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Development of "Abnormal" Fischer Indolization to Syntheses of 3,6′-Biindole and Its Derivatives[1]

In the previous paper,[2] we showed that Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (I) with ethanolic hydrogen chloride abnormally gave 6-substituted indole products and others. The proposed mechanism[2] suggested us that some nucleophile present in the reaction mixture could react with I to give a 6-substituted indole derivative, if a suitable condition was adopted. We would like to show a development of the above "abnormal" reaction to the synthetic method of 3,6′-biindole and its derivatives in this paper.

For the sake of confirmation of our postulate, we examined cyclization of I in the presence of an enolizable dicarbonyl compound which would act as a nucleophile even in acidic media. Treatment of a solution of I and acetylacetone in benzene with TsOH gave ethyl

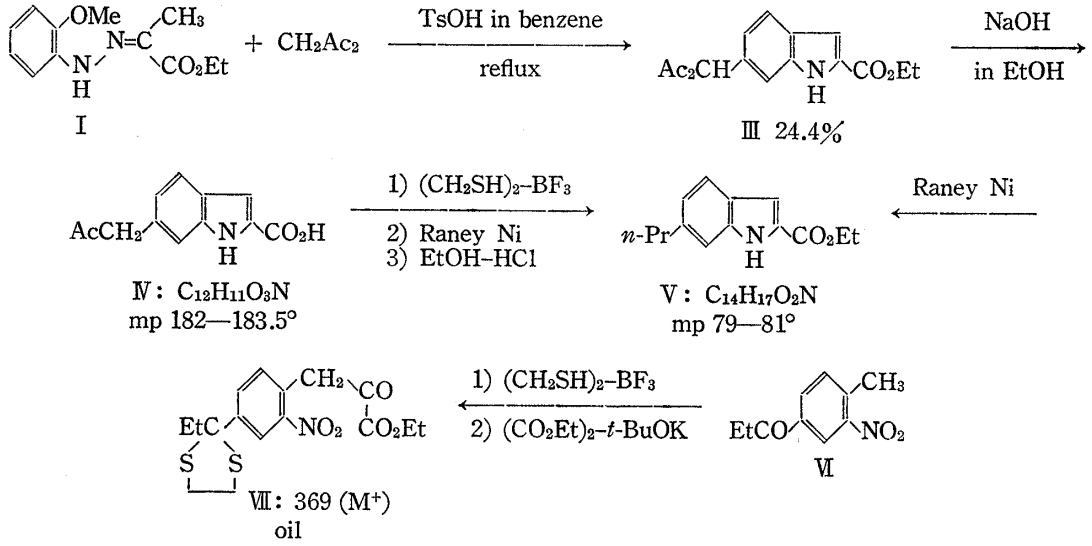


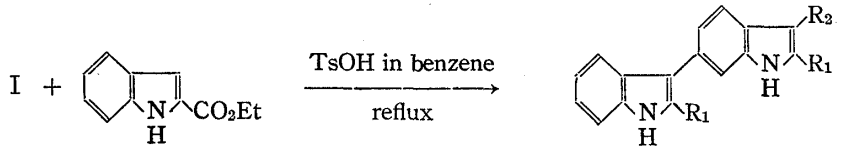
Chart 1

6-(1-acetyl-2-oxopropyl) indole-2-carboxylate (III), [$C_{16}H_{17}O_4N$],[3] mp 149—151°. A sequence of degradative reaction of III gave ethyl 6-n-propylindole-2-carboxylate (V), which was identical with sample prepared from 4-methyl-3-nitropropiophenone[4] (VI) *via* Reissert's method[5] as shown in Chart 1. These chemical evidences established the correctness of our assumption.

It is well known that an indole derivative is subject to an electrophilic attack to give an N- or C_3-substituted product. Some indole derivatives, therefore, may be nucleophiles on the above indolization. However, it is also well known that indole itself is polymerized under the acidic condition.[6] Then, we examined the behavior of indole when refluxed with TsOH in benzene and observed its polymerization to a trimer. On the other hand, ethyl

1) This communication forms Part IV of this series, "H. Ishii, *et al.*, Fischer indolization and Its Related Compounds"; Part III: H. Ishii, K. Harada, K. Abe, K. Doki and N. Ikeda, *Yakugaku Zasshi*, **91**, 947 (1971).
2) H. Ishii, Y. Murakami, Y. Suzuki and N. Ikeda, *Tetrahedron Letters*, **1970**, 1181.
3) All compounds given by formulae afforded satisfactory elemental analyses.
4) W.H. Hartung and J.C. Munch, *J. Am. Chem. Soc.*, **51**, 2570 (1929).
5) R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York and London, 1970.
6) G.F. Smith, "Advances in Heterocyclic Chemistry," ed. by A.R. Katritzky, Academic Press, New York and London, 1963, Vol. 2, p. 300.

indole-2-carboxylate[7] (VIII) was found to be suitable for our purpose. A mixture of I and VIII (1:2) was treated under the above condition to give diethyl 3,6′-biindole-2,2′-dicarboxylate (IX), mp 203—204°, [$C_{22}H_{20}O_4N_2$, NMR (DMSO-d_6) τ: 2.81 (1H, d, J=1.5 Hz, C_3-H), −1.77 (2H, s, 2×NH)], in 36% yield. The fact that IX has only one C_3-H signal means that a C_3-carbon of one indole unit links with a benzene protion of the other. However, the signals due to aromatic protons of IX are so complicated by overlapping that no information on the benzene terminus of the linkage can be obtained.



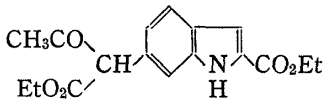
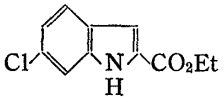
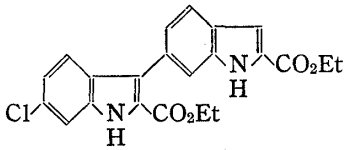
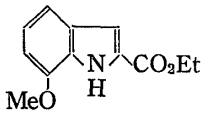
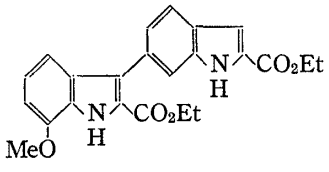
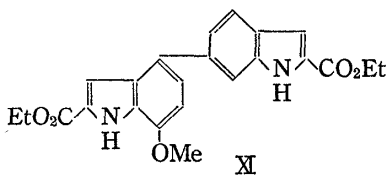
VIII

IX: R_1=CO_2Et, R_2=H
X: R_1=CO_2Et, R_2=CHO
II: R_1=R_2=H

Chart 2

Formylation of IX with Vilsmeier reagent gave its 3-formyl derivative (X), mp >290°, [$C_{23}H_{20}O_5N_2$], in 87.6%, whose structure was confirmed by the fact that two NH signals were observed as singlets at −1.87 and −2.74 τ in its nuclear magnetic resonance (NMR) spectrum (DMSO-d_6), but not the C_3-H signal. The formyl derivative (X) has a 1H doublet (J=8.8 Hz) at 1.70 τ which can be assigned to C_4-H, since it appeared in the lower field by 50—130 Hz than other six aromatic protons of X. This phenomenon can be understood in terms of an anisotropic effect of the C_3-aldehydic carbonyl group. Decoupling experiments allowed us to distinguish the C_5-H quartet (J=8.8 and 1.5 Hz) from other signals. These spectral evidences imply the presence of protons at C_4, C_5 and C_7 of the formylated indole nucleus. In other words, another terminus of the biindole linkage is placed on C_6. The evidences mentioned so far completely established the structure of IX.

Table I

Nucleophile	Product	Yield (%)	mp (°C)
$CH_3COCH_2CO_2Et$		19.4	116—118
		3.75	243—244
		16.3	205—207
	 XI	10.8	234—236

7) J. Elks, D.F. Elliott and B.A. Hems, *J. Chem. Soc.*, **1944**, 629.

Hydrolysis of IX with KOH followed by decarboxylation with copper chromite[8] in quinoline gave II, mp 157—158.5°, [$C_{16}H_{12}N_2$], in 60% yield.

Moreover, we synthesized some other 6-substituted indole and 3,6′-biindole derivatives listed in Table I. When ethyl 7-methoxyindole-2-carboxylate[2] was used as a nucleophile, two isomeric biindole derivatives were isolated. In 1969, Gannon, *et al.*[9] reported the isolation of an undefined biindole derivative, mp 233—235°, from the reaction mixture of Fischer indolization of I with ethanolic hydrogen chloride. From the identities of the physical properties of both products, we believe that Gannon, *et al.* obtained diethyl 7-methoxy-4,6′-biindole-2,2′-dicarboxylate (XI) on their experiment.

Now, we can develop the abnormal Fischer indolization to a unique synthetic method.

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8) W.A. Lazier and H.A. Arnold, *Org. Synth. Coll. Voll.*, **2**, 142 (1943).
9) W.F. Gannon, J.D. Benigni, D.E. Dickson and R.L. Minnis, *J. Org. Chem.*, **34**, 3002 (1969).

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Stereostructure of Rhodojaponin V and VII, Toxins of *Rhododendron japonicum*

From the flowers of *Rhododendron japonicum* SURINGER (Ericaceae), a famous poisonous tree in Japan, four toxic diterpenoids, rhodojaponin I, II, III,[1] and IV,[2] have been isolated. We have further noticed in the flowers the presence of other constituents which have been isolated and termed as rhodojaponin V and VII (R–V and R–VII). R–V has also been found in the roots, together with sparassol[3] and methyl orsellinate.

R–V, $C_{22}H_{34}O_7$ (M^+—18 *m/e* 392), mp 240—242°, was shown by the infrared and nuclear magnetic resonance (NMR) spectra to have four tertiary methyls (1.35, 1.47, 1.55, 1.87 ppm), hydroxyls (3560, 3440 cm^{-1}) one of which is secondary (4.00 ppm), one secondary O-acetyl (1725, 1230 cm^{-1}, 2.02, 6.10 ppm), and an epoxide (3.24, 4.15 ppm). Alkaline hydrolysis and acetylation of R–V were carried out to give deacetyl-R–V and R–V monoacetate, respectively, which were found to be identical with R–III (III)[1] and R–I (IV),[1] respectively. The C-14 hydrogen signal in the NMR spectrum of R–V appears at a lower-field region (6.10 ppm) as compared with that of R–III (III) (4.94 ppm), demonstrating that the C-14 hydroxyl is acetylated. R–V is thus concluded to have stereostructure I.

R–VII, $C_{24}H_{38}O_9$, mp 231—234°, was indicated by the spectral properties to possess four tertiary methyls (1.34, 1.46, 1.47, 1.80 ppm), hydroxyls (3425 cm^{-1}) two of which are secondary (3.98, 5.01 ppm, formation of di-O-acetyl-R–VII (V)), and two secondary O-acetyls

1) H. Hikino, K. Ito, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1078 (1969).
2) H. Hikino, N. Shoji, S. Koriyama, T. Ohta, Y. Hikino, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 2357 (1970).
3) K. Kinoshita, *Nippon Kagaku Kaishi*, **53**, 865 (1932).