[Chem. Pharm. Bull. 19(12)2561—2566(1971)]

UDC 547.751.057 : 547.574.3.04 : 547.291.04

# The Fischer Indole Synthesis with Formic Acid. II.[1] The Synthesis of Hexahydrocyclopent (*b*) indoles

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(Received June 11, 1971)

2-Alkylcyclopentanone phenylhydrazones (Ia, b) were refluxed with 98—100% formic acid to solely afford *cis*-1: 2: 3: 3a: 4: 8b-hexahydro-8b-alkyl-cyclopent(*b*)indoles (IVa, b) in the yields of 34% and 33%, respectively. Similar treatment of cyclopentanone phenylhydrazone with formic acid gave indoline (IVc) and indoles (IIc) and its N-formyl derivative (IIe). The reaction mechanism and stereochemistry of these products are discussed.

Since the procedure of the Fischer indolization with 98—100% formic acid was described,[1] this method has been shown to have a useful applicability to the syntheses of *aspidosperma* and *iboga* alkaloids by using the ketones of the polycyclic ring system.[3] An advantageous feature of this method consists in isolation of the formyl-indolines (IV) as relatively stable products which have been formed by reduction and formylation with formic acid immediately after cyclization to the indolenine(III) occurred, since most of the latters are less stable on treatment.

Meanwhile, the difficulties experienced in the Fischer indolization of 2-alkylcyclopentanone phenylhydrazones (I, R=alkyl, $n$=3) by acid are known in the literature.[4-6] For example, Buu-Hoï reported that an attempt to effect indolization of 2-ethylcyclopentanone (Ia) by acid resulted in failure.[4] Afterwards, Kelly, *et al.* described a new method of the thermal indolization, by which they obtained a mixture of IIb and IIIb in the yield ratio of approximately 1: 5, on boiling 2-methylcyclopentanone phenylhydrazone(Ib) in diethylene glycol without acid, though in a poor total yield of 15%.[5] They described nothing, however, about cyclization of 2-ethylcyclopentanone phenylhydrazone (Ia). Now, Ia has been substantially cyclized to the formyl-indoline(IVa) as a sole product in 34% yield according to the present standard procedure.

The initial material (Ia, orange oil, $bp_3$ 151—153°) was mixed with anhydrous formic acid in the molar ratio 1:5, on which an intense exothermic reaction proceeded with concurrent evolution of carbon dioxide. The whole mixture was further refluxed at 130—135° for a half hour. The crude product was purified by chromatography on alumina, and the main fraction eluted by benzene–hexane (1:1) afforded the formyl indoline (IVa), [ultraviolet spectrum (UV) $\lambda_{max}^{EtOH}$ 254, 294 mμ. infrared spectrum (IR) $\nu_{max}$ 1666 $cm^{-1}$ (C=O). nuclear magnetic resonance (NMR) ($CDCl_3$) $\tau$ 1.1 (N-CHO)]. In spite of the careful search for the other neutral or the basic material on this operation, no characterized product was obtained. For proof of the structure, IVa was reduced with lithium aluminum hydride to the methylindoline (Va) as a colorless oil, $bp_4$ 110—111°, UV: $\lambda_{max}^{EtOH}$ 261, 313 mμ; NMR, ($CDCl_3$) $\tau$ 7.2 (N-Me),

1) Part I, Y. Ban, T. Oishi, Y. Kishio and I. Iijima, *Chem. Pharm. Bull.* (Tokyo), **17**, 2604 (1969).
2) Location: *Kita-12-jo, Nishi-6-chome, Sapporo.*
3) *a*) I. Inoue and Y. Ban, *J. Chem. Soc.*, **1970**, 602; *b*) M. Ikezaki, T. Wakamatsu and Y. Ban, *Chem. Comm.*, **1969**, 88; *c*) Y. Ban, T. Wakamatsu, Y. Fujimoto and T. Oishi, *Tetrahedron Letters*, **1968**, 3383; *d*) Y. Ban and I. Iijima, *ibid.*, **1969**, 2523; *e*) M. Akagi, T. Oishi and Y. Ban, *ibid.*, **1969**, 2063; *f*) Y. Ban, I. Iijima, I. Inoue, M. Akagi and T. Oishi, *ibid.*, **1969**, 2067.
4) N.P. Buu-Hoï, P. Jacquignon and T.B. Loc, *J. Chem. Soc.*, **1958**, 738.
5) A.H. Kelly, D.H. McLeod and J. Parrick, *Can. J. Chem.*, **1965**, 296.
6) *a*) B. Robinson, *Chem. Rev.*, **63**, 373 (1963); *b*) B. Robinson, *ibid.*, **69**, 227 (1969); *c*) R.E. Lyle and L. Skarlos, *Chem. Comm.*, **1966**, 644.

which formed the picrate, yellow needles, mp 145—146°, giving satisfactory elemental analyses.

Similarly, Ib was treated with formic acid under a similar condition to give the formylindoline (IVb) as a single isolable product in a state of oil [UV $\lambda_{max}^{EtOH}$ 253, 293 mμ. IR $\nu_{max}$ 1675 $cm^{-1}$ (N-CHO). NMR ($CDCl_3$) $\tau$ 1.07 (N–CHO)] in 33% yield. IVb was also reduced to the methylindoline (Vb), colorless oil, $bp_3$ 88—89°, which was characterized as the picrate, mp 152—154°. It is interesting to compare the present result with the indolization of 2-methylcyclopentanone 4-benzyloxyphenylhydrazone (VIII) in boiling monoethylene glycol affording 52% yield of the indole (IX) as only one product without generation of the corresponding indolenine (III type).[7]

It is readily noticed that the direction of the Fischer cyclization (*e.g.* Ia,b,d→IIa,b,d and/or IIIa,b,d, respectively) will be affected by various conditions of catalysis, the kind of the

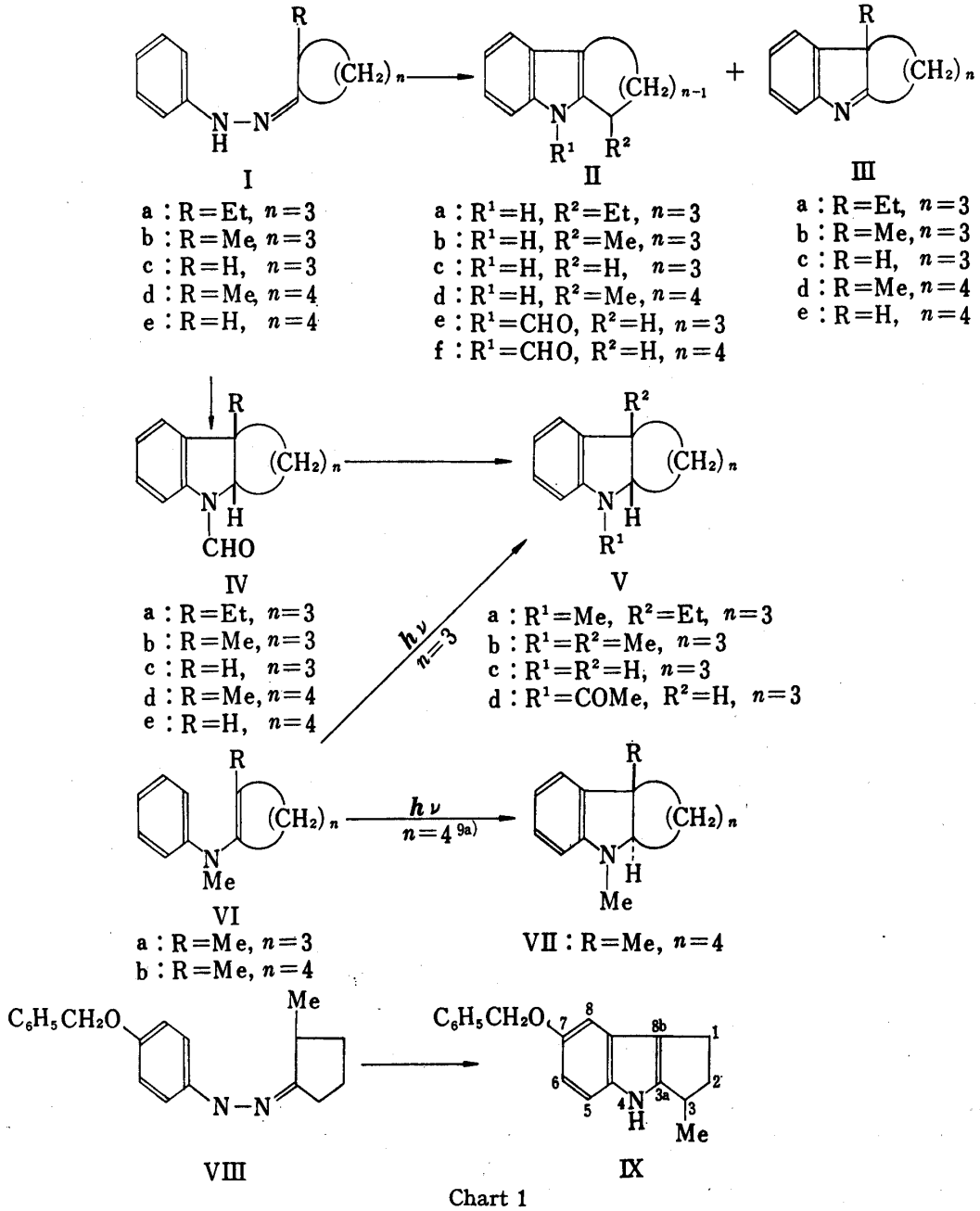


Chart 1

7) M. Ahmed, M. Sc. Thesis, University of Manchester, Manchester, England, 1966, quoted by B. Robinson.[6b]

substituent on α-position to carbonyl and the size of cyclic ketones, *etc.*[6] But, it seems also likely that the substituent attached to the phenyl ring of phenylhydrazone may exert an effect on the direction of cyclization.[8]

As for the stereochemistry at B/C ring juncture of these indolines, the *cis*-configuration has been generally approved,[9a] although without conclusive evidences, mainly by analogy with relative stabilities of *cis*- and *trans*-bicyclo (3.3.0)octane(pentalane) derivatives, of which the *cis*-isomer is far more stable on comparison with the energetically unfavorable *trans*-isomer.[10] Meanwhile, the stereochemistry of 4a-alkyl-1,2,3,4,4a,9a-hexahydro-carbazole (*e.g.* IVd) which was produced by the present method, was established to be *cis* mainly based on the NMR spectral data,[11] although the stable *trans*-isomer(VII) has been obtained as a major product by Chapman[9a] on photoisomerization of the N-arylenamine (VIb), which excited state should take the conrotatory cyclization course, followed by a suprafacial (1,4) hydrogen shift.[9b] Photoisomerization of VIa, however, carried out by us according to the Chapman's method[9a] gave the identical *cis*-indoline (Vb) as only one product, whose physicochemical properties were in good agreement with those of Vb on the Fischer cyclization. Thus, the present work indicates that the Woodward-Hoffmann's rule[9b] well explaining formation of the *trans*-isomer (VII), is not applicable to the cyclization of VIa. These results suggest that the compounds with two fused five-membered rings in the *cis*-configuration are extremely preferable to the *trans*-isomer, even though the latter could be present, but further direct evidences should be required.

Subsequently, cyclopentanone phenylhydrazone (Ic) was submitted to the Fischer indolization with anhydrous formic acid under a similar condition. The product was chromatographed on alumina to give the indole (IIc, 16% yield), the formyl indole (IIe, 1% yield) and unexpectedly, the formylindoline (IVc, 17% yield). The last product had not been anticipated to generate, since any Fischer indolization of the ketones with no substituent at α-positions of the carbonyl had never furnished the indolenine derivative, and the present product (IVc) must have taken place by reduction of such an indolenine (IIIc), if formed.

According to the so far known works, the indoline (Vc) was prepared only by reduction IIc electrolytically in acid solution[12] or by hydrogenation of IIc under a high pressure of hydrogen (in dioxane, Raney Ni, 70—75°, 75 atom.).[13] It was also reported that an attempted reduction of IIc with tin and hydrochloric acid gave no indoline (Vc).[14]

Therefore, for establishment of the structure of the present product, the compound (IVc), red orange oil, was hydrolyzed to Vc, which was characterized as the acetyl derivative (Vd), colorless prisms, mp 79—80° (lit.[13] 77—79°), providing the satisfactory spectral and analytical results for support of these assignments.

In contrast to this fact, Ib was similarly treated with formic acid to give the formyl indole (IIf) in 93% yield, but the formyl indoline (IVe) was not detected at all, although

8) It was experienced that 6a-ethyl-octahydro-4H-pyrrolo[3,2,1-*i*,*j*]quinoline 2,9-dione(A/B, A/C: *trans*, *cis*) phenylhydrazones with a methoxyl group or with no substituent in the aromatic ring were submitted to the Fischer indolization with formic acid, providing the corresponding formyl indole and indoline in different ratios. Y. Ban and I. Iijima, Unpublished work.[3f]

9) *a*) O.L. Chapman and G.L. Eian, *J. Am. Chem. Soc.*, **90**, 5329 (1968); *b*) R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry" Verlag Chemie, GmbH. Weinheim, **1970**, p. 59.

10) *a*) R.P. Linstead and E.M. Meade, *J. Chem. Soc.*, **1934**, 935; J.W. Barrett and R.P. Linstead, *ibid.*, 611 (1936); *b*) A.C. Cope and M. Brown, *J. Am. Chem. Soc.*, **80**, 2859 (1958).; *c*) E. Coxworth, "The Alkaloids, Chemistry and Physiology" edited by R.H.F. Manske, Academic Press, New York, **1965**, Vol. VIII, p. 31; *d*) E.L. Eliel, "Stereochemistry of Carbon Compounds" McGraw-Hill Book Co., Inc. 1962, p. 273.

11) Y. Ban, H. Kinoshita, S. Murakami and T. Oishi, Tetrahedron Letters **1971**, 3687.

12) S.G.P. Plant and D.M.L. Rippon, *J. Chem. Soc.*, **1928**, 1906.

13) H. Booth, F.E. King and J. Parrick, *J. Chem. Soc.*, **1958**, 2302.

14) B. Witkop and J.B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951). B. Witkop, J.B. Patrick and M. Rosenblum, *ibid.*, **73**, 2641 (1951).

naturally. Thus, the reaction processes leading to IVc are significantly interesting in light of the most reliable mechanism which was originally proposed by Robinson and Robinson[15] and later modified by Carlin and Fischer,[6,16] who indicated it as follows:

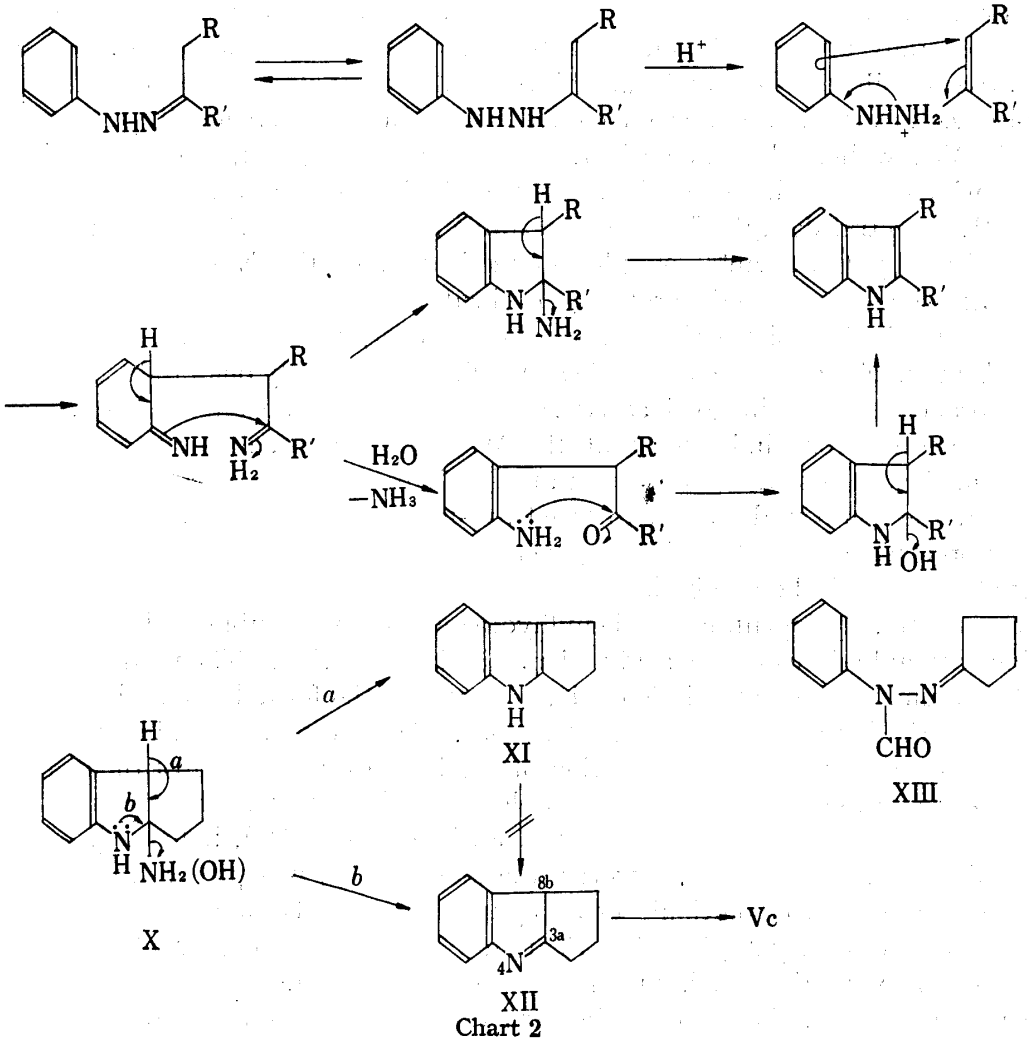


Chart 2

In the present particular case, the final intermediate(X) could be assumed to afford the indole (XI) through the pathway of (*a*), and give the indolenine (XII) *via* the (*b*) route, the latter product should be immediately reduced to Vc and then to the formyl derivative IVc. The alternative possibility that there might be an equilibrium between XI and XII in the presence of formic acid was presumably considered, but this assumption was discarded by a result of the experiment, in which (IIc=XI) was heated with formic acid not to afford IVc at all. This experiment also demonstrates that XI could not be the direct precursor of Vc in the present synthesis. The other possibility that the phenylhydrazone Ic should have been initially formylated to XIII is not likely, at least for formation of IVc, since such an intermediate (XIII) could have afforded the formyl indole (II), but not the IVc. The generation of IVc is thus only compatible with the pathway of (*b*) delineated in Chart 2. The initial formation of a double bond at N(4)—C(3a) [exocyclic to C-ring] as well as at C(3a)—C(8b) might be acceptable on consideration of the high strain present in two fused five membered rings. As a consequence, the proposal on the pathway (*b*) leading to XII in the Robinson's mechanism should be limited to the Fischer indolization with a five membered cyclic ketone of no substituent at 2-position.

15) G.M. Robinson and R. Robinson, *J. Chem. Soc.*, **1918**, 639.
16) R.B. Carlin and E.E. Fischer, *J. Am. Chem. Soc.*, **70**, 3421 (1948).

## Experimental[17]

***cis*-1,2,3,3a,4,8b-Hexahydro-4-formyl-8b-ethylcyclopent(b)indole(IVa)**——To 850 mg of 2-ethylcyclopentanone phenylhydrazone (Ia, $bp_3$ 151—153°, orange oil) was added anhydrous (98—100%) formic acid (902 mg), during which time an exothermic reaction occurred with concurrent evolution of carbon dioxide. The bright red solution was refluxed at 130—135° in an oil bath for 35 min. The excess of formic acid was removed *in vacuo*, the residual solution was made alkaline with sodium bicarbonate, and was extracted with ethyl acetate. The extract was shaken with 10% HCl to remove a basic material, washed with water, 10% $NaHCO_3$, and again with water. The solvent was removed to furnish an oil which indicated five spots on thin-layer chromatography (TLC) (eluted by benzene: ethyl acetate (1: 1)). The crude oil was chromatographed on alumina, and the fraction eluted by benzene–hexane (1: 1) furnished 246 mg of IVa as a red brownish oil (UV: $\lambda_{max}^{EtOH}$ 254, 294 m$\mu$. IR $\nu_{max}^{film}$ 1666 $cm^{-1}$ (CHO). NMR ($CDCl_3$) $\tau$ 1.1 (N-CHO)). The crude neutral product (301 mg) which was indicated by TLC to contain IVa, was submitted to the lithium aluminum hydride reduction and purified by chromatography to give Va which provided 197 mg of the picrate, mp 145—146°, identical with the authentic sample. (See the next procedure for preparation of Va.) The amount of this picrate was corresponding to 57 mg of IVa, and the total yield of IVa was 33.6% (303 mg) of the theoretical amount. The 10% HCl solution containing the basic material which had been transfered from the ethyl acetate extract after the reaction, was made alkaline, but nothing was obtained.

***cis*-1,2,3,3a,4,8b-Hexahydro-4-methyl-8b-ethylcyclopent(b)indole(Va)**——A solution of the formylindoline (Va, 246 mg) in THF was gradually added to a suspension of $LiAlH_4$ (434 mg) in THF at room temperature, and the whole solution was refluxed with stirring for 2 hr on cooling, the whole mixture was worked up in the usual manner to give 192 mg (83.8%) of Va as a colorless oil, $bp_4$ 110—111°, [UV: $\lambda_{max}^{EtOH}$ 261, 313 m$\mu$. NMR: $\tau$ 7.2 (N-$CH_3$)], which afforded the picrate, yellow needles, mp 145—146° (decomp.). *Anal.* Calcd. for $C_{20}H_{22}O_7N_4$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.42; H, 5.03; N, 12.89.

***cis*-1,2,3,3a,4,8b-Hexahydro-4-formyl-8b-methylcyclopent(b)indole (IVb)**——Anhydrous formic acid (4.632 g, 5 molar equivalent of formic acid to Ib) was mixed with 2-methylcyclopentanone phenylhydrazone (3.770 g), on which an exothermic reaction occurred with concurrent evolution of carbon dioxide. The whole solution was refluxed at 130° in an oil bath for 30 min. On cooling, the reaction mixture was extracted with benzene, the benzene layer was washed with 10% $NaHCO_3$, and with water. The solvent was removed, the residue was submitted to chromatography on alumina, on which the fraction eluted with benzene–hexane (1: 1) furnished 971 mg of the formyl indoline (IVb) as an oil [UV: $\lambda_{max}^{EtOH}$ 253, 293 m$\mu$. IR: $\nu_{max}^{film}$ 1675 $cm^{-1}$ (N-CHO). NMR ($CDCl_3$) $\tau$ 1.07 (N-CHO)]. The acidic layer containing the basic material was made alkaline, but nothing was obtained. In a similar way that was done with the ethyl derivative, the fraction being indicated by TLC to contain IVb, was reduced with lithium aluminum hydride to give Vb, which was purified by chromatography and collected as the picrate (1.009 g), mp 152—154°, identical with the authentic specimen. (See the next procedure for preparation of Vb). The amount of this picrate corresponded to 1.307 g of IVb, and the total yield of IVb was 32.8% from Ib.

***cis*-1, 2, 3, 3a,4, 8b-Hexahydro-4-methyl-8b-methylcyclopent(b)indole(Vb)**——Method-A: The synthesis from IVb: A solution of the formylindoline (IVb, 971 mg) in THF was gradually added to a suspension of $LiAlH_4$ (2.76 g) in THF at room temperature, and the whole solution was refluxed with stirring for 2 hr, then worked up in the usual manner. The N-methylindoline (Vb, 764 mg, $bp_3$ 88—89°) was obtained as a colorless oil [UV: $\lambda_{max}^{EtOH}$ 258, 308 m$\mu$. NMR ($CDCl_3$) $\tau$ 7.2 (N-$CH_3$) which formed the picrate, yellow needles, mp 152—154°. *Anal.* Calcd. for $C_{19}H_{20}O_7N_4$: C, 54.80; H, 4.84; N, 13.46. Found: C, 54.66; H, 4.84; N, 13.29].

Method-B: Photochemical synthesis from (VIa): The enamine VIa was prepared by refluxing N-methylaniline (9.0 g), 2-methylcyclopentanone (8.4 g) and toluene containing a small amount of *p*-toluenesulfonic acid in a Dean–Stark apparatus for removal of the water produced during the reaction for 24 hr. The product VIa was purified by distillation, $bp_5$ 115—120°, which was found by TLC to be contaminated with a small amount of N-methylaniline. The enamine (VIa) thus obtained, without further purification, was submitted to photoisomerization according to the Chapman's method.[9] The degassed ethereal solution (300 ml) of the enamine (VIa, 2.2 g) was irradiated by a pyrex-jacket immersion lamp (400 W) for 3.5 hr. The ether was removed, and the residual oil was purified by chromatography on silica-gel to afford 450 mg of N-methyl indoline (Vb), [IR $\nu_{max}^{film}$ 2800 (N-$CH_3$), UV: $\lambda_{max}^{EtOH}$ 261, 312 m$\mu$. Mass: $M^+$=187; NMR ($CDCl_3$)

17) Melting points were determined on the Yanagimoto Micromelting Apparatus (hot stage type). Ultraviolet spectra were taken with the Hitachi EPS-3T recording spectrophotometer and infrared spectra were determined with the Koken DS-301 spectrophotometer. NMR spectra were measured with the Hitachi–Perkin Elmer H-60 spectrometer [60 Mc/sec with tetramethylsilane] as the internal reference. Mass spectra were taken with the Hitachi RMD-6D spectrometer. The plates for thin layer chromatography were prepared by developing Silica $Gel_{254}$ according to Stahl (E. Merck AG), followed by heating.

$\tau$ 8.67 (3H, s, C-Me), 8.75—8.80 (6H, m, methylene), 7.28 (3H, s, N-$CH_3$), 6.3—6.7 (1H, m, methine) 3.9—2.9 (4H, m, atrom.)]. Picrate, mp 147—150°, was identified with the sample prepared by the procedure of Method-A.

**Indolization of Cyclopentanone Phenylhydrazone (Ic)**——A solution of 4.001 g (0.0228 mol) of Ic in 98—100% formic acid (5 ml) was refluxed at 130° in an oil bath for 3 hr, during which time evolution of carbon dioxide was observed. The reaction mixture became dark red and turned viscous. The formic acid was removed *in vacuo*, and 3.906 g of the residue was chromatographed on silica-gel.

(1) 1st fraction: The fraction eluted by benzene–hexane (1: 1) afforded 52 mg of 1,2,3,4-tetrahydro-4-formyl-cyclopent(*b*)indole (IIe) as colorless needles, mp 85—86° (IR: $\nu_{max}^{Nujol}$ 1690 $cm^{-1}$ (N-CHO). UV: $\lambda_{max}^{EtOH}$ 247, 304 m$\mu$; $\lambda_{max}^{EtOH\text{-}NaOH}$ 280 m$\mu$. NMR ($CDCl_3$) $\tau$ 1.10 (N-CHO)]. The formyl group of this compound is readily removable.

(2) 2nd fraction: The second fraction of chromatography eluted by benzene–hexane (1: 1) afforded 1,2,3,4-tetrahydro-cyclopent(*b*)indole (IIc) as 777 mg (16%) of colorless plates, mp 102—104° (Lit.[13] mp 108°) (IR: $\nu_{max}^{Nujol}$ 3460 $cm^{-1}$ (NH); UV: $\lambda_{max}^{EtOH}$ 280 m$\mu$).

(3) 3rd fraction: The third fraction eluted by the same solvent furnished 809 mg (17%) of *cis*-1,2,3,3a,4,8b-hexahydro-4-formyl-cyclopent(*b*)indole (IVc) as an orange red oil which indicated one spot on TLC. IR: $\nu_{max}^{film}$ 1670 $cm^{-1}$ (N-CHO). UV: $\lambda_{max}^{EtOH}$ 253 m$\mu$. NMR ($CDCl_3$) $\tau$ 6.12 (1H, m, C-(8b)-H), 5.20 (1H, m, C-(3b)-H).

For proof of the structure of IVc, the following chemical conversions were carried out for characterization.

A solution of 560 mg of IVc in 15% HCl (10 ml) was refluxed for 5 hr. On cooling, the whole solution was made alkaline with 10% NaOH under ice cooling, and extracted with benzene. The benzene extract was washed with water, dried over sodium sulfate, and the solvent was removed to leave 99 mg of a red oil (Vc), IR $\nu_{max}^{film}$ 3400 $cm^{-1}$ (NH).

A mixture of 80 mg of the above oil (Vc) in acetic anhydride (5 ml) and pyridine (5 ml) was heated at reflux for 2 hr. The excess of acetic anhydride and pyridine were removed *in vacuo* to give *cis*-1,2,3,3a,4-8b-hexahydro-4-acetylcyclopent(*b*)indole (Vd) as colorless prisms, mp 79—80° (lit.[18] 77—79°). IR: $\nu_{max}$ 1650 $cm^{-1}$ (N-$COCH_3$). UV: $\lambda_{max}^{EtOH}$ 254 m$\mu$. NMR ($CDCl_3$) $\tau$ 7.67 (N-$COCH_3$). *Anal.* Calcd. for $C_{13}H_{15}NO$: C, 77.59; H, 7.51; N, 6.96. Found: C, 77.64; H, 7.44; N, 6.94.

**Acknowledgement** The authors express their thanks to all the staffs of the central laboratory of this Institute for elemental analyses, NMR and Mass spectral measurements. This work was supported in part by the Toyo Rayon Science Foundation and the National Institutes of Health (MH-08187), which were greatly acknowledged.

18) W.H. Perkin, Jr. and S.G.P. Plant, *J. Chem. Soc.*, 1923, 3242.