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1-Acylindoles. IV.[1] Novel Syntheses of 1-Benzoylindole-3-aliphatic Acids

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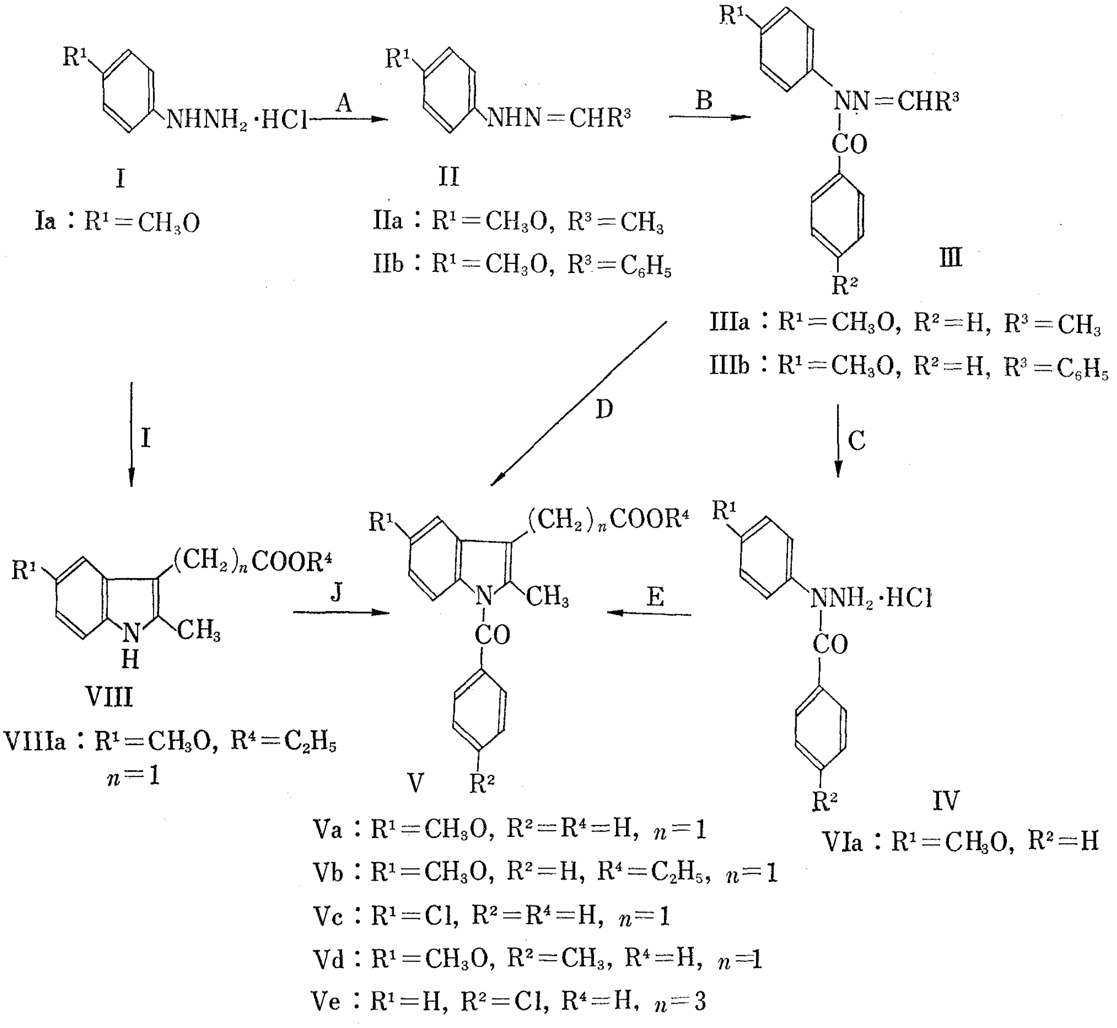
1) Some novel procedures for syntheses of 1–aroylindole–3–aliphatic acids are developed.

2) According to these methods new 1–benzoylindole–3–aliphatic acid derivatives are prepared for pharmacological test.

3) Some reaction mechanisms on these methods are suggested.

1–Aroylindole derivatives have been prepared from the corresponding indole derivatives by acylating with aroyl halides. However, substitution to the nitrogen atom of indole ring is difficult in general from the point of its aromaticity.



I

Ia : $R^1=CH_3O$

II

IIa : $R^1=CH_3O$, $R^3=CH_3$

IIb : $R^1=CH_3O$, $R^3=C_6H_5$

III

IIIa : $R^1=CH_3O$, $R^2=H$, $R^3=CH_3$

IIIb : $R^1=CH_3O$, $R^2=H$, $R^3=C_6H_5$

VIII

VIIIa : $R^1=CH_3O$, $R^4=C_2H_5$
$n=1$

V

Va : $R^1=CH_3O$, $R^2=R^4=H$, $n=1$

Vb : $R^1=CH_3O$, $R^2=H$, $R^4=C_2H_5$, $n=1$

Vc : $R^1=Cl$, $R^2=R^4=H$, $n=1$

Vd : $R^1=CH_3O$, $R^2=CH_3$, $R^4=H$, $n=1$

Ve : $R^1=H$, $R^2=Cl$, $R^4=H$, $n=3$

IV

VIa : $R^1=CH_3O$, $R^2=H$

Chart 1

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[1] Part III: H. Yamamoto, *J. Org. Chem.*, 32, 3693 (1967).

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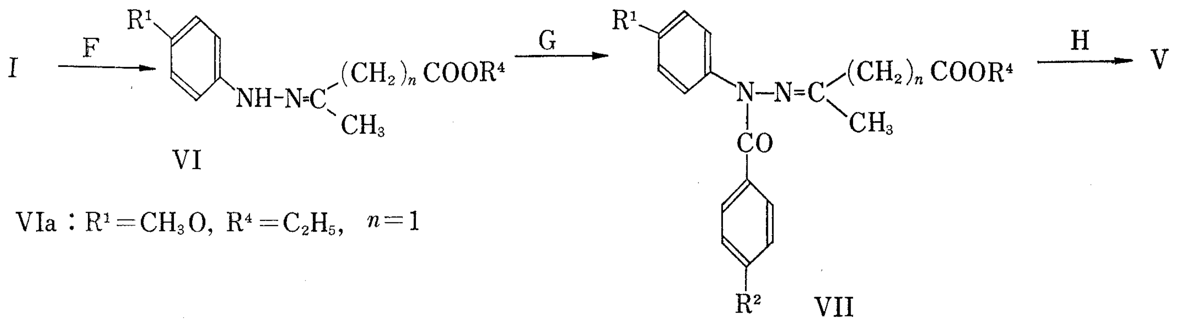
Moreover, esterification of indole-3-aliphatic acids by a suitable radical, for example alkyl group, benzyl group, *etc.*, is demanded in order to protect the carboxylic group from acylation.

Some novel procedures for syntheses of 1-aroylindole-3-aliphatic acids are developed,[3] on which we describe in this paper (Chart 1 and 2).


VI

VIa : $R^1=CH_3O$, $R^4=C_2H_5$, $n=1$

VII

VIIa : $R^1=CH_3O$, $R^2=H$, $R^4=C_2H_5$, $n=1$

Chart 2

When phenylhydrazine derivative (I) is acylated directly by benzoyl chloride in the presence of a hydrogen chloride acceptor, the benzoyl group is substituted unselectively to the N^1-position and the N^2-position to yield N^1-acylated, N^2-acylated and N^1,N^2-diacylated phenylhydrazine derivatives. The formation ratio of these derivatives depends on a sort of substituent R_1 group and a relative amount of acyl chloride.

Formation of hydrazone compound (II) by ketone or aldehyde is necessary for inhibition of N^2-substituted compound formation. Hydrazone of acetaldehyde or benzaldehyde is most preferable for this purpose. These hydrazones are so unstable that they are decomposed slowly in the air.

Benzoylation of the N^1-position of phenylhydrazones by benzoyl chloride proceeds quantitatively in the presence of hydrogen chloride acceptor.

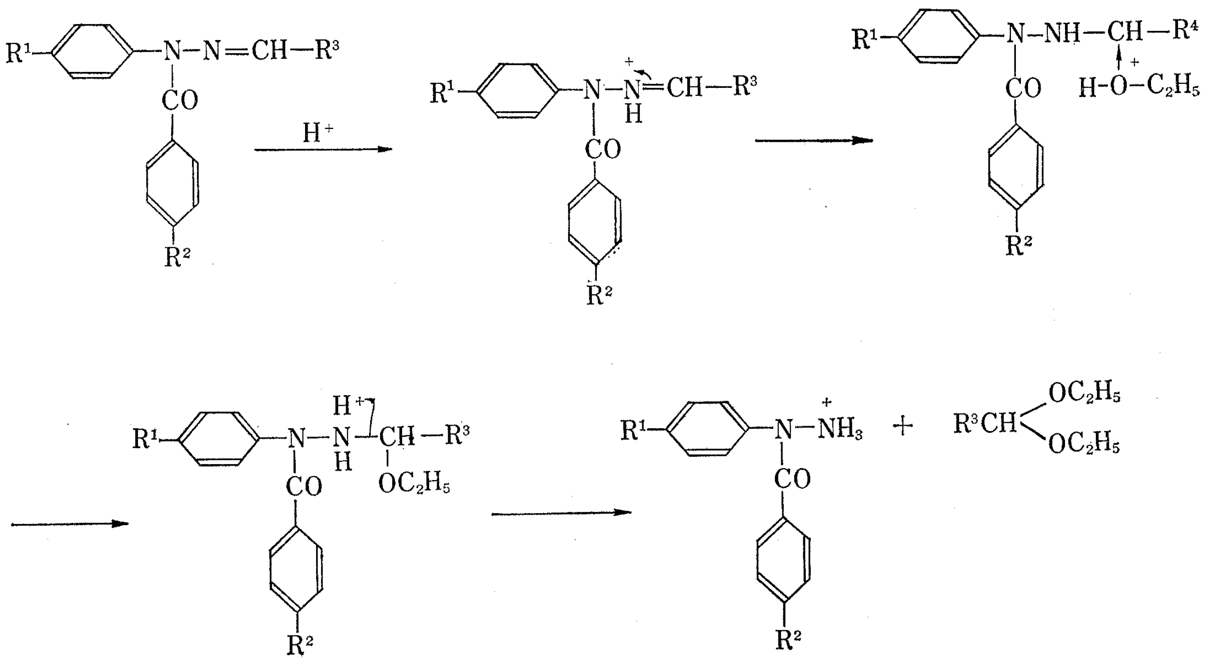


Chart 3

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[3] H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 17 (1968).

The double bond of –N=CH– of N^1–benzoylphenylhydrazones (III) is cleaved by excess mineral acid to yield N^1–benzoylphenylhydrazines in an alcohol solvent or a mixture of inert solvent and alcohol (Chart 3).

In case of $R^3=CH_3$ (IIIa), the double bond is easily cleaved in alcohol saturated with hydrogen chloride even below 0°. While, the double bond of a compound of $R^3=C_6H_5$ is stable under the same condition, but under the more severe condition the same cleavage is occurred to give N^1–benzoylphenylhydrazines.

When N^1–benzoylphenylhydrazone derivative of an aldehyde or ketone compound is heated with equimolar hydrogen chloride and another kind of aldehyde or ketone compound, some part of these aldehyde or ketone compounds is exchanged with each other under chemical equilibrium between the N^1–benzoylphenylhydrazone derivative and the aldehyde or ketone compounds. It has been reported that a similar equilibrium was observed between 2,4–dinitrophenylhydrazones of acetone and 3–methylcrotonaldehyde.4)

When an aldehyde N^1–benzoylphenylhydrazone derivative (III) is treated with levulinic acid in the presence of equimolar hydrogen chloride, the same chemical equilibrium between the aldehyde N^1–benzoylphenylhydrazone derivative and levulinic acid might be formed, but levulinic acid N^1–benzoylphenylhydrazone derivative causes cyclization actually and leaves from the system. Therefore, the equilibrium is moved to the right side of the equilibrium formula, that is the reaction progresses smoothly (Chart 5).

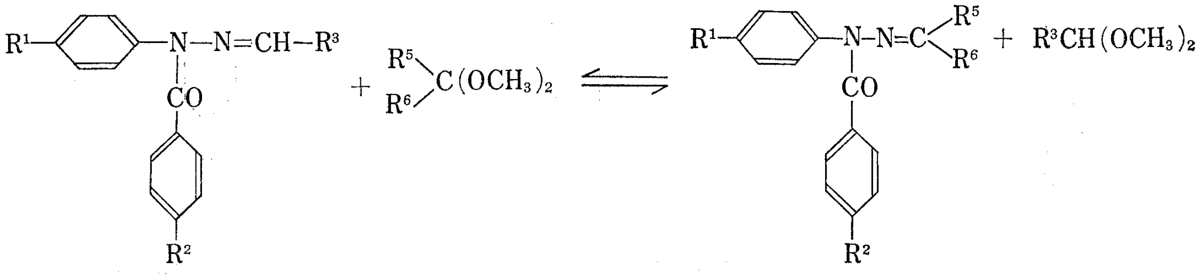

Chart 4

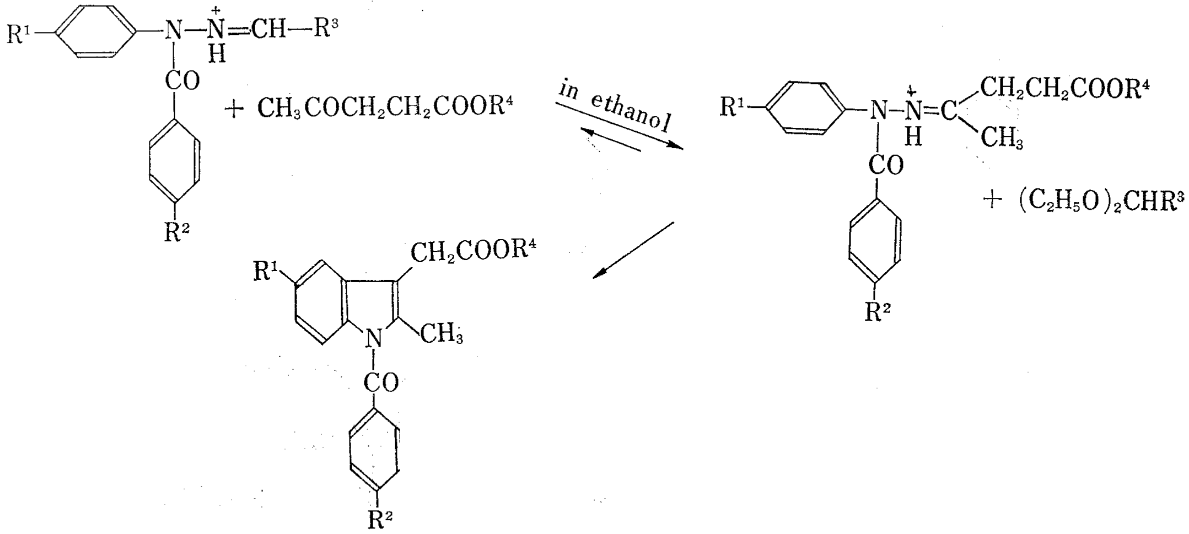

Chart 5

It is found that reaction of N^1–benzoylphenylhydrazine derivative hydrochloride (IV) with ketoalphatic acid generally gives a 1–benzoyl–2–methylindole–3–aliphatic acid derivative

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4) H. Marxeier and E. Pfeil, *Ber.*, **97**, 815 (1964).

in good yield. However, the yield of a cyclized product is notably affected by electro-inductive effect (I-effect) of a substituent R^1. The study on the cyclization reactivity is in progress, which will be published in other opportunity.

Levulinic acid N^1-benzoylphenylhydrazone derivative must be produced as an intermediate in the cyclization reaction, but the fact is not confirmed yet. The hydrazone formation of N^1-benzoylphenylhydrazine derivative hydrochloride (IV) and levulinic acid is rather difficult in comparison with other hydrazone formation of acetaldehyde or benzaldehyde, because the corresponding hydrazone (VII) from IV and levulinic acid is not produced at all even at 50°. However, at the temperature higher than 65° the reaction smoothly progresses and a cyclized product (V) is given in good yield. From these results, it is able to say that it is impossible to isolate VII from the reaction system.

The mechanism for the formation of 1-benzoylindole-3-aliphatic acid derivative from corresponding N^1-benzoylphenylhydrazine derivative hydrochloride is proposed as following: (1) formation of the hydrazones from N^1-benzoylphenylhydrazines and levulinic acid, (2) migration of the double bond, (3) the new C-C bond formation caused by electron transfer

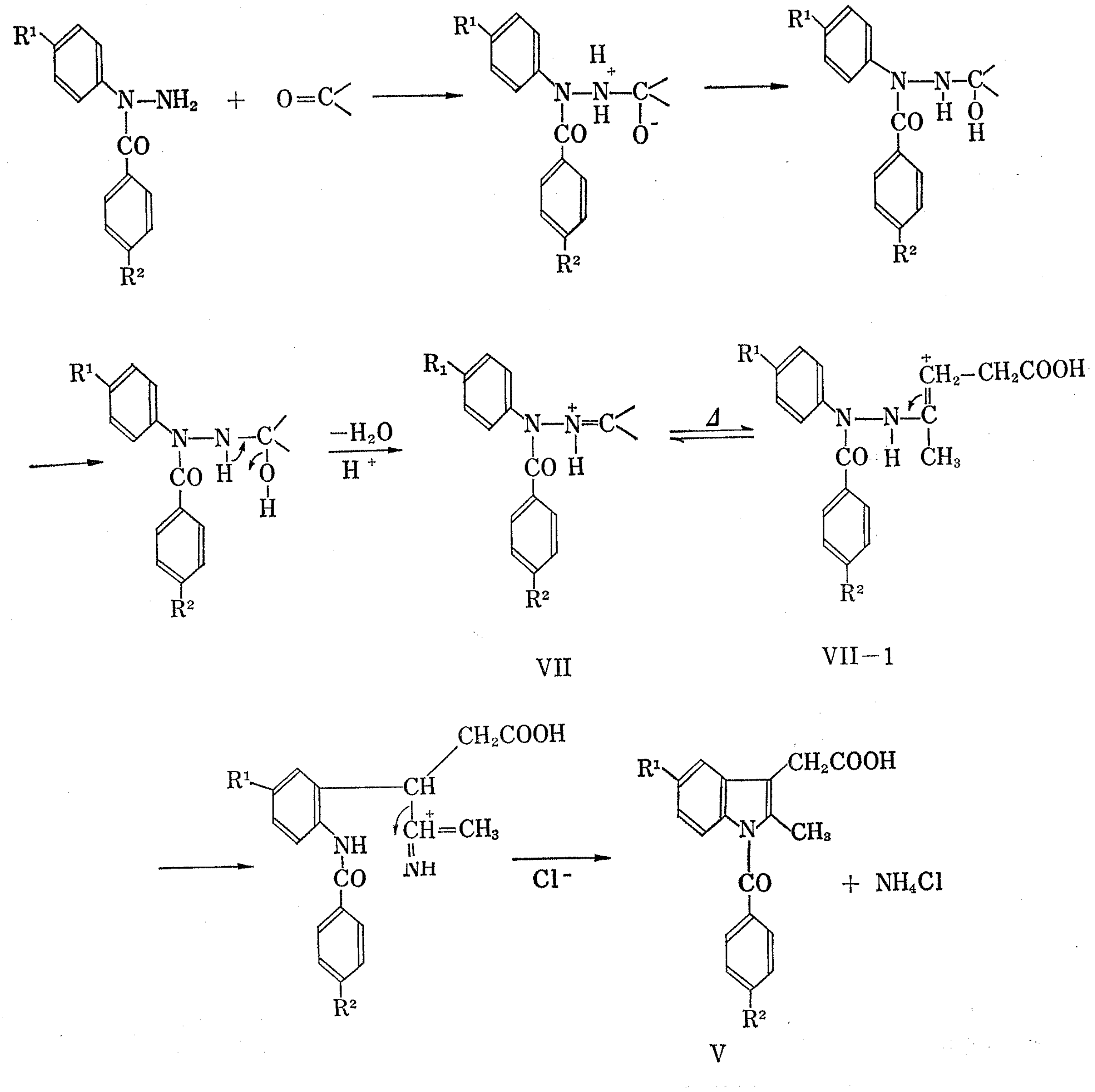
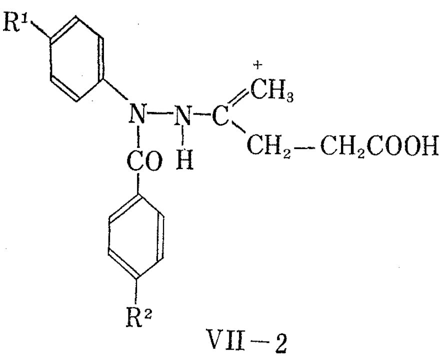


Chart 6

and (4) indole ring closure (Chart 6). This reaction mechanism is thought to be the same with the case of a N^1-unsubstituted-phenylhydrazine derivative.5)



VII−2

Chart 7

The structure of Va is confirmed from NMR spectra of 1-benzoyl-5-methoxyphenylindoleacetic-3-acid (Va) and its ethyl ester (Vb), which is prepared under heating in ethyl alcohol containing a small quantity of conc. hydrochloric acid.

Migration of the double bond of –N=CH– is theoretically thought to cause the production of VII–2 as well as VII–1. However, from the point of the last product obtained quantitatively, VII–2 seems to be a small amount or not produced as an intermediate in the reaction system (Chart 7). The double bond of VII–2 must be more unstable than that of VII–1 in a reaction mixture because of interference of hyperconjugation.

When ethyl levulinate *p*-methoxyphenylhydrazone (VIa) is acylated with benzoyl chloride in a mixture of pyridine and ether, a crude oily product is obtained in high yield. The infrared absorption spectra (λ_{max}) show 1730 cm^{-1} (CO of COOEt) and 1650 cm^{-1} (CO of NCO), and infrared absorption band of NH is not observed. Refluxing of this product in ethanol containing hydrogen chloride causes production of ethyl 1-benzoyl-2-methyl-5-methoxyindole-3-acetate, the spectra of which are identical with those of authentic sample. From these results, the benzoylated product is confirmed to be ethyl levulinate N^1-benzoyl-*p*-methoxyphenylhydrazone (VII).

The acid amide linkage of 1-benzoyl-2-methylindole-3-aliphatic acids is unstable even in pH lower than 10. Ethyl 1-benzoyl-2-methyl-5-methoxyindole-3-acetate (Vb) is easily hydrolyzed in an alkaline aqueous solution to yield ethyl 2-methyl-5-methoxyindole-3-acetate (VIIIa).

So many 1-benzoylindole-3-aliphatic acid derivatives were prepared already from corresponding N^1-benzoylphenylhydrazine derivatives and ketoaliphatic acid by the mentioned new method E. These compounds have been shown to have a remarkable anti-inflammatory activity against carrageenin edema of rat's hind paws. These pharmacological studies will be published in the future.

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 spectorometer and NMR spectra were taken on a Varian A-60 spectrophotometer.

Acetaldehyde *p*-Methoxyphenylhydrazone (IIa)——Method A_1: To a stirred mixture of 41.4 g (0.3 mole) of *p*-methoxyphenylhydrazine and 150 ml of ether maintained below 10° was added 16.5 g of 80% acetaldehyde dropwise under nitrogen stream. The reaction mixture was stirred for an additional 30 min. Thereto was added 50 ml of water and the mixture solution was throughly shakened. The organic layer was separated and dried over anhydrous potassium carbonate. The mixture was distilled to an oily residue, which was distilled *in vacuo*, to give 43 g (88%) of dark yellow liquid of IIa, bp 145—147° (8 mmHg). It was allowed to stand in a refrigerator to give yellow crystalline solid, mp 59—62°. It was slowly decomposed in the air. UV_{max}^{EtOH} mμ (ε): 274 (4.22), 310 (3.62). IR cm^{-1}: 3290 (NH). *Anal.* Calcd. for $C_9H_{12}ON_2$: C, 65.83; H, 7.36; N, 17.06. Found: C, 65.69; H, 7.08; N, 17.22.

Benzaldehyde *p*-Methoxyphenylhydrazone (IIb)——Method A_2: In a little excess sodium hydroxide aqueous solution was warmed 35 g (0.2 mole) of I. The cooling caused precipitation of the free base which was collected by filtration. To a suspension of the wet cake in 400 ml of ether was added 23 g. of benzaldehyde under nitrogen stream with stirring. The stirring was continued for additional 1 hr, and the organic layer was then concentrated to nearly dryness. The crystalline solid was collected by filtration,

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5) C.F.H. Allen and C.V. Wilson, *J. Am. Chem. Soc.*, **65**, 611 (1943).

washed with cold ether, and dried over phosphorous pentoxide in a vaccum dryer to yield 32 g (71%) of yellow needles of benzaldehyde *p*-methoxyphenylhydrazone (IIb). IR cm^{-1}: 3429 (NH).

This compound was so unstable, that it was used without purification for the next procedure.

Acetaldehyde N^1-Benzoyl-*p*-methoxyphenylhydrazone (IIIa)——Method B$_1$: A mixture of 32.8 g (0.2 mole) of acetaldehyde *p*-methoxyphenylhydrazone (IIa) and 120 ml of dry pyridine was maintained at a temperature of below 5° while 30.9 g (0.22 mole) of benzoyl chloride was added dropwise to the mixture for 30 min. The reaction mixture was stirred for 4 hr under cooling with ice, and the mixture was then poured into 600 ml of water. The resultant precipitate was filtered, and washed with water to give 53 g (99%) of crude IIIa, mp 98—102. Recrystallization from 90% ethanol gave 40 g (73%) of light yellow prisms, mp 106—107°. IR cm^{-1}: 1650(CO). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 229 (4.29). *Anal.* Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.63; H, 6.01; N, 10.44. Found: C, 71.49; H, 5.98; N, 10.64.

Benzaldehyde N^1-Benzoyl-*p*-methoxyphenylhydrazone (IIIb)——Method B$_2$: To a solution of 29 g (0.128 mole) of IIb in 300 ml of tetrahydrofuran was added 12.2 g (0.154 mole) of pyridine. The mixture was maintained at the temperature of below 5°, while 21.7 g (0.154 mole) of benzoyl chloride was added dropwise thereto for 20 min with stirring. The stirring was continued for additional 4 hr under cooling with ice, and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to nearly dryness. The resultant crystalline solid was collected by filtration, washed with water, and dried over anhydrous calcium chloride in a vacuum dryer to give 42 g (99%) of crude IIIb, mp 144—146°. Recrystallization from ethanol gave 30 g (71%) of colorless needles of IIIb, mp 148—149. IR cm^{-1}: 1646 (CO), UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 220 (4.41), 277 (4.31), 282 (4.32), 291 (4.32), 299 (4.28). *Anal.* Calcd. for $C_{21}H_{18}O_2N_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.16; H, 5.42; N, 8.67.

N^1-Benzoyl-*p*-methoxyphenylhydrazine Hydrochloride (IV)——Method C$_1$: Gaseous hydrogen chloride was slowly absorbed in a mixture of 15 g of IIIa, 180 ml of ether and 15 ml of methanol for 1 hr at ice-salt temperatures. After saturation of hydrogen chloride, the mixture was stirred for 2 hr under cooling with ice. The resultant crystals were collected by filtration, washed with ether, and dried in a vacuum dryer to give 14.3 g (92%) of crude IV, mp 174° (decomp.). Recrystallization from methanol-ether gave 13.1 g (84%) of colorless needles of IV, mp 174° (decomp.). IR cm^{-1}: 1683 (CO) UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 225 (4.12), 270 (3.84). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2Cl$: C, 60.33; H, 5.42; N, 10.05; Cl, 12.72. Found: C, 60.65; H, 5.32; N, 10.17; Cl, 12.61. Method C$_2$: To a suspension of 3.3 g of IIIb in 60 ml of ether was added 10 g of 10% ethanolic hydrogen chloride. The mixture was refluxed for 3 hr with stirring. The reaction mixture was allowed to stand at room temperature. The resultant crystals were collected by filtration, washed with 20 ml of ether, and dried to give 2.0 g (72%) of colorless needles of IV, mp 174° (decomp.). The infrared absorption spectra of the product were identical with that of authentic sample.

1-Benzoyl-2-methyl-5-methoxyindole-3-acetic Acid (Va)——Method D$_1$: A mixture of 13.4 g of IIIa and 40 g of levulinic acid containing 1.8 g of hydrogen chloride was heated at 75° for 2 hr with stirring. After cooling, an addition of 200 ml of water to the pasty reaction mixture caused precipitation of crystalline solid which was collected by filtration, washed with water and dried to give 16 g (98%) of crude Va. Recrystallization three times from acetone-water gave 6.4 g (39%) of colorless needles, mp 175—176°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1730 (CO of COOH), 1645 (CO of NCO). This infrared absorption spectra was identical with that of authentic sample prepared from IV by method E$_1$. *Anal.* Calcd. for $C_{19}H_{17}O_4N$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.19; H, 5.22; N, 4.40.

Method D$_2$: A mixture of 10 g of IIIb, 5.8 g of levulinic acid and 24 g of acetic acid containing 1.1 g of hydrogen chloride was heated at 75—80° for 2 hr with stirring. After cooling, an addition of 100 ml of water to the reaction mixture caused precipitation of crystalline solid which was collected by filtration, washed with water and dried to give 10 g of crude Va. Recrystallization twice from acetone-water gave 6.5 g (66%) of colorless needles of Va, mp 175—176°. Identical infrared absorption spectra were obtained from this material and from authentic sample prepared from IV by method E$_1$. *Anal.* Calcd. for $C_{19}H_{17}O_4N$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.21; H, 5.10; N, 4.55.

Method E$_1$: A mixture of 5 g of IV and 15 g of levulinic acid was stirred with slowly heating in a water-bath. When a temperature of the bath attained to 70°, crystals of ammonium chloride were immediately produced with exothermic reaction. After completion of the exothermic reaction, heating in a water-bath of 75° was continued for additional 1.5 hr. After cooling, an addition of 50 ml of water caused precipitation of a crystalline solid, which was removed by filtration, washed with water, and dried over anhydrous calcium chloride in a vacuum dryer to give 5.8 g (100%) of crude Va. Recrystallization from acetone-water gave 4.7 g (81%) of colorless needles of Va, mp 175—176°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1730 (CO of COOH), 1645 (CO of NCO). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 219 (4.36), 268 (4.15), 318 (3.81). NMR τ: 7.12 (Singlet, 3H, CH_3 of 2-substituent of the indole ring), 6.32 (Singlet, 2H, CH_2 of $-CH_2COOH$), 6.17 (Singlet, 3H, CH_3 of CH_3O), 3.02—3.32 (Multiplet, 3H, ring protons of indole ring), 2.24—2.51 (Multiplet, 5H, ring protons of benzene ring). *Anal.* Calcd. for $C_{19}H_{17}O_4N$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.39; H, 5.15; N, 4.21.

The esterification of Va: A drop of conc. hydrochloric acid was added to a solution of 1.0 g of Va in 30 ml of dry ethanol, and the mixture was refluxed for 4 hr. And, the reaction mixture was concentrated to dryness under reduced pressure. The resultant crystalline solid was recrystallized from alcohol-water to give

1 g (92%) of Vb, mp 68—69°. IR and NMR spectra of the crystals were identical with those of authentic sample.

1-Benzoyl-2-methyl-5-methoxyindole-3-acetic Acid (Vc)——By Method E_1, Vc were prepared from N^1–benzoyl–*p*–chlorophenylhydrazine hydrochloride. Recrystallization from acetone–water gave colorless needles, mp 176—177°. IR cm^{-1}: 1693 (CO of COOH), 1681 (CO of NCO). *Anal.* Calcd. for $C_{18}H_{14}O_3NCl$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.94; H, 4.39; N, 4.18.

1-(*p*-Methylbenzoyl)-2-methyl-5-methoxyindole-3-acetic Acid (Vd)——By Method E_1, colorless needles of Vd, were prepared from N^1–(*p*–methylbenzoyl)–*p*–methoxyphenylhydrazine hydrochloride, which yield was 66%. Recrystallization from acetone–water gave colorless needles, mp 157—158°. IR cm^{-1}: 1706 (CO of COOH), 1668 (CO of NCO). *Anal.* Calcd. for $C_{19}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.16; H, 5.77; N, 4.10.

γ-(1-(*p*-Chlorobenzoyl)-2-methylindol-3-yl)butyric Acid (Ve)——By Method E_1, colorless prisms of Ve were prepared from N^1–(*p*–chlorobenzoyl)–phenylhydrazine hydrochloride in 66% of yield. Recrystallization from acetone–water gave colorless prisms, mp 147—148°. IR cm^{-1}: 1710 (CO of COOH), 1680 (CO of NCO). *Anal.* Calcd. for $C_{20}H_{18}O_3NCl$: C, 67.70; H, 4.82; N, 3.94. Found: C, 67.66; H, 4.90; N, 4.07.

2-Methyl-5-methoxindole-3-acetic Acid (VIIIa)——Method J: A solution of Va in 10 ml of 5% sodium hydroxide aqueous solution was heated at 60° for 3 min. After cooling, the solution was acidified with conc. hydrochloric acid to give a white precipitate, which was collected by filtration and washed with water throughly. Recrystallization from ethanol gave 0.2 g (73%) of VIIIa, mp 161—162°. The product was confirmed by identity of IR spectra and undepress of miscible melting point with authentic sample prepared from *p*–methoxyphenylhydrazine and levulinic acid by method I.[6]

Ethyl 1-Benzoyl-2-methyl-5-methoxyindole-3-acetic Acid (Vb)——Method E_2: A mixture of 5 g of IV, 3 g of ethyl levulinate and 25 ml of dry ethanol was refluxed for 1.5 hr. After cooling, the alcohol was removed by distillation *in vacuo*. Addition of 30 ml of water to the resultant residue caused precipitation of crystalline solid, which was collected by filtration, washed with water and dried over anhydrous calcium chloride in a vacuum dryer to give 5.6 g (89%) of crude Vb. Recrystallization from ethanol aqueous solution gave 3.9 g (62%) of colorless needles, mp 68—69°. IR ν_{max}^{Nujol} cm^{-1}: 1727 (CO of COOEt), 1677 (CO of NCO). UV λ_{max}^{EtOH} mμ (log ε): 219 (4.37), 268 (4.14), 318 (3.80). NMR τ: 8.87—8.63 (triplet, 3H, CH_3 of $COOCH_2CH_3$), 7.64 (Singlet, 3H, CH_3 of 2–substituent of the indole ring), 6.34 (Singlet, 2H, CH_2 of $CH_2\text{–}\overset{\overset{O}{\|}}{C}\text{–}O\text{–}$), 6.17 (Singlet, 3H, CH_3 of OCH_3), 6.02—5.67 (qualtet, 2H, CH_2 of $-COOCH_2CH_3$); 3.32—3.01 (Multiplet, 3H, ring protons of the indole ring), 2.60—2.23 (Multiplet, 5H, ring protons of the benzene ring). *Anal.* Calcd. for $C_{24}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99; Found: C, 72.23; H, 6.04; N, 4.01.

Ethyl Levulinate *p*-Methoxyphenylhydrazone (VI)——Method F: In a little excess sodium hydroxide aquous solution was warmed 35 g (0.2 mole) of I. The cooling caused crystallization of the free base, which was collected by filtration. To a solution of the wet cake in a mixture of 50 ml of acetic acid and 180 ml of water was added slowly 28.8 g (0.2 mole) of ethyl levulinate at room temperature with stirring. After stirring for additional 1 hr, resultant crystals were collected by filtration, washed with water, and dried over potassium hydroxide and phosphorous pentoxide in a vacuum dryer to give 38 g (72%) of VI, mp 77—78°. IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH), 1720 (CO). This compound was so unstable that it was used without purification for a next procedure.

Ethyl Levulinate N^1-Benzoyl-*p*-methoxyphenylhydrazone (VII)——Method G: A mixture of 13.2 g (0.05 mole) of VIa, 25 ml of dry pyridine and 100 ml of ether was maintained at a temperature of 0—5° while a mixture of 7.7 g of benzoyl chloride and 50 ml of ether was added dropwise thereto for 40 min in a nitrogen gas with stirring. Stirring was continued for additional 4 hr under cooling with ice, and then the mixture was refluxed for 2 hr. After cooling, the reaction mixture was washed three times with each of 50 ml of water, and the ether layer was dried over anhydrous sodium sulfate. Thereafter, ether was removed by distillation to give an oily residue. This substance was thought to be crude VIIa, judging from data of the infrared absorption spectra. IR cm^{-1}: 1730 (CO of COOEt), 1650 (CO of NCO). This product was used without purification for a next procedure.

Ethyl 1-Benzoyl-2-methyl-5-methoxyindole-3-acetate (Vb)——Method H: To the oily residue, which was obtained by the mentioned procedure (Method G), was added 30 ml of dry ethanol containing 1.8 g of hydrogen chloride, and the mixture was refluxed for 1.5 hr. After cooling, ethanol was removed by distillation to give an oily residue, which was added to 100 ml of ether. The insoluble material was removed by filtration, and the filtrate was concentrated to nearly dryness. The resultant crystals were collected by filtration to give 11.1 g of crude Vb, mp 62—74°. Recrystallization from aqueous ethanol solution gave 7.1 g of Vb, mp 68—69°. Infrared absorption spectra of this product were identical with that of Vb prepared by Method E_2. *Anal.* Calcd. for $C_{21}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.57; H, 5.96; N, 4.11.

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6) E. Shaw, *J. Am. Chem. Soc.*, 77, 4322 (1955).