Diese Arbeit wurde unter der gütigen Leitung von Herrn Prof. E. Ochiai und mit Hilfe der Unterstützung des Unterrichtsministeriums zur Förderung der Naturwissenschften durchgeführt, wofür ich mich zu grossem Dank verpflichtet fühle.

Experimental

Die oben erwähnten Versuchsmaterien sind, ausgenommen 5,7-Dimethyl-1,2,3,4-tetrahydro-1,6-naphthyridin (V) und 3-Dimethylaminopyridn, alle bekannt.

5,7-Dimethyl-1,2,3,4-tetrahydro-1,6-naphthyridin (V)—Über seine Synthese wird bald veröffentlicht werden.

3—Dimethylaminopyridin—Durch Methylierung von 3-Aminopyridin mit Formaldehyd und Ameisensäure hergestellt. Kp$_6$ 95°. Pikrat : Nadeln vom Schmp. 179~181°(aus MeOH). $C_7H_{10}N_2\cdot C_6H_3N_3O_7$—Ber. C, 44.5 : H, 3.9 : N, 19.9. Gef. : C, 44.33 : H, 3.70 : N, 19.47. Die freie Base wurde durch ihr Pikrat gereinigt und kurz vor der Messung im Vakuum destilliert.

Zusammenfassung

An Hand der vergleichenden UV-spektrographischen Untersuchung von Dehydro-α-matrinidin und synthetischen Aminopyridinderivaten wurde das Vorliegen des 4-Aminopyridin-Skelettes im ersteren nachgewiesen.

(Eingegangen am 26. April, 1956)

U.D.C. 547.754 : 542.941.7

50. Tomoyoshi Komai : Reduction of Ethyl Indoxylate. I. Catalytic Reduction of Acetyl Derivatives of Ethyl Indoxylate.

(*National Institute of Health, Tokyo**)

In high pressure catalytic reduction, the hydrogenation of indole is known to occur preferably in its pyrrole ring and the reaction occurs more easily when some substituted groups are attached to the pyrrole ring.[1] Adkins and Coonradt suggested that on selective hydrogenation[1] of indole under conditions of 250~300 atms. at 220~250°, copper chromite gave indoline and Raney nickel gave octahydroindole, but they doubted the occurrence of tetrahydro compound. Broun and Bayer,[2] Willstätter, Seitz, and Broun,[3] Broun, Bayer, and Blessing,[4] and Willstätter and Jacquet[5] reported that on reduction with nickel or platinum under high pressure and temperature, indole and its alkyl derivatives are hydrogenated to indoline and octahydroindole, more or less accompanied with decomposition products of the pyrrole ring. King, Bartrop, and Walley[6] showed that in ethanol or methanol solution under high pressure, Raney nickel converted indole into hydrogenated N-ethyl- or N-methylindole, respectively.

With respect to the reduction of indoxyl,[7] it has been reported that the simple indoxyl produces indoline, indole, and 2,3-dihydroindoxyl with copper-nickel-kieselgur under high pressure and that O,N-diacetylindoxyl gives N-acetyldihydroindoxyl with nickel-kieselgur.

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[1] H. Adkins, H. L. Coonradt : J. Am. Chem. Soc., **63**, 1563(1941).

[2] J. v. Broun, O. Bayer : Ber., **58**, 387(1925).

[3] R. Willstätter, J. Seitz, J. v. Broun : *Ibid.*, **58**, 385(1925).

[4] J. v. Broun, O. Bayer, G. Blessing, *Ibid.*, **57**, 392(1924).

[5] R. Willstätter, Jacquet : *Ibid.*, **51**, 767(1918).

[6] F. E. King, J. A. Bartrop, R. J. Walley : J. Chem. Soc., **1945**, 277.

[7] D. R. P. 515,544, 516,675, 515,676, 518,515(1928).

Johnson, *et al.*[8] showed that an antibiotic, Gliotoxin, involves a substituted 3-hydroxyindoline-2-carboxylic acid (I) moiety in its structure, and as a standard compound of this structural part they synthesized methyl 1-acetyl-3-hydroxyindoline-2-carboxylate (II) from methyl 1-acetylindoxylate by means of low-pressure catalytic hydrogenation with Adams' platinum catalyst.[9] The latter is the only investigation reported with respect to the indoxylate hydrogenated in its pyrrole ring system.

In the course of a research on the catalytic hydrogenation of ethyl indoxylate derivatives, an attempt was made for the catalytic reduction of ethyl indoxylate (IV) with platinum or Raney nickel under various conditions, but no reaction products were isolated other than the starting material. However, three acetyl derivatives of ethyl indoxylate, ethyl 3-acetyl- (V), 1,3-diacetyl- (VI), and 1-acetylindoxylate (VIII) were found to be hydrogenated with Raney nickel under high pressure to form reaction products in good yield. The hydrogenation occurred on different parts of the structure of (IV) according to the position of the acetyl group in the starting compounds.

Ethyl indoxylate (IV), which was prepared according to the method reported by Vorländer and Mumme,[10] was treated with acetyl chloride to form ethyl 3-acetylindoxylate (V), which was further acetylated with anhydrous sodium acetate and acetic anhydride to ethyl 1,3-diacetylindoxylate (VI). Ethyl 1-acetylindoxylate (VIII) was prepared from diethyl N-acetylphenylglycine-*o*-carboxylate (VII) derived from (III) by an intramolecular condensation. These three acetyl derivatives were reduced catalytically under almost the same conditions.

On hydrogenation of ethyl 3-acetylindoxylate (V) in ethanolic solution over nickel catalyst at 100~110°, 85 atms., colorless fine prisms (IX), m.p. 144.5~146°, $C_{13}H_{17}O_4N$, were obtained. This product gave a positive tetranitromethane reaction. The ultraviolet absorption curve of (IX) showed the maximum absorption band at 280 mμ, characteristic to the pyrrole ring, but lacked the characteristic absorption for the benzene ring. Further gentle saponification of (IX) with ethanolic potassium hydroxide yielded a compound (X), m.p. 94.5~94.6°, $C_{11}H_{15}O_3N$, which showed a positive ferric chloride test. On oxidative degradation with potassium permanganate, (IX) gave an aliphatic dicarboxylic acid which was identified with authentic adipic acid. From these reactions (IX) was proved to be ethyl 3-acetoxy-4,5,6,7-tetrahydroindole-2-carboxylate, produced from the starting compound (V) by the partial hydrogenation of the benzene ring, and thus (X) must be ethyl 3-hydroxy-4,5,6,7-tetrahydroindole-2-carboxylate, in which O-acetyl group of (IX) had been saponified. This result showed that the partial hydrogenation of indole ring does not always preferentially occur in its pyrrole ring system as mentioned by Adkins.[1] The resistance of ethoxycarbonyl group of (IX) against saponification is comparable with that of ethyl indoxylate.[11]

Hydrogenation of ethyl 1,3-diacetylindoxylate (VI) under similar conditions as for (V) (100~110°, 85 atms.) gave a compound (XI), m.p. 62.5~64°, $C_{13}H_{15}O_3N$, which gave an acid (XII), m.p. 191~192°, $C_{11}H_{11}O_3N$, on saponification with dilute ethanolic potassium hydroxide. Both (XI) and (XII) showed positive tetranitromethane test. The analytical data of (XI) and (XII) showed that the O-acetyl group attached on the 3-position of the parent compound (VI) had liberated by reduction. There are many examples of such hydrogenolysis of O-acetyl group in literatures.[12,13,14] Thus, the mode of the

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[8] J. D. Dutcher, J. R. Johnson, W. F. Bruce : J. Am. Chem. Soc., **67**, 1736(1945).
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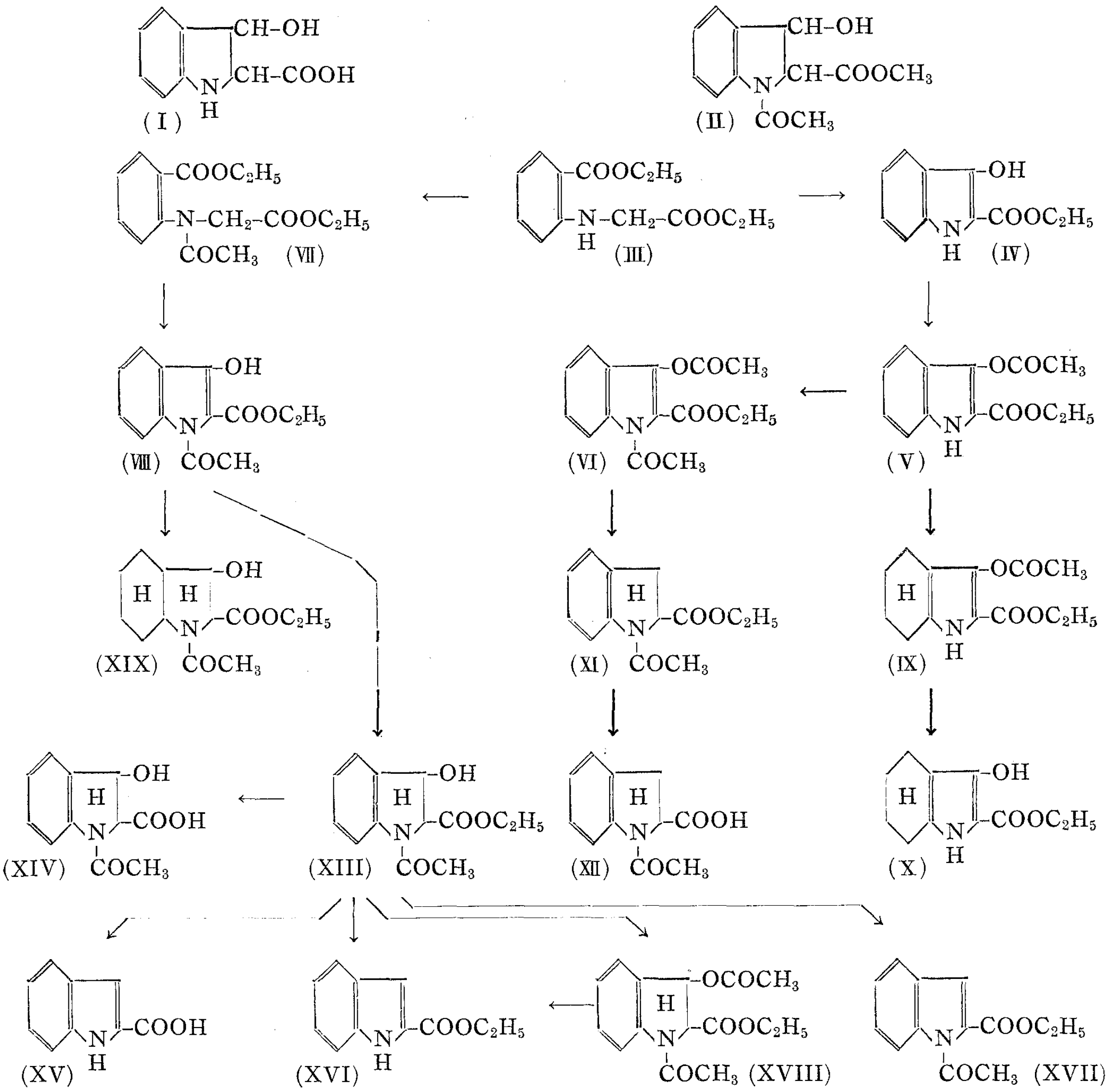
CH-OH
CH-COOH
N
H
(I)
CH-OH
CH-COOCH3
N
COCH3
(II)
-COOC2H5
-N-CH2-COOC2H5
COCH3
(VII)
-COOC2H5
-N-CH2-COOC2H5
H
(III)
-OH
-COOC2H5
N
H
(IV)
-OH
-COOC2H5
N
COCH3
(VIII)
-OCOCH3
-COOC2H5
N
COCH3
(VI)
-OCOCH3
-COOC2H5
N
H
(V)
H
H
-OH
-COOC2H5
N
COCH3
(XIX)
H
-COOC2H5
N
COCH3
(XI)
H
-OCOCH3
-COOC2H5
N
H
(IX)
-OH
H
-COOH
N
COCH3
(XIV)
-OH
H
-COOC2H5
N
COCH3
(XIII)
H
-COOH
N
COCH3
(XII)
H
-OH
-COOC2H5
N
H
(X)
-COOH
N
H
(XV)
-COOC2H5
N
H
(XVI)
-OCOCH3
H
-COOC2H5
N
COCH3 (XVIII)
-COOC2H5
N
COCH3 (XVII)

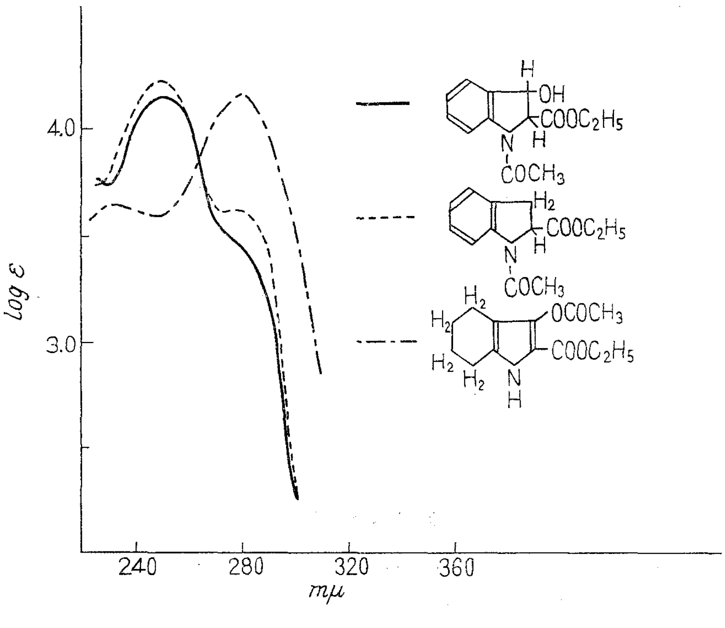
log ε
4.0
3.0
240
280
320
360
mμ
H
OH
COOC2H5
N H
COCH3
H2
COOC2H5
N H
COCH3
H2
H2
OCOCH3
H2
COOC2H5
H2
H2
N
H

Fig. 1.

hydrogenation reaction in this case was definitely different from that of (V) as mentioned above. The ultraviolet absorption spectrum of (XI) was almost identical with that of ethyl 1-aectyl-3-hydroxyindoline-2-carboxylate (XIII) (q.v.), exhibiting the strong absorption of benzene ring at 240∼250 mμ but no band for the pyrrole ring. Therefore, (XI) and (XII) must be ethyl 1-acetylindoline-2-carboxylate and 1-acetylindoline-2-carboxylic acid, respectively.

On hydrogenation under similar conditions (100∼110°, 85 atms.) as described above ethyl 1-acetylindoxylate (VIII) gave a mixture, from which a crude compound melting at about 120° as a major product and another one melting at 165∼167° as a by-product were obtained. Uuder milder conditions (60°, 60 atms.), the compound (XIII), m.p. 120.5∼121.5°, $C_{13}H_{15}O_4N$, was quantitatively isolated. This showed a positive tetranitromethane test but no ferric chloride coloration. The ultraviolet absorption spectrum of (XIII) is almost similar to that of (XI), strong absorption band of benzene ring appearing at 240∼250 mμ with an extremely slight absorption at 280 mμ. Therefore, (XIII) should correspond to ethyl 1-acetyl-3-hydroxyindoline-2-carboxylate, in which the hydrogenation occurs at positions 2 and 3. In this hydrogenation the hydroxyl group at 3-position of (VIII) remained unaffected. On gentle saponification with 0.5% ethanolic potassium hydroxide (XIII) gave 1-acetyl-3-hydroxyindoline-2-carboxylic acid (XIV), m.p. 164∼165°, $C_{11}H_{11}O_4N$. However, 3% ethanolic potassium hydroxide and ethanolic hydrochloric acid converted (XIII) into indole-2-carboxylic acid (XV) and ethyl indole-2-carboxylate (XVI), respectively, by simultaneous N-deacetylation and dehydration of 2 and 3-positions. Acetyl chloride caused only dehydration of (XIII) to give ethyl 1-acetylindole-2-carboxylate (XVII), while acetic anhydride and anhydrous sodium acetate converted the former into O,N-diacetate (XVIII), m.p. 104∼105°, $C_{15}H_{17}O_5N$. When treated with dilute ethanolic hydrochloric acid, (XVIII) gave ethyl indole-2-carboxylate (XVI) with simultaneous O,N-deacetylation and formation of a double bond between the 2 and 3-positions.

As a result of these reactions, it is suggested that the hydroxyl group at 3-position is comparatively stable to dehydration so long as the nitrogen is acetylated. A similar effect of the N-acetyl group has also been observed by Johnson, *et al.*,[9] and it is also reported that 1-acetyl-3-hydroxyindoline is similarly stable.[7]

When a more drastic conditions, 150 atms., 110∼120°, were used, (VIII) gave another hydrogenated product (XIX), m.p. 167∼168.5°, $C_{13}H_{21}O_4N$. This compound showed negative tetranitromethane and ferric chlorids tests and no absorption was observed in ultraviolet region. (XIX) gave a corresponding acid and a diacetate by saponification with dilute ethanolic potassium hydroxide and acetylation with acetic anhydride, respectively. Further, on drastic oxidation with alkaline potassium permanganate, (XIX) formed adipic acid. Consequently this reduction product must be ethyl 1-acetyl-3-hydroxyoctahydroindole-2-carboxylate (XIX).

Thus, it was found that on hydrogenation under almost similar conditions (110°—150 atms., 100°—85 atms., or 60°—60 atms.), the three acetyl derivatives of ethyl indoxylate gave partial or complete ring-saturated products depending on the position of the acetyl group in the starting compounds.

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Experimental

Ethyl 3-Acetylindoxylate (V)—To 15 g. of ethyl indoxylate, 10 g. of AcCl was added and boiled gently for 1 hr. After cooling, the mixture was poured into ice water to decompose the excess

AcCl and fine crystals that separated showed m.p. 134.5~135.5° after recrystallization from EtOH.

Ethyl 3-Acetoxy-4,5,6,7-tetrahydroindole-2-carboxylate (**IX**)—A solution of 5 g. of (V) in 170 cc. of EtOH containing approx. 3 g. of Ni catalyst was shaken in H_2 atmosphere at 85 atms. and 100~110°. The mixture was filtered and concentrated to afford crystals which on recrystallization from EtOH melted at 144.5~146°. Yield, 90%. *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.15; H, 6.82; N, 5.58. Found : C, 62.15; H, 6.79; N, 5.79.

Ethyl 3-Hydroxy-4,5,6,7-tetrahydroindole-2-carboxylate (**X**)—1.0 g. of (IX) was dissolved in 100 cc. of 0.5% EtOH-KOH and saponified by boiling gently for 1 hr. The mixture was treated as usual to furnish fine crystals which after recrystallization from EtOH melted at 94.5~96°. No acidic product was obtained. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.70. Found: C, 62.81; H, 7.17; N, 6.91.

Oxidation of (**IX**) **with Potassium Permanganate**—To a stirred solution of 0.2 g. of (IX) in 30 cc. AcOH, pulverized $KMnO_4$ was added until no more decolorization of the reagent occurred. The mixture was poured into water and extracted with $CHCl_3$. The extract was evaporated and the residue, purified by recrystallization from water, m.p. 145~147°, showed no depression when mixed with authentic specimen of adipic acid.

Ethyl 1,3-Diacetylindoxylate (**VI**)—A solution of 6.0 g. of (V) and 2 g. of anhyd. AcONa in 30 cc. Ac_2O was boiled for 1 hr. After decomposition of Ac_2O with water, crystals were obtained. On recrystallization from EtOH, the colorless crystals melted at 83~84°. Yield, 4.7 g.

Ethyl 1-Acetylindoline-2-carboxylate (**XI**)—The hydrogenation was carried out on 4.0 g. of (VI) as described in the previous experiment. After filtration and evaporation of the hydrogenated solution, the colorless residue was distilled under a reduced pressure. The distillate which boiled at 153~154°/0.5 mm. solidified on standing. It gave colorless crystals with m.p. 62.5~64° after recrystallization from benzene-ligroine. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found : C, 67.26; H, 6.51; N, 6.05.

1-Acetylindoline-2-carboxylic Acid (**XII**)—(XI) was saponified with 1% EtOH-KOH to furnish an acidic compound, which recrystallized to colorless needles, m.p. 191.5~192.5°. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found : C, 64.43; H, 5.71; N, 6.77.

Ethyl 1-Acetylindoxylate (**VIII**)—A cold solution of EtONa, prepared from 1.4 g. of Na and 25 cc. of dehyd. EtOH was added under shaking to a solution of 18 g. of diethyl N-acetyl-N-phenylglycine-*o*-carboxylate (VII) in 50 cc. of the same solvent. The mixture was allowed to stand at room temperature for 0.5 hr. and then acidified with 20% AcOH solution, separating colorless crystals. This was combined with another crop obtained by the addition of 75 cc. of water to the filtrate. The total yield of (VIII) thus obtained amounted to approx. 10.5 g. It showed m.p. 114.5~116° and was pure enough for the following reactions.

Ethyl 1-Acetyl-3-hydroxyindoline-2-carboxylate (**XIII**)—A solution of 10 g. of (VIII) in 150 cc. of EtOH containing approx. 7 g. of Ni catalyst was shaken in H_2 atmosphere at 60 atms. and 60°. After filtration and evaporation of the solvent, colorless needles were obtained in almost quantitative yield. It showed a melting point of 121~122.5° on recrystallization from benzene. *Anal.* Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found : C, 62.68; H, 5.98; N, 5.65.

1-Acetyl-3-hydroxyindoline-2-carboxylic Acid (**XIV**)—(XIII) was hydrolysed with 0.5% EtOH-KOH by gentle boiling. The mixture was acidified and extracted with AcOEt. On evaporation of the solvent, a colorless crystalline substance was obtained which was recrystallized from EtOH-benzene to melt at 164~165°(decomp.). *Anal.* Calcd. for $C_{11}H_{11}O_4N\cdot H_2O$: C, 55.25; H, 5.48; N, 5.86. Found : C, 55.26; H, 5.47; N, 5.90.

Indole-2-carboxylic Acid (**XV**)—(XIII) was hydrolysed with 3% EtOH-KOH by boiling. The acidic product was recrystallized from benzene to melt at 203~204°(decomp.). It showed no depression when mixed with authentic sample of indole-2-carboxylic acid.

Action of Dilute Hydrochloric Acid on (**XIII**) : **Formation of Ethyl Indole-2-carboxylate** (**XVI**)—A mixture of 50 cc. EtOH, 1.0 g. of (XIII), and 1 cc. HCl was boiled for 2 hrs., and the solvent was removed under diminished pressure to give colorless crystals, which recrystallized from benzene to colorless plates, m.p. 121.5~122°. Yield, 0.6 g. It showed no depression when mixed with authentic sample of ethyl indole-2-carboxylate synthesized from *o*-nitrophenylpyruvic acid.

Action of Acetyl Chloride on (**XIII**) : **Formation of Ethyl 1-Acetylindole-2-carboxylate** (**XVII**)—A mixture of 1 g. of (XIII) and 5 g. of AcCl was boiled for a few mins. and poured into ice water. The crystals that separated melted at 51.5~52.5° after recrystallization from EtOH. Yield, 0.7 g.

Ethyl 1-Acetyl-3-acetoxyindoline-2-carboxylate (**XVIII**)—A mixture of 20 cc. Ac_2O, 2.0 g. of (XIII), and 1 g. of anhyd. AcONa was refluxed for 1 hr. The reaction mixture was poured into cold water and the crystals, on recrystallization from EtOH, melted at 104.5~105.5°. Yield, 1.6 g. *Anal.* Calcd. for $C_{15}H_{17}O_5N$: C, 61.85; H, 5.88; N, 4.81. Found : C, 61.86; H, 5.87; N, 4.71.

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.

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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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