[Chem. Pharm. Bull. 20(10)2163—2171(1972)]

UDC 547.757.04 : 547.292'596.4.04

Photo-induced Friedel-Crafts Reactions. IV. Indoleacetic Acids[1]

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(Received March 21, 1972)

The photoreaction of indole with methyl chloroacetate afforded a mixture of seven isomeric methyl indoleacetates, mainly the 4-isomer, whose separation into each component was carried out by repeated column chromatographies. The structues of all of them confirmed by their spectral data and by the unequivocal sysntheses.

The unusual reactivity of the 4-position on the indole nucleus was explained on the basis of the calculation data by SCF-CI-MO method.

The photocyclizations and photorearrangements of N-chloroacetyl derivatives of aromatic amino acids and pharmacodynamic amines have produced many novel heterocycles.[3] A common process of these photoreactions appears to be homolytic or heterolytic cleavage of the C-Cl bond by the intramolecular energy transfer or by the intramolecular electron transfer from the excited singlet state of the aromatic chromophore.[4,5]

The intermolecular photoreaction of electron-rich aromatics such as phenol or anisol with chloroacetamide gave phenylacetic acid derivatives, which provided an example of photo-induced Friedel–Crafts reaction.[6]

In the present paper, the intermolecular photoreaction has been extended to another electron-rich aromatic, indole.

Photoreaction of Indole with Methyl Chloroacetate

After irradiation of an aqueous methanol solution of indole (I) in the presence of 3 equivalents of methyl chloroacetate (II) with 500 W high pressure mercury lamp under nitrogen for 12 hr, the tarry photoproduct was chromatographed on a short column of silica gel to yield a mixture of methyl indoleacetates containing all of seven possible isomers. The separation of the mixture into their components was very difficult because of their similar chemical and chromatographic properties, however it was finally accomplished by repeated column chromatographies on silica gel and alumina. By means of chromatography over silica gel column the mixture was first separated into six fractions (A_1—A_6).

The first fraction A_1 was the recovered indole (I).

The parent peak at *m/e* 189 in the mass spectrum of the fraction A_2 corresponds to methyl indoleacetate, $C_{11}H_{11}O_3N$. The infrared (IR) spectrum has no signal of the NH group and in the nuclear magnetic resonance (NMR) spectrum the six aromatic protons remained unchanged. These data suggest this compound to be methyl indole-1-acetate (III), which

1) Part III: S. Naruto and O. Yonemitsu, *Tetrahedron Letters*, **1971**, 2297.
2) Location: *Kita-12, Nishi-6, Sapporo*; *a*) Present Adress: *Central Research Laboratories, Sankyo Co., Ltd., Hiromachi 1-chome, Shinagawa-ku, Tokyo.*
3) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 5686 (1970); O. Yonemitsu, H. Nakai, Y. Kanaoka, I.L. Karle, and B. Witkop, *ibid.*, **92**, 5691 (1970); Y. Okuno, K. Hemmi, and O. Yonemitsu, *Chem. Commun.*, **1971**, 745; Y. Okuno, K. Hemmi, and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **20**, 1164 (1972), and references cited therein.
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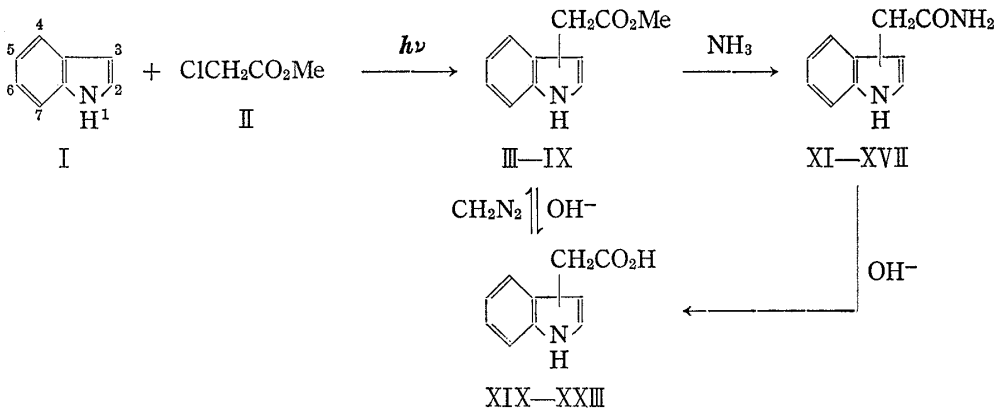

Chart 1

was confirmed by comparing in IR, ultraviolet (UV), NMR, and mass spectra, thin-layer chromatography (TLC) and gas-liquid chromatography (GLC) with the authentic sample.

According to the GLC there are two components in almost equal proportion in the fraction A_3. This mixture was separated into each component by a acid-washed alumina column chromatography. In the NMR spectrum of the compound eluted more rapidly, the aromatic proton at the 3-position in the indole nucleus appears as a multiplet, which changed to a doublet (J=3 Hz) by the addition of D_2O. The presence of the NH group was also confirmed by IR and NMR spectra. These data indicate that a acetate residue is not attached to the pyrrole moeity of indole nucleus. The aromatic protons other than that of 3-position in the NMR spectrum appear so complicate to assign the position of the residue. However, it seems to be reasonable that a loosely bounded hydrogen bond of the NH with the ester group in methyl indole-7-acetate (IX) caused the more rapid elution in the chromatography. The catalytic reduction with 5% $Pd(OH)_2/BaSO_4$[7] gave methyl indoline-7-acetate (XVIII), which was identical with the authentic sample with regard to TLC, IR, UV, and mass spectra and the mixed melting point.

The slower eluted compound must be methyl indole-2-acetate (IV), because in its NMR spectrum the 3-position's proton appears as a broad singlet, which was sharpened by the addition of D_2O with the concominant disappearance of the NH signal. The structure was confirmed by comparing with the authentic sample.

The fraction A_4 was easily found to be a ester substituted at the benzene portion. This ester was hydrolyzed to indole-4-acetic acid (XX), which was identical with the known authentic sample.[8] Its methyl ester (VI) and amide (XIV) were also identified.

The fraction A_5 was a mixture of methyl indole-3-acetate (V), methyl indole-4-acetate (VI), methyl indole-5-acetate (VII) and methyl indole-6-acetate (VIII), attempts of whose separation into each component were unsuccessful, therefore the mixture was converted to amides and then chromatographed on a silica gel column. From the first eluent another fraction of indole-4-acetamide (XIV) was isolated. The second eluent was containing a small amount of indole-5-acetamide (XV), whose structure though difficult to assign by the spectral data was confirmed by comparing with the authentic sample synthesized unequivocally.

The final eluent, a mixture of indole-3-acetamide (XIII) and indole-6-acetamide (XVI) was hydrolyzed to acids, recrystallization from benzene–ether gave indole-3-acetic acid (XIX). The mother liquor was esterified with diazomethane, followed by the treatment with ammonium hydroxide to yield indole-6-acetamide (XVI). The separation of 3- and 6-isomers was also performed after the catalytic reduction with $Pd(OH)_2/BaSO_4$, followed by acetylation

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Table I. Photo-Friedel-Crafts Reaction of Indole with Methyl Chloroacetate

Reaction position	Product	Yield (%)	Spin density
1	III	0.24	0.0914
2	IV	2.55	0.1679
3	V	1.35	0.2280
4	VI	6.2	0.2413
5	VII	0.13	−0.0054
6	VIII	1.69	0.1117
7	IX	1.9	0.1948

Table II. Analytical Data of Methyl Indoleacetate: Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40.

Compound	mp (°C) bp (°C)	Recryst. solvent[a)]	Found		
			C	H	N
III	128—129/0.03 mmHg		69.67	5.99	7.38
IV	70.5—71.5	B-H	69.82	6.00	7.44
VI	66.5—67.5	A–H	69.97	5.82	7.41
VII	oil		69.57	5.92	7.38
VIII	52.5—53.5	E–H	69.64	5.80	7.40
IX	95 —96	C–H	69.91	5.77	7.30

a) B: benzene; H: *n*-hexane; A: ethyl acetate; C: methylene chloride

Table III. Spectral Data of Methyl Indoleacetate

	UV λ_{max} nm (ε)	IR ν_{max} cm^{-1}		NMR δ^{CDCl_3}				
		NH	CO	CH_3	CH_2	NH	C_3–H	others
III	269 (5920), 280 (5550), 291.5 (4230)		1755	3.65	4.73		6.50	7.00—7.70
IV	273 (8060), 279 (7860), 282 (6850), 289.5 (6390)	3400	1730	3.70	3.78	8.70	6.30	6.90—7.70
VI	275 (7370), 280 (7600), 290 (8070)	3380	1725	3.62	3.88	8.30	6.55	6.90—7.30
VII	276.5 (5780), 283 (5630), 293 (4100)	3530	1740	3.64	3.69	8.20	6.45	6.90—7.55
VIII	275.5 (6490), 282 (6570), 292 (5260)	3520	1730	3.65	3.69	8.20	6.45	6.85—7.65
IX	273 (6570), 281 (6600), 290 (5120)	3430	1740	3.62	3.80	8.95	6.49	6.90—7.70

Table IV. Analytical Data of Indoleacetamide: Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08

Compound	Position	mp (°C)	Recryst. solvent[a)]	Found		
				C	H	N
XI	1	181—182	Et	69.17	5.91	16.09
XII	2	180—181	Et	68.83	5.93	15.84
XIV	4	140—142	W	68.98	5.81	16.10
XV	5	150—151	Et–H	69.17	6.06	15.93
XVI	6	189—191	Et	68.70	5.92	16.05
XVII	7	173—174	A	69.06	5.79	16.15

a) Et: ethanol; W: water; H: *n*-hexane; A: ethyl acetate

Table V. Analytical Data of Indoleacetic Acid: Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00

Compound	Position	mp (°C)	Recryst. solvent	Found		
				C	H	N
XXI	5	149—150	A–H	68.37	5.10	8.04
XXII	6	142—144	E–H	68.55	5.36	8.04
XXIII	7	153—155	B–H	68.63	5.28	8.01

Table VI. Spectral Data of Indoleacetamide and Indoleacetic Acid

Compound	UV λ_{max}^{EtOH} nm (ε)	IR ν^{Nujol} cm^{-1}
XI	270 (6350), 280.5 (5990), 285.5 (sh. 5540), 292 (4430)	3370, 3170, 1670, 1630
XII	272.5 (8300), 279 (8080), 282 (8020) 290 (6560)	3450, 3180, 1655
XIV	274 (7430), 280 (7660), 290 (6130)	3450, 3200, 1655, 1625
XV	277 (6730), 283 (5630), 294 (4010)	3440, 3180, 1650, 1620
XVI	275.5 (6530), 282 (6630), 292.5 (5340)	3440, 3180, 1650, 1635
XVII	273 (6500), 281 (6480), 290.5 (4920)	3510, 3310, 1670, 1620
XXI	272 (5620), 276.5 (5690), 283 (5530) 293.5 (3940)	3500, 1710
XXII	275 (6400), 281 (6450), 291.5 (5150)	3440, 1695
XXIII	273 (6510), 280.5 (6480), 294 (4010)	3500, 1705

to methyl N-acetylindolineacetates (XXIV and XXV). However, since these separation yields were far from quantitative, the yields of 3- and 6-isomers in the photoreaction were determined by comparing of intensities in the NMR signals of the mixture of XIII and XIV, and that of V and VIII.

The final fraction A_6 was a deep brown tarry oil, since in which no methyl indoleacetate was detected, no further purification was carried out.

The yields of the photoreaction are summerized in Table I, and some physical data of methyl indoleacetates, indoleacetamides and indoleacetic acids in Table II—VI.

Syntheses of Indoleacetic Acid Derivatives

Since seven isomeric methyl indoleacetates, especially benzene-substituted isomers have so similar chemical and physical properties to determine unequivocally their structures, all of indoleacetic acids, their methyl esters and amides were synthesized.

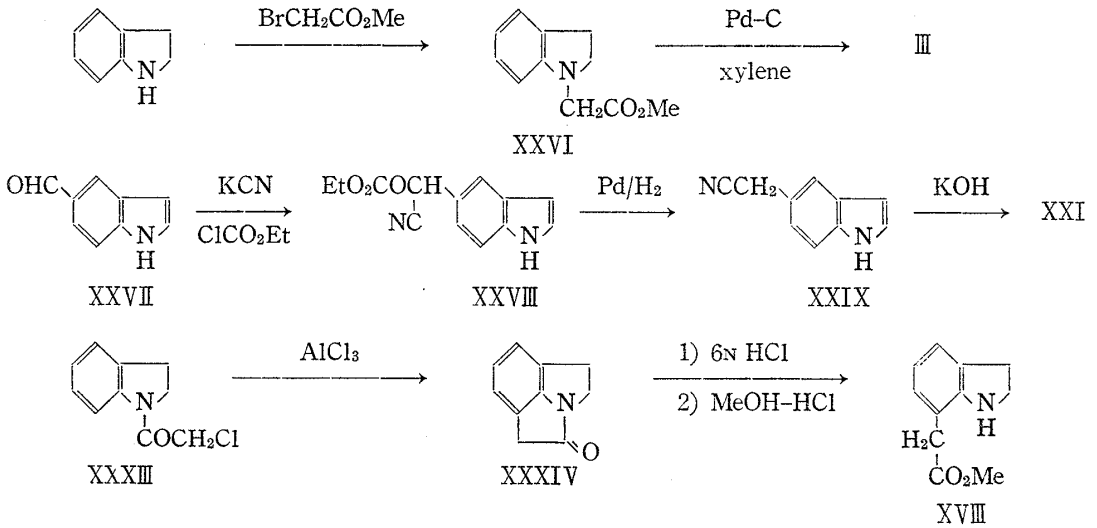

Chart 2

Indole-1-acetic acid has already synthesized from indole and ethyl chloroacetate by Erdtman, *et al.*[9] however its derivatives were given another way in this paper. Indoline was heated at 60° with methyl bromoacetate to yield easily methyl indoline-1-acetate (XXVI), which was dehydrogenated to methyl indole-1-acetate (III) in 95% yield by heating 5% Pd on charcoal. By the treatment with concentrated ammonium hydroxide III was converted to indole-1-acetamide (XI), which was hydrolyzed with potassium hydroxide to indole-1-acetic acid.

Indole-2-,[10] 3-, and 4-acetic acids,[8] methyl indole-3-acetate (V)[11] and indole-3-acetamide (XIII)[12] were already known, therefore unknown methyl esters and amides were synthesized in the usual way.

The synthesis of indole-5- or 6-acetic acid was rather difficult. After several unsuccessful trials, only the cyanhydrine method[13] gave satisfactory results. Indole-5-aldehyde (XXVII)[14] was treated with potassium cyanide and ethyl chlorocarbonate to yield XXVIII. Hydrogenation of crude XXVIII using Pd-black catalyst gave indole-5-acetonitrile (XXIX) in good yield (77% from XXVII), which was hydrolyzed by heating with 1 N sodium hydroxide to yield indole-5-acetic acid (XXI). Indole-6-acetic acid (XXII) was also synthesized from indole-6-aldehyde (XXX)[14] in a similar manner described above.

Indole-7-acetic acid (XXIII) seems to be synthesized similarly from indole-7-aldehyde, however 1-chloroacetylindoline (XXXIII) was chosen as a starting material because it was easily available.[15] When XXXIII was heated with $AlCl_3$ at 365—375° for 40 sec, tricyclic compound (XXXIV) was isolated though in poor yeild, which was hydrolyzed with 6 N hydrochloric acid followed by esterification to yield methyl indoline-7-acetate (XVIII). Compound XVIII was easily dehydrogenated to methyl indole-7-acetate (IX) as described for methyl indole-1-acetate (III).

Discussion

It is well known that the electrophilic substitution on indole nucleus usually takes place at its pyrrole moiety. Even in the radical reaction the similar result is obtained.[16] However the photoreaction in this paper mainly occurs at the 4-position though in very poor yield suggesting that this substitution must not take place through the reaction of the ground state molecule of indole with the alkyl radical.

On the basis of the fluorescence quenching study on electron-rich aromatics such as indole or anisol with chloroacetamide or methyl chloroacetate[17] and the solvent effect in the photolysis of N-chloroacetylphenethylamines,[5] it was proposed that this type of the photoreaction in aqueous solution may be initiated by electron-transfer from the excited electron-rich aromatic to the chlorinated amide or ester group *via* a loosely bound exciplex, followed by the cleavage of the C-Cl bond.[5] The flash-photolysis study of *N*-chloroacetyl-*m*-tyramine probably supported the mechanism.[4] Therefore, the photo-Friedel–Crafts reaction of indole with methyl chloroacetate may proceed as shown in Chart 3. The radical cation (XXXV) of indole may be the species to condense with ethoxycarbonylmethylene radical (XXXVI). If this is the mechanism, the reactivity of each position on indole may depend on the elec-

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10) R. Ginliano and M.L. Stein, *Ann. Chem.* (Rome), **48**, 1284 (1958).
11) R.W. Jackson, *J. Biol. Chem.*, **88**, 659 (1930).
12) K.N.F. Shaw, A. McMillan, A.G. Gudmundson, and M.D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).
13) K. Kindler, *Arch. Pharm.*, **283**, 190 (1950).
14) F. Troxler, A. Harnisch, G. Bormann, and L. Szabo, *Helv. Chem. Acta*, **51**, 1616 (1968).
15) J. Blake, J.R. Tretter, G.J. Juhasz, W. Bonthrone, and H. Rapoport, *J. Amer. Chem. Soc.*, **88**, 4060 (1966).
16) J. Hutton and W.A. Waters, *J. Chem. Soc.*, **1965**, 4253.
17) M.T. McCall, G.S. Hammond, O. Yonemitsu, and B. Witkop. *J. Amer. Chem. Soc.*, **92**, 6991 (1970).

tron spin density[18] of the cation-radical (XXXV). As shown in Table I the calculated spin density of each position by SCF-CI-MO method[19] explains the high reactivity of the 4-position of indole in this photoreaction, and these data provide another support for the proposed mechanism.

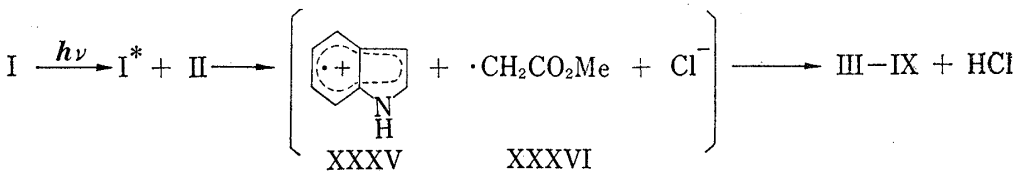

Chart 3

Experimental

A. Photoreaction of Indole (I) with Methyl Chloroacetate (II)

A solution of 1.17 g (10 mmol) of indole (I), 3.24 g (30 mmol) of methyl chloroacetate (II) and 1.5 g (20 mmol) of sodium bicarbonate in 500 ml of 30% aqueous methanol was irradiated with 500 W high pressure mercury lamp inside a quartz water-cooling jacket in a steady stream of nitrogen for 12 hr. The irradiated red solution with a small amount of a deep brown oil floated was concentrated *in vacuo* to a volume of *ca.* 80 ml and extracted with ethyl acetate for several times. The combined extracts were dried over sodium sulfate and evaporated to leave a deep brown oil. Four batches were combined to yield 10 g of a oil, which was chromatographed on a column of silica gel (60 g). Elution with methylene chloride gave 3.76 g of a mixture of methyl indole acetates as a pale brown oil, which was rechromatographed on a column of 500 g of silica gel. Elution with methylene chloride gave six fractions (A_1—A_6).

Fraction A_1 was 50 mg of recovered indole (I), mp 48—50°, which was identical with the authentic sample by TLC, IR and the mixed mp.

Methyl Indole-1-acetate (III)——Fraction A_2 was 18 mg (0.24%) of methyl indole-1-acetate (III) as a pale yellow oil, Mass Spectrum *m/e*: 189 (M^+), 130 (base peak), which was identical with the authentic sample by IR, UV, NMR, Mass, TLC, and GLC.

Methyl Indole-7-acetate (IX)——Fraction A_3 was 320 mg of a mixture of methyl indole-7-acetate (IX) and methyl indole-2-acetate (IV), which was chromatographed on a column of acid-washed alumina. The column was eluted with methylene chloride–*n*-hexane (1:1) to yield 143 mg (1.9%) of methyl indole-7-acetate (IX), which was recrystallized from methylene chloride–*n*-hexane to give colorless plates, mp 95—96°. Mass Spectrum *m/e*: 189 (M^+), 130 (base peak).

Methyl Indoline-7-acetate (XVIII)——A solution of 52.3 mg (0.276 mmole) of IX in 2.5 ml of acetic acid and 1 ml of 2N hydrochloric acid was hydrogenated using 50 mg of 5% $Pd(OH)_2$ on $BaSO_4$ catalyst for 45 min. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the residue was allowed to stand at room temperature in 7 ml of 3N hydrogen chloride in methanol overnight to yield 61.6 mg (98%) of methyl indoline-7-acetate (XVIII) hydrochloride as a pale red crystalline powder, which was recrystallized from ethanol to afford colorless small prisms, mp 198—201° (decomp.). *Anal.* Calcd. for $C_{11}H_{18}O_2NCl$: C, 58.02; H, 6.20; N, 6.15. Found: C, 57.96; H, 6.08; N, 6.10. IR ν_{max}^{Nujol} cm^{-1}: 1750. UV λ_{max}^{EtOH} nm(ε): 241 (8100), 296 (3210). Mass Spectrum *m/e*: 191 (M^+), 130, 119(base peak). NMR δ^{D_2O}: 3.35 (2H, t, J=8 Hz), 3.74 (3H, s), 3.89 (2H, s), 3.93 (2H, t, J=8 Hz), 7.30—7.55 (3H, ,m)

Methyl Indole-2-acetate (IV)——Further elution with the same solvent from the acid-washed alumina column gave 170 mg (2.25%) of crude methyl indole-2-acetate (IV), which was recrystallized from benzene–*n*-hexane to afford colorless prisms, mp 70.5—71.5°. Mass Spectrum *m/e*: 189 (M^+), 130 (base peak).

Methyl Indole-4-acetate (VI)——Fraction A_4 was 170 mg of a viscous oil containing mainly methyl indole-4-acetate (VI), which was allowed to stand at room temperature overnight in concentrated ammonium hydroxide. After evaporation of ammonium hydroxide *in vacuo*, the residue was purified by preparative TLC to give 120 mg of indole-4-acetamide (XIV). Recrystallization from water afforded colorless needles, mp 140—142°. Mass Spectrum *m/e*: 174 (M^+), 130 (base peak).

Fraction A_5 was 940 mg of a mixture of methyl indole-4-acetate (VI), methyl indole-5-acetate (VII), methyl indole-3-acetate (V) and methyl indole-6-acetate (VIII), which was treated with concentrated ammonium hydroxide as described above to give a mixture of indoleacetamides. Chromatography on 50 g of a silica gel column eluting with ethyl acetate–methylene chloride (1:2) gave 311 mg of XIV, 107 mg of a mixture of indole-3-acetamide (XIII), indole-5-acetamide (XV) and indole-6-acetamide (XVI), and 166 mg of a mixture of XIII and XVI.

18) N. Kanamaru and S. Nagakura, *Bull. Chem. Soc. Japan*, **43**, 3443 (1970).
19) H.C. Longuet-Higgins, and J.A. Pople, *Proc. Phys. Soc.*, **A68**, 591 (1955).

Combined indole-4-acetamide (XIV) (431 mg, 6.2%) was heated at 110° in 3N potassium hydroxide for 4 hr. The solution was cooled and acidified with 10% hydrochloric acid to precipitate indole-4-acetic acid (XX). Recrystallization from ethanol to afford colorless needles, mp 206° (decomp.), which was identical with the authentic sample[8] by IR, UV, Mass, and the mixed mp.

A ether solution of XX was treated with excess of a ether solution of diazomethane for 5 min to give methyl indole-4-acetate (VI) quantitatively. Recrystallization from ethyl acetate–*n*-hexane afforded colorless needles, mp 66.5—67.5°, Mass Spectrum *m/e*: 189 (M^+), 130 (base peak).

Methyl Indole-5-acetate (VII)——Above 107 mg of the mixture of XIII, XV, and XVI was chromatographed on a preparative silica gel TLC using a mixture of ethyl acetate–methylene chloride (1:1) as a solvent to give 9 mg (0.13%) of indole-5-acetamide (XV) and 46 mg of a mixture of XIII and XVI. Recrystallization of XV from ethanol–*n*-hexane gave colorless needles, mp 150°, Mass Spectrum *m/e*: 174 (M^+), 130 (base peak), which was identical with the authentic sample (see below) by IR, TLC, and the mixed mp. Indole-5-acetamide (XV) was converted to methyl indole-5-acetate (VII) as described above, a colorless oil, Mass Spectrum *m/e*: 189 (M^+), 130 (base peak), which was identical with the authentic sample with regard to TLC, IR, UV, and mass spectra.

Methyl Indole-3-acetate (V)——A combined mixture (212 mg, 3.04%)[20] of XIII and XVI was heated at 110°in 3N potassium hydroxide for 4 hr. The solution was cooled and acidified with 10% hydrochloric acid to precipitate a mixture of indole-3-acetic acid (XIX) and indole-6-acetic acid (XXII), which was extracted with ether. The ether extract was dried over sodium sulfate and evaporated to leave a colorless solid, which was recrystallized from benzene–ether to afford indole-3-acetic acid (XIX), mp 158—160°. Esterification with diazomethane gave its methyl ester (V) as a oil, which was identical with the authentic sample with regard to TLC and spectral data.

Methyl Indole-6-acetate (VIII)——The mother liquor from recrystallization of the mixture of XIX and XXII was esterified with diazomethane, followed by the treatment of concentrated ammonium hydroxide to give a mixture of amides XIII and XVI. Recrystallization from ethanol gave indole-6-acetamide (XVI) as colorless plates, mp 189—190°, Mass Spectrum *m/e*: 174 (M^+), 130 (base peak), which was identical with the authentic sample (see below) by TLC, IR, NMR, and the mixed melting point. Indole-6-acetamide (XVI) was reconverted to methyl indole-6-acetate (VIII), which was recrystallized from ether–*n*-hexane to afford colorless needles, mp 52.5—53.5°, Mass Spectrum *m/e*: 189 (M^+), 130 (base peak).

Methyl 1-Acetylindoline-3-acetate (XXIV)——Fifty mg of the mixture of V and VIII was hydrogenated in acetic acid at 60° using 5% $Pd(OH)_2$ on $BaSO_4$ catalyst[7] for 20 min. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the residue was esterified by the treatment of hydrogen chloride in methanol overnight. After evaporation of the methanol, the residue was heated at 120° in 4 ml of acetic anhydride for 1 hr. Evaporation of acetic anhydride *in vacuo* left a red oil, which was decolorized by a short column of 2 g of silica gel to give a pale red solid. Chromatography on a preparative silica gel TLC using methylene chloride as solvent gave two fractions. From the upper fraction 40.6 mg of methyl 1-acetyl indoline-3-acetate (XXIV) was isolated as a colorless solid, which was recrystallized from water to afford colorless needles, mp 59.5—61°. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.85; H, 6.46; N, 6.08. IR $\nu^{Nujol}cm^{-1}$: 1750, 1655. UV λ_{max}^{EtOH} nm(ε): 253 (15630), 280 (3970), 290 (3150). Mass Spectrum *m/e*: 233 (M^+), 191, 160, 130, 108 (base peak). NMR δ^{CDCl_3}: 2.17 (3H, s), 2.2—2.8 (3H, m), 3.68 (3H, s), 3.75—4.25 (2H, m), 6.95—7.30 (3H, ,m) 8.1—8.25 (1H, m).

Methyl 1-Acetyl indoline-6-acetate (XXV)——The lower fraction of the preparative TLC gave 6.8 mg of methyl 1-acetylindoline-6-acetate (XXV), which was recrystallized from water to give colorless needles, mp 101—102.5°. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.81; H, 6.40; N, 6.12. IR $\nu^{Nujol}cm^{-1}$: 1750, 1660. UV λ_{max}^{EtOH} nm(ε): 255 (14400), 273 (12370), 285 (4500), 295 (4340). Mass Spectrum *m/e*: 233 (M^+), 191 (base peak), 175, 132, 130. NMR δ^{CDCl_3}: 2.19 (3H, s), 3.11 (2H, t, J=8 Hz), 3.60 (2H, s), 3.67 (3H, s), 4.04 (3H, t, J=8 Hz), 6.8—7.2 (2H, m), 8.10 (1H, broad).

B. Syntheses of Indoleacetic Acid Derivatives

Methyl Indoline-1-acetate (XXVI)——A solution of 7.016 g (60 mmole) of indoline and 4.183 g (40 mmole) of methyl bromoacetate in 35 ml of tetrahydrofuran was heated at 60° for 1.5 hr under nitrogen. After evaporation of the solvent, to the residue 15 ml of 3% hydrochloric acid and 15 ml of ethyl acetate were added. The ethyl acetate layer was washed with water and dried over sodium sulfate. Evaporation of the solvent left 4.614 g of a brown oil, $bp_{0.05}$ 113—115°, 3.555 g (31%) of a colorless oil. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.17; H, 6.86; N, 7.28. IR $\nu^{Nujol}cm^{-1}$: 1755. Mass Spectrum *m/e*: 191 (M^+). UV λ_{max}^{EtOH} nm(ε): 251 (9440), 302 (3550). NMR δ^{CDCl_3}: 2.97 (2H, d, J=7 Hz), 3.50 (2H, d, J=7 Hz), 3.69 (3H, s), 3.85 (2H, s), 6.30—7.20 (4H, m).

Methyl Indole-1-acetate (III)——A xylene solution of 1.116 g (5.84 mmol) of XXVI with 500 mg of 5% Pd on charcoal was heated under reflux for 1 hr. After removal of the catalyst by filtration and of

20) The mixture was reconverted to a mixture of esters V and VIII, and by the comparison of intensities in its NMR signals the yields of respective compounds in the photoreaction were determined as 1.35 and 1.69%.

the solvent by evaporation *in vacuo*, the residual pale yellow oil (1.106 g) was chromatographed on a column of 10 g of silica gel. Elution with methylene chloride gave 1.048 g (95%) of a colorless oil of methyl indole-1-acetate (III). *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C 69.82; H, 5.86; N, 7.40. Found: C, 69.67; H, 5.99; N, 7.38. IR $\nu^{neat}cm^{-1}$: 1760. Mass Spectrum *m/e*: 189 (M^+), 130 (base peak).

Indole-1-acetamide (XI)——To a methanol solution (20 ml) of 1.148 g (6.08 mmole) of III concentrated ammonium hydroxide (20 ml) was added and allowed to stand overnight. After evaporation of the solvent, a colorless crystalline powder was recrystallized from ethanol to afford 811 mg (77%) of colorless needles, mp 181—182°. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.65; H, 5.86; N, 15.87. IR $\nu^{Nujol}cm^{-1}$: 3370, 3170, 1670, 1630. Mass Spectrum *m/e*: 174 (M^+), 130 (base peak).

5-(1-Ethoxycarbonyloxy)indoleacetonitrile (XXVIII)——To a stirred solution of 145 mg (1 mmole) of indole-5-aldehyde[14] (XXVII) in 2 ml of ethanol was added under ice-cooling 101 mg (1.5 mmole) of potassium cyanide, followed by the dropwise addition of 165 mg (1.5 mmole) of ethyl chlorocarbonate. As the carbonate was added a white powder precipitated gradually. After 1.5 hr the ethanol was evaporated *in vacuo* at 10—20°. The precipitate was collected by filtration, washed with a small amount of water and dissolved in methylene chloride. The methylene chloride solution was washed with water, dried over sodium sulfate and concentrated *in vacuo* to leave 236 mg of a pale yellow solid, which was recrystallized from benzene–*n*-hexane to afford colorless small prisms, mp 98.5—99.5° (decomp.). *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$: C, 63.92; H, 4.95; N, 11.40. Found: C, 63.79; H, 4.99; N, 11.47. IR $\nu^{Nujol}cm^{-1}$: 3470, 1770. UV λ_{max}^{EtOH} nm(ε): 230 (46500), 276 (5050), 282 (5100), 292 (4490). Mass Spectrum *m/e*: 244 (M^+), 171, 155 (base peak). NMR δ^{CDCl_3}: 1.28 (3H, t, J=7 Hz), 4.22 (2H, q, J=7 Hz), 6.30 (1H, s), 6.5—6.6 (1H, m), 7.2—7.4 (3H, m), 7.77 (1H, s), 8.35 (1H, broad).

Indole-5-acetonitrile (XXIX)——A methanol solution (2.5 ml) of 236 mg of crude XXVIII was hydrogenated using 63 mg of Pd-black catalyst. After 1.25 hr 37 mg of another Pd-black was added and the hydrogenation was continued for additional 2 hr. After removal of the catalyst by filtration and of the solvent by evaporation, the residual yellow oil was chromatographed on a silica gel (4 g) column. Elution with methylene chloride gave 120 mg (77% from XXVII) of a colorless crystalline powder, which was recrystallized from benzene–*n*-hexane to afford colorless plates, mp 65.5—66°. *Anal.* Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.85; H, 5.15; N, 18.05. IR $\nu^{Nujol}cm^{-1}$: 3470, 3340, 2290. UV λ_{max}^{EtOH} nm(ε): 271 (shoulder, 5820), 276 (6160), 282 (6280), 293 (4900). Mass Spectrum *m/e*: 156 (M^+, base peak), 130. NMR δ^{CDCl_3}: 3.78 (2H, s), 6.45—6.6 (1H, m), 6.95—7.64 (4H, m), 8.3 (1H, broad).

Indole-5-acetic Acid (XXI)——Indole-5-acetonitrile (XXIX) (120 mg, 0.77 mmole) in 2 ml of 3N potassium hydroxide was heated at 110° for 3 hr. The solution was cooled and acidified with 10% hydrochloric acid to precipitate a white powder, which was extracted with ether three times. The combined ether extracts were washed with water, dried over sodium sulfate and concentrated *in vacuo* to leave 109 mg (74.5% of a pale yellow crystalline powder, which was recrystallized from ethyl acetate–*n*-hexane to afford colorless needles mp 149—150°, Mass Spectrum *m/e*: 175 (M^+), 130 (base peak).

6-(1-Ethoxycarbonyloxy)indoleacetonitrile (XXXI)——From 145 mg (1 mmole) of indole-6-aldehyde (XXX),[14] 253 mg of 6-(1-ethoxycarbonyloxy)indoleacetonitrile (XXXI) was synthesized as described above for XXVIII. Recrystallization from benzene–*n*-hexane gave colorless prisms, mp 96—97.5° (decomp.). *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.17; H, 4.98; N, 11.68. IR ν^{Nujol} cm^{-1}: 3550, 1760. UV λ_{max}^{EtOH} nm(ε), 230 (33380), 280 (7820), 293 (shoulder, 6030). Mass Spectrum *m/e*: 244 (M^+), 171, 156, 155 (base peak), 130. NMR δ^{CDCl_3}: 1.29 (3H, t, J=7 Hz), 4.24 (2H, q, J=7 Hz), 6.32 (1H, s), 6.5—6.6 (1H, m), 7.15—7.8 (4H, m), 8.35 (1H, broad).

Indole-6-acetonitrile (XXXII)——From 253 mg of XXXI, 82 mg of indole-6-acetonitrile (XXXII) was synthesized as described above for indole-5-acetonitrile (XXIX). Recrystallization from benzene–*n*-hexane gave colorless needles, mp 105—106°. *Anal.* Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 77.12; H, 5.12; N, 17.73. IR $\nu^{Nujol}cm^{-1}$: 3380, 2290. UV λ_{max}^{EtOH} nm(ε), 276 (5960), 282 (6190), 292 (5100) Mass Spectrum *m/e*: 156 (M^+, base peak), 130. NMR δ^{CDCl_3}: 3.75 (2H, s), 6.45—6.55 (1H, m), 6.80—7.70 (4H, m), 8.20 (1H, broad).

Indole-6-acetic Acid (XXII)——Indole-6-acetonitrile (XXXII) (35.8 mg, 0.23 mmole) was heated at 110° in 0.8 ml of 1N sodium hydroxide for 2 hr. After cooling, the solution was acidified by the addition of 10% hydrochloric acid and the precipitate was extracted with ether. The ether extract was washed with water, dried over sodium sulfate and evaporated *in vacuo* to leave 29 mg (72%) of a colorless solid, which was recrystallized from ether–*n*-hexane to afford colorless plates, mp 142—144°, Mass Spectrum *m/e*: 175 (M^+), 130 (base peak).

2-Keto-1,2,4,5-tetrahydropyrrolo[3,2,1,hi]indole (XXXIV)——A mixture of 782 mg (4 mmole) of 1-chloroacetylindoline (XXXIII) and 1.2 g (9 mmole) of aluminium chloride was heated at 365—375° on a metal bath for 40 sec. After cooling, to a brown solid was added ice–water and 10% hydrochloric acid and the mixture was extracted with methylene chloride for three times. The combined extracts were washed with water, dried over sodium sulfate, concentrated *in vacuo* to leave 611 mg of a deep brown solid, which was decolorized by a silica gel (6 g) column eluting with methylene chloride to give 166 mg of a pale brown solid. Chromatography on a preparative silica gel TLC gave 79.2 mg (12.4%) of a colorless crystalline powder, which was recrystallized from ethyl acetate–*n*-hexane to afford colorless needles, 129—131°. *Anal.*

Calcd. for $C_{10}H_9ON$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.36; H, 5.97; N, 8.77. IR $\nu^{Nujol}cm^{-1}$: 1715, 1695, 1660. UV λ_{max}^{EtOH} nm(ε): 250 (9550), 254 (9980), 257 (shoulder, 9190), 261 (shoulder, 7580), 265 (shoulder, 5370), 298 (2110). Mass Spectrum *m/e*: 159 (M^+), 130 (base peak). NMR δ^{CDCl_3}: 3.50 (2H, t, $J=7$ Hz), 3.70 (2H, s), 4.00 (2H, t, $J=7$ Hz), 6.8—7.1 (4H, m).

Methyl Indoline-7-acetate (XVIII) Hydrochloride——Compound XXXIV (21.7 mg, 0.136 mmole) was suspended in 1.2 ml of 6N hydrochloric acid and heated at 100° for 15 min. The clear solution was concentrated *in vacuo* to dryness, and the dried residue was dissolved in 4 ml of 1N hydrogen chloride in methanol and allowed to stand overnight. After removal of the solvent, the crystalline powder was recrystallized from ethanol to afford colorless small prisms, mp 202—203° (decomp.).

Methyl 1-Acetylindoline-3-acetate (XXIV)——Indole-3-acetic acid (525 mg, 3 mmole) was hydrogenated in 25 ml of acetic acid and 25 ml of 2N hydrochloric acid using 500 mg of 5% $Pd(OH)_2$ on $BaSO_4$ catalyst at 60° for 45 min. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the dried residue was dissolved in 3N hydrogen chloride in methanol and allowed to stand overnight. After evaporation of the solvent, to the residue was added slightly excess of anhydrous sodium acetate and 15 ml of acetic anhydride. The solution was heated under reflux for 1.5 hr. Evaporation of the acetic anhydride left a deep brown oil, which was chromatographed on a silica gel column (13 g). Elution with methylene chloride gave 628 mg (90%) of a pale red crystalline powder, which was recrystallized from water to afford colorless needles, mp 59.5—61°.

Methyl Indoleacetates——Indoleacetic acids were esterified with diazomethane for 5 min. After chromatographed on a silica gel column eluting methylene chloride, methyl indoleacetates were isolated almost quantitatively.

Indoleacetamides——Methanol solutions of methyl indoleacetates were treated with concentrated ammonium hydroxide overnight. Evaporation of the solvent and purification by silica gel chromatography eluting with ethyl acetate gave indoleacetamides in 80—90% yields.