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1-Acyl-indoles. II.[1] A New Syntheses of 1-(*p*-chlorobenzoyl)-5-methoxy-3-indolylacetic Acid and Its Polymorphism

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1-(*p*-Chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid, a potent anti-inflammatory drug, was directly prepared from N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride and levulinic acid in excellent yield by the new method. The recrystallization of 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid from solvents gave crystals of polymorphism -α, β, and γ-types.

1-(*p*-Chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid (I)(generic name: Indomethacin) is an excellent anti-inflammatory drug having a high degree of anti-inflammatory and remarkable antipyretic activities.[3,4]

About its syntheses, Shen, *et al.*[3] has reported that 2-methyl-5-methoxy-3-indolylacetic acid was converted to its anhydride, which was treated with *t*-butanol to give *t*-butyl 2-methyl-5-methoxy-3-indolylacetate, then *p*-chlorobenzoylation and pyrolysis of the *t*-butyl ester afforded I.

A nitrogen atom of 1st position of indole ring is so weakly basic, that it is generally difficult to direclty acylate the nitrogen atom by benzoyl halide derivative, but it has been

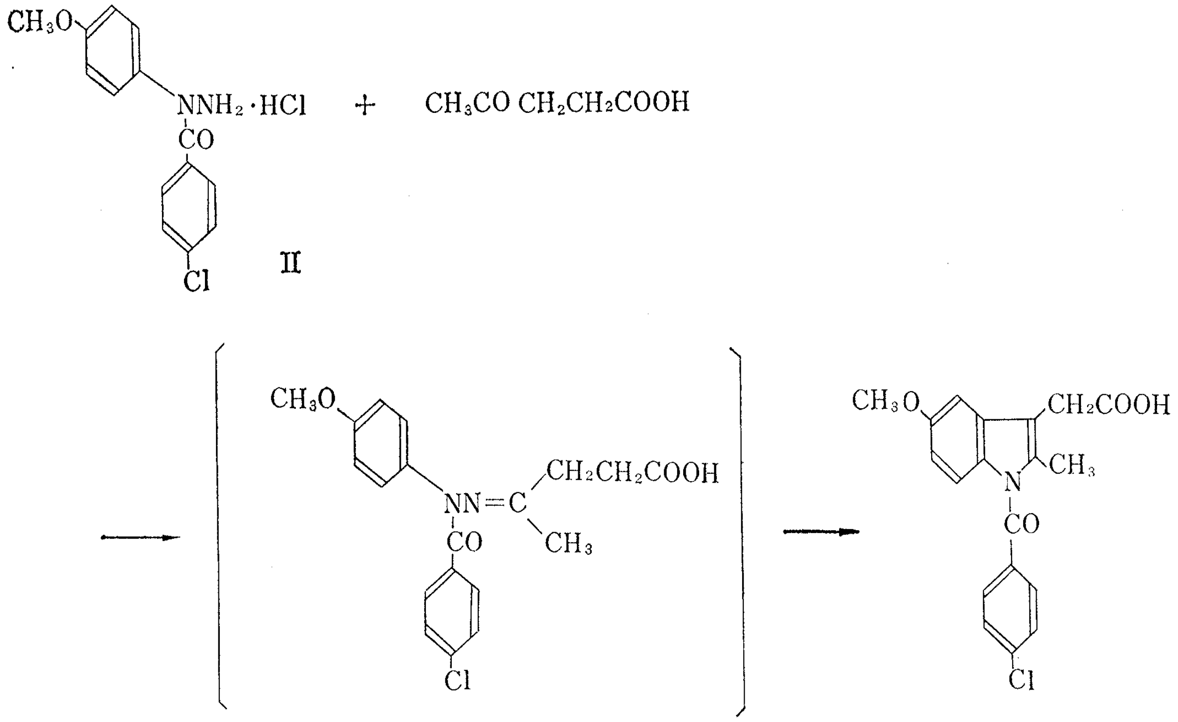

Chart 1

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[1] Part I: *Bull. Chem. Soc. Jap.*, **40** (1967).

[2] Location: *Kasugade-cho, Konohana-Ku, Osaka.*

[3] T.Y. Shen, *et al. J. Am. Chem. Soc.*, **85**, 488—489 (1963).

[4] C.A. Winter, E.A. Risley and G.W. Nuss, *J. Pharm. Exptl. Therap.*, **141**, (3) 369—376 (1963).

done under activation of the nitrogen atom by indole salt of magnesium iodide or metalic sodium.

Further, a side chain of 3rd position of the ring is free acid in this case, so it must be protected from acylation of acid by esterification before benzoylation of the nitrogen atom of the ring. And a condition of hydrolysis for preparing a free acid derivative from the ester must be fairly mild in order to keep acid–amide $(-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-)$ bonding.

The author, however, found that I was directly obtained from N^1–(*p*–chlorobenzoyl)–*p*–methoxyphenylhydrazine hydrochloride (II) and levulinic acid in excellent yield.

II and levulinic acid were stirred in acetic acid at 70—95° for a few hours, and the reaction mixture was chilled to give crystals, which was filtered, washed with water and dried. Then recrystallization from an appropriate solvent gave pure cyrstals of I.

Formic acid, propionic acid, butyric acid, lactic acid, hexane, cyclohexane, *etc.* were able to be used as solvent of this reaction instead of acetic acid, and each of these solvents gave I in more than 60% yield (62—90%). While, benzene, toluene, dioxane, butanol, *etc.* gave I in poor yield.

The new reaction smoothly proceeds in mild conditions and finishes within a few hours to give I in a nearly quantitative yield. Therefore a free *p*–electron pair of N^1–nitrogen atom seems to scarcely participate the C–C new bond formation in indole cyclization.[5]

And the author found that the recrystallization from solvents gave three types of crystals, which have been named α, β, and γ–types. This polymorphism was recognized by infrared absorption spectra, X–ray spectra, differential thermal analysis and melting points. And each of these types was able to be identified by X–ray spectra and infrared spectra. Effects of solvents on types of crystals, their stability, their mutual transformation, X–ray analysis, *etc.* are studying now, which will be reported in later opportunity.

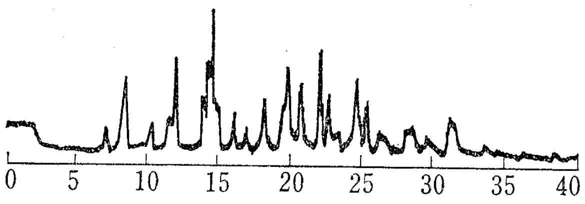

Fig 1.[6] X–ray Spectrum of α–Type

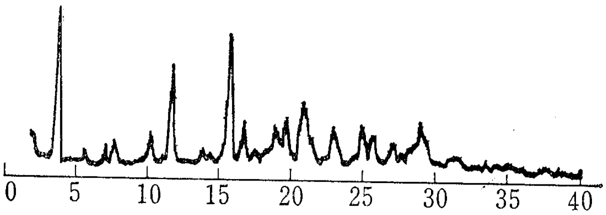

Fig. 2.[6] X–ray Spectrum of β–Type

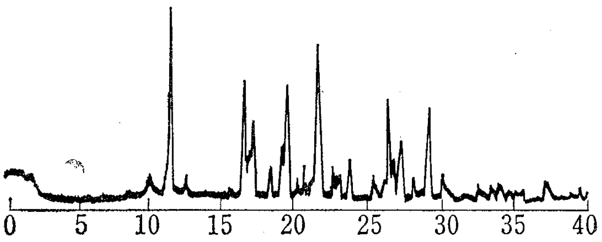

Fig. 3.[6] X–ray Spectrum of γ–Type

TABLE I

Type	Typical recrystallization Solvent	Appearance	mp	IR $\nu_{\text{paraffin}}^{\text{cm}^{-1}}$
α	ethanol	white needle	154.5—155.5°	1690
β	benzene	white	158—160.5°	1690, 1675
γ	ether	white prism	160—161.5°	1715, 1690

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[5] H. Yamamoto, *Bull. Chem. Soc. Jap.*, **40** (1967).

[6] Tube Cu, Filter Ni, Slit 1°—0.15 mm.

Experimental

Melting points are uncorrected. Infrared absorption spectra were corded on Hitachi EPI–S2 type and X–ray spectra were taken on Rigakudenki D–S type.

Synthesis of 1–(*p*–Chlorobenzoyl)–2–methyl–3–methoxy–5–indolyl Acetic Acid (I)——(1) N^1–(*p*–chlorobenzoyl)–*p*–methoxyphenylhydrazine hydrochloride (II)[7] was able to be quantitatively prepared from acetaldehyde N^1–(*p*–chlorobenzoyl)–*p*–methoxyphenylhydrazone by gaseous hydrogen chloride in a solvent mixture of ethanol and toluene.

(2). 6.0 g of II and 2.6 g of levulinic acid were stirred in acetic acid at 80° for 3 hr. The reaction mixture was allowed to stand at room temperature overnight to give 6.8 g (95.8%) of crystals, which were filtered, and washed with water three times. Recrystallization twice from a mixture solution of acetone and water gave 6.0 g (85%) of I, mp 160—161.5°. It showed no melting point depression with the authentic sample recrystallized from a solution of acetone and water. Infrared adsorption spectra of a product prepared from I by deacylation of 10% alcoholic sodium hydroxide was indentical with that of an authentic sample of 2–methyl–5–methoxy–3–indolylacetic acid. *Anal.* Calcd. for $C_{19}H_{16}O_4NCl$: C, 63.78%; H, 4.48%; N, 3.92%; Cl, 9.93%. Found: C, 63.95%; H, 4.46%; N, 3.88%; Cl, 10.11%. Molecular Weight Calcd. for $C_{19}H_{16}O_4NCl$: 357.8 Found: 358 (by Rast method). UV_{max}^{EtOH} $m\mu$ (ε): 320 (6,400), 229 (20,800)

Polymorphism of I——Recrystallization of I from solvents gave three types of crystals; α ,β, and γ–types. Each of these types showed different appearance, melting point, infrared adsorption spectra and X–ray spectra.

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[7] H. Yamamoto, *J. Org. Chem.*, **32**, (11) 3693—3695 (1967).