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107. Kikuo Ishizumi, Takayuki Shioiri, and Shun-ichi Yamada: Studies in the Indole Series. II.*1 A General Synthesis of Cycloalkan[*b*]indolones.

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A general synthesis of cycloalkan[*b*]indolones from 3-indolealkanoic acids is described. Effect of 1-alkyl substitution of indole was observed on the ultraviolet spectra of 1-methyl-3-indolealkanoic acids. Cyclization of 3-indolealkanoic acids was mostly effected with polyphosphoric acid. Ring closure of Vc and Vd with PPA brought about concomitant expected monomers (VIIc and VIId) and dimers (VIIIa and VIIIb). The structure proof of the dimers was obtained from analytical and spectral data.

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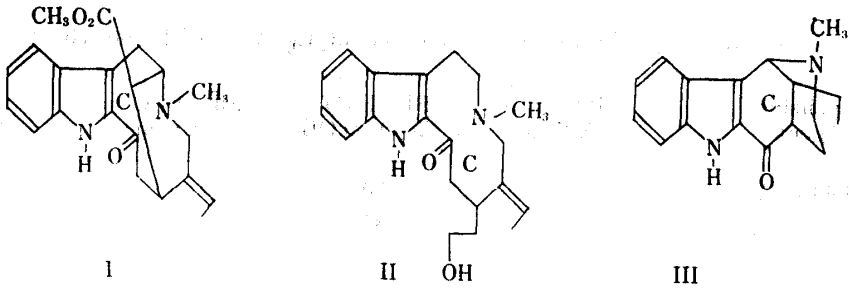
In recent years there have been outstanding developments in the structural elucidation of indole alkaloids. A surprisingly large number of new indole alkaloids have been isolated mainly from a variety of apocynaceous plants.[1] 2-Acylindole alkaloids,[2] above all, are one of the representatives and vobasine (I) was the first of 2-acylindole alkaloids to be elucidated structurally.[3] Vobasine (I) and its congeners have an eight-membered ketonic ring C. A second type of 2-acylindole alkaloids is represented by burnamicine (II),[4] which is characterized by a ten-membered ketonic ring C containing a basic nitrogen. Dasycarpidone (III),[5] which contains a six-membered ketonic ring C, is one of a third type. These 2-acylindole alkaloids in common are composed of cycloalkan[*b*]indolone skeleton.



I II III

Chart 1.

As a basic experiment for the synthetic approaches to the 2-acylindole alkaloids, we have investigated a general synthetic method of cycloalkan[*b*]indolones from 3-indolealkanoic acids. 1-Unsubstituted 3-indolealkanoic acids (IV) were synthesized from indole by the methods given in the literatures.[6] From IV, 1-methyl-3-indolealkanoic acids (V) were prepared by methylation according to the procedure of our previous report.[7]

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*1 Part I. This Bulletin, **15**, 499 (1967).

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1) R. H. F. Manske (Ed.): The Alkaloids, Vol. II, VI, VIII, Academic Press, New York and London.

2) *a*) J. A. Weisbach, B. Douglas: Chem. & Ind. (London), **1965**, 623; *Idem*: Lloydia, **27**, 374 (1964). *b*) *Idem*: Chem. & Ind., **1966**, 233.

3) U. Renner, D. A. Prins, A. L. Burlingame, K. Biemann: Helv. Chim. Acta, **46**, 2186 (1963).

4) M. F. Bartlett, W. I. Taylor: J. Am. Chem. Soc., **85**, 1203 (1963).

5) J. A. Joule, M. Ohashi, B. Gilbert, C. Djerassi: Tetrahedron, **21**, 1717 (1965).

6) For IVa, *a*) R. Majima, T. Hoshino: Ber., **58**, 2044 (1925). For IVb, *b*) F. N. Stepanov: U. S. S. R. Patent, 66,681; C. A., **41**, 2087 (1947). For IVc, IVd; *c*) H. E. Fritz: J. Org. Chem., **28**, 1384 (1963).

7) S. Yamada, T. Shioiri, T. Itaya, T. Hara, R. Matsueda: This Bulletin, **13**, 88 (1965).

The ultraviolet spectra of these 1-methyl-3-indolealkanoic acids (V) in 90% aqueous ethanol showed the same 1-alkyl effect as that of 1-alkyltryptophans.[7]

Table I. Ultraviolet Spectra of 3-Indolealkanoic Acids (IV and V)

n	Compound	λ_{max} mμ ($\varepsilon \times 10^{-3}$)			
5	IVa	222 (34.2)	275 (5.78)	282 (6.27)	291 (5.44)
	Va	225.5 (34.2)		289 (5.45)	
6	IVb	223 (32.5)	275 (5.61)	282 (5.97)	292 (5.40)
	Vb	226 (38.2)		290 (6.04)	
7	IVc	222 (32.0)	275 (4.76)	282.5 (5.21)	291 (4.52)
	Vc	226 (37.2)		290 (5.57)	
8	IVd	223 (31.6)	276 (5.25)	283 (5.76)	291 (5.09)
	Vd	227 (35.0)		291 (5.60)	

It may be concluded that generally the introduction of 1-alkyl substituent in 3-alkylindoles gives rise to a bathochromic displacement in a maximum near 280 mμ to 290 mμ along with decrease or disappearance of maxima near 270 and 290 mμ. A 220 mμ absorption band of 1,3-dialkylindoles also is displaced to slightly longer wave lengths than that of 3-monoalkylindoles. Recently Jackson, *et al.* reported that 1-methyltryptamines[8a] and 1-alkylskatoles[8b] in ethanol showed the 1-alkyl effect on the ultraviolet spectra.

Preliminary investigations of intramolecular cyclization reaction were carried out about 4-(3-indolyl)butyric acid (IVb) and its 1-methyl derivative (Vb). The results are summarized in Table II. The cyclization procedure of phosphorus pentoxide in boiling

Table II. Ring Closure of 4-(3-Indolyl)butyric Acids (IVb and Vb) (%)

Cyclizing Agent	P_2O_5 in Xylene	$BF_3 \cdot Et_2O$ in Ac_2O-AcOH	$BF_3 \cdot Et_2O$ in Dioxane	PPA
Yield of VIb	22	50	—	55
VIIb	—	87	26	90

xylene was virtually identical with that described by Jennings,[9] who obtained VIa from IVa in 11% yield. Plieninger, *et al.*[10] prepared indolo-α-pyrone derivatives from 3-indoleacetic acid and several acid anhydrides with boron trifluoride etherate. Under this condition, the expected ketones (VIb and VIIb) were obtained in moderate yield. The most effective cyclizing agent examined, however, was polyphosphoric acid (PPA).[11]

Table III shows summary of PPA cyclizations of IV and V. A typical ring closure

Table III. PPA Cyclization of 3-Indolealkanoic Acids (IV and V) (%)

Ring size n	5	6	7	8
Yield of VI	44	55	95	30
VII	77	90	11	trace

8) *a*) A.H. Jackson, A.E. Smith: J. Chem. Soc., **1964**, 5510. *b*) *Idem*: Tetrahedron, **21**, 989 (1965).
9) K.F. Jennings: J. Chem. Soc., **1957**, 497.
10) H. Plieninger, W. Müller, K. Weinerth: Chem. Ber., **97**, 667 (1964).
11) *a*) H.R. Snyder, F.X. Werber: J. Am. Chem. Soc., **72**, 2962, 2965 (1950). *b*) F.D. Popp, W.E. McEwen: Chem. Revs., **58**, 321 (1958). *c*) F. Uhlig, H.R. Snyder: Advances in Organic Chemistry, Vol. 1, 35 (1960), Interscience Publishers, Inc., New York.

was run by treating each starting material in 10~50 parts of PPA at 95° for 10~30 minutes. The color development was used to determine the time of each reaction according to Koo and Uhligs' suggestions.[12]

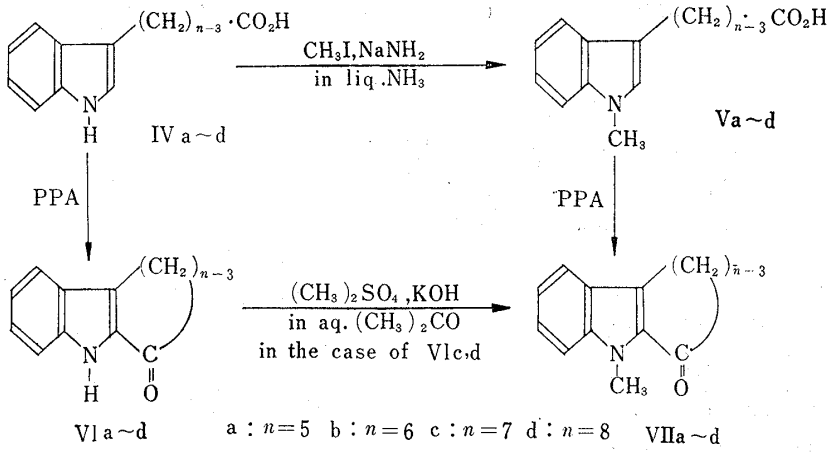


Chart 2.

The structures of the cyclized products were proved to be cycloalkan[*b*]indolones (Ⅵ and Ⅶ) from analytical and spectral data. All cyclized products have two ultraviolet absorption bands at about 237 and 310 mμ (ε>10,000) with two infrared absorption bands at about 1650 and 740 cm^{-1} attributable to aromatic ketone and *O*-disubstituted benzene moiety. Both absorption patterns are characteristic of the 2-acylindoles having no substituent on the benzene portion of the indole nucleus.[2] This assignment is corroborated by the nuclear magnetic resonance spectra showing the aromatic four-protons at about 2.7τ. A detailed discussion on the spectral properties will be reported in the following paper.[13]

In the case of Ⅴc, three products were obtained after purification by chromatography over alumina and fractional crystallization. The one came as pale yellow scales, m.p. 64.5~65.5°, and was identified with Ⅶc prepared by methylation of Ⅵc according to the method of Stevens, *et al.*[14] The second came as a crystalline powder, m.p. 118~119°, which was ascribed to have the dimeric structure (Ⅷa) as discussed below. The third, m.p. 201~202°, could not be elucidated its structure owing to small quantities,

When Ⅴd was treated with 40 parts of PPA at 95° for 30 minutes, it afforded a dimer (Ⅷb) and only a trace of Ⅶd, which was detected on thin-layer chromatography by comparison with the authentic sample prepared by methylation of Ⅵd. At 150° for 3 minutes, Ⅴd afforded a substance whose spectral data were quite similar to the third product obtained by ring closure of Ⅴc. The methyl ester of Ⅴd also gave Ⅷb only. Acetylation at the 2-position occurred when Ⅴd was treated with boron trifluoride etherate in acetic anhydride-acetic acid.*3

The molecular formula of Ⅷb was determined by the microanalysis and the molecular weight measurement to be $C_{30}H_{34}O_2N_2$, which was twice the formula of Ⅶd. The spectral similarities between Ⅷa and Ⅷb, together with microalytical data, allowed Ⅷa to be a dimer.

*3 Skatole and 3-(3-indolyl)propionic acid (Ⅳa) also afforded their 2-acetyl derivatives under this condition (see Experimental). The position of the acetylation was confirmed by the ultraviolet spectra[13] of the acetylated products.

12) *a*) J. Koo : J. Am. Chem. Soc., **75**, 1889, 1891 (1953). *b*) F. Uhlig : Angew. Chem., **66**, 435 (1954).

13) T. Shioiri, K. Ishizumi, S. Yamada : This Bulletin, in press.

14) T.S. Stevens, S.H. Tucker : J. Chem. Soc., **123**, 2140 (1923). cf. L.J. Dolby, D.L. Booth : J. Org. Chem., **30**, 1550 (1965).

The nuclear magnetic resonance spectrum of Ⅷa shows two three-proton singlet N-methyl peaks at 6.30 and 6.01τ as well as a one-proton singlet at 3.25τ characteristic of the indolic α-proton signal.[15] A typical 1,2,4 aromatic proton pattern (ortho splitting J=9.0 c.p.s., meta splitting J=2.0 c.p.s.) was observed at 1.78, 2.27 and 2.75τ accompanied with the unsubstituted aromatic indole moiety (complex pattern at about 2.9τ) (Fig. 1).

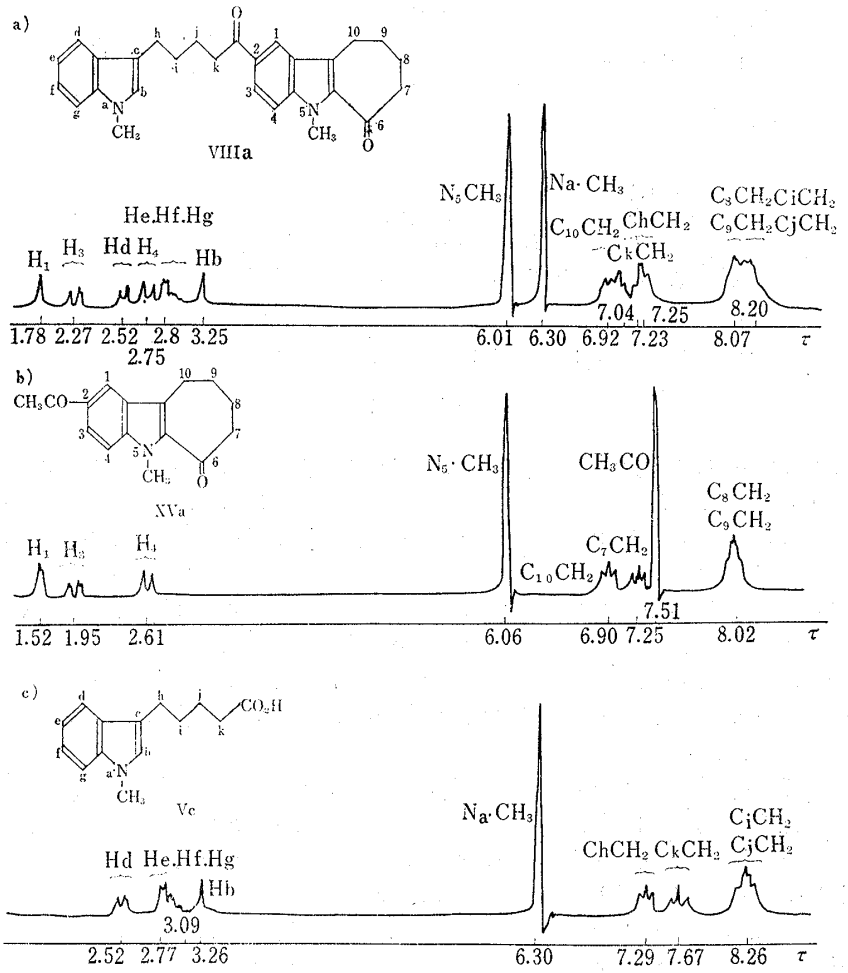


Fig. 1. Nuclear Magnetic Resonance Spectra of Ⅷa, XVa and Vc in CCl_4

A similar consideration on the nuclear magnetic resonance spectrum of Ⅷb yields an analogous interpretation. Peaks at 6.33, 5.99 and 3.33τ are assigned to the same structural groupings as those of Ⅷa. The aromatic proton pattern is also very similar to Ⅷa (Fig. 2).

The above data suggested these dimers (Ⅷa and Ⅷb) to be 2 or 3*4-acylcycloalkan-[*b*]indolones. The position of the acyl group could be settled at 2 from the spectral comparison of the dimers and the synthetic model compounds (Ⅺ, XVa and XVb).

The synthesis of 1,3-dimethyl-2,5-diacetylindole (Ⅺ), one of the model compounds, was accomplished in three steps starting from skatole. Methylation of skatole in liquid ammonia led to 1,3-dimethylindole (Ⅸ), which furnished 2-acetyl-1,3-dimethylindole (X) on acetylation with boron trifluoride etherate in acetic anhydride-acetic acid.*3

*4 2 or 3 position in the seven or eight-membered cycloalkan[*b*]indolones (Ⅶc, d and Ⅷc, d) corresponds to 5 or 6 position in a simple indole derivative such as skatole.

15) *a*) L. A. Cohen, J. W. Daly, H. Kny, B. Witkop: J. Am. Chem. Soc., **82**, 2184 (1960). *b*) R. V. Jardine, R. K. Brown: Canad. J. Chem., **41**, 2067 (1963). *c*) M. G. Reinecke, H. W. Johnson, J. F. Sebastian: Chem. & Ind., **1964**, 151.

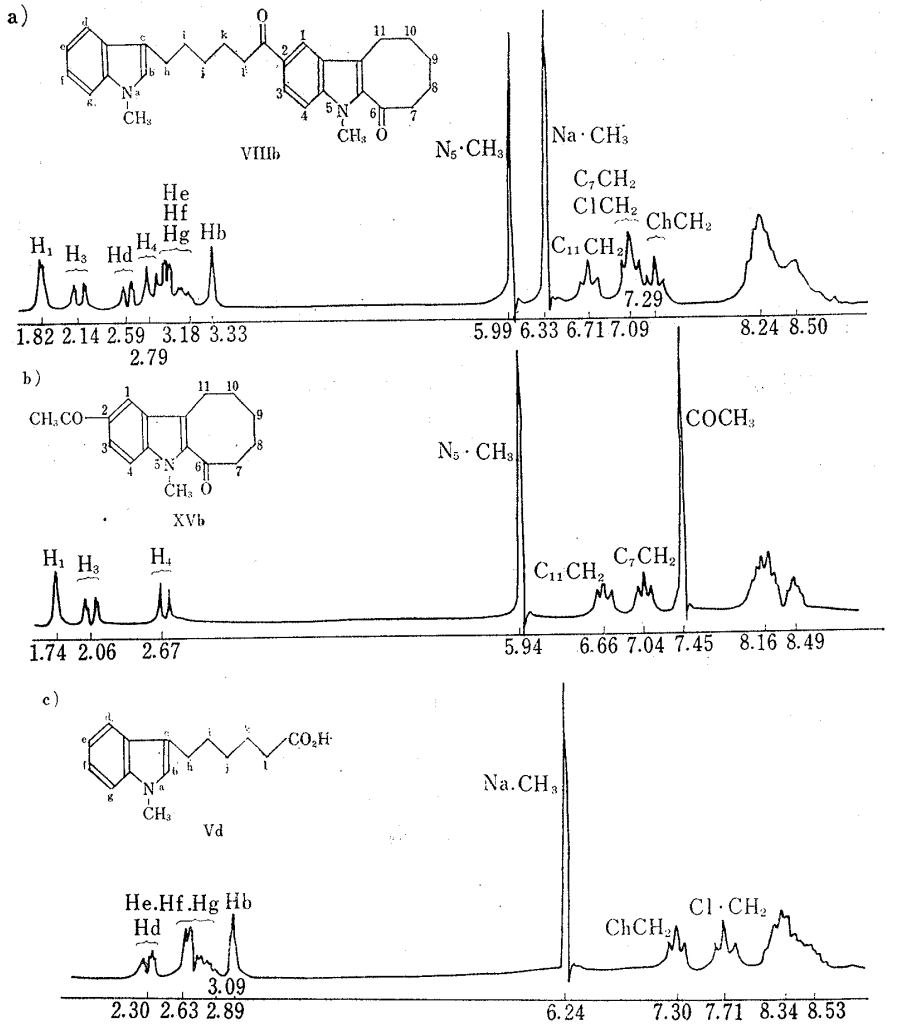
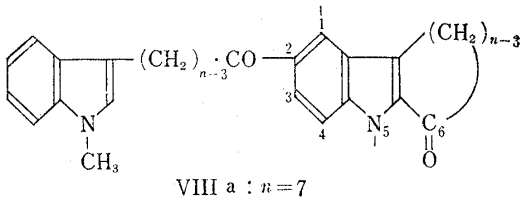


Fig. 2. Nuclear Magnetic Resonance Spectra of VIIIb, XVb and Vd in CCl_4

The compound (X) was further subjected to acetylation with PPA and acetic anhydride-acetic acid. The structure of the resultant 1,3-dimethyl-2,5-diacetylindole (XI) was confirmed by an unambiguous synthesis following the line of the Strandtman synthesis of 5-acetylindole derivatives,[16] using the Japp-Klingemann reaction of *p*-acetylphenyldiazonium



VIII a : $n=7$
VIII b : $n=8$

Chart 3.

Table IV. Infrared and Ultraviolet Spectra of 2,5-Diacylindole Derivatives

	Infrared Spectra in Nujol (cm^{-1})				Ultraviolet Spectra in 90% aq. EtOH λ_{max} mμ ($\varepsilon \times 10^{-3}$)		
	$\nu_{5-C=O}$	$\nu_{2-C=O}$	$\nu_{C=C}$	$\delta_{arom.}$			
XIV	1667	1633	1615	722	220 (8.48)	280.5(58.4)	326 (11.5)
XI	1660	1644	1606	817, 795	223 (10.8)	282 (61.0)	325 (10.3)
XVa	1665	1658	1612	825	223 (8.46)	282 (57.6)	325 (9.50)
XVb	1669	1645	1609	808	225.5(7.64)	284 (57.9)	327.5(9.75)
VIIIa	1683	1645	1605	779, 731	226 (41.2)	283 (58.8)	325 (9.93)
VIIIb	1679	1643	1607	803, 739	226 (40.5)	284.5(58.6)	327 (9.78)

16) M. V. Strandtmann, C. Puchalski, J. Shavel : J. Med. Chem., **7**, 141 (1964).

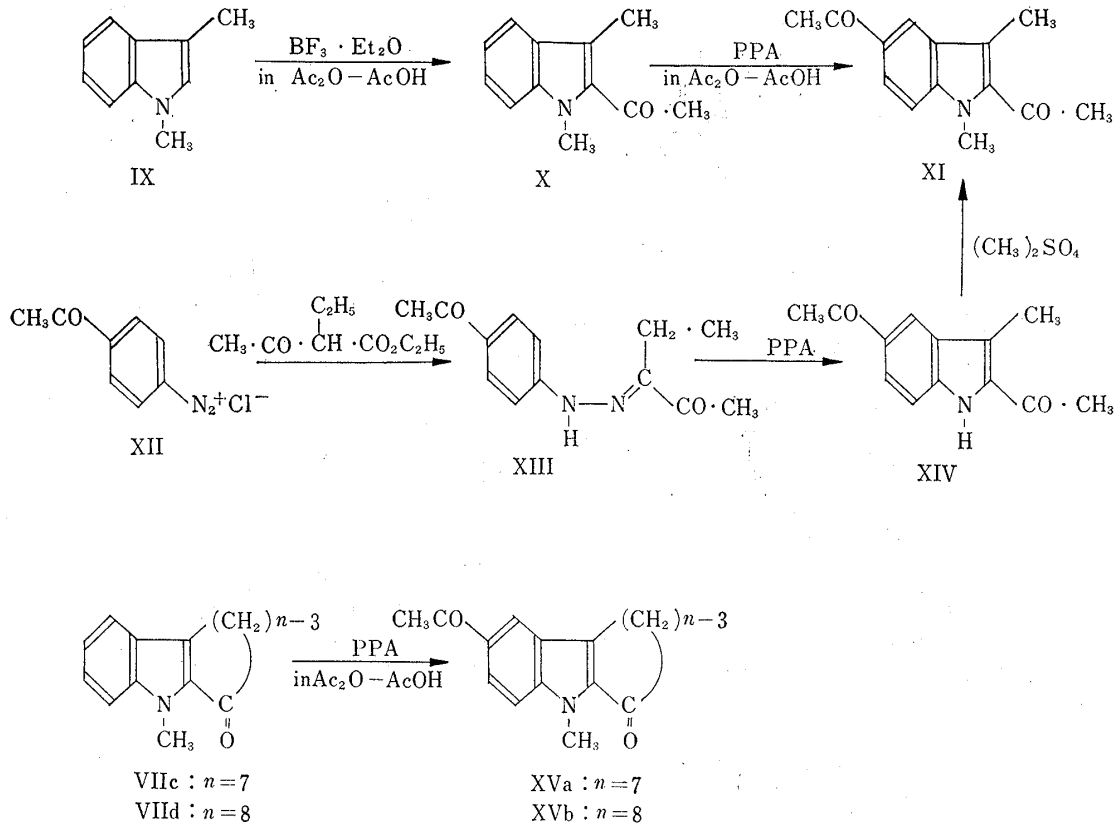


Chart 4.

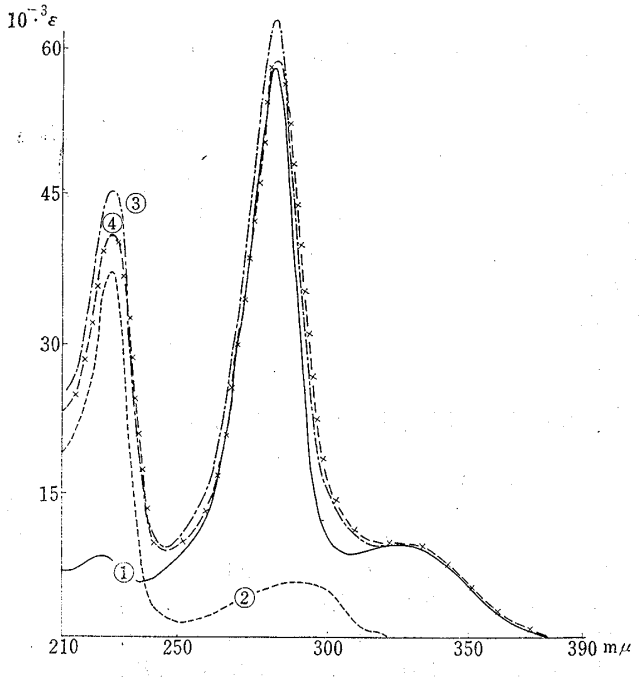


Fig. 3. Ultraviolet Spectra of XVa, Vc, VIIIa and the Summation of the Curves of XVa and Vc in 90% aq. EtOH

① ——— XVa ② ------- Vc
③ —·— XVa+Vc ④ – – × – – VIIIa

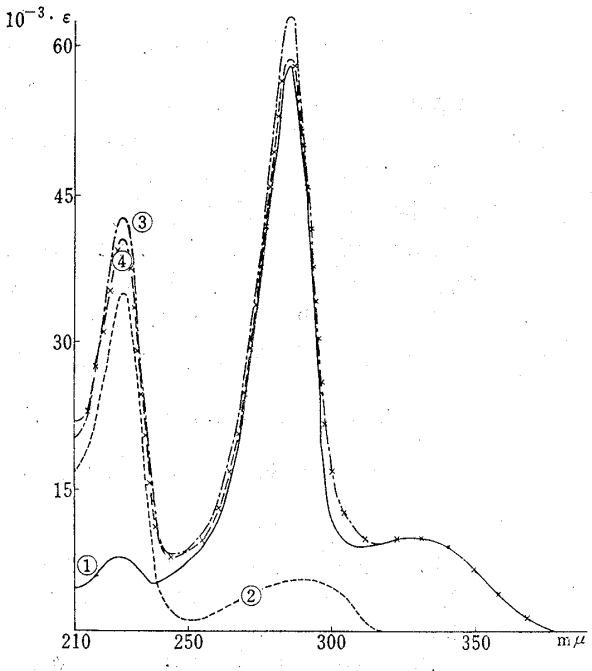


Fig. 4. Ultraviolet Spectra of XVb, Vd, VIIIb and the Summation of the Curves of XVb and Vd in 90% aq. EtOH

① ——— XVb ② ------- Vd
③ —·— XVb+Vd ④ – – × – – VIIIb

chloride (XII) and ethyl 2-acetylbutyrate followed by the Fischer indole synthesis and methylation, as shown in Chart 4.

This identification permitted that when a 2-acyl-1,3-dialkylindole was treated with PPA and acetic anhydride-acetic acid acetylation at the 5-position would occur. Then, VIIc and VIId were subjected to the acetylation to give XVa and XVb.

The spectral data of XI, XIV, XVa and XVb were closely similar to those of the dimers (VIIIa and VIIIb) as shown in Table V. The assignment of the two carbonyl stretching bands in these 2,5-diacetylindole derivatives was based on the fact that the carbonyl frequency of 2-acylindole derivatives (*ca.* 1650 cm^{-1})[2,13] was lower than that of alkyl aryl ketones (*ca.* 1690 cm^{-1}).[17] In addition, the ultraviolet absorption curve of VIIIa (or VIIIb) is well superimposable with a synthetic curve obtained by summation of the curves of Vc and XVa (or Vd and XVb) (Figs. 3 and 4). The comparison of the nuclear magnetic resonance spectrum of VIIIa with those of XVa and Vc (Fig. 1), similarly the spectrum of VIIIb with those of XVb and Vd (Fig. 2) gave reasonable results.

The above data have established the structures of VIIIa and VIIIb as 2-[5-(1-methyl-3-indolyl)pentanoyl]-5-methyl-7, 8, 9, 10-tetrahydrocyclohept[*b*]indol-6(5*H*)-one and 2-[6-(1-methyl-3-indolyl)hexanoyl]-5-methyl-5,7,8,9,10,11-hexahydro-6*H*-cycloöct[*b*]indol-6-one.

Experimental

All m.p.s are uncorrected. The UV and IR absorption spectra were respectively taken in 90% aq. EtOH with a Cary Model 11, and in nujol with a Koken Model DS-402G spectrophotometer. The NMR spectra were obtained in CCl_4 solution containing tetramethylsilane as an internal reference at 100 Mc. on a Varian HR-100 high resolution NMR spectrometer. Solvents used for extraction in all experiments were dried over anhyd. Na_2SO_4 after extraction, and removed under reduced pressure.

1-Methylation of 3-Indolealkanoic Acids (IV)

3-(1-Methyl-3-indolyl)propionic Acid (Va)——Metallic Na (6.4 g., 0.28 atom) was added with stirring in small pieces to liquid NH_3 (*ca.* 21.) containing ferric nitrate nonahydrate (0.5 g.). After dissolution was complete, 3-(3-indolyl)propionic acid (IVa)[6a] (22.7 g., 0.12 mole) suspended in anhyd. Et_2O was added to the stirred mixture. After 2 hr., MeI (22.8 g., 0.16 mole) was added dropwise, and stirring was continued to evaporate NH_3. Water (120 ml.) was added to the residue and the mixture was heated to dissolve the residue and filtered, and the filtrate was acidified with conc. aq. HCl. The resultant white precipitates were collected and washed with H_2O. One recrystallization from H_2O afforded colorless needles (18.3 g., 75%), m.p. 124~124.5°. One more recrystallization furnished an analytical sample, m.p. 124~125°. (Reported m.p. 125.5°).[18] *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.82; H, 6.49; N, 7.19. IR cm^{-1}: 1714 (COOH), 1625 (C=C), 733 (*O*-disubstituted benzene).

4-(1-Methyl-3-indolyl)butyric Acid (Vb)——4-(3-Indolyl)butyric acid (IVb)[6b] was methylated as above in 56% yield. Recrystallizations from *n*-hexane furnished colorless needles, m.p. 100~101°. (Reported m.p. 101~102°).[19] *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.56; H, 7.27; N, 6.55. IR cm^{-1}: 1707, 1702 (COOH), 1608 (C=C), 740, 729 (*O*-disubstituted benzene).

5-(1-Methyl-3-indolyl)valeric Acid (Vc)——The reaction was carried out as above from 5-(3-indolyl)-valeric acid (IVc).[6c] The product (yield, 56%) was purified from MeOH to colorless crystals, m.p. 88°. *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.52; N, 6.08. IR cm^{-1}: 1706 (COOH), 739, 735 (*O*-disubstituted benzene).

6-(1-Methyl-3-indolyl)caproic Acid (Vd)——Methylation of 6-(3-indolyl)caproic acid (IVd)[6c] afforded Vd in 55% yield. Recrystallizations from MeOH gave colorless prisms, m.p. 61~63°. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.56; H, 7.76; N, 5.85. IR cm^{-1}: 1711 (COOH), 1614 (C=C), 734, 722 (*O*-disubstituted benzene).

Methyl 6-(1-Methyl-3-indolyl)hexanoate——A mixture of Vd (5.0 g.) and 25 w/v% MeOH-HCl (50 ml.) was refluxed for 5.5 hr. After excess MeOH was evaporated, the residue was dissolved in benzene, and the benzene solution was washed successively with H_2O, sat. aq. $NaHCO_3$ and H_2O, dried, and evaporated. The residual oil was distilled to give the methyl ester of Vd (3.0 g., 58%), $b.p_5$ 202°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.25; H, 8.06; N, 5.57.

17) L. J. Bellamy: The Infra-red Spectra of Complex Molecules, 132 (1958), Methuen & Co., Ltd. (London).
18) M. Julia, J. Bagot: Bull. soc chim. France, **1964**, 1924.
19) M. Julia, J. Bagot, O. Siffert: *Ibid.*, **1964**, 1939.

Cyclization of 4-(3-Indolyl)butyric Acids (IVb and Vb)

2,3,4,9-Tetrahydro-1*H*-carbazol-1-one (VIb). i) P_2O_5 in Xylene——To a refluxing solution of 4-(3-indolyl)butyric acid (IVb) (1.0 g.) in xylene (200 ml.) was added portionsweise P_2O_5 (8 g.) during 30 min. After further refluxing for 1 hr., the solution was decanted and washed with sat. aq. $NaHCO_3$. Dried solution was concentrated to yield VIb (0.2 g., 22%) as short yellow needles, m.p. 148~157°. Recrystallizations from *n*-hexane raised the m.p. to 164~165°. (Reported m.p. 168~170°).[20] *Anal.* Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.03; H, 5.99; N, 7.46.

ii) BF_3•Et_2O in Ac_2O-AcOH——To an ice-cooled solution of IVb (1 g.) in Ac_2O (1 ml.)-AcOH (5 ml.) was added dropwise BF_3•Et_2O (1.1 ml.) during 2 min. After stirring at room temperature for 45 min., the mixture was poured into ice-water (30 ml.) and extracted with benzene. The benzene layer was washed with sat. aq. $NaHCO_3$, dried and evaporated to give a yellow oil, which was solidified on standing for a long time. The solid (m.p. 151~157°) weighed 0.45 g. (50%).

The $NaHCO_3$ layer was acidified with conc. aq. HCl to give precipitates (0.42 g., m.p. 137~142°), 0.2 g. of which was refluxed in NaOH (0.13 g.)-EtOH (1.2 ml.)-H_2O (1.6 ml.) for 0.5 hr. and acidified to recover IVb (0.1 g.), m.p. 117~120°.

iii) PPA——To hot PPA (11 g.) was added IVb (1 g.) and the mixture was stirred at 95° for 25 min. The dark red reaction mixture was poured into ice-water (60 ml.) and extracted with benzene. After washing with sat. aq. $NaHCO_3$, the benzene layer was dried and evaporated to yield VIb (0.5 g., 55%), m.p. 159~163°.

The three products obtained from i), ii) and iii) were identified through the admixture and the comparison of IR spectra.

9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (VIIb). i) BF_3•Et_2O in Ac_2O-AcOH——4-(1-Methyl-3-indolyl)butyric acid (Vb) was subjected to ring closure as above (stirring at room temperature for 2 hr.) in 87% yield. Recrystallizations from MeOH gave colorless prisms, m.p. 98~99° (Reported m.p. 100~102°).[20] *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.53; H, 6.63; N, 7.18.

ii) BF_3•Et_2O in Dioxane——BF_3•Et_2O (1.1 ml.) was added to a solution of Vb (1.0 g.) in dioxane (5 ml.). The mixture was stirred at room temperature for 2 hr., and refluxed for 4 hr. After evaporation of dioxane, the residue was dissolved in benzene-Et_2O (1:1) and the organic layer was washed with sat. aq. $NaHCO_3$, dried and evaporated to give VIIb (0.23 g., 25%), m.p. 86~94°. Vb (0.15 g.) was recovered from the sat. aq. $NaHCO_3$ layer.

iii) PPA——A mixture of Vb (1 g.) and PPA (14 g.) was stirred at 95° for 30 min. and worked up as above. Yield 0.83 g., 90%.

The products obtained by ii) and iii) were found to be identical with one obtained by i) through admixture and spectral comparison.

PPA Cyclization of 3-Indolealkanoic Acids (IV and V)

1,2-Dihydrocyclopent[*b*]indol-3(4*H*)-one (VIa)——IVa (2 g.) was treated with 30 g. of PPA at 95° for 10 min. The reaction mixture was poured into ice-water, filtered, extracted with AcOEt-hot benzene, and worked up as usual. Yield 44%. VIa crystallized from EtOH as short yellow needles, m.p. 245~248° (Reported m.p. 252~252.5°).[9] *Anal.* Calcd. for $C_{11}H_9ON$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.94; H, 5.42; N, 8.04. IVa (0.1 g.) was recovered from the sat. aq. $NaHCO_3$ layer.

4-Methyl-1,2-dihydrocyclopent[*b*]indol-3(4*H*)-one (VIIa)——A mixture of Va (3 g.) and PPA (40 g.) was stirred at 95° for 13 min. The dried, extracted benzene layer was decolorized with Al_2O_3 before evaporation. Yield 77%. The crude VIIa was purified from EtOH to give colorless needles, m.p. 133~134° (Reported m.p. 80~100°).[21] *Anal.* Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.87; H, 6.00; N, 7.62.

7,8,9,10-Tetrahydrocyclohept[*b*]indol-6(5*H*)-one (VIc)——A mixture of IVc (6.0 g.) and PPA (180 g.) was heated with stirring at 85° for 12 min. Work-up as usual gave VIc (5.2 g., 95%), m.p. 140~144°. Two recrystallizations from EtOH afforded colorless prisms, m.p. 145.5~147° (Reported m.p. 148°).[22] *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.08; H, 6.71; N, 6.72.

5-Methyl-7,8,9,10-tetrahydrocyclohept[*b*]indol-6(5*H*)-one (VIIc)——To a stirred solution of VIc (5.0 g). in Me_2CO (20 ml.) was added 66% aq. KOH (36 ml.), followed by the dropwise addition of Me_2SO_4 (15 ml.). After refluxing for 45 min., removal of Me_2CO, extraction with benzene and washing with sat. aq. NaCl and finally drying and concentration gave an oil (5.0 g.), which was chromatographed over Al_2O_3 (150 g.) in benzene to give VIIc (3.5 g., 63%), m.p. 61~63°. Purification from EtOH gave slightly yellow scales, m.p. 64.5~65.5°. *Anal.* Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.02; H, 7.12; N, 6.60.

PPA Cyclization of 5-(1-Methyl-3-indolyl)valeric Acid (Vc)——A mixture of Vc (3.0 g.) and PPA (90 g.) was stirred at 80° for 25 min., and then poured into ice-water (200 ml.). The aq. suspension was extracted with benzene, and the benzene layer was washed with sat. aq. $NaHCO_3$, dried and evaporated to give a brown oil (2.6 g.), which was subjected to chromatography on Al_2O_3 (80 g.) in benzene. From the first

20) B. Douglas, J. L. Kirkpatrick, B. P. Moore, J. A. Weisbach: Aust. J. Chem. **17**, 246 (1964).
21) M. Renxen: Bull. soc. chim. Belges, **68**, 258 (1959); C. A., **54**, 494d (1960).
22) M. Mühtstädt, W. Treibs: Ann., **608**, 38 (1957).

fraction 1.6 g. of solid was obtained. One recrystallization from EtOH gave 0.3 g. of crystals, m.p. 180～186°. Two more recrystallizations from EtOH raised the m.p. to 201～202°. *Anal.* Found : C, 81.38; H, 6.70; N, 6.67. IR cm^{-1} : 1655, 1613, 740. UV λ_{max} mμ : 222, 234, 278, 316. The structure was not pursued.

The mother liquor from the first recrystallization was evaporated, and the residue was recrystallized from *n*-hexane to give prisms (0.3 g., 11%), m.p. 57～61°. This was identified with Ⅶc through admixture and spectral comparison with the sample obtained from Ⅵc.

From the second fraction of Al_2O_3 chromatography 0.3 g. of solid (m.p. 114～116°) was obtained. Purification from EtOH afforded a colorless crystalline powder, m.p. 118～119°. *Anal.* Calcd. for $C_{28}H_{30}O_2N_2$: C, 78.84; H, 7.09; N, 6.57. Found : C, 78.85; H, 7.16; N, 6.82. The structure of this compound was determined as 2-[5-(1-methyl-3-indolyl)pentanoyl]-5-methyl-7,8,9,10-tetrahydrocyclohept[*b*]indol-6(5*H*)-one (Ⅷa).

5,7,8,9,10,11-Hexahydro-6*H*-cycloöct[*b*]indol-6-one (Ⅵd)——A mixture of Ⅳd (2.0 g.) and PPA (93 g.) was stirred at 95° for 8 min. and worked up as usual to give a yellow powder (0.92 g.), m.p. 130～155°. Chromatography on Al_2O_3 (30 g.) using benzene as the eluent gave a crystalline product (0.55 g., 30%), m.p. 170～180°. Two recrystallizations from EtOH afforded colorless crystals, m.p. 183° (Reported m.p. 186～187°).[23] *Anal.* Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09; N, 6.57. Found : C, 78.75; H, 6.99; N, 6.65.

5-Methyl-5,7,8,9,10,11-hexahydro-6*H*-cycloöct[*b*]indol-6-one (Ⅶd)——Under the same conditions as described above for methylation of Ⅵc, but with 1.5 hr. refluxing, Ⅵd gave 16% conversion to Ⅶd. Purifications from EtOH afforded colorless scales, m.p. 91°. *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found : C, 79.39; H, 7.66; N, 6.21.

PPA Cyclization of 6-(1-Methyl-3-indolyl)caproic Acid (Vd)——Vd (2.0 g.) was treated with PPA (80 g.) at 95° for 30 min. Work-up as above gave a yellow oil (1.8 g.) after evaporation of benzene. It was chromatographed over Al_2O_3 (45 g.) in benzene. After exclusion of the first effluent (10 ml.) (Ⅶd was detected on thin-layer chromatography), a yellow solid (0.98 g.) was obtained from the subsequent effluents, and purified from EtOH to give colorless prisms, m.p. 118～119.5°. *Anal.* Calcd. for $C_{30}H_{34}O_2N_2$: C, 79.26; H, 7.54; N, 6.16; mol. wt., 454.58. Found : C, 79.18; H, 7.58; N, 5.99; mol. wt. (Rast), 409. The structure of these prisms was determined as 2-[6-(1-methyl-3-indolyl)hexanoyl]-5-methyl-5,7,8,9,10,11-hexahydro-6*H*-cycloöct-[*b*]indol-6-one (Ⅷb).

PPA cyclization of Vd (2.0 g.) at 150° for 3 min. gave an unknown substance (85 mg.) from the first effluent of benzene on Al_2O_3 chromatography and Ⅷb (0.59 g.) from the subsequent effluents. The former (m.p. 215～218°) was recrystallized twice from EtOH. *Anal.* Found : C, 81.60; H, 7.46; N, 6.11. IR cm^{-1} : 1646, 1621, 747. UV λ_{max} mμ : 221, 233, 279, 320.

The methyl ester of Vd only afforded Ⅷb.

Acetylation at the 2-Position of 3-Alkylindole Derivatives[*3]

2-Acetyl-3-methylindole——To a cooled solution of skatole[*5] (2.0 g.) in Ac_2O (2 ml.)-AcOH (10 ml.) was added dropwise $BF_3 \cdot Et_2O$ (2 ml.). The mixture was stirred at room temperature for 1¾ hr., and poured into ice-water (150 ml.) to yield yellow precipitates, which were filtered and purified from *n*-hexane to give colorless needles (0.7 g., 27%), m.p. 144～145°. Two more recrystallizations from *n*-hexane raised the m.p. to 146～147° (Reported m.p. 146～147°).[24] *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found : C, 76.33; H, 6.38; N, 8.10.

3-(2-Acetyl-3-indolyl)propionic Acid——To a cooled solution of Ⅳa (4.0 g.) in Ac_2O (4 ml.)-AcOH (20 ml.) was added dropwise $BF_3 \cdot Et_2O$ (4.5 ml.). The mixture was stirred at room temperature for 45 min., poured into ice-water (100 ml.), extracted with benzene and Et_2O. The combined organic layer was further extracted with sat. aq. $NaHCO_3$. The alkaline layer was acidified with conc. aq. HCl to give an oil, which was solidified with benzene. The solid (1.2 g., 25%), m.p. 167～170°, was recrystallized from EtOH to give colorless minute needles, m.p. 173～175°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67; N, 6.06. Found : C, 67.49; H, 5.59; N, 6.22. Jennings[9] gave a 125～127° value for the m.p. of 3-(2-acetyl-3-indolyl)propionic acid. From a consideration on his ultraviolet spectral data of the compound (λ_{max} 225, 285, 290, 310 mμ) and our data (λ_{max} 236, 313 mμ),[13] the assignment by Jennings is probably in error.

6-(1-Methyl-2-acetyl-3-indolyl)caproic Acid——Acetylation of Vd was carried out as above, but with 22 hr. stirring at room temperature, and work-up as usual and recrystallizations from *n*-hexane gave the 2-acetyl derivative of Vd, m.p. 98～99°, as colorless scales. Yield 34%. *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found : C, 71.15; H, 7.26; N, 4.82.

Synthesis of 2,5-Diacetylindole Derivatives

1,3-Dimethylindole (Ⅸ)[25]——Skatole[*5] (19.5 g., 0.15 mole) suspended in Et_2O was added to a solution of sodium amide in liquid NH_3 (from 3.85 g., 0.165 atom, of Na in *ca.* 21. of NH_3) with efficient

[*5] Kindly furnished by Dr. T. Hino.

23) B. Witkop, J. B. Patrick, M. Rosenblum : J. Am. Chem. Soc., **73**, 2641 (1951).

24) H. Yasuda : Kagaku Kenkyusho Hokoku, **30**, 139 (1954); C. A., **49**, 6832 h (1955).

25) Cf. K. T. Potts, J. E. Saxton : J. Chem. Soc., **1954**, 2641; Org. Syntheses, **40**, 68.

stirring. After 1 hr., MeI (28.5 g., 0.20 mole) was added carefully and the solution was kept at room temperature until all the NH_3 had evaporated. H_2O (100 ml.) was added to the residue, and the mixture was extracted with Et_2O (150 ml.). The Et_2O layer was washed with H_2O, dried, and evaporated. Distillation of the residue gave a slightly yellow oil (17 g., 78%), b.p_{10} 127~131°. Redistillation at 118°/10 mm. Hg (reported b.$p_{0.4}$ 72~73°)[26] gave a colorless oil. *Anal.* Calcd. for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.52; H, 7.37; N, 9.47.

2-Acetyl-1,3-dimethylindole (X)——In a similar manner as described for acetylation of skatole, IX afforded X in 78% yield. Purification from EtOH gave minute needles, m.p. 86~87°(Reported m.p. 84~85°).[20] *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.19; H, 6.97; N, 7.50.

***p*-Aminoacetophenone**[27]——To a solution of *p*-nitroacetophenone (38 g.) in AcOH (300 ml.)-H_2O (75 ml.) was added portionsweise iron powder (50 g.) during 1¼ hr. The addition of iron raised the temperature of the solution to 75°. After 30 min. from the beginning of the addition, the mixture was heated at 90°, followed by the addition of H_2O (75 ml.). After all iron powder was added, the reaction mixture was stirred for 30 min., cooled, diluted with H_2O and extracted with Et_2O. Drying and evaporation of Et_2O gave a yellow solid (20 g., 65%), m.p. 102~103°. Recrystallization from H_2O afforded 15.3 g. of pale yellow crystals, m.p. 104~105°(Reported m.p. 106°).[28]

2,3-Pentanedione 3-*p*-acetylphenylhydrazone (XIII)——A solution of NaOH (5.7 g.) in H_2O (16 ml.) was added to ethyl 2-acetylbutyrate[29] (18 g.) in EtOH (32 ml.). Shortly after the formation of a semisolid gelatinous mass, H_2O (320 ml.) was added and the mixture was stirred until only a small amount of oil remained unreacted upon. This was removed by passing the solution through a wet filter paper and the filtrate was added at 0~2° to a solution of *p*-acetylphenyldiazonium chloride (XII) prepared by diazotization of *p*-aminoacetophenone (15 g.) in H_2O (97 ml.)-conc. aq. HCl (54 ml.) with $NaNO_2$ (8 g.) in H_2O (200 ml.) at 0~5°. The addition of crystallized AcONa (63 g.) caused the rapid precipitation of the phenylhydrazone (XIII), which was carried to the surface by the liberated CO_2, collected, and washed with H_2O. The substance was recrystallized from benzene to red powders (20 g., 78%), m.p. 120~121°. Purification from MeOH gave red prisms, m.p. 130~132°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.42; H, 7.05; N, 11.96. IR cm^{-1}: 3272 (NH), 1665, 1652 (C=O), 1601 (C=N). UV λ_{max} mμ (ε): 237.5 (9940), 355 (39000).

2,5-Diacetyl-3-methylindole (XIV)——A mixture of XIII (3.5 g.) and PPA (70 g.) was warmed in an oil bath. Liberation of NH_3 began at 70°(internal temperature). The mixture was heated with stirring at 110~120°(internal temperature) for 45 min., poured into ice-water, filtered and extracted with benzene. Washing of the benzene layer with H_2O, sat. aq. $NaHCO_3$ and H_2O, drying and evaporation gave the residue (0.15 g., 4.7%), m.p. 220~225°. The analytical sample was obtained by two recrystallizations from AcOEt as crystalline powders, m.p. 228~228.5°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.42; H, 6.07; N, 6.35.

1,3-Dimethyl-2,5-diacetylindole (XI). **i) From X**——A solution of X (1.5 g.) in Ac_2O (1.5 ml.)-AcOH (1.5 ml.) was added to hot PPA (3.2 g.). The mixture was stirred at 70°(internal temperature) for 10 min., and poured into ice-water (100 ml.). The aq. solution was extracted with benzene, and the benzene layer was washed with sat. aq. $NaHCO_3$, H_2O and dried. Evaporation of solvent furnished XI (1.63 g., 89%), m.p. 125.5~126°. XI crystallized from EtOH as colorless minute needles, m.p. 127~128°. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.20; H, 6.68; N, 6.30.

ii) From XIV——Methylation of XIV was carried out as described for methylation of VIc in 30% yield. Purification from MeOH afforded colorless needles, m.p. 122~124°. This compound was identified with the one obtained from X through admixture and spectral comparison.

2-Acetyl-5-methyl-7,8,9,10-tetrahydrocyclohept[*b*]indol-6(5*H*)-one (XVa)——VIIc was subjected to acetylation with PPA in Ac_2O-AcOH as described for acetylation of X. Yield 77%. Repeated recrystallizations from MeOH gave colorless needles, m.p. 149.5~150°. *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.13; H, 6.91; N, 5.59.

2-Acetyl-5-methyl-5,7,8,9,10,11-hexahydro-6*H*-cycloöct[*b*]indol-6-one (XVb)——XVb was prepared from VIId through the same manner as above. The internal reaction temperature was 65°. Yield 78%. Purification from EtOH produced colorless needles, m.p. 141~142°. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.11; H, 7.07; N, 5.28.

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26) C. W. Rees, C. E. Smithen: J. Chem. Soc., **1964**, 938.
27) Cf. J. C. E. Simpson, C. M. Atkinson, K. Schofield, O. Stephenson: *Ibid.*, **1945**, 646.
28) E. H. Rodd (Ed.): "Chemistry of Carbon Compounds," 538 (1954), Elsevier Publishing Corp., London.
29) M. Conrad, L. Limpath: Ann., **192**, 153 (1878).