# A NOVEL DIMERIZATION OF 1-HYDROXYINDOLES[1]

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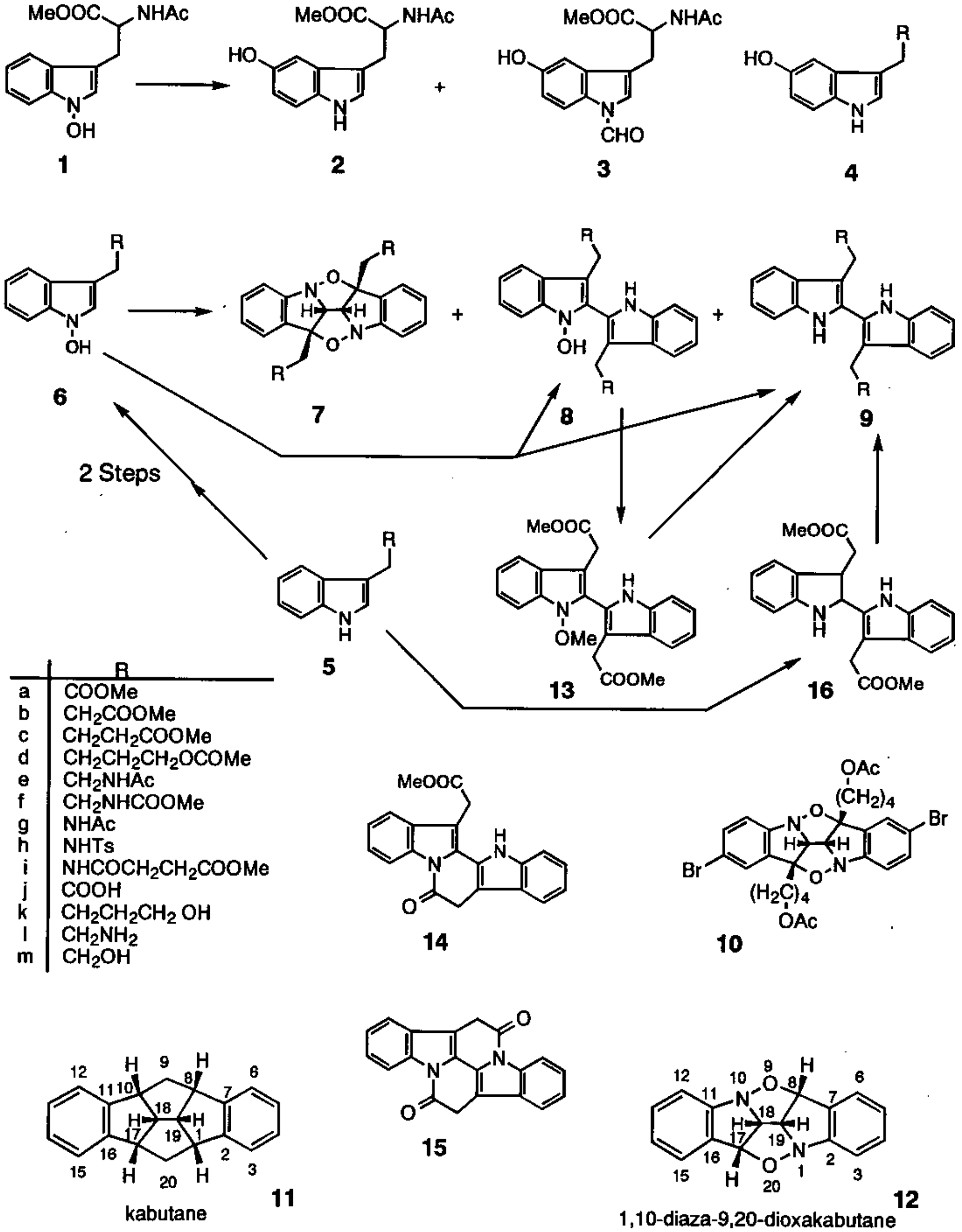
*Abstract* —— 1-Hydroxyindoles are sensitive to acids and undergo four types of competing reactions; dehydroxylation, nucleophilic substitution, dimerization, and formation of hexacyclic dimer. The direction of the reaction seems to be determined depending on the subtle balance of substrate structures, acids, and reaction conditions. Stuctures of variety of products are unequivocally determined by X-ray single crystallographic analyses and chemical correlations.

We have disclosed that 1-hydroxy-[2] and 1-methoxyindoles[2] undergo nucleophilic substitution reactions.[3] For example, treatment of *N*b-acetyl-1-hydroxytryptophan methyl ester (**1**) with 85% formic acid (HCOOH) at 61°C produced 5-hydroxy- (**2**) and 1-formyl-5-hydroxytryptophan derivatives (**3**) in 67 and 12% yields, respectively (Scheme 1).[3b,d,f]

On the basis of these experiments, we examined the reaction of methyl 1-hydroxyindole-3-acetate (**6a**), readily available from methyl indole-3-acetate (**5a**),[2] with 85% HCOOH expecting the formation of methyl 5-hydroxyindole-3-acetate (**4 a**). Surprisingly **4a** was not formed at all, instead a novel type of dimerization occurred resulting in the formation of hexacyclic dimer (**7a**), 1-hydroxydimer (**8a**), and **5a** in 20, 8, and 14% yields, respectively. Whereas a mixture of trifluoroacetic acid (TFA) and acetonitrile (1:1, v/v) reacted with **6a** affording 3% yield of another dimer (**9a**) together with **7a** (27%), **8a** (5%), and **5a** (14%). When TFA alone was used at room temperature, formation of **7a** was not observed, and **8a** and **9a** were produced in 48 and 17% yields, respectively.

Methyl 1-hydroxyindole-3-propionate (**6b**) also afforded **7b**, **8b**, and **5b** in 39, 11, and 26% yields, respectively, by the reaction with 85% HCOOH. Under similar reaction conditions, methyl 1-hydroxyindole-3-butylate (**6c**) gave **7c** (47%) and **5c** (28%), while 1-hydroxy-3-(4-acetoxybutyl)indole (**6d**) produced **7d** (36%) and **8d** (41%). By contrast, *N*b-acetyl- (**6e**) and *N*b-methoxycarbonyl-1-hydroxytryptamine (**6f**) produced only 5-hydroxy compounds (**4e**, **4f**, and its formyl derivatives) in the reaction with 85% HCOOH as reported previously.[3] Of particular interest are the reactions of these compounds (**6e** and **6f**) with other acids. Thus, when **6e** was reacted

## Scheme 1



| | R |
|---|---|
| a | COOMe |
| b | $CH_2COOMe$ |
| c | $CH_2CH_2COOMe$ |
| d | $CH_2CH_2CH_2OCOMe$ |
| e | $CH_2NHAc$ |
| f | $CH_2NHCOOMe$ |
| g | NHAc |
| h | NHTs |
| i | $NHCOCH_2CH_2COOMe$ |
| j | COOH |
| k | $CH_2CH_2CH_2$ OH |
| l | $CH_2NH_2$ |
| m | $CH_2OH$ |

kabutane

all-*cis* -dibenzo[*b,g*]tetracyclo-[7.2.1.$0^{4,11}$. $0^{6,10}$]dodecane

1,10-diaza-9,20-dioxakabutane

all-*cis* -1,10-diaza-9,20-dioxadibenzo[*b,g*]-tetracyclo[7.2.1.$0^{4,11}$. $0^{6,10}$]dodecane with TFA, **7e**, **9e**, and *N*b-acetyl-5-hydroxytryptamine (**4e**) were produced in 33, 17, and 13% yields, respectively. However, if 85% phosphoric acid was employed to **6e**, **4e** was not formed, and **7e**, **5e**, and unreacted starting material (**6e**) were obtained in 44, 16, and 5% yields, respectively. The carbamate (**6f**), contrasted with seemingly similar substrate (**6e**), produced 5-hydroxy-*N*b-methoxycarbonyltryptamine (**4f**, 16%) together with **7f** (9%) and **5f** (13%) by the reaction with 85% phosphoric acid.

In the cases of 3-aminomethyl-1-hydroxyindole derivatives, such as **6g**, **6h**, and **6i**, no isolable products were obtained because tar was formed immediately after addition of such weak acid as 85% HCOOH.

Alkaline hydrolysis of **7a**, **7d**, and **7e** with aqueous 2N-NaOH afforded **7j** (97%), **7k** (98%), and **7l** (75%), respectively. Reduction of **7a** and **7c** with $LiAlH_4$ produced **7m** (81%) and **7k** (99%), respectively. Since the diazotization of **7l** with $NaNO_2$-AcOH and subsequent alkaline treatment produced **7m** in 71% yield, structures of **7a** and **7e** are correlated each other. Furthermore, bromination of **7d** in $CHCl_3$ afforded dibromo compound (**10**) in 66% yield. Among these various derivatives, only **7a** was found to be suitable for structural determination by X-ray single crystallographic analysis. The results shown in Figure 1 clearly show that the hexacyclic dimer (**7a**) has characteristic Kabuto (Japanese ancient soldiers helmet) like structure in shape. So, we would like to give kabutane as the short name for this type of parent skeleton, all-*cis*-dibenzo[*b*,*g*]tetracyclo[$7.2.1.0^{4,11}.0^{6,10}$]-dodecane (**11**). Accordingly, mother skeleton (**12**) of hexacyclic dimers is termed 1,10-diaza-9,20-dioxakabutane. The structure of **8a** was established as follows. Thus, methylation with diazomethane led **8a** to 1-methoxy dimer (**13**) in 92% yield revealing the existences of 1-hydroxy and 1-methoxy group in the respective molecules (**8a** and **13**). The compound (**13**) was also suitable crystals for X-ray single crystallographic analysis and the results shown in Figure 2 confirmed its structure.

Catalytic hydrogenation of **13** with 10% Pd/C removed 1-methoxy group to afford dimer (**9a**) in 94% yield. Although subsequent treatment of **9a** with 2N-$H_2SO_4$ afforded **14** in 93% yield, formation of **15** was not observed at all. On the other hand, 2,3-dihydro-2,2'-bisindole (**16**) was prepared in 94% yield according to Bergman's report[3] reacting **5a** with TFA. Oxidation of **16** with dichlorodicyanoquinone produced **9a** (75%), which was identical with that derived from 1-methoxy dimer (**13**).

In conclusion, we found that 1-hydroxyindole compounds are sensitive to acids and undergo four types of competing reactions; dehydroxylation, nucleophilic substitution, dimerization, and formation of hexacyclic dimer. The direction of the reaction seems to be determined depending on the subtle balance of substrate structures, acids, and reaction conditions. We are continuing investigations to clarify these complex factors and to expand the chemistry of 8,17-disubstituted 1,10-diaza-9,20-dioxakabutanes.

**Figure 1**

**ORTEP Drawing of 7a**

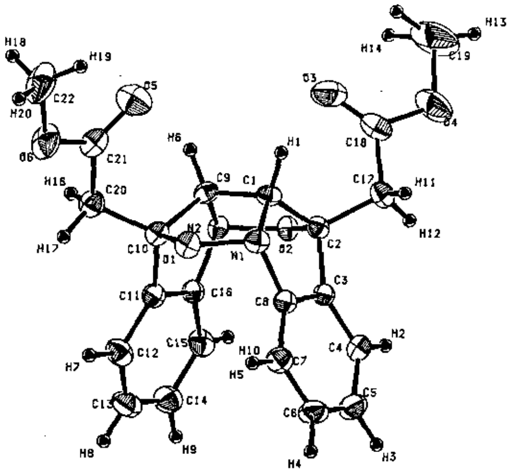
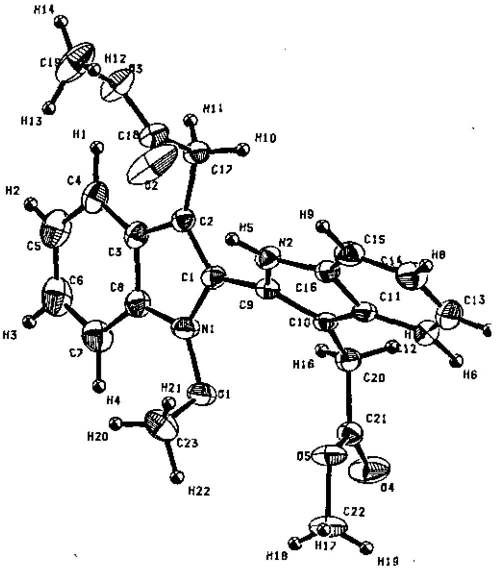


**Figure 2**

**ORTEP Drawing of 13**



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