CDCl_3$, τ) 8.61(3H, t., J=7.5cps, CH_3), 8.56(3H, t., J=7.5cps, CH_3), 5.95(2H, q., J=7.5cps, $-OCH_2-$), 5.63(2H, q., J=7.5cps, $-OCH_2$)].

[*1] All compounds given for formulae gave satisfactory elementary analyses.

Structure of these three compounds were confirmed by direct comparison with samples prepared by Reissert's cyclization of the corresponding nitrotoluene derivatives. Furthermore, we eventually prepared ethyl 5-chloroindole-2-carboxylate (6), mp 171-172°, and confirmed this indole was not identical with the chloroindole (3), obtained above. When sulfuric acid was used in place of hydrogen chloride as a reagent, (5) was isolated with two other indolic compounds. (see Table I on yielding). Therefore, it seems that the substitution of methoxyl group with a nucleophile would be fairly common in Fischer indolization of derivatives of 2-methoxyphenylhydrazone.

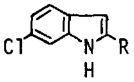
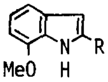
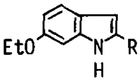
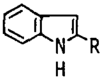
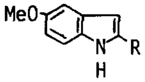
On the other hand, treatment of (1) with boron trifluoride in acetic acid or ethyl acetate gave a mixture of three indolic compounds showed two new spots on t.l.c. and separated by chromatography on silicic acid. In the order of elution, these indoles were respectively identified as ethyl indole-2-carboxylate (7) [$C_{11}H_{11}O_2N$, mp 123-124°, NMR no OCH_3], (4) and ethyl 5-methoxyindole-2-carboxylate (8) [$C_{12}H_{13}O_3N$, mp 160-161.5°, NMR($CDCl_3$, τ), 6.18(3H, s., OCH_3)] by comparison with authentic samples which were prepared by Fischer indolization of ethyl pyruvate phenyl- and p-methoxyphenylhydrazone. Furthermore, treatment of (1) with mixed acetic and sulfuric acids gave three indolic compounds, (4), (7) and (8), while Pappalardo et al isolated (4) as a sole product of the same reaction. Carlin et al[3], two decade ago, found the migration of halogen from ortho to para in the Fischer indolization of 2,6-dichlorophenylhydrazone derivatives, but such a migration of methoxyl group is still remained as unknown up to now.

In the current paper, Gannon et al[4] reported on the cyclization of (1) with the saturated ethanolic hydrogen chloride and offered a mechanism of substitution of methoxyl group with chlorine atom. They isolated two indolic compounds from the reaction mixture, 3 -chloroindole-2-carboxylate (9), and pointed out the presence of two other indolic compounds in the recrystallization mother liquors, (4) by t.l.c. and (5) by the fact that the mass spectrum of the indolic mixture showed a peak at m/e 233. Superficially, their results are slightly different from ours, particularly on the yielding of each indoles, but such discrepancies may depend upon the concentration of hydrogen chloride in the reaction mixture.

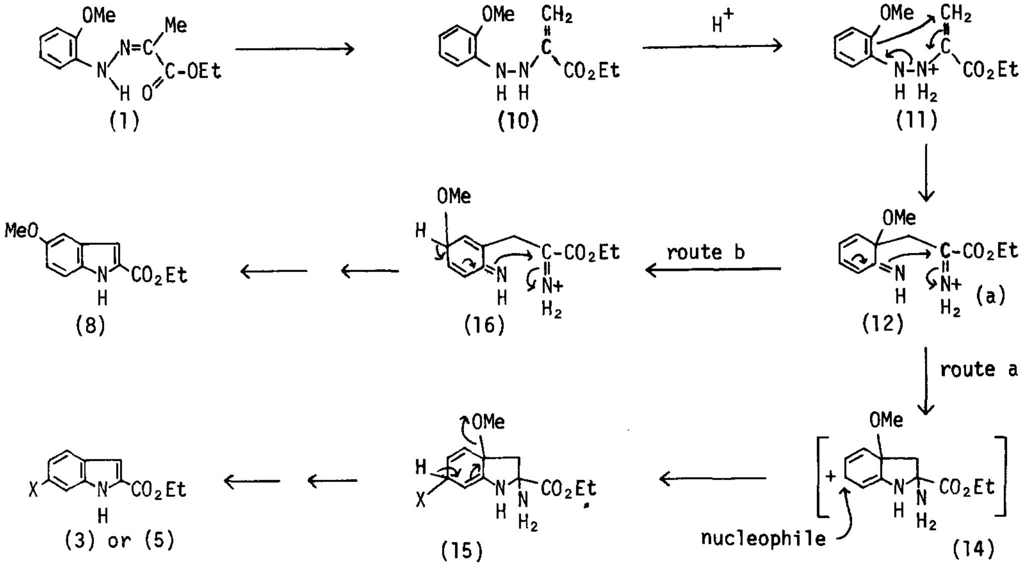
Now, we would like to propose our mechanism including the substitution and migration of methoxyl group as illustrated in Scheme I. According to the Robinson's mechanism[5] of Fischer indolization accepted most widely, carbon-carbon bond formation of the ene-hydrazine intermediate (11) gives (12) which by attack of the ring imino nitrogen to the immonium carbon and shift of the double bond leads to the formation of more stable carbonium ion at C_6 of indole (14). Consequently, entering of chlorine atom or ethoxyl group into C_6 is explained by attack of the

Table I. Products of the Fischer Indole Syntheses of Ethyl Pyruvate 2-Methoxyphenylhydrazone

$R = CO_2Et$

products / reagents	 (3)	 (4)	 (5)	 (7)	 (8)
3N·HCl-EtOH	18.4 %	15.8 %	3.8 %	not isolated	not isolated
H_2SO_4-EtOH		12.8 %	2.0 %	0.2 %	not isolated
$BF_3\cdot OEt_2$-AcOH		13.5 %		2.1 %	0.85 %
$BF_3\cdot OEt_2$-AcOEt		15.0 %		2.7 %	4.7 %
H_2SO_4-AcOH		5.0 %		0.22 %	0.32 %

Scheme I (nucleophile = X^- or EtOH)



nucleophile to the carbonium ion or perhaps this process could be concertedly occurred with cyclization of pyrrole ring, route (a). On the other hand, if the cyclization is preceded by the migration of methoxyl group from ortho to para position, deprotonation from C_5 occurred more easily than entering of a nucleophile into C_6 to give a 5-methoxyindolic compound, route (b). Work on the mechanism of the migration of methoxyl group is still in progress.

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