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Acylindoles. VIII.[1] New Procedures for 1-Heteroaroylindole-3-acetic Acid Derivatives

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1-Heteroaroyl-2-methylindole-3-acetic acid derivatives are prepared by reacting the corresponding N^1-heteroaroylphenylhydrazine derivatives with levulinic acid. And these indole derivatives are also prepared by some other procedures. In one of these compounds, 1-nicotinoyl-2-methyl-5-methoxyindole-3-acetic acid, the existence of its dimorph is suggested by the infrared spectrum. The indole derivatives show a remarkable experimental anti-inflammatory activity having extremely low toxicity.

In the previous paper[3,4] it was reported that 1-benzoyl-2-methylindole-3-acetic acid derivatives were prepared by reacting levulinic acid. This paper reports that 1-heteroaroyl-2-methylindole-3-acetic acid derivatives also could be synthesized by the same procedure described as previously. For example, a reaction of acetaldehyde or benzaldehyde phenylhydrazones with heteroaroyl chloride affords N^1-heteroaroylphenylhydrazones, by which degradation with acids corresponding N^1-heteroaroylhydrazines are prepared. And, these compounds are in high yield converted to the corresponding objective 1-heteroaroylindole-3-acetic acids by reacting with levulinic acid.

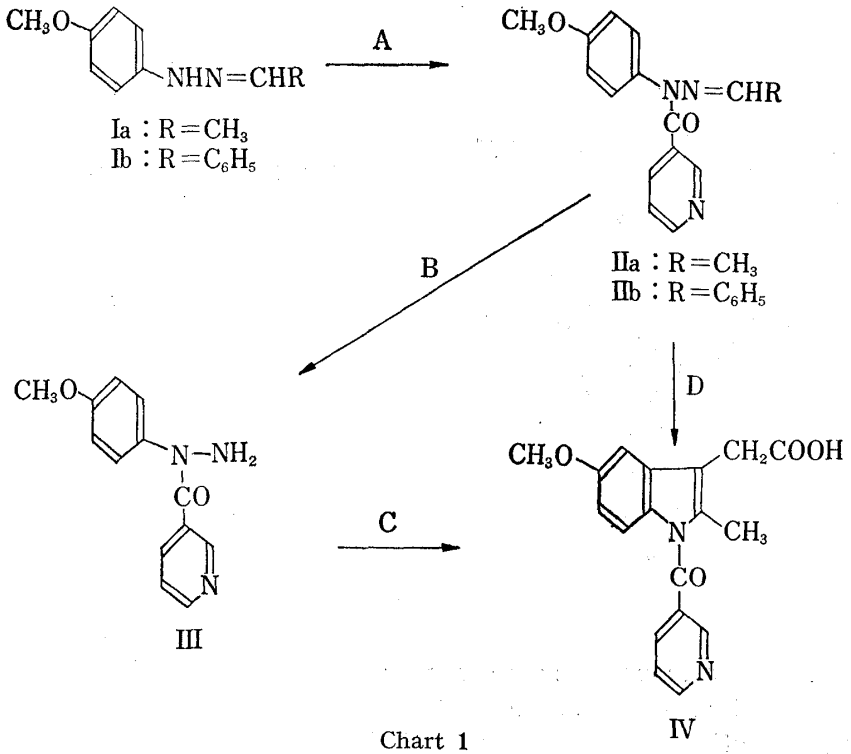

Chart 1

1) Part VII: *Chem. Pharm. Bull* (Tokyo), in press.
2) Location: *278, Kasugade-cho, Konohana-ku, Osaka.*
3) H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 17 (1968).
4) H. Yamamoto, M. Nakao and A. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 647 (1968).

According to this method, various 1–heteroaroylindole–3–acetic acid derivatives, which are substituted by nicotinoyl, isonicotinoyl, thenoyl or furoyl group in 1–position and one of methoxy, methyl, chlor group, *etc.* in 5–position, have been prepared for antiinflammatory agent.

Treating *p*–methoxyphenylhydrazine with nicotinoyl chloride directly in the presence of triethylamine gave N^2–nicotinoyl–*p*–methoxyphenylhydrazine (III) as well as N^1–nicotinoyl isomer, the latter of which only participates in the formation of 1–nicotinoyl–2–methyl–5–methoxyindole–3–acetic acid (IV) from levulinic acid, but the former compound can not essentially participate in the reaction system. Therefore, the remove of N^2–nicotinoyl isomer from the mixture is not necessary for employing it as the starting material of the reaction.

In these formations of a indole ring, N^1–heteroaroylphenylhydrazone derivative of levulinic acid must be formed as an intermediate during the reaction, though this fact is not confirmed. Because this compound is considered to be so unstable to change rapidly into a corresponding indole derivative.

However, methyl levulinate N^1–nicotinoyl–*p*–methoxyphenylhydrazone (VI) is prepared by reacting methyl levulinate *p*–methoxyphenylhydrazone (V) with nicotinoyl chloride in tetrahydrofuran in the presence of pyridine. The compound (VI) is so considerably unstable on exposure to air that unsuccessful attempts were made to be fully purified for elementary analysis, but a formation of indole ring (VII) is accomplished by employing the crude compound (VI) as the starting material.

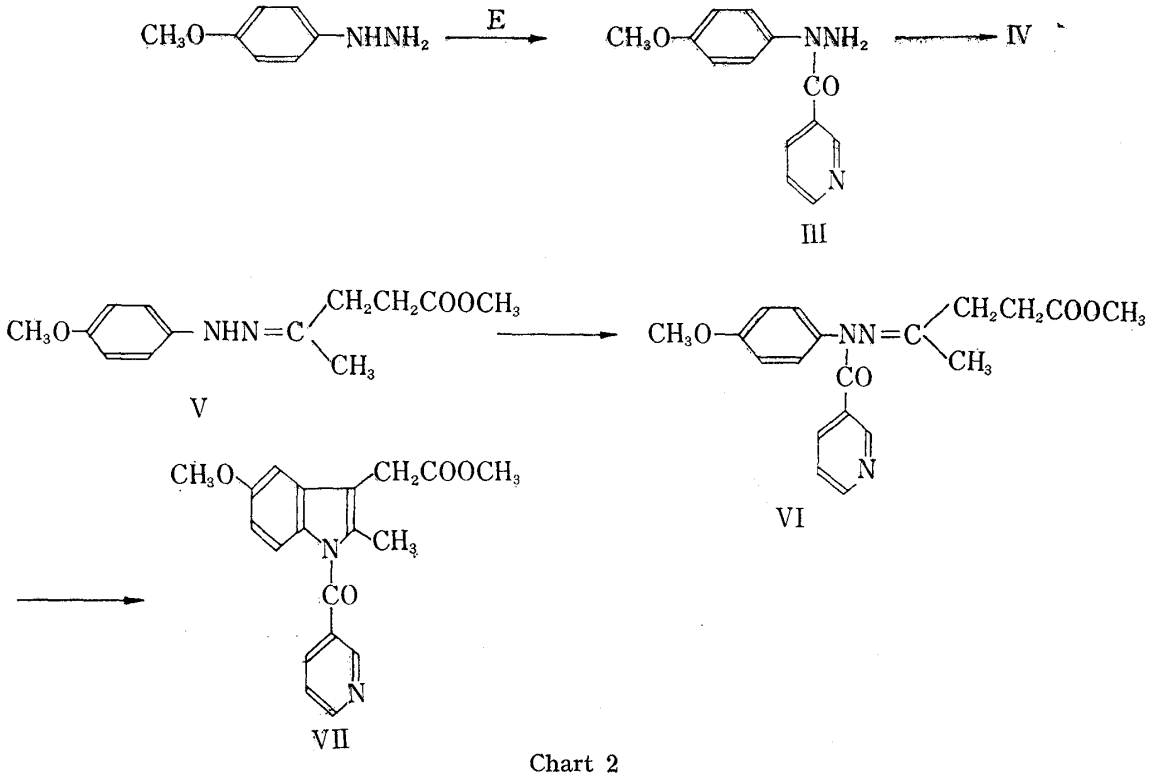

Chart 2

Evidence for the existence of the dimorph of IV, which is named α– and β–form is given by IR spectra. The β–form crystals are given by recrystallization of IV from ethylene glycol monomethyl ether, acetic acid and ethanol, while the α–form crystals are prepared by pouring the solution of IV in ethylene glycol monomethyl ether into cold water or petroleume–ether. Further, when the solution of IV in dilute aqueous ammonia is adjusted to pH 4 by addition of dilute hydrochloric acid, the α–form crystals are obtained. The α–form crystals are wet at about 170°, thereafter solidified and melted at 200—201°, the temperature of which is the same with the melting point of β–form. According to the differential

thermal analysis of the α-form crystals, the exothermic curve is exhibited at about 175°, suggesting that the α-form crystals transform to the stable β-form at the temperature.

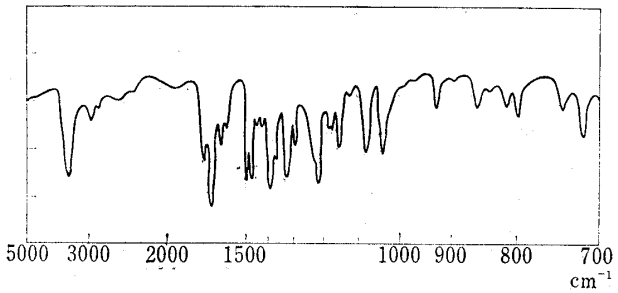

Fig. 1. IR Spectrum (KBr Tablet Method) of α-Type Ⅳ

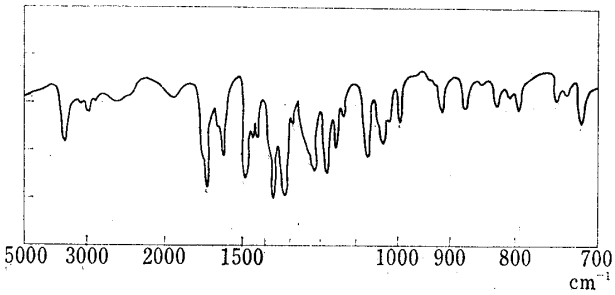

Fig. 2. IR Spectrum of β-Type Ⅳ (KBr Tablet Method)

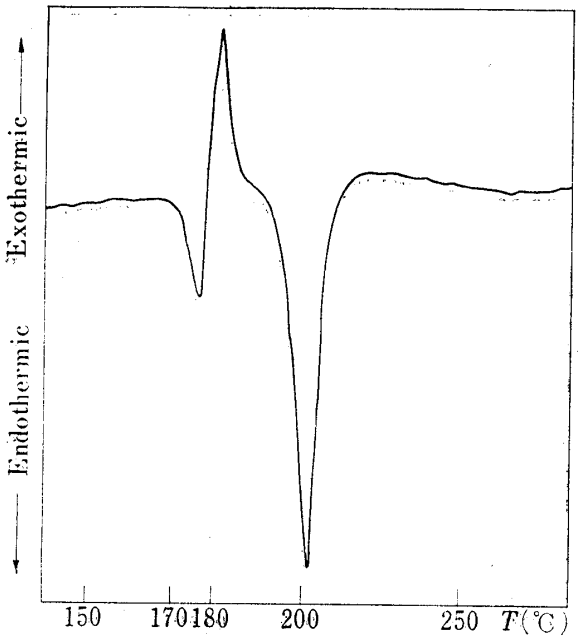

Fig. 3. α-Form of 1-Nicotinoyl-2-methyl-5-methoxy-3-indolylacetic Acid

standard sample, α-Al_2O_3; heating rate, 5°/min

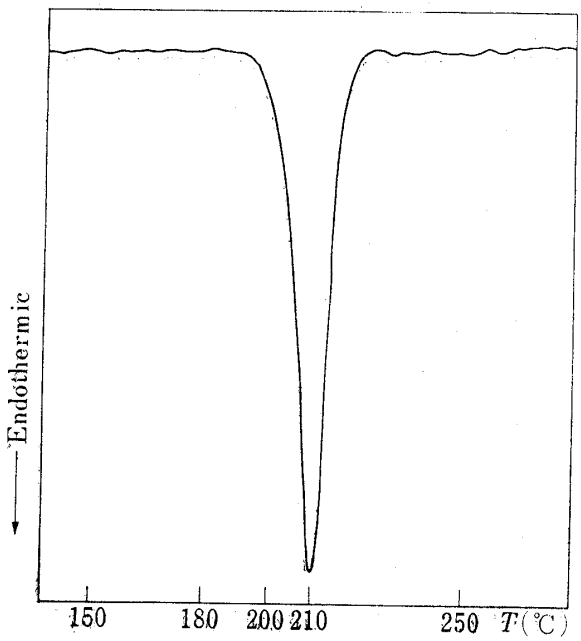

Fig. 4. β-Form of 1-Nicotinoyl-2-methyl-5-methoxy-3-indolylacetic Acid

standard sample, α-Al_2O_3; heating rate, 5°/min

Several compounds have remarkable activities in experimental inflammation tests. For example, Ⅳ shows over 50% inhibition of volum of carrageenin-induced edema of rat's hind paw in 100 mg/kg *per os*. The activity is greater than that of oxyphenbutazone. In spit of the potential activity, acute, subacute and chronic toxities are extremely low. These biological aspects will be published later.

Experimental

Melting points are uncorrected. Infrared absorption spectra were recorded on a Simadzu-27G spectrophotometer, ultraviolet absorption spectra were recorded on a Simadzu RS-27 spectrophotometer, nuclear magnetic resonance (NMR) spectra were taken on a Varian A-60 spectrophotometer and DTA data were recorded on a Simadzu DT-2B apparatus.

Acetaldehyde N¹-Nicotinoyl-*p*-methoxyphenylhydrazone (IIa)——A) A mixture of 16.4 g (0.1 mole) of acetaldehyde *p*-methoxyphenylhydrazone (Ia), 9.5 g (0.12 mode) of pyridine and 110 ml of tetrahydrofuran was kept at 0—5° while 17.0 g (0.12 mole) of nicotinoyl chloride was added dropwise for 15 min. The reaction mixture was stirring on cooling for 2 hr and at room temperature for 1 hr. A precipitate was removed by filtration and the filtrate was concentrated under redudced perssure to a red oily substance, which is solidified on treatment of 200 ml water. After cooling in a ice-bath, the mixture was filtered to

give 23 g of crude IIa. Recrystallization from ethyl acetate—hexane gave 16.4 g (61%) of light brown prisms, mp 100—101°. UV λ_{max}^{EtOH} mμ (log ε): 226 (4.26), 264 (3.99). IR ν_{max}^{Nujol} cm^{-1}: 1650 (NCO). *Anal.* Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.78; H, 5.56; N, 15.83.

Benzaldehyde N^1-Nicotinoyl-*p*-methoxyphenylhydrazone (IIb)—(A) To a solution mixture of 400 ml dry ether and 200 ml of dry tetrahydrofuran was added 56.5 g (0.25 mole) of benzaldehyde *p*-methoxyphenylhydrazone (Ib) and 23.7 g dry pyridine. To the mixture was added dropwise 42.4 g (0.3 mole) of nicotinoyl chloride below 2°. After stirring at 5° for 3 hr, a precipitate produced was collected by filtration, washed with water and dried to give 44.5 g of crude IIb of mp 142—144°. Recrystallization from ethanol gave 40.5 g of white scales, mp 145—146°. IR ν_{max}^{Nujol} cm^{-1}: 1665 (NCO), 1605 (benzene ring), 1580. *Anal.* Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.80; H, 5.01; N, 12.49.

N^1-Nicotinoyl-*p*-methoxyphenylhydrazine (III)——(B) To a solution of 10 g of IIa in 100 ml of benzene was added 40 ml of 30% of methanolic HCl on cooling, and the mixture was allowed to stand in a refrigerator overnight. Crystals were collected by filteration and washed with ether to give 11.3 g of III dihydrochloride, mp 196—197° (decomp.). Recrystallization from methanol–ether gave 10.2 g (87%) of colorless prisms, mp 197—198° (decomp). UV λ_{max}^{EtOH} mμ (log ε):229 (4.05), 266 (3.85). IR ν_{max}^{Nujol} cm^{-1}: 1608. A treatment with dilute sodium carbonate aqueous solution followed by recrystallization from benzene gave colorless needles, of III, mp 109—110°. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.23), 267 (4.06). IR ν_{max}^{Nujol} cm^{-1}: 3360, 3200 (NH_2), 1640 (NCO). *Anal.* Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.31; H, 5.33; N, 17.14.

1-Nicotinoyl-2-methyl-5-methoxyindole-3-acetic Acid (IV)——(C) A mixture of 6.3 g (0.02 mole) of III dihydrochloride, 2.8 g of levulinic acid (0.03 mole) and 10 ml of acetic acid was heated in a water-bath of 90° for 40 min with stirring. After cooling, the reaction mixture was poured into 400 ml of water and a precipitate produced after standing in a refrigerator overnight was filtered, washed with water and recrystallized from ethylene glycol monomethyl ether to yield 4.9 g (76%) of yellow prisms of IV, mp 200—201°. UV λ_{max}^{EtOH} mμ (log ε): 265 (4.15), 320 (3.76). IR ν_{max}^{Nujol} cm^{-1}: 1700 (COOH), 1668 (NCO). NMR (τ in DMSO): 7.77 (3H, s, $-CH_3$), 6.29 (2H, s, $-CH_2COOH$), 6.20 (3H, s, $-OCH_3$), 3.35—1.05 (7H, m, ring protones).

(D) A mixture of 5.38 g of acetaldehyde N^1–nicotinoyl–*p*–methoxyphenylhydrazone and 15 g of levulinic acid contained 1 g of hydrogen chloride was heated in a water–bath of 95° for 30 min. After cooling, the mixture was poured into 500 ml of cold water and a yellowish brown precipitate was collected by filteration. Recrystallization from acetic acid–water twice gave yellow crystals of IV, mp 200—201°, undepressed when admixed with an authentic sample prepared in C. Identical infrared absorption spectra were obtained from this material and from the authentic sample.

According to the procedure mentioned above, 0.5 g of yellow IV of mp 200—201° was prepared from 2 g of benzaldehyde N^1–nicotinoyl–*p*–methoxyphenylhydrazone (IIB) and 15 ml of levulic acid. This material was identified by undepression of mixture melting point and identity of infrared absorption spectra with an authentic sample.

(E) To 17.45 g (0.1 mole) of *p*–methoxyphenylhydrazine hydrochloride, 22.2 g of triethylamine and 450 ml of toluene was added dropwise 15 g of nicotinoyl chloride at 10—15°. Stirring was continued for additional 17 hr. After filteration gaseous hydrogen chloride was blowed into the filtrate. A crystalline solid produced was collected by filtration and dried. This material was added to a solution mixture of 20 ml of acetic acid and 100 ml of levulinic acid, and the mixture was heated and stirred at 90° for 40 min. Pouring the reaction mixture into 1600 ml of water caused production of 1.4 g of gray crystals. Recrystallization from ethylene glycol monomethyl ether gave 1.05 g (3.2%) of IV, identified by the same method mentioned above.

Methyl Levulinate *p*-Methoxyphenylhydrazone (V)——According to the procedure described in the previous paper,[4] 35 g (70%) of V, mp 77—78°, was prepared from 35 g of *p*–methoxyphenylhydrazine hydrochloride. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1720 (COO). These crystals were unstable on exposure to air.

Methyl 1-Nicotinoyl-2-methyl-5-methoxyindole-3-acetate (VII)——A solution of 7.0 g of nicotinoyl chloride in 10 ml of tetrahydrofuran was added dropwise to a mixture of 11.2 g of V, 5 ml of pyridine and 60 ml of dry tetrahydrofuran and stirring was continued at 25° for additional 3.5 hr. The filtrate obtained by filtering the reaction mixture was concentrated in reduced pressure to give 1.57 g of an oily substance, which was suggested to be methyl levulinate N^1–nicotinoyl–*p*–methoxyphenylhydrazone (VI) from the infrared absorption spectrum (IR ν_{max}^{Nujol} cm^{-1}: 1725 ($-COOCH_3$), 1645 (NCO)). To this oily substance was added 35 ml of acetic acid containing 2 g of hydrogen chloride and the mixture was heated at 85—90° for 2 hr with stirring. After cooling, water was added to the reaction mixture which was extracted with benzene. The benzene layer was washed with water and dried. Benzene was evaporated leaving 9.9 g of an oily substance, which was solidified slowly. Recrystallization from ethyl acetate—ether twice gave 3 g (22.2%) of VII, mp 110—111°. UV λ_{max}^{EtOH} mμ(log ε): 165 (4.16), 320 (3.77). IR ν_{max}^{Nujol} cm^{-1}: 1730 ($COOCH_3$), 1680 (NCO). *Anal.* Calcd. for $C_{19}H_{18}O_4N_2$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.42; H, 5.33; N, 8.13.

Dimorph of IV——The existence of the dimorph, α– and β–form of the compound (IV) was suggested by the infrared spectra.

Recrystallization from ethylene glycol monomethyl ether, acetic acid and ethanol gave the β–form crystals. While, when a solution of IV in ethylene glycol monomethyl ether at elevated temperatures was poured into cold water or petroleum ether, the α–form crystals were obtained. Further, when a solution

of the compound IV in a dilute aqueous ammonia was adjusted to pH 4 by addition of dilute hydrochloric acid, the α-form crystals were precipitated.

The infrared spectra showed that the α-form crystals were transformed to the β-form by following treatments: (1) cooling after melting the α-form crystals at 200—210°, (2) recrystallizing the α-form crystals from ethylene glycol monomethyl ether or acetic acid.

On the contrary, it was shown by infrared spectra that the α-form crystals were prepared from the β-form crystals by following tratments: (1) pouring a solution of the β-form crystals in ethylene glycol monomethyl ether into water, (2) adding petroleum ether to a solution of the β-form crystals in ethylene glycol monomethyl ether, and (3) adjusting a solution of the β-form crystals in dilute aqueous ammonia to pH 4 with dilute hydrochloric acid.

Identical ultraviolet absorption spectra in an ethanol solution were obtained from the both forms of crystals. The β-from crystals were melted at 200—201°, while the α-form crystals were wet at nearly 170°, but thereafter solidified and then melted at 200—201°. In the case of the α-form crystals, an exothermic curve of DTA data was exhibited at about 175°.

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