the synthesis of fatty acid in the liver was activated by addition of malonate but the synthesis of anethole was obviously inhibited by malonate.

When Foeniculum plant was cultivated in a greenhouse in winter, the plant grows rapidly, and the content of fennel oil is low, but the content of *p*-hydroxycinnamic acid is rather great. By the inhibition method, it seems that *p*-hydroxycinnamic, cinnamic, and phenylpyruvic acids are present as the powerful intermediates from phenylalanine to anethole. This fact is in good agreement with accumulation of a large amout of *p*-hydroxycinnamic acid in the plant and with the recent studies on the synthesis of lignin and flavone.[2,3]

A part of expenses for the present work was defrayed by the Grant-in-Aid for Institutional Research from the Ministry of Education which is gratefully acknowledged. The author thanks Prof. H. Mitsuhashi for his advices and is indebted to Mr. N. Yoshida for cultivation of the plant.

Summary

The cell-free enzyme system of Foeniculum plant synthesized anethole from phenylalanine on addition of ATP, DPN^+, Mg^{2+}, and 2-oxoglutarate in anaerobic condition. In this enzyme reaction, *p*-hydroxycinnamic, cinnamic, and phenylpyruvic acids seem to be a powerful intermediate of the anethole biosynthesis, which was detected by the inhibition method.

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144. Shigehiko Sugasawa[*1] and Yoshio Deguchi[*2]: Synthesis of β-Carboline Derivatives. III. A Synthesis of Dimethoxybenzindoloquinolizine.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*)

In the first paper of this series,[1] Sugasawa, Terashima, and Kanaoka described a new synthesis for hexahydrobenzindolo[3,2-*h*]quinolizine, which appeared to have opened a new general route for synthesis of β-carboline derivatives. Syntheses of tetrahydrobenzindoloquinolizines from isoquinolyl- and quinolyl-indoles provided additional examples.

In this paper will be described a synthesis of 2,3-dimethoxy-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (XIII) as a more probable prototype of a fundamental skeleton not yet met in the vegetable kingdom reported in the previous paper.[2]

Thus, ethyl 2-indolecarboxylate was condensed with 3,4-dimethoxyphenethylamine to yield the amide (I) and this was cyclized to give 1-(2-indolyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (II), from which tetrahydro derivatives (III and III′) were prepared by the conventional method. Since the gramine formation of (II) did not proceed neatly, being accompanied by a side reaction, this was dehydrogenated first to give (IV), which then yielded

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1) Part I. S. Sugasawa, M. Terashima, Y. Kanaoka: This Bulletin, **4**, 16(1956).

2) Part II. S. Sugasawa, S. Takano: *Ibid.*, **7**, 417(1959).

the gramine (V) but only after a more prolonged treatment with formaldehyde and diethylamine than in the previous cases.[1,2]

The methiodide (VI) of (V), prepared in a good yield directly from (V) and methyl iodide in benzene solution in the presence of acetic acid, was converted into the ester (IX) via a general route shown in Chart 1, in which the intermediate nitrile (VII) was not isolated in a pure state. The reduction of this ester with lithium aluminium hydride in tetrahydrofuran solution proceeded smoothly to give the corresponding alcohol (X) without affecting the isoquinoline ring as could be judged from its ultraviolet spectral curve as compared with that of (IV) (Fig. 1).

On being treated with phosphorus tribromide in chloroform solution, the alcohol (X) gave the hydrobromide of the corresponding bromide (XI) in contrast to the case reported previously.[1] (XI) was purified from dilute hydrobromic acid solution to form a well-defined

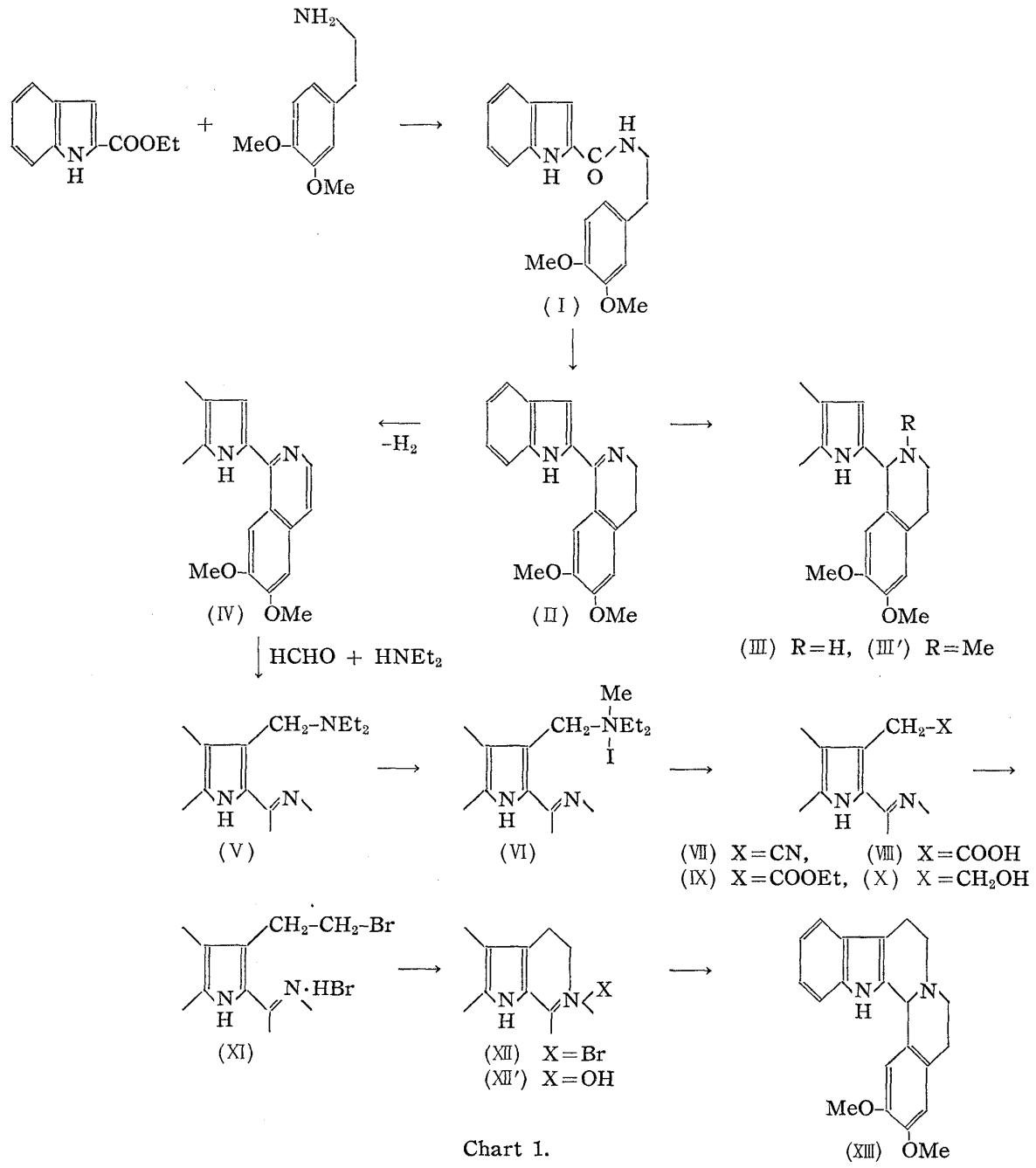

Chart 1.

crystals, which gave good analyses for (XI), but when recrystallized from a mixture of ethanol and ether the purified crystal (XI) as well as the crude (XI) furnished the cyclized quinolizinium bromide (XII) as was confirmed through its analyses. The chloroform solution of (XI) and (XII), when treated with dilute sodium hydrogencarbonate solution, bacame red and, after some time, red crystalline solid (XII′) began to separate, which no longer contained halogen but was again converted to the yellow (XII) by the action of hydrobromic acid. These compounds (XI, XII, and XII′) gave practically identical ultraviolet curves in ethanolic solution as shown in Fig. 2.

In contrast to (XII), which showed an identical ultraviolet curve in 50% ethanolic *N* hydrobromic acid solution as in ethanol, (XI) gave a different curve in 50% ethanolic *N* hydrobromic acid solution (Fig. 3) from the one given in Fig. 2. If (XI) remained uncyclized in the ethanolic hydrobromic acid solution it should give an ultraviolet curve similar to that of the hydrobromide of the alcohol (X), whose ultraviolet curve was, however, different from that of (XI), as can be seen in Fig. 3. Judging from the shape of the curve of (XI) shown in Fig. 3, as compared to those of (X)-hydrobromide and (XII), this compound is considered to cyclize completely in ethanolic solution to form (XII), whereas only partial cyclization takes place in ethanolic hydrobromic acid solution. The slight bathochromic shift of the maximum of the ultraviolet curve of (XII′) in 50% ethanolic 1.5*N* sodium hydroxide solution (Fig. 3), as compared with that in ethanol (Fig. 2), is probably due to the

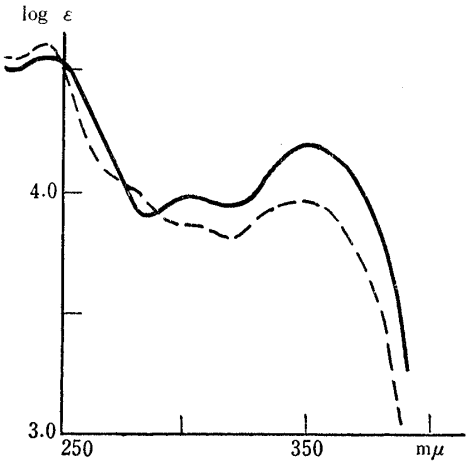

Fig. 1.
——— (IV)
--------- (X) (in EtOH)

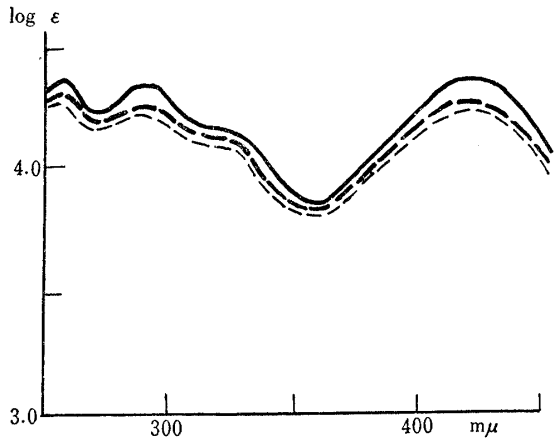

Fig. 2.
——— (XII)
------ (XI)
--------- (XII′) (in EtOH)

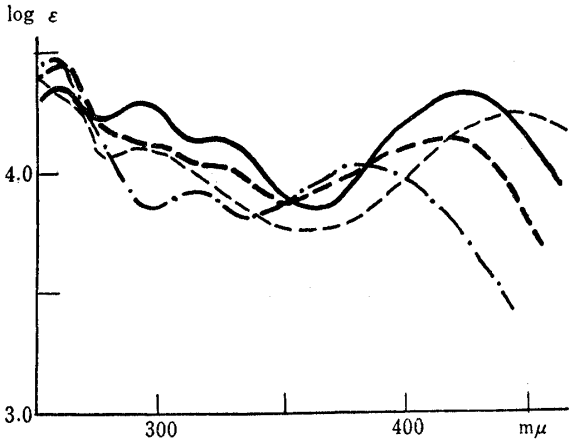

Fig. 3.
——— (XII) } (in 1*N* HBr-50% EtOH)
------ (XI) }
-·-·-· (X) HBr (in 1*N* HBr-H_2O)
--------- (XII′) (in 1.5*N*·NaOH-50% EtOH)

formation of an anhydronium base from (XII').[2,3]

The reduction of (XII') was achieved by means of hydrogen activated over the Adams platinum catalyst to yield colorless (XIII), whose ultraviolet curve was practically identical with those of (III) and (III') in conformity with its structure. (XII') was also reduced by sodium borohydride in hydrous methanol[4] to give a product, whose identity with (XIII) obtained as above was proved beyond doubt by mixed melting point test and through comparison of ultraviolet and infrared spectral data of the hydrochloride of the two compounds.

Experimental

N-3,4-Dimethoxyphenethyl-2-indoleacetamide (I)—A mixture of ethyl 2-indolecarboxylate[5] (1.8 g.) and 3,4-dimethoxyphenethylamine (1.8 g.) was heated in an oil bath (175~185°) for 6 hr. After cool, the resultant reddish substance was dissloved in $CHCl_3$, the solution was washed with dil. HCl and H_2O, dried, and the solvent was evaporated to leave a syrup, which solidified on being triturated with Et_2O. Yield, 2.3 g. Purified from AcOEt this formed colorless minute pillars, m.p. 154~155°. *Anal.* Calcd. for $C_{19}H_{20}O_3N_2$: C, 70.35; H, 6.2; N, 8.6. Found : C, 70.4; H, 6.3; N, 8.3.

1-(2-Indolyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (II)—A benzene solution (30 cc.) of the amide (I) (3.3 g.) and $POCl_3$ (10 g.) was refluxed for ca. 3 hr. When cooled, petr. ether (300 cc.) was added to the reaction mixture to precipitate a dark resinous substance. The precipitate was dissolved in hot H_2O (charcoal), filtered, and the filtrate was allowed to cool, separating orange-brown hydrochloride of (II), which became orange when washed with a little Me_2CO. Purified from hot water this formed deep yellow minute needles, m.p. 146° (decomp.). Yield, 3.1 g. (89%).

The free base formed faint yellow pillars, m.p. 149° (from MeOH), which was indifferent to the Ehrlich reagent. UV mμ (log ε) : λ_{min}^{EtOH} 266 (3.74), λ_{max}^{EtOH} 317 (4.34). *Anal.* Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.5; H, 5.9; N, 9.15. Found : C, 74.3; H, 6.2; N, 9.0.

1-(2-Indolyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III)—The hydrochloride of (II) was reduced catalytically over Adams Pt catalyst in MeOH. The free base formed colorless minute needles, m.p. 132~134°, which gave reddish purple Ehrlich color test. UV mμ (log ε) : λ_{min}^{EtOH} 251 (3.67), λ_{max}^{EtOH} 281 (4.08).

The N-methyl derivative (III') was prepared by catalytic reduction of the methiodide, m.p. 216° (decomp.), of (II) as usual. The free base (III') separated in colorless slender leaflets from AcOEt, m.p. 187~188°. UV mμ (log ε) : λ_{min}^{EtOH} 250 (3.68), λ_{max}^{EtOH} 282 (4.09). *Anal.* Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.5; H, 6.9; N, 8.7. Found : C, 74.3; H, 7.1; N, 8.7.

1-(2-Indolyl)-6,7-dimethoxyisoquinoline (IV)—A mixture of (II) (0.3 g.), ethyl cinnamate (0.3 g.), 30% Pd-C (0.2 g.), and *p*-cymene (10 cc.) was refluxed for 6 hr. with vigorous stirring and filtered while hot. The cooled filtrate separated orange yellow crystalline solid, which was purified from EtOH to yellow featherly needles, m.p. 222°; yield, 0.2 g. *Anal.* Calcd. for $C_{19}H_{16}O_2N_2$: C, 75.0; H, 5.3; N, 9.2. Found : C, 74.6; H, 5.5; N, 9.3.

The methiodide formed yellow pillars from MeOH, m.p. 239° (decomp.). *Anal.* Calcd. for $C_{20}H_{20}O_2N_2I$: C, 53.8; H, 4.3; N, 6.3. Found : C, 53.9; H, 4.4; N, 6.2.

1-(3-Diethylaminomethyl-2-indolyl)-6,7-dimethoxyisoquinoline (V)—A mixture of 50% Et_2NH (0.3 g.) solution, AcOH (0.25 g.), and HCHO (0.15 g.) was prepared in the cold and then the foregoing (IV) (0.5 g.) was suspended into this solution forming a reddish brown solution after being warmed at 50° on a steam bath with stirring. Addition of dil. NaOH solution with ice cooling caused light brown solid to separate, which was collected, washed with H_2O, dried, and used directly in the next step. Yield, 0.5 g., soluble in EtOH, Et_2O, benzene, etc.

Monopicrate : Yellow minute needles (from EtOH-Me_2CO), m.p. 218° (decomp.). *Anal.* Calcd. for $C_{30}H_{30}O_9N_6$: C, 58.25; H, 4.9; N, 13.6. Found : C, 58.0; H, 4.9; N, 13.1.

Dipicrate : Yellow minute needles (from EtOH-Me_2CO), m.p. 181° (decomp.). *Anal.* Calcd. for $C_{36}H_{33}O_{16}N_9$: C, 57.8; H, 4.4; N, 16.9. Found : C, 57.7; H, 4.7; N, 16.8.

The methiodide (VI) was prepared by dissolving (V) (1.0 g.) in anhyd. benzene (undissolved matter if any was removed by filtration) and adding AcOH (0.3 g.) and CH_3I (0.6 g.) (some anhyd. EtOH may be added to insure a clear solution). The whole was allowed to stand at room temp. for 4~8 days to complete the separation of (VI). When purified from MeOH this formed yellow plates, m.p. 250° (decomp.); yield, 0.85 g. *Anal.* Calcd. for $C_{25}H_{30}O_2N_3I$: C, 56.5; H, 5.7; N, 7.9. Found : C, 56.5; H, 5.6; N, 8.1.

3) L. H. Groves, A. G. Swan : J. Chem. Soc., **1952**, 650.
4) R. Mirza : *Ibid.*, **1957**, 4400.
5) J. Elks, D. F. Elliot, B. H. Hems : *Ibid.*, **1944**, 629.

2-(6,7-Dimethoxy-1-isoquinolyl)-3-indoleacetic Acid (VIII)—A mixture of above-obtained (VI) (1.7 g.), KCN (0.25 g.), EtOH (40 cc.), and H_2O (60 cc.) was refluxed in a steam bath for 2 hr., EtOH was evaporated *in vacuo*, and the crude nitrile (VII) so obtained was extracted with benzene. The residue of this benzene solution was heated on a steam bath with 20% KOH solution (40 cc.) and EtOH (20 cc.) for 10 hr. EtOH was evaporated, residual solution was filtered, and the filtrate was made acid with AcOH, when a yellow solid (0.7 g.) separated. This acid (VIII) is very sparingly soluble in common organic solvents and for analysis, a small portion was purified from a large amount of EtOH, when minute yellow needles, m.p. 262° (decomp.), were obtained. *Anal.* Calcd. for $C_{21}H_{18}O_4N_2$: C, 69.6; H, 5.0; N, 7.7. Found : C, 70.0; H, 5.3; N, 7.9.

Ethyl 2-(6,7-Dimethoxyisoquinolyl)-3-indoleacetate (IX)—A suspension of the foregoing acid (VIII) (0.4 g.) in anhyd. EtOH (50 cc.) was saturated with dry HCl gas in the cold. The whole was then transferred on a steam bath, dry HCl being introduced continuously under reflux until a clear brownish yellow solution resulted. EtOH was then evaporated, the residue was dissolved in H_2O, and basified with K_2CO_3 to separate the free basic ester, which was taken up in Et_2O. Et_2O solution was dried and the solvent was removed. The residue came in colorless scales with cinnamic ester-like fragrance from a mixture of benzene and petr. ether, m.p. 94~96°; yield, 0.3 g.

The methiodide formed minute yellow needles, m.p. 202°. *Anal.* Calcd. for $C_{24}H_{25}O_4N_2I$: N, 5.3. Found : N, 5.2.

2-(6,7-Dimethoxy-1-isoquinolyl)tryptophol (X)—To a solution of the ester (IX) (1.0 g.) in tetrahydrofuran (10 cc.) an Et_2O suspension of $LiAlH_4$ (0.25 g. in 30 cc. Et_2O) was added with ice cooling. The whole was then stirred for 1 hr. at room temp. and an additional 1.5 hr. under reflux. When cool the product was decomposed by adding water (1 cc.), filtered, and the residue was repeatedly extracted with Et_2O and then with warm $CHCl_3$. The residue obtained after evaporation of the organic solvents was purified from EtOH to yield faint yellow minute pillars, m.p. 212~214°; yield, 0.25 g. *Anal.* Calcd. for $C_{21}H_{20}O_3N_2$: C, 72.4; H, 5.8; N, 8.0. Found : C, 72.3; H, 5.9; N, 8.0.
Hydrochloride : Yellow needles (from EtOH), m.p. 228° (decomp.).
Picrate : Yellow needles (from EtOH), m.p. 230° (decomp.). *Anal.* Calcd. for $C_{27}H_{30}O_{10}N_5$: C, 56.4; H, 4.25; N, 11.9. Found : C, 56.15; H, 4.0; N, 12.15.

1-[3-(2-Bromoethyl)-2-indolyl]isoquinoline (XI)—A solution of the foregoing alcohol (250 mg.) in $CHCl_3$ (20 cc.) was mixed with PBr_3 (0.2 g.) in $CHCl_3$ (20 cc.) and the whole was refluxed on a steam bath for 5 hr. $CHCl_3$ was then evaporated *in vacuo* and the reddish syrupy residue was triturated with Et_2O to form a yellow solid, which was collected on a filter, washed with Et_2O, and then purified from 0.5% HBr solution. (XI) separated as minute yellow needles, m.p. 190° (decomp.); yield, 250 mg. *Anal.* Calcd. for $C_{21}H_{20}O_2N_2Br_2$: C, 51.2; H, 4.1; N, 5.7. Found : C, 51.6; H, 4.1; N, 5.8.

2,3-Dimethoxy-8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizinium Bromide (XII)—The foregoing compound (XI) was repeatedly crystallized from a mixture of MeOH and Et_2O until the product formed yellow needles with a definite m.p. of 254° (decomp.). *Anal.* Calcd. for $C_{21}H_{19}O_2N_2Br$: C, 61.3; H, 4.7; N, 6.8. Found : C, 61.5; H, 4.6; N, 6.4.

2,3-Dimethoxy-5,6,8,9,14,14*b*-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (XIII)—A yellow solid obtained by treating (X) (194 mg.) with PBr_3 as above was dissolved in $CHCl_3$ and the resultant solution was shaken with 5% $NaHCO_3$ solution to separate a reddish solid probably (XII′); yield, 150 mg. This formed a rather indefinite reddish purple crystalline solid from EtOH, m.p. 199° (decomp.). *Anal.* Calcd. for $C_{21}H_{20}O_3N_2 \cdot H_2O$: C, 68.8; H, 6.05; N, 7.65. Found (in a substance dried at 100° at 10 mm. Hg for 10 hr.) : C, 68.05; H, 5.7; N, 7.6.

i) EtOH solution of (XII′) (80 mg.) was reduced with H_2 activated over the Adams Pt catalyst, absorbing 1 molar equivalent of H_2 to give a yellow solution. The reduction solution was now faintly acidified by adding a few drops of dil. HCl and reduction was continued by adding fresh catalyst, if necessary, until a few drops of the reduction solution did not develop any more red coloration by adding $CHCl_3$ and 5% $NaHCO_3$ solution. The filtrate from the catalyst was evaporated and the residue was purified from EtOH to colorless long needles, m.p. 248° (decomp.); yield, 50 mg. UV mμ (log ε) : λ_{min}^{EtOH} 252 (3.69), λ_{max}^{EtOH} 282 (4.08). *Anal.* Calcd. for $C_{21}H_{23}O_2N_2Cl$: C, 68.0; H, 6.25; N, 7.6. Found : C, 68.0; H, 6.3; N, 7.4.

The free base separated in colorless needles (from EtOH), m.p. 216~217°. UV mμ (log ε) : λ_{min}^{EtOH} 252 (3.54), λ_{max}^{EtOH} 282 (4.08). *Anal.* Calcd. for $C_{21}H_{22}O_2N_2$: C, 75.4; H, 6.6; N, 8.4. Found : C, 75.5; H, 6.8; N, 8.3.

ii) (XII′) (50 mg.) was reduced with $NaBH_4$ (20 mg.) in hydr. MeOH according to the method of Mirza,[4] the product was dissolved in dil. HCl (charcoal), and the filtrate was evaporated. The resultant residue was purified from EtOH to form colorless needles, m.p. 248° (decomp.); yield, 20 mg. UV mμ (log ε) : λ_{min}^{EtOH} 252 (3.61), λ_{max}^{EtOH} 283 (4.09). IR spectra of the two hydrochlorides were also identical.

The authors are grateful to members of the analysis rooms of this Faculty and Laboratories of Applied Microbiology, University of Tokyo, for micro-analytical data.

Summary

A new method for synthsis of β-carboline derivatives reported in the previous papers was now extended to include the preparation of tetrahydrobenzindoloquinolizine derivative (XIII). Thus, N-(3,4-dimethoxyphenethyl)-2-indoleacetamide was cyclized by Bischler-Napieralski-Perkin method to yield the corresponding 3,4-dihydroisoquinoline. The latter, after being dehydrogenated, was condensed with formaldehyde and diethylamine to give the gramine-type compound (V), from which benzindoloquinolizinium base (XII) was prepared as previously. Reduction of the latter to (XIII) was effected either catalytically or by means of sodium borohydride.

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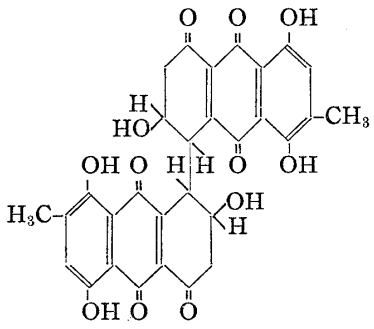
UDC 547.976 : 582.282.12

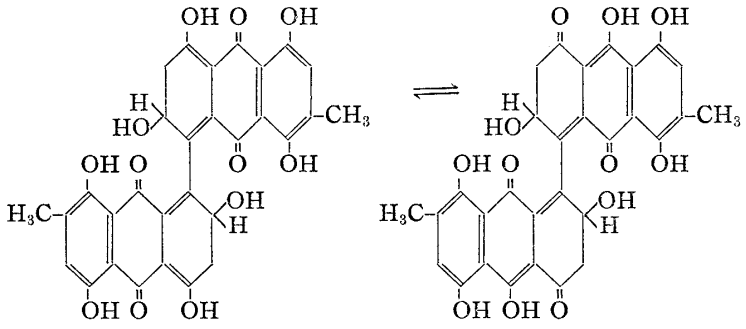
145. Shoji Shibata and Isao Kitagawa : Metabolic Products of Fungi. XVI.*2 The Structures of Rubroskyrin and Luteoskyrin. (2).

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

In a previous paper on the coloring matters of *Penicillium islandicum*,[1] the structures of rubroskyrin (I) and luteoskyrin (II) were proposed and an isomerization reaction of rubroskyrin into luteoskyrin was described.



Rubroskyrin (I)



Luteoskyrin (II)

The properties of both pigments are summarized in Table I.

The present paper deals with the infrared spectral analysis of rubroskyrin and luteoskyrin, and provides some additional evidences for the presence of alcoholic hydroxyls in the molecules of both pigments.

The infrared stretching absorption band of carbonyl in rubroskyrin undergoes a shift towards higher frequency (1703 cm^{-1}) than that usually expected for a six-membered α,β-unsaturated ring ketone.

As the model compounds for rubroskyrin and luteoskyrin, 3,4-dihydro-1,9,10(2*H*)-anthracenetrione[2] (VII), 3,4-dihydro-8-hydroxy-1,9,10(2*H*)-anthracenetrione (VIII), 1-hydroxy-

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*1 Hongo, Tokyo (柴田承二, 北川 勲).

*2 Part XV. S. Shibata, S. Natori, K. Fujita, I. Kitagawa, K. Watanabe : This Bulletin, **6**, 608(1958).

1) Part (1). S. Shibata, I. Kitagawa : *Ibid.*, **4**, 309(1956).

2) K. Zahn, H. Koch : Ber., **71**, 172(1938).