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著者	Hasegawa Masakazu, Tabata Matsuko, Satoh Keiichi, Yamada Fumio, Somei Masanori
journal or publication title	Heterocycles
volume	43
number	11
page range	2333-2336
year	1996-01-01
URL	http://hdl.handle.net/2297/4340

doi: <https://doi.org/10.3987/com-96-7588>

A NOVEL DIMERIZATION OF 1-HYDROXYINDOLES¹

Masakazu Hasegawa, Mutsuko Tabata, Keiichi Satoh, Fumio Yamada, and
Masanori Somei*

Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920, Japan

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. Structures 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-methoxyindoles² undergo nucleophilic substitution reactions.³ For example, treatment of *Nb*-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 (**4a**). 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-butyrate (**6c**) gave **7c** (47%) and **5c** (28%), while 1-hydroxy-3-(4-acetoxybutyl)indole (**6d**) produced **7d** (36%) and **8d** (41%). By contrast, *Nb*-acetyl- (**6e**) and *Nb*-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

with TFA, **7e**, **9e**, and *Nb*-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-*Nb*-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 LiAlH₄ produced **7m** (81%) and **7k** (99%), respectively. Since the diazotization of **7l** with NaNO₂-AcOH and subsequent alkaline treatment produced **7m** in 71% yield, structures of **7a** and **7e** are correlated each other. Furthermore, bromination of **7d** in CHCl₃ 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[7.2.1.0⁴.11.0⁶.10]-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-H₂SO₄ 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 report³ 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

REFERENCES AND NOTES

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Received, 22nd July, 1996