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New Indole Trimer[1]

When treated with *p*-toluenesulfonic acid in benzene, indole itself formed a trimer which was different from the known trimer.

The structure of the new trimer was established.

Keywords——trimerization; structure establishment; acid catalyzed rearrangement; indole; Vilsmeier reaction

It is well known that indole itself was easily polymerized under various acid conditions to give a dimer and/or a trimer.[2] A sole compound (**1**) has been known as a indole trimer until now, and its structure (**1**) was proposed by Smith[3] and Noland.[4] Recently, in the course of studies on the advanced Fischer indolization,[5] we occasionally obtained another new indole trimer (**2**). In this paper, we wish to report the structural establishment of **2**.

Refluxing a benzene solution of indole in the presence of TsOH for 3 hr gave colourless dimorphic crystals, mp 105—107° or mp 186.5—187.2°, [IR($CHCl_3$): 3475 (NH)] in 39.7% yield. Dimorphism of **2** was confirmed by the cross-seeding experiment. The molecular formula $C_{24}H_{21}N_3$ of **2** was shown by the facts that the elemental analysis agreed with the empirical formula $(C_8H_7N)_n$ and that the mass spectrum of **2** shows a parent peak at *m/e* 351 corresponding to the molecular ion of the trimeric indole.

2 provided the monoacetate (**3**), colourless needles, mp 168.5—171°, [$C_{26}H_{23}N_3O$[6]; IR (KBr): 3400, 3355 (NH), 1680 (C=O)] in 70.1% yield by treatment with Ac_2O at 100° for 3 min.

In order to compare with the properties of **2** and **3**, the known trimer[7] (**1**), mp 173—177° (lit.[8] mp 169°), and its monoacetate (**4**), mp 209—212° (lit.[9] mp 202°) were prepared according to the reported method.[8,9] Non-identity of **2** with **1** was confirmed by comparison of their infrared (IR) spectra in a solution and *Rf* values on TLC [SiO_2; ether–*n*-hexane (3: 1)]. A clue for structural elucidation of **2** came from the comparative inspection of the spectral data on these four compounds mentioned above. As shown in Table I, the nuclear magnetic resonance (NMR) spectra of **1** and **2** show the presence of an $ArCH_2CH<$ and two NH functions. The mass spectra of both trimers have a common base peak at *m/e* 245 corresponding to a bisindolylmethine ion. These data indicate that these two trimers should be allocated to two of three possible isomers, (**1**), (**2**) or (**5**).

In the trial of the Vilsmeier reaction of **3** and **4** using DMF and $POCl_3$, the former (**3**) gave the monoformyl derivative (**6**), mp 252—255°, [$C_{27}H_{23}N_3O_2$[6]; IR (Nujol): 3370, 3170

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[1] This paper forms Part XI of "Fischer Indolization and Its Related Compounds," by H. Ishii.

[2] For a review of polymerization of indole with acid, see R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 6—8; W.A. Remers and R.K. Brown, "Indoles" (ed. by W.J. Houlihan), Part 1, Wiley-Interscience, New York, 1972, pp. 66—70; G.F. Smith, "Advances in Heterocyclic Chemistry," (ed. by A.R. Katritzky), Vol. 2, Academic Press, New York, 1963, pp. 300—309.

[3] G.F. Smith, *Chem. and Ind.* (London), **1954**, 1451.

[4] W.E. Noland and W.C. Kuryla, *J. Org. Chem.*, **25**, 486 (1960).

[5] H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, **29**, 1991 (1973); H. Ishii, Y. Murakami, K. Hosoya, T. Furuse, H. Takeda, and N. Ikeda, *Chem. Pharm, Bull.* (Tokyo), **20**, 1088 (1972).

[6] The compound gave satisfactory elemental analysis for the formula given.

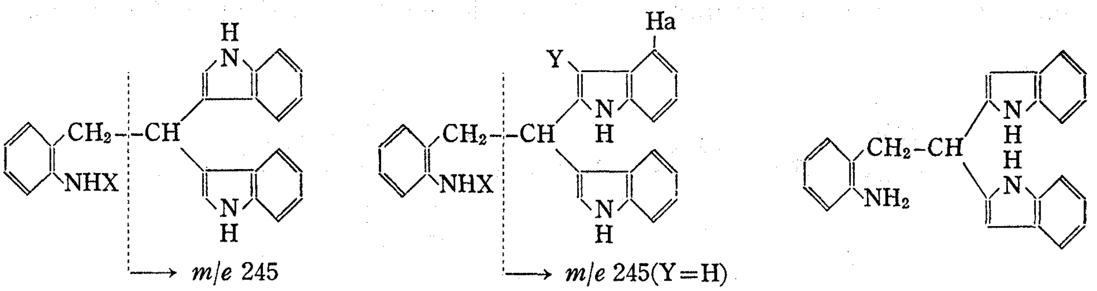
[7] This compound (**1**) also shows dimorphism. Another crystal form melted at 110—113°. This fact was confirmed by the cross-seeding experiment.

[8] O. Schmitz-Dumont, B. Nicolojannis, E. Schnorrenberg, and H.H. Saenger, *J. Prakt. Chem.*, **131**, 146 (1931).

[9] K. Keller, *Chem. Ber.*, **46**, 726 (1913).

Table I. The NMR Spectra of Indole Trimers (in $CDCl_3$, δ)

	The known trimer (**1**)	The new trimer (**2**)
$-C\underline{H}_2-CH\langle$	3.33(2H, d, $J=7.0$ Hz)	3.35(2H, diff. d, $J=7.0$ Hz)
$-CH_2-C\underline{H}\langle$	4.78(1H, t, $J=7.0$ Hz)	4.62(1H, t, $J=7.0$ Hz)
Arom. protons	6.38—6.68(2H, m)	6.35—6.72(3H, m)
	6.76—7.30(10H, m)	6.77—7.40(10H, m)
	7.41(2H, d, $J=7.8$ Hz)	7.43—7.62(1H, m)
N$\underline{H}$	3.20(2H, br. s)	2.98(2H, br. s)
	7.66(2H, br. s)	7.77(2H, br. s)



1: X=H
4: X=Ac

2: X=Y=H
3: X=Ac; Y=H
6: X=Ac; Y=CHO

5

Chart 1

(NH), 1680, 1620 (C=O)] in 81.9% yield, while the latter (**4**) resulted in the recovery of the starting material. These evidences indicate that there is no unsubstituted C_3 position of indole moieties in **1**, but one in **2**, because it is well known that the Vilsmeier reaction easily takes place at the C_3 position of indole nucleus, when remained unsubstituted. The chemical deduction was also supported by the spectral evidences. In the NMR spectrum, there is no signal attributable to the C_3-proton of an indole part in **4** and **6**, while it can be observed at 6.19 δ as 1H singlet in the starting **3**. Furthermore, in **6**, the 1H multiplet appeared at 8.00 δ attributable to the C_4-proton of the formylated skeleton. The down-field shift of this signal should be caused by an anisotropic effect of the peri C_3-formyl group. Finally, in the mass spectrum, **6** has a base peak at *m/e* 273 corresponding to the formylated bisindolylmethine ion.

Table II. The NMR Spectra of Derivatives of the Indole Trimers (in DMSO-d_6, δ)

		4	**3**	**6**
$-C\underline{H}_2-CH\langle$		3.45(2H, d, $J=7.8$ Hz)	3.46(2H, d, $J=7.5$ Hz)	3.36—3.84(2H, m)
$-CH_2-C\underline{H}\langle$		4.71(1H, t, $J=7.8$ Hz)	4.66(1H, t, $J=7.5$ Hz)	5.34(1H, diff. t, $J=7.5$ Hz)
Arom. $\underline{H}$	C_3-H	—	6.19(1H, s)	—
	Others	6.68—7.36(12H, m)	6.73—7.52(13H, m)	6.76—7.50(12H, m)
		7.46(2H, d, $J=7.5$ Hz)		
	Ha			8.00(1H, m)
N$\underline{H}$		8.93(1H, s)	9.08(1H, s)	9.35(1H, s)
		10.60(2H, s)	10.72(2H, s)	10.91(1H, s)
				11.71(1H, s)
$COC\underline{H}_3$		1.88(3H, s)	1.96(3H, s)	2.04(3H, s)
C$\underline{H}$O		—	—	10.04(1H, s)

In 1960, Noland[4] condensed *o*-nitrophenylacetaldehyde[10] (**7**) with indole itself in AcOH to give the *o*-nitro-bisindolyl product (**8**), which was converted to **1** by the reduction of the nitro group. We, however, found that the similar treatment of the same reactants in the presence of anhydr. $ZnCl_2$ gave a mixture of **8** and an isomeric nitro derivative (**9**) as a labile crystalline mass, mp 85° [IR(Nujol): 3400 (NH), 1522, 1348 (NO_2); NMR (DMSO-d_6) δ: 3.70 (2H, d, J=8.0 Hz, $\mathrm{ArC\underline{H}_2CH}<$), 4.64 (1H, t, J=8.0 Hz, $\mathrm{ArCH_2C\underline{H}}<$), 6.16 (1H, s, indolic C_3–H), 6.62—7.00 (4H, m, arom. H), 7.00—7.45 (8H, m, arom. H), 7.65—7.80 (1H, m, arom. Hx), 10.66 (2H, br. s, NH, exchangeable); MS *m/e*: 381 (M^+, 8.8%), 245 (bisindolylmethine ion, base peak)] in 13.0 and 32.2% yields, respectively. Formation of **9** should be explained by the acid catalyzed rearrangement of the initially formed **8** to **9** during the reaction, because treatment of the pure **8** with anhydr. $ZnCl_2$ in AcOH under the same condition mentioned above afforded the same product mixture. Catalytic reduction of the pure **9** provided **2**.

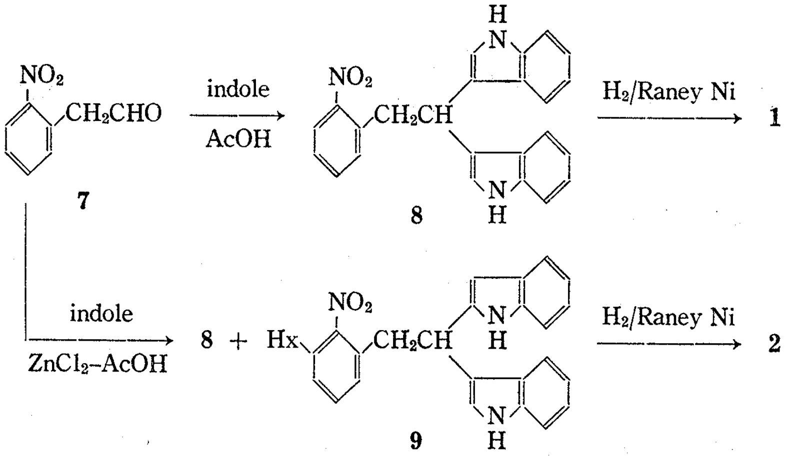


Chart 2

The evidence described so far indicates that the structure of the new indole trimer should be depicted by the formula (**2**). Although the mechanism for the formation of **2** could be supposed by the acid catalyzed rearrangement of **1** on the basis of the rearrangement of **8** to **9**, the precise discussion on this matter will be described in our full paper in the near future.

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Faculty of Pharmaceutical Sciences
Chiba University, 1-33, Yayoi-cho,
Chiba, 280, Japan

HISASHI ISHII[11]
KEIKO MURAKAMI
YASUOKI MURAKAMI
KATSUHIRO HOSOYA

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10) *a*) M. Mousseron-Canet and J.-P. Boca, *Bull. Soc. Chim. France*, **1967**, 1296; e) R.A. Weerman, *Ann.*, **401**, 1 (1913); *c*) W.E. Noland and J.H. Sellstedt, *J. Org. Chem.*, **31**, 345 (1966). We prepared 7 according to the reported method in the reference.[10a]

11) The author to whom correspondence should be addressed.