Action of Dilute Hydrochloric Acid on (XVIII) : Formation of Ethyl Indole-2-carboxylate (XVI)—A solution of 0.5 g. of (XVIII) in 30 cc. EtOH containing 1% HCl was refluxed for 2 hrs. and after evaporation of the solvent under reduced pressure, the crystals that separated were recrystallized from benzene to melt at 121.5～122°. No depression was observed when mixed with ethyl indole-2-carboxylate previously obtained.

Ethyl 1-Acetyl-3-hydroxyoctahydroindole-2-carboxylate (XIX)—A solution of 250 cc. of EtOH containing 10 g. of (Ⅷ) and approx. 20 g. of Ni catalyst was shaken in H_2 atmosphere at 110～120° and 150 atms. After filtration, EtOH was removed under diminished pressure to give colorless crystals, which were washed with a small volume of ether to remove a sticky substance. On recrystallization from EtOH-benzene it melted at 167～168.5°. Yield, 4.7 g. *Anal.* Calcd. for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29; N, 5.49. Found : C, 61.84; H, 8.19; N, 5.27.

Oxidation of (XIX) with Potassium Permanganate—To a hot stirred suspension of (XIX) in 5% KOH solution, a solution of 2% $KMnO_4$ was added until a permanent violet color appeared. After acidification with HCl the mixture was continuously extracted with ether. The ether solution was evaporated to afford colorless crystals which on recrystallization from water melted at 145～147°, without depression when mixed with authentic adipic acid.

Summary

The high-pressure catalytic hydrogenation of the acetyl derivatives of ethyl indoxylate was investigated. Under 85 atms. of hydrogen atmosphere at 100～110°, nickel catalyst converted ethyl 3-acetoxyindole-2-carboxylate (Ⅴ) into ethyl 3-acetoxy-4,5,6,7-tetrahydroindole-2-carboxylate (Ⅸ), and ethyl 1-acetyl-3-acetoxyindole-2-carboxylate (Ⅵ) into ethyl 1-acetylindoline-2-carboxylate (Ⅺ), but ethyl 1-acetylindoxylate (Ⅷ) was hydrogenated to ethyl 1-acetyl-3-hydroxyindoline-2-carboxylate (XIII) at 60 atms. and 60°, and to ethyl 1-acetyl-3-hydroxyoctahydroindole-2-carboxylate (XIX) at 150 atms. and 110～120°.

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51. **Tomoyoshi Komai** : Reduction of Ethyl Indoxylate. II. Lithium Aluminum Hydride Reduction of Ethyl Indoxylate.

(*National Institute of Health, Tokyo**)

It was shown[1] that several acetyl derivatives of ethyl indoxylate were hydrogenated by catalytic reduction with Raney nickel under high pressure and the mode of the saturation of indole ring was found to depend on the position of acetyl group in the starting materials. The present paper deals with the reduction of ethyl indoxylates with lithium aluminum hydride.

By the lithium aluminum hydride reduction of indole derivatives, Taylor[2] obtained the corresponding primary alcohol from ethyl 3-alkylindole-2-carboxylate or 3-alkyl-2-formylindole. It was shown by the same author, that the yield of reaction products varied, depending on the number of carbon atoms attached to 3-position. In the absence of carbon atom at 3, the yield of reaction product is the best and the product is relatively stable, but when one or more carbon atoms are present at 3-position, more unstable products are obtained with poorer yields. Julian, *et al.*[3] applied this reaction to the synthesis of the ring system of yohimbine, where the carbonyl group of oxindole

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* Chojamaru, Kamiohsaki, Shinagawa-ku, Tokyo (駒井知好).

[1] Part. I : This Bulletin, **4**, 261(1956).

[2] W.J. Taylor : Helv. Chim. Acta, **33**, 164(1950).

[3] P.L. Julian, A. Magnani : J. Am. Chem. Soc., **71**, 3207(1949).

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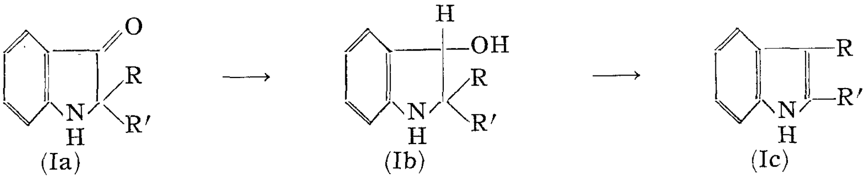
derivative was reduced, and β-carboline derivative was obtained by the reductive ring closure between 2-position of indole ring and 3′-position of the isoquinoline ring attached to the end of a side chain in the 3-position of the indole ring. It was also reported that indole-2-carboxylic acid is reduced by lithium aluminum hydride to form 2-hydroxymethylindole.⁴⁾

Witkop⁵⁾ has shown in a series of investigations that pseudoindoxyl type (Ia) is reduced by lithium aluminum hydride to (Ib), which in the presence of a trace of acid, undergoes rearrangement to form (Ic) type compound.



This reaction was used in the reduction of ethyl indoxylate. In this reduction two pathways can be considered. First, if ethyl indoxylate is present in enol form, designated by (IIa), 2-hydroxymethylindoxyl (III) should be obtained, because lithium aluminum hydride would attack only the ethoxycarbonyl group. Second, if ethyl indoxylate is present in keto form (IIb), 2-hydroxymethyl-3-hydroxyindoline (IV) should be the main product, because the same reagent would attack both the ethoxycarbonyl and carbonyl groups at 2- and 3-positions to form primary and secondary alcohols, respectively. The latter compound, however, should be dehydrated to 2-hydroxymethylindole, as reported in the previous paper.

The solution of ethyl indoxylate was added to a suspension of excess lithium aluminum hydride. The color of the reaction mixture was considerably complicated and finally a gray sticky precipitate was formed. The three products were isolated from the mixture in the usual manner, but during this operation a dark brown coloration of the solution was observed. From the reaction mixture the three products, fine pale yellow needles, m.p. 192～193°(decomp.), yellow prisms, m.p. 209～210°(decomp.), and an acidic colorless crystals, m.p. 182～183°, were obtained.

If ethyl indoxylate gives compounds such as (III) or (IV) by the above-mentioned reaction mechanism the products would have had no color with lower melting points. Actually, however, the three products obtained here had relatively high melting point and only one was colorless with acidic nature, so that it was considered that the reaction had not proceeded as planned.

From the result of analyses, it was revealed that the colorless crystals, m.p. 182～183°, was N-acetylanthranilic acid (V) which was identified with an authentic specimen. It is rather unexpected that such a compound was produced by lithium aluminum hydride reduction of ethyl indoxylate.

The analytical data of the two yellow crystalline products, m.p. 209～210°(decomp.), and m.p. 192～193°(decomp.), corresponded to the molecular formula of $C_{18}H_{16}ON_2$ and $C_{18}H_{16}O_2N_2$, respectively, which showed that both these products should be a dimer. It has long been known that oxygen, air, hydrogen peroxide, Caro's acid, or peracetic acid⁶⁾ converts 2-methylindole into a yellow compound, $C_{18}H_{16}ON_2$, which has been regarded as bis(2-methyl-3-indyl) ether. Witkop⁷⁾ pointed out that the ether structure is incorrect and showed by the infrared data that it should have the structure represented by (VI) via the route shown in Chart 1.

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4) W. J. Brehm : *Ibid.*, **71**, 3541(1949).
5) B. Witkop : *Ibid.*, **72**, 614(1950).
6) B. Witkop : Ann., **558**, 98(1947).
7) B. Witkop, J. B. Patrick : J. Am. Chem. Soc., **73**, 713(1951).

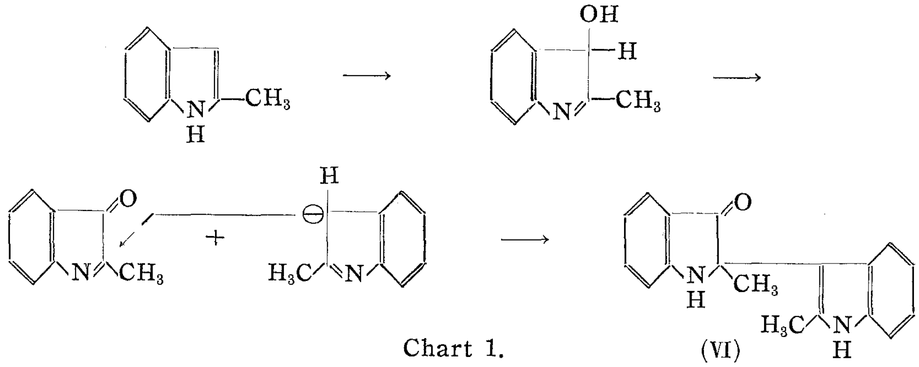
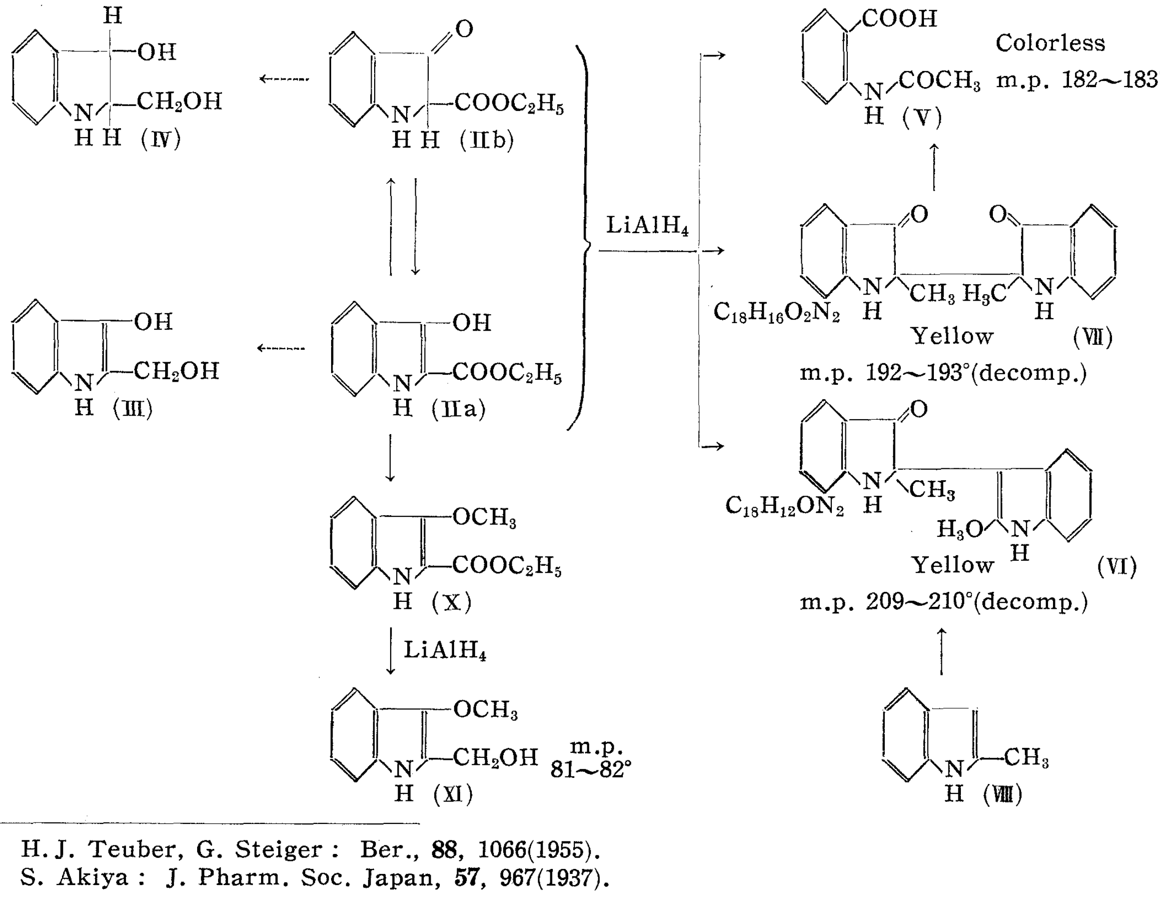


Chart 1.

Recently, Teuber and Steiger reported that potassium nitrosodisulfonate converted 2-methylindole into the same compound (VI).⁸⁾ One of the reduction products obtained in the present work was found to have the same molecular formula, $C_{18}H_{16}ON_2$, m.p. 209~210°(decomp.), as Witkop's compound, m.p. 212°(decomp.). Further, both compounds showed good agreement in their ultraviolet and infrared absorption spectra. The oxidation of 2-methylindole (VIII), with peracetic acid was repeated and a yellow product, m.p. 209~210°(decomp.), showed no depression when admixed with the reduction product (VI) and a good agreement in ultraviolet and infrared absorption curves. Consequently, Witkop's compound was proved to be identical with the reduction product, m.p. 209~210°(decomp.).

Another yellow crystals (VII), m.p. 192~193°(decomp.), obtained by lithium aluminum hydride reduction showed a molecular weight of approximately 310 and 294 by the Akiya-Barger⁹⁾ and Rast method, respectively, and on analysis it was shown to have a molecular formula of $C_{18}H_{16}O_2N_2$ (molecular weight, 292). This product did not react



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8) H. J. Teuber, G. Steiger: Ber., **88**, 1066(1955).
9) S. Akiya: J. Pharm. Soc. Japan, **57**, 967(1937).

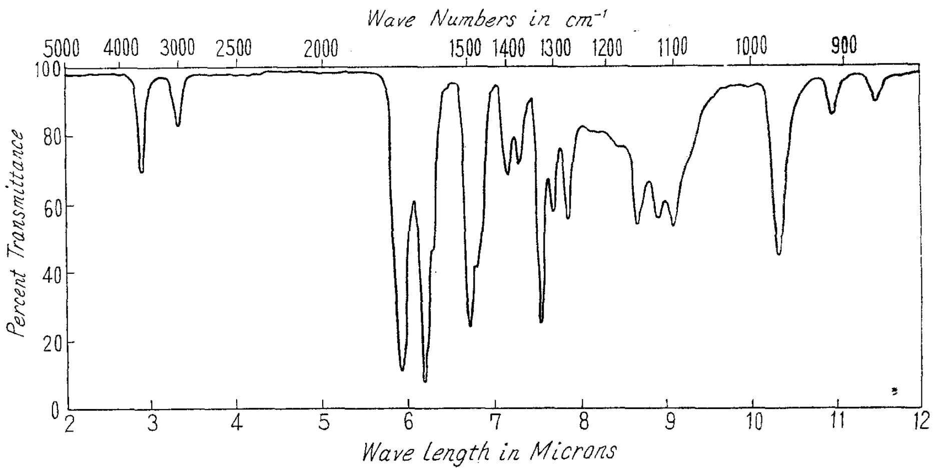

Fig. 1.

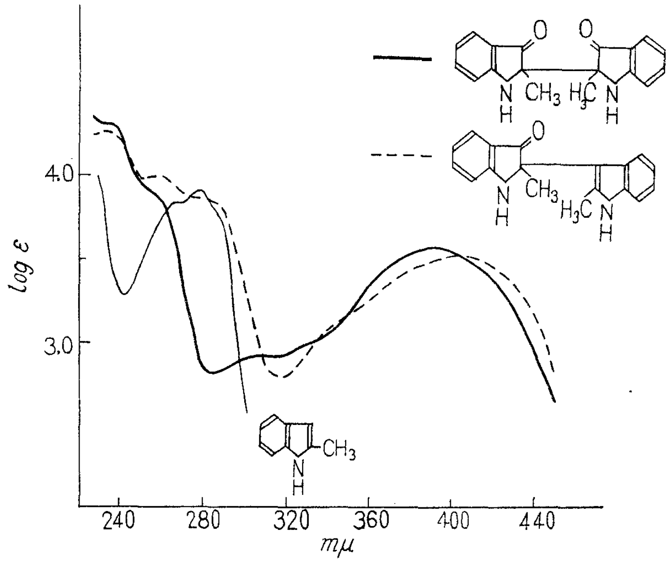

Fig. 2.

with carbonyl or hydroxyl reagents as in the case of (VI) and was very unstable to acids or alkalis to form a brownish resinous substance. Potassium permanganate converted this yellow compound into N-acetylanthranilic acid, the methyl group of which was presumed to be derived from ethoxycarbonyl of ethyl indoxylate by lithium aluminum hydride reduction. The ultraviolet absorption spectrum of the yellow compound (VII), m.p. 192~193°(decomp.), showed a maximum at 390~400 mμ, which is closely similar to that of (VI), but lacked an absorption band at 280 mμ, which suggests the presence of an indyl residue. The infrared spectrum of this compound was also closely similar to that of (VI) and recorded a band at 5.8 μ characteristic for a carbonyl in a five-membered ring and one band at 6.2 μ, typical for the structural element $C_6H_5{-}\underset{|}{N}{-}\overset{\diagup}{\underset{\diagdown}{C}}{-}$, where the carbon atom does not have a double bond.[7] These experimental data reasonably illustrate that the yellow compound, m.p. 192~193°(decomp.), should have a structure (VII) as proposed. In the following paper,[10] the identification of (VII) with synthetic specimen will be reported.

Thus, ethyl indoxylate on lithium aluminum hydride reduction did not form the expected products but three compounds resulted by condensation or decomposition. This may lead to an assumption that the keto-enol form of tautomerism of ethyl

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[10] This Bulletin, **4**, 314(1956).

indoxylate participates in this reduction, because the methyl ether (X) of ethyl indoxylate gave the expected product, 2-hydroxymethyl-3-methoxyindole (XI), m.p. 81∼82°, by reduction with the same reagent, although the product was not so stable a compound.

The next step is to elucidate the mechanism of the formation of three products (V), (VI), and (VII). Recently, Dreding and Hartman[11] investigated the mechanisms of lithium aluminum hydride reduction of some enolizable β-ketocarboxylic acids, such as 2-ethoxycarbonylcyclohexanone. In this reaction, three compounds were obtained; 2-methylenecyclohexanol (A), 1-cyclohexenemethanol (B), and 2-hydroxymethylcyclohexanol (C). The formation of unsaturated alcohols, (A) and (B), in this reduction would be explained by the scheme shown in Chart 2.

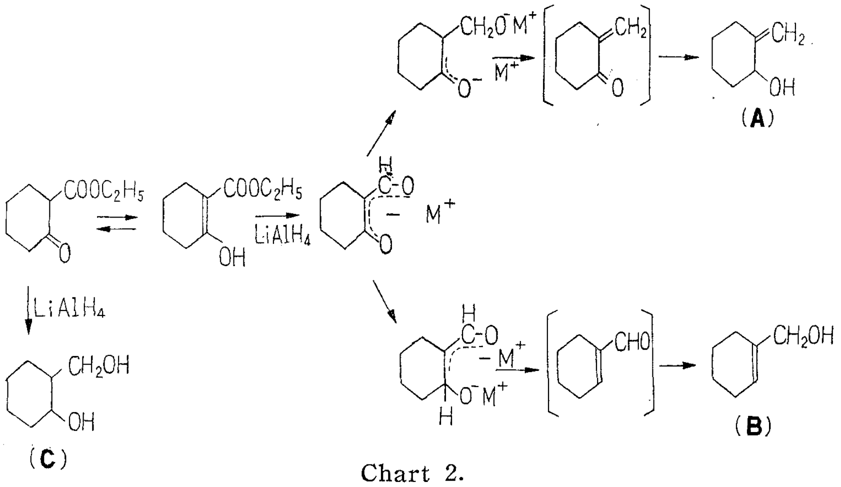

Chart 2.

It is likely that, when ethyl indoxylate (IIa, b) enters the chain of reaction, the enolizable portion reacts with lithium aluminum hydride to form the enolate salt (XII) and the ethoxyl group may be replaced by hydrogen (XIII) from the hydride. The hydride may attack the acid residue of (XIII) to form an intermediate (XIV). While the enolate salt portion would resist reduction by lithium aluminum hydride, (XIV) might be deoxygenated as in the case of Grignard reaction[12] to form (XVa), which forms a reversible indolenine-type compound (XVb). Lithium aluminum hydride would further convert the carbonyl group of (XVb) into (XVIa), which is reversible with (XVIb). Since (XVb) has a reactive double bond of an indolenine form, $-N{=}C<$[13], the carbon-2 of (XVIb) can be substituted with the nucleophilic center of (XVb) to eventually form yellow crystals (VII), m.p. 192∼193°(decomp.), $C_{18}H_{16}O_2N_2$.

On the other hand, the carbonyl group of (XVIb) partly remained would further be reduced by lithium aluminum hydride to an intermediate (XVII) and subsequent dehydration would give rise to 2-methylindole (VIII). The indolenine form (XVIII) of the latter should be capable of undergoing condensation at the 2-position of (XVb), as shown by Witkop, to form the yellow crystals (VI), m.p. 209∼210°(decomp.), $C_{18}H_{16}ON_2$.

The formation of N-acetylanthranilic acid may be explained as follows : In the course of isolation of the reaction products, water molecule is added to the 1- and 2-positions of (XVb) and the bond between 2 and 3 of the hydrated compound would be cleaved to form 2-acetylaminobenzaldehyde. This mechanism should be similar to the cleavage of camphoquinone to form camphoric acid semialdehyde in alkaline

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11) A.S. Dreding, J.S. Hartman : J. Am. Chem. Soc., **75**, 939(1953).
12) G.F. Wood, J.W. Tucker : *Ibid.*, **70**, 2174(1948).
13) B. Witkop : *Ibid.*, **72**, 2311(1950).

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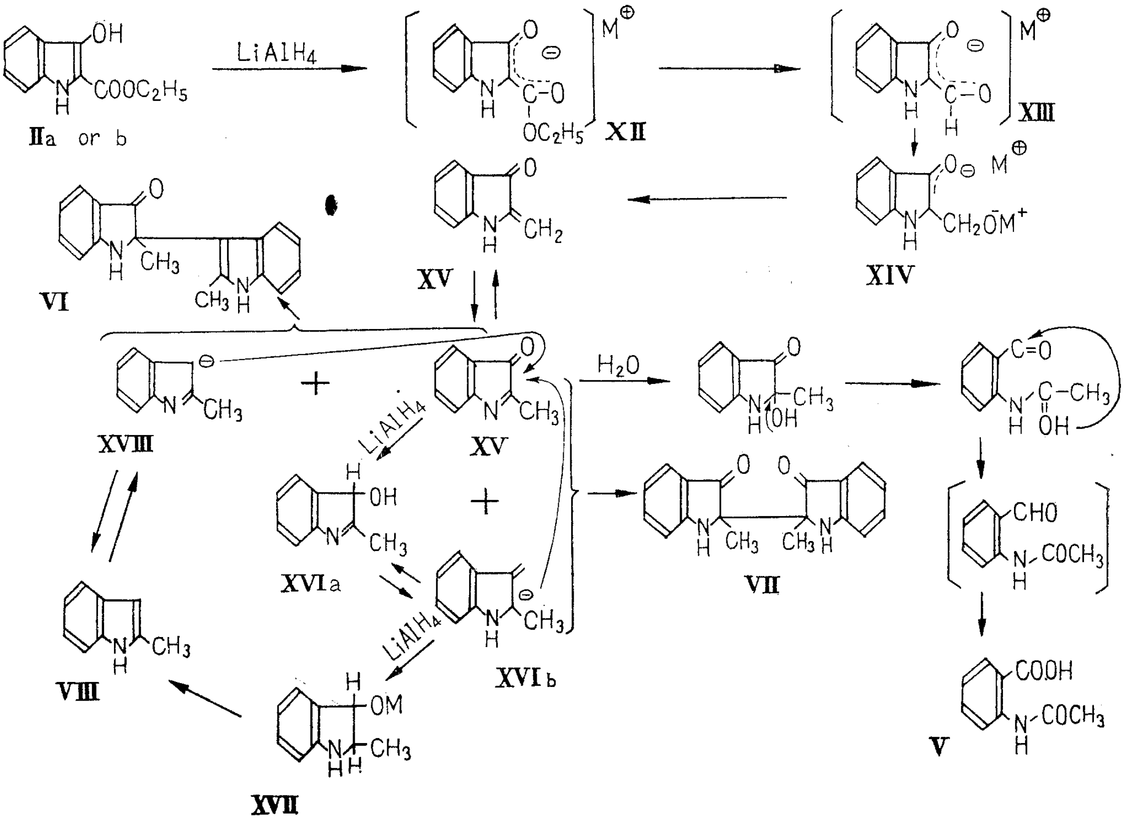

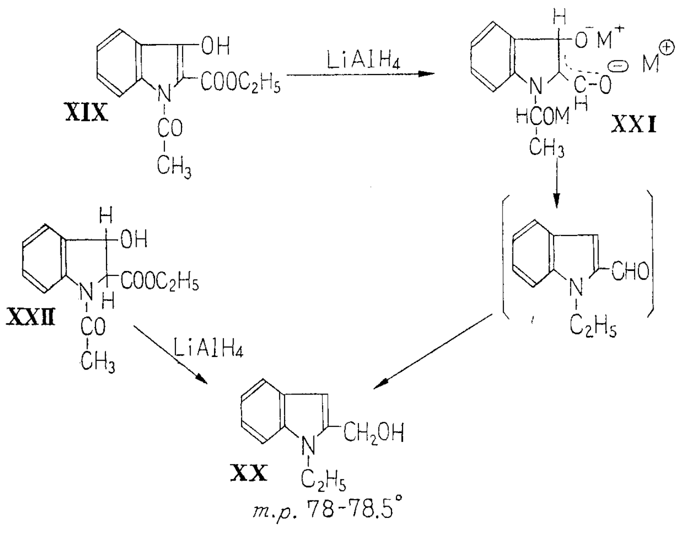

reaction conditions.[14] Further oxidation by air of 2-acetylaminobenzaldehyde would result in the acid (V).

Ethyl N-acetylindoxylate (XIX) on reduction under the same conditions gave 1-ethyl-2-hydroxymethylindole (XX) without any side reaction. This phenomenon is well explained by the fact that, after the formation of a (XIII)-type intermediate, lithium aluminum hydride would mainly attack the 3-position to form (XXI). Then the latter would be converted into 1-ethyl-2-hydroxymethylindole (XX) via the deoxygenation at 2- and 3- positions and followed by reduction of the aldehyde group. The compound (XX) was also derived from ethyl 1-acetyl-3-hydroxyindoline-2-carboxylate (XXII) by lithium aluminum hydride reduction.

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[14] J. Bredt : J. prakt. Chem., **95**, 63(1917).

Thus, the isolation of the unusual products from the lithium aluminum hydride reduction of ethyl indoxylate can be explained by assuming that it gives several intermediates which would further condense with one another, and the occurrence of such intermediates under these reaction conditions is specific for an enolizable β-dicarbonyl compounds.

The author is grateful to Prof. S. Akiya and Assist. Prof. T. Ukita, Institute of Infectious Diseases, and Dr. D. Mizuno, the Chief of Chemical Division, National Institute of Health, for their interest and encouragement in this work. Thanks are due to Assist. Prof. T. Isshiki for advice on electronic theory, to Dr. H. Kamata for the measurement of the infrared spectra, and to Miss R. Ota, Miss E. Kondo, Mr. B. Kurihara, and Mr. S. Tanaka for microanalysis. The author is also indebted to Mr. K. Muto for technical assistance in this work.

Experimental

Lithium Aluminum Hydride Reduction of Ethyl Indoxylate—A solution of 3 g. of ethyl indoxylate in 50 cc. of dehyd. ether was added cautiously to a stirred solution of 3.0 g. of $LiAlH_4$ in 30 cc. of dehyd. ether. In the early phase of the reaction, a white to lemon yellow precipitate appeared and this changed to a gray sticky precipitate. The mixture was refluxed for 1 hr. followed by careful decomposition of excess hydride and the complex formed, with approximately 200 cc. of 30% aq. Rochell salt solution. The ethereal layer was separated and the aq. layer extracted several times with purified AcOEt. The combined organic solution was washed with saturated $NaHCO_3$ solution. The washings were combined and on acidification with HCl colorless crystals were obtained. It melted at 182∼183° after recrystallization from benzene and showed no depression with authentic specimen of N-acetylanthranilic acid.

The organic solution washed with $NaHCO_3$ solution was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The brownish yellow residue obtained was recrystallized from benzene. The first yellow crystals appeared from the solution melted at 155∼159°, in an yield of 180 mg. After repeated recrystallization from EtOH it formed pale yellow needles or prisms, m.p. 192∼193°(decomp.). *Anal.* Calcd. for $C_{18}H_{16}O_2N_2$ (VII) : C, 73.95; C, 5.50; N, 9.58. Found : C, 74.19; H, 5.24; N, 9.70.

The second product, which crystallized out from the filtrate of the first crop after concentration to a small volume, formed brownish yellow crystals, m.p. 150∼157°(decomp.). Yield, 360 mg. On repeated recrystsllization from MeOH, it melted at 209∼210°(decomp.).

2-Methyl-2-(2′-methylindyl-3′)pseudoindoxyl (VI)—To a solution of 2 g. of 2-methylindole in 12 cc. of glacial AcOH was added 2 cc. of 30% H_2O_2. The mixture was stirred for 20 mins. Fine yellow crystals obtained melted at 209∼210°(decomp.) after recrystallization from MeOH and showed no depression when admixed with the yellow compound, m.p. 209∼210°, obtained above. *Anal.* Calcd. for $C_{18}H_{16}ON_2$ (VI) : C, 78.24; H, 5.84; N, 10.10. Found : C, 78.29; H, 5.75; N, 10.39.

Oxidation of (VII) with $KMnO_4$—To a suspension of 0.42 g. of (VII) in a mixture of 10 cc. of water and 2 cc. of 50% aq. KOH was added dropwise a solution of 0.8 g. of $KMnO_4$ in 30 cc. water. The mixture was boiled for 10 mins. and after filtration, the reaction mixture was acidified with a few drops of conc. H_2SO_4 to give N-acetylanthranilic acid. On recrystallization from water and benzene, the product melted at 182∼183°. On mixed fusion with authentic specimen of N-acetylanthranilic acid, it showed no depression.

Lithium Aluminum Hydride Reduction of Methyl Ether of Ethyl Indoxylate (X)—A solution of 1.0 g. of ethyl 3-methoxyindole-2-carboxylate in 20 cc. of dehyd. ether was added cautiously to a stirred suspension of 0.5 g. of $LiAlH_4$ in 10 cc. of dehyd ether. The mixture was refluxed for 30 mins. followed by careful decomposition of the excess hydride and the complex formed with a small amount of water. Approximately 70 cc. of 30% aq. Rochell salt was added to the mixture, the ethereal layer was separated, and the aq. layer extracted twice with ether. The combined ethereal solution was washed with water, dried, and evaporated. The residue, approx. 0.7 g., was recrystallized several times from xylene to colorless crystals, m.p. 81∼82°. *Anal.* Calcd. for $C_{10}H_{11}O_2N$ (2-Hydroxymethyl-3-methoxyindole) (XI) : C, 67.78; H, 6.26; N, 7.91. Found : C, 67.60; H, 5.99; N, 8.10,

Lithium Aluminum Hydride Reduction of Ethyl 1-Acetylindoxylate (XIX)—A solution of 1.0 g. of $LiAlH_4$ in approx. 70 cc. of dehyd, ether was placed in the flask of a Soxhlet extractor and 2.0 g of ethyl 1-acetylindoxylate was placed in the extractor tube. By heating gently, the hydride solution was maintained at a moderate rate of boiling until all the compound in the tube had been carried into the flask. The flask was then cooled, the extractor tube was removed, and the condenser was connected directly to the flask. The decomposition was carried out in the usual manner. The water layer was extracted several times with AcOEt, the extract solution

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was washed with water, dried, and evaporated under a reduced pressure. The residue, approx. 0.5 g., was purified by sublimation or distillation under a diminished pressure or recystallization from xylene. The colorless crystals thus obtained melted at 78~78.5°, b.p$_{0.5}$ 127~129°. There was no depression of the melting point on admixture with the compound obtained from ethyl 1-acetyl-2,3-dihydroindoxylate (XXII) by $LiAlH_4$ reduction. *Anal.* Calcd. for $C_{11}H_{13}ON$ (XX): C, 75.44; H, 7.48; N, 8.00. Found: C, 75.69; H, 7.04; N, 7.86.

Summary

When ethyl indoxylate was treated with lithium aluminum hydride, three compounds were obtained. Two of these compounds were identified as N-acetylanthranilic acid (Ⅴ) and 2-methyl-2-(2′-methylindyl-3′)pseudoindoxyl (Ⅵ), and the remaining one was assumed to be bis(2-methyl-2-indolin-3-one) (Ⅷ). The mechanisms of their formation were discussed.

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U.D.C. 547.677.4.07

52. **Michitoshi Ohta**: Azaditerpenoids. IV.[1] Synthesis of 1-Methoxycarbonyl-1,12-dimethyl-7-amino-1,2,3,4,9,10,11,12-octahydrophenanthrene.

(*Kowa Chemical Laboratories**)

In Part Ⅱ of this series,[2] it was shown that the permanganate oxidation of dehydroabietic acid and purification of the product as its methyl ester by chromatography afforded 1-methoxycarbonyl-1,12-dimethyl-7-acetyl-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene (Ⅲ) in 0.8% yield as a by-product. Later, this reaction condition was examined in order to increase the yield of (Ⅲ) and it was found that the oxidation of methyl dehydroabietate (I) with chromium trioxide in glacial acetic acid at about 80° afforded methyl 9-oxodehydroabietate (Ⅱ) in 25% yield, together with about 5% yield of (Ⅲ). Similar oxidation of (Ⅱ) was found to give (Ⅲ) in 14% yield. Recently, Zeiss, *et al.*[3] reported that oxidation of (I) in a large amount of glacial acetic acid with chromium trioxide at 70° gives (Ⅲ) in a good yield of 17~20%.

Heating of (Ⅲ) with equimolar amount of iodine in pyridine at 100° results in the formation of a corresponding pyridinium iodide but the substance remains uncrystallizable. Decomposition of this iodide by boiling with two moles of ethanolic sodium hydroxide affords 1-methoxycarbonyl-7-carboxy-9-oxo-1,12-dimethyloctahydrophenanthrene (Ⅳ), m.p. 200~202°. Use of an excess of ethanolic sodium hydroxide naturally results in the saponification of the ester at 1-position and a dicarboxylic acid of m.p. 290°(decomp.) is obtained. Attempted oxidation of (Ⅲ) with sodium hypobromite, followed by methylation of the acid so obtained with diazomethane, and purification of the methyl ester afforded rhomboprismatic crystals of m.p. 152.5~154°, which gave positive halogen test and whose analytical values agreed with $C_{20}H_{23}O_5Br$. These facts indicated that the desired oxidation of the acetyl group was accompanied with the introduction of bromine.

Reduction of (Ⅳ) by the Huang-Minlon method and recrystallization of the product from methanol-benzene mixture afforded crystals (V′) of m.p. 240~242°(sint. at around

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[1] Part Ⅲ: J. Pharm. Soc. Japan, **75**, 445(1955).

[2] M. Ohta: *Ibid.*, **75**, 289(1955).

[3] H. H. Zeiss, *et al.*: J. Am. Chem. Soc., **77**, 6707(1955).

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