*UDC 547.837.2.07*

# 78. Shigehiko Sugasawa and Seiichi Takano : Syntheses of β-Carboline Derivatives. II.[1] Pentacyclic β-Carboline Analogs of Alstoniline and Tetrahydrobenzindoloquinolizines.

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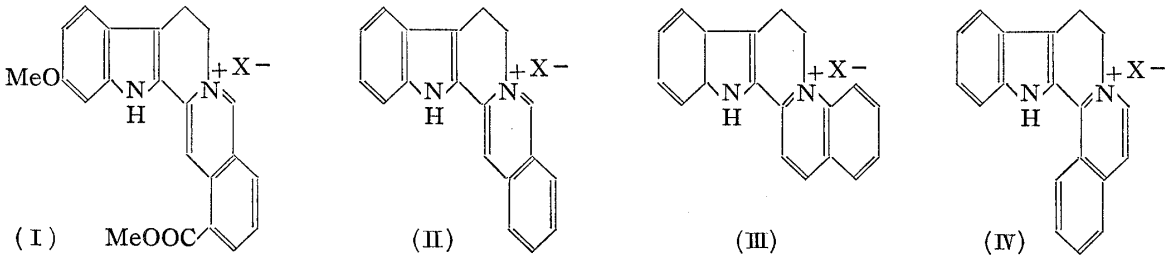
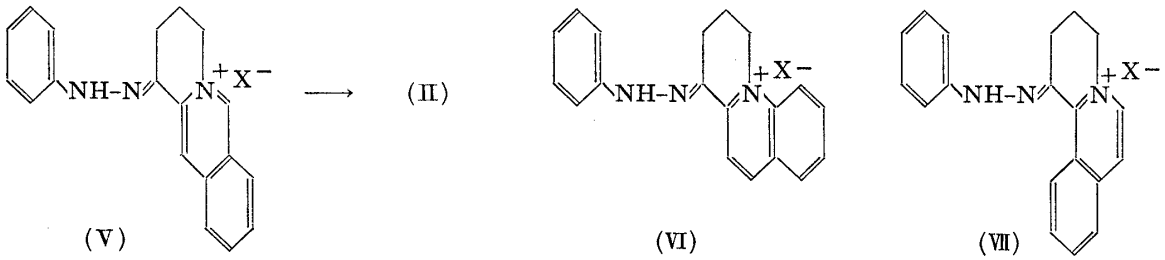
The structure of alstoniline, a minor alkaloid of *Alstonia constricta* F. MUELL, has been shown by Elderfield, *et al.*[2] to be represented by (I).



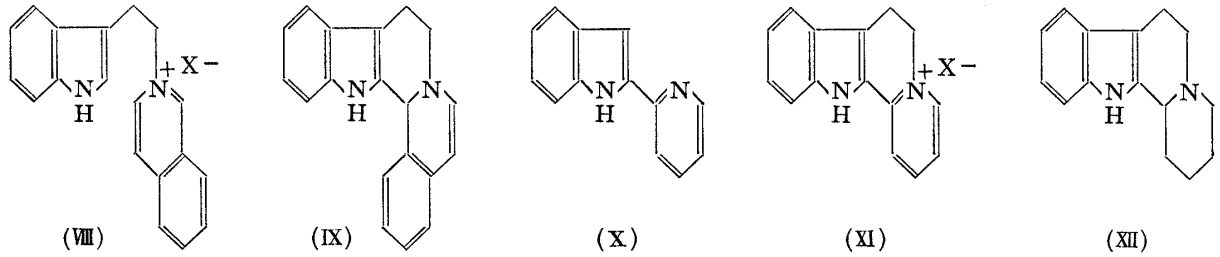

(I) (II) (III) (IV)

Recently, among alstoniline-like pentacyclic β-carbolinium salts (II), (III), and (IV), (II) has been synthesized independently by four groups,[3~6] all of whom used the phenylhydrazone (V) as a starting material, cyclizing it to the corresponding indole by the Fischer method.




(V) ⟶ (II) (VI) (VII)

On the other hand, Prasad and Swan[7] undertook to synthesize (III) and (IV) in the same way from the corresponding phenylhydrazones (VI and VII) but their attempt was reported to result in failure, recovering the starting materials. Robinson and others[8] expected that a quaternary salt (VIII) would yield the base (IX) in dissociating solvent and under the influence of bases, but an unequivocal result has not been obtained.




(VIII) (IX) (X) (XI) (XII)

* Hongo, Tokyo (菅澤重彦, 高野誠一).

1) Part I : This Bulletin, **4**, 16(1956).
2) R.C. Elderfield, S.L. Wythe : J. Org. Chem., **19**, 683(1954).
3) R. C. Elderfield, *et al.* : *Ibid.*, **23**, 435(1958).
4) G.A. Swan : J. Chem. Soc., **1958**, 2038.
5) E.E. Glover, G. Jones : *Ibid.*, **1958**, 1750.
6) Jacobs, Fouché : The 16th Congress, I.U.P.A.C., Paris, 1957, Résumés des Comm., Vol. II, 316.
7) K.B. Prasad, G.A. Swan : J. Chem. Soc., **1958**, 2024.
8) K.T. Potts, R. Robinson : *Ibid.*, **1955**, 2675.

Previously Sugasawa, Terashima, and Kanaoka[9] prepared various 2-pyridylindoles in a good yield by heating the phenylhydrazone of corresponding methyl pyridyl ketone with polyphosphoric acid and 2-(2-pyridyl)indole (X) thus obtained was converted to the quaternary salt (XI) by spanning $-CH_2-CH_2-$ bridge from 3-position of indole to nitrogen of pyridine ring. (XI) was then hydrogenated to 1,3,4,6,7,12b-hexahydro-2*H*,12*H*-indolo-[2,3-*a*]quinolizine (XII). This method was now successfully applied to (XIII) and (XIV), and thus the synthesis of (III) and (IV) was achieved for the first time. The synthetic route is shown in Chart 1.

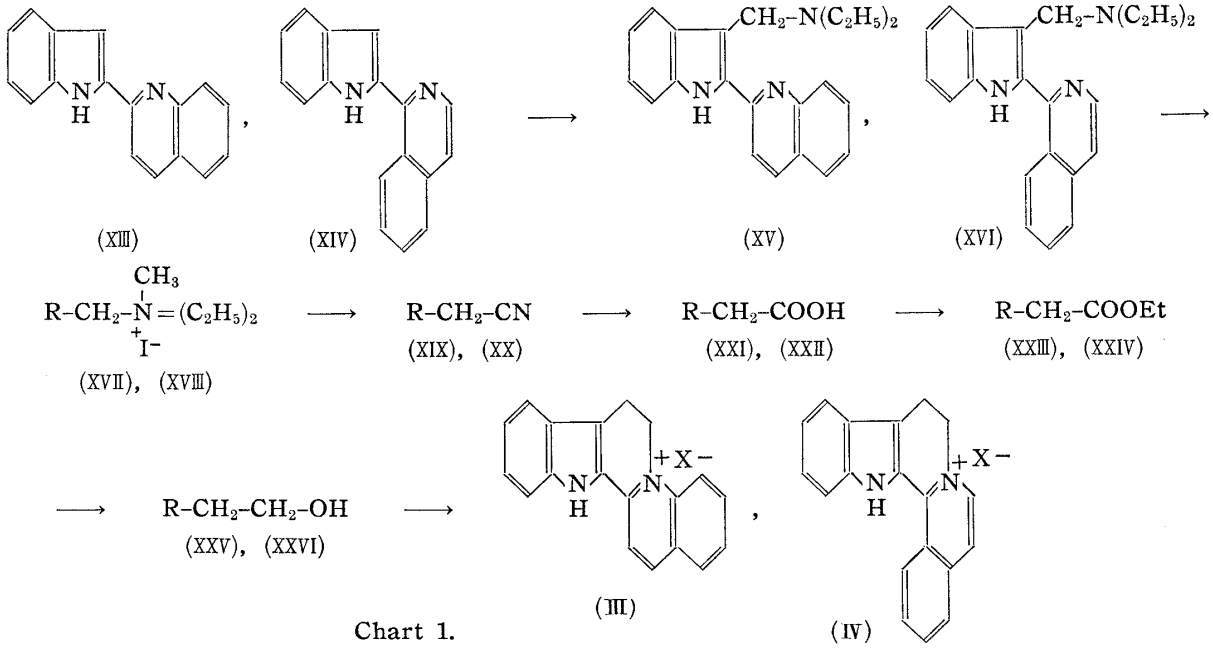


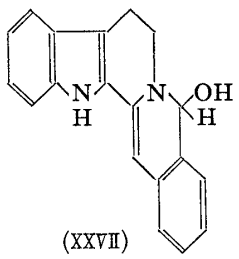

Chart 1.

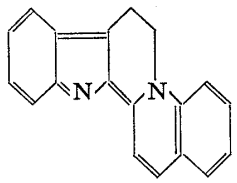
The starting materials (XIII and XIV) were prepared in good yields by heating the phenylhydrazones of methyl 2-quinolyl ketone[10] and methyl 1-isoquinolyl ketone[11] with polyphosphoric acid, both of which were prepared by the known procedure. (XIII) and (XIV) were treated with formaldehyde and diethylamine giving the corresponding gramine-type compounds (XV and XVI), the methiodides of which were then converted into the acetonitriles (XIX and XX) by treating them with sodium cyanide in hydrous ethanol. The nitriles were hydrolysed with alkali to the carboxylic acids (XXI and XXII), followed by reduction of the corresponding esters (XXIII and XXIV) with lithium aluminum hydride to give the alcohols (XXV and XXVI). The alcohols were treated with phosphorus tribromide in chloroform, separating yellow precipitate which was probably the hydrobromide of the 3-(2-bromoethyl)indole derivatives (Br instead of OH in (XXV) and (XXVI)).

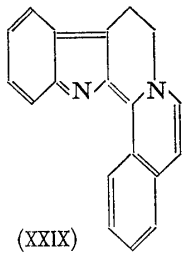
When the precipitate was crystallized from ethanol, the compounds were easily cyclized to the $\beta$-carbolinium salts (III and IV), as in the case of (XI).[9] The quaternary bromides (II, III, and IV) are all orange-red crystals melting above 300°. The behavior of (III) and (IV) towards alkali is probably worth mentioning in contrast to that of (II).

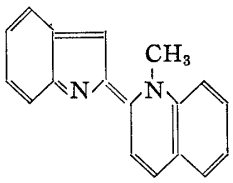
Swan[4] had reported that (II) easily afforded the pseudo-base (XXVII) in dilute alkaline solutions and the ultraviolet absorption spectrum of (XXVII) showed no remarkable shifts in acidic and alkaline ethanol solutions, while the orange aqueous solution of (III) and (IV) immediately turned dark red when basified with alkali, which color was transferred to the organic layer when shaken with benzene. The color was again transferred

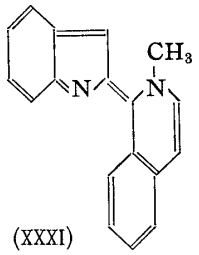
9) S. Sugasawa, M. Terashima, Y. Kanaoka : This Bulletin **4**, 16(1956).
10) K.N. Campbell, *et al.* : J. Am. Chem. Soc., **68**, 1841(1946).
11) J.J. Padbury, H.G. Lindwall : *Ibid.*, **67**, 1268(1945); A. Kaufmann, M. Kunkler : Chem. Ber., **45**, 3093(1932).

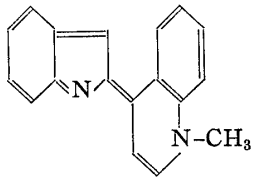

(XXVII)


(XXVIII)


(XXIX)


(XXX)


(XXXI)


(XXXII')

to the aqueous layer on acidification, giving an orange solution. The ultraviolet absorption spectra of (III) and (IV) measured in acid, neutral, and alkaline hydrous ethanol are shown in Fig. 1, and suggest the formation of anhydronium bases (XXVIII and XXIX) under alkaline conditions.

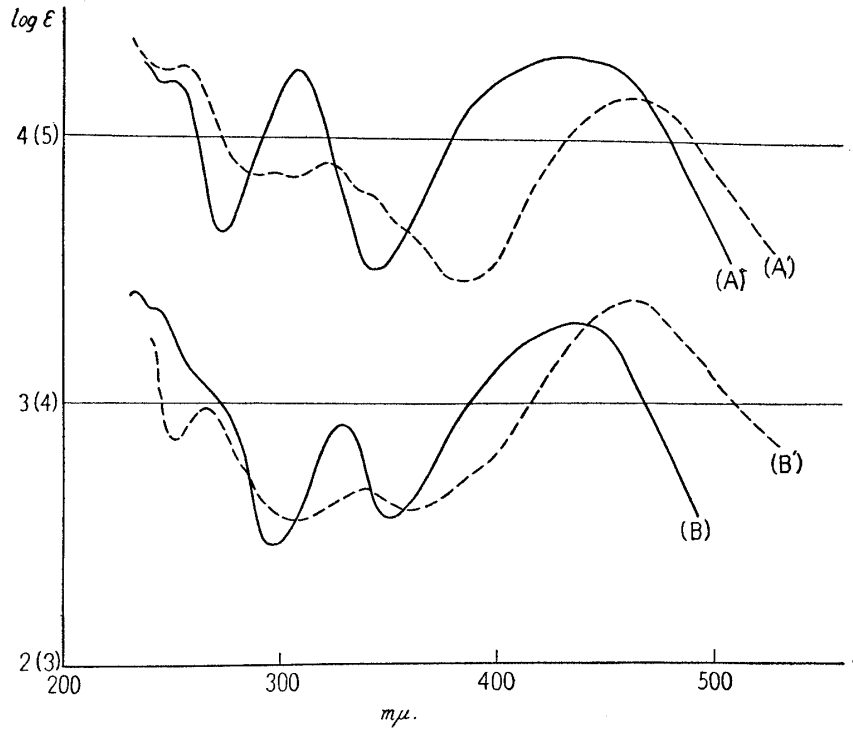



Fig. 1.

Ultraviolet Absorption Spectra (in 95% EtOH)

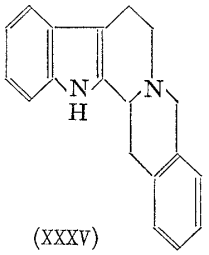
(A)——(III)
(A')------(III) in 0.01*N*KOH
(B)——(IV)
(B')------(IV) in 0.01*N*KOH

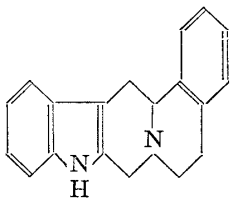
This is also the case in the metho-salts of (XIII), (XIV), and 2-(4-quinolyl)indole (XXXII) which do not contain the β-carboline structure and thus the formation of anhydronium bases (XXX, XXXI, and XXXII') is suggested. Recently Prasad and Swan[7] observed a similar phenomenon in the metho-salts of 2-pyridylindoles.

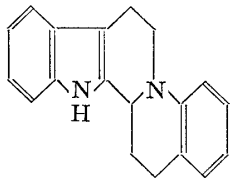
(XIII), (XIV), and (XXXII), as in the case of 2-pyridylindole,[9] gave a negative Ehrlich color test and the corresponding quaternary salts behaved similarly, but when these quaternary salts were reduced with sodium borohydride in ethanolic solutions, the products then gave positive Ehrilch tests (reddish violet). 1-Methyl-2-(2-indolyl)-1,2,3,4-tetrahydroquinoline (XXXIII) and 1-(2-indolyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (XXXIV), which were obtained by catalytic reduction of the methosalts of (XIII) and (XIV), also gave

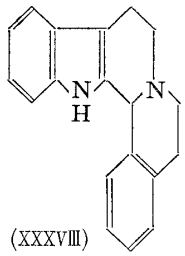
distinct Ehrlich color tests (violet).

Speculation that certain highly potent calabash-curare alkaloids might contain a tetrahydrobenzindoloquinolizine ring led Boekelheide, *et al.*[12] and Swan[7] to synthesize (XXXVI) and (XXXV), respectively. Accordingly, an attempt was made to reduce the quaternary salts (III and IV) to the corresponding tetrahydrobenzindoloquinolizines (XXXVII and XXXVIII).


(XXXV)


(XXXVI)


(XXXVII)


(XXXVIII)

The quaternary salts (XI[9] and II[13]) were easily reduced catalytically with hydrogen activated over Adams' platinum to furnish (XII) and (XXXV), respectively, whereas in the case of (III) no absorption of hydrogen occurred under the same condition. It was reported[14] that the salts of alstonine were resistant to catalytic hydrogenation, although they were reduced to tetrahydroalstonine under the influence of alkali where an anhydronium base might be formed. Therfore, the catalytic reduction of (III) was attempted in ethanolic sodium hydroxide over platinum oxide or Raney nickel, when ca. 1 mole of hydrogen was absorbed, the dark red solution becoming pale red but not colorless. The solution was therefore acidified and the yellow solution obtained was shaken again in the presence of Adams' platinum but no hydrogen uptake was observed and the solution turned dark red when basified with alkali.

The tetrahydro base (XXXVII) was now obtained when sodium borohydride in ethanolic solution was used in combination with Raney nickel catalyst. Thus sodium boro-

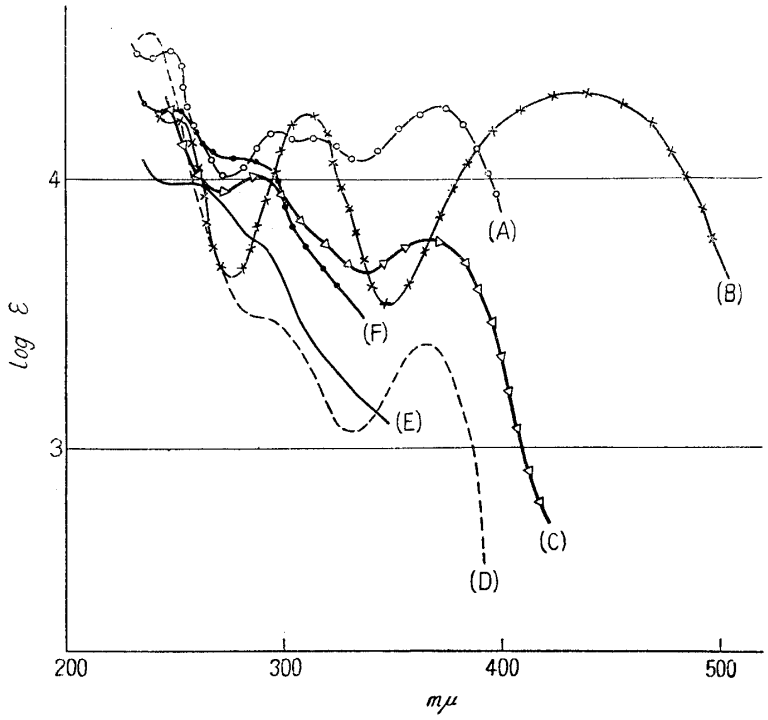



Fig. 2.

Ultraviolet Absorption Spectra (in 95% EtOH)

(A) -○—○- (XXV)
(B) -×—×- (III)
(C) -◁—◁- (III) (treated with $NaBH_4$)
(D) ----- (XXXIX)[16]
(E) ——— (XXXVII)
(F) -•—•- (XXXIII)

12) V. Boekelheide, C. Ainsworth : J. Am. Chem. Soc., **72**, 2134(1950).
13) G. A. Swan : J. Chem. Soc., **1949**, 1720.
14) N. J. Leonard, R. C. Elderfield : J. Org. Chem., **7**, 556(1942).

hydride was added to an orange solution of (III) in hydrous ethanol,[15] when the reduction proceeded with effervescence, giving a pale yellow solution. The ultarviolet absorption spectrum of this solution is shown in (Fig. 2 (C)) which differs distinctly from those of the alcohol (XXV) and the quaternary salt (III) but resembles that of 1-methyl-2-phenyl-1,2-dihydroquinoline (XXXIX) (shown in Fig. 2 (D)) prepared by Karrer and Schmid.[16] These facts suggest that (III) was reduced in the $>C=\overset{+}{N}<$ grouping. An attempt to isolate the reduction product at this stage resulted in failure, only affording a dark red resinous material.

Accordingly the pale yellow solution obtained by reduction with sodium borohydride was directly shaken with Raney nickel in hydrogen atmosphere, becoming completely colorless. The ultraviolet absorption spectrum of this colorless solution is illustrated in Fig. 2 (E), which is similar to that of 2-(2-indolyl)-1-methyl-1,2,3,4-tetrahydroquinoline (XXXIII) (Fig. 2 (F)), easily obtained by catalytic reduction of the metho-salt of (XIII). These spectral data support (XXXVII) as the structure of the reduction product of (III) by the present hydrogenation method. The colorless solution obtained above, however, was sensitive to air oxidation, becoming colored rapidly. This was worked up quickly in corbon dioxide atmosphere to give a pale brown vitreous substance in a good yield. Recrystallized from a little quantity of hydrous ethanol, it changed mostly to a dark red resinous product, affording only a small amount of almost colorless (somewhat pinkish) crystals of m.p. 173~175°, the ultraviolet absorption spectrum of which is the same with Fig. 2 (E) to show that the crystals had the structure (XXXVII). (XXXVII) is very sensitive to air oxidation, gradually becoming brown and the ethanol solution turned dark red in a day or so.

On the contrary, (IV) gave (XXXVIII) in one step when treated with an excess of sodium borohydride in boiling hydrous ethanol.[15] When, however, the quaternary salt (IV) was treated with sodium borohydride in hydrous ethanol at room temperature, the orange solution became colorless under effervescence. The ultraviolet absorption spectrum is shown in Fig. 3 (B), which is similar to that of 2-butyl-1,2-dihydroisoquinoline (XL).[16] This fact suggests that the $>C=\overset{+}{N}<$ grouping was selectively reduced. The above

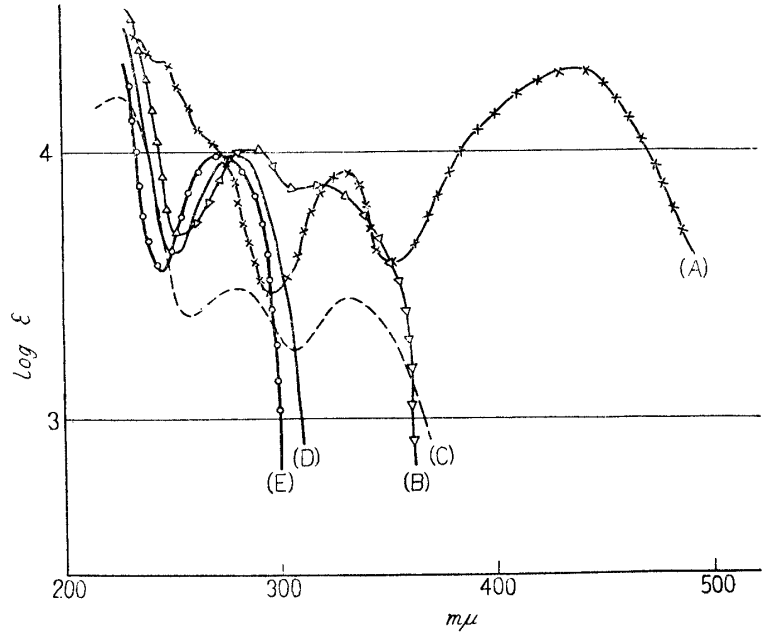



Fig. 3.

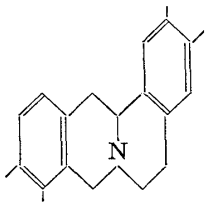
Ultraviolet Absorption Spectra (in 95% EtOH)

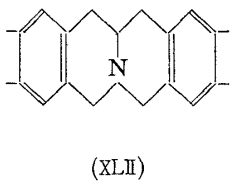
(A) -×—×- (IV)
(B) -▷—▷- (IV) (treated with $NaBH_4$)
(C) ----- (XL)[16]
(D) ——— (XXXVIII)
(E) -○—○- (XXXIV)

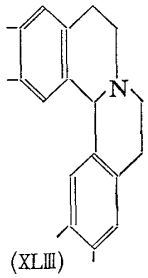
15) R. Mirza : J. Chem. Soc., **1957**, 4400.
16) H. Schmid, P. Karrer : Helv. Chim. Acta, **32**, 960(1949).

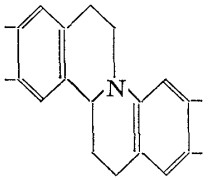
solution was then refluxed with an excess of sodium borohydride for an hour and then water added to precipitate a crystalline substance. The ultraviolet absorption spectrum of the crystals, shown in Fig. 3 (D), is closely similar to that of 1-(2-indolyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (XXXIV) and shows the formation of the desired tetrahydrobenzindoloquinolizine (XXXVIII). Though gradually turned yellow on standing in the air, (XXXVIII) was fairly stable when compared with (XXXVII).

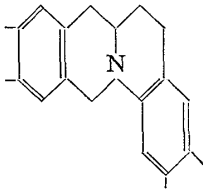
These facts are strongly reminiscent of the following facts. Among tetramethoxytetrahydrodibenzoquinolizines (XLI to XLV) prepared by Sugasawa, *et al.*,[17] (XLI), (XLII), and (XLIII) formed through fusion of two tetrahydroisoquinoline rings were rather stable in the air, whereas (XLIV) and (XLV), having fused hydroquinoline and hydroisoquinoline ring


(XLI)


(XLII)

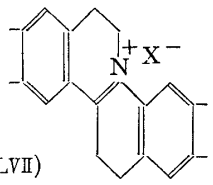

(XLIII)

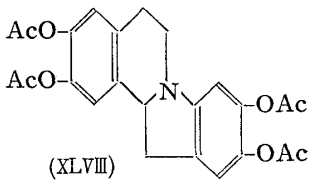

(XLIV)


(XLV)

in their structure, were quite susceptible to air oxidation, turning yellow to reddish rapidly. The compound (XLVI), having the skeleton of (XLV) but none of methoxyl group, was synthesized by Ochiai, *et al.*[18] and it was also very unstable in the air.

Furthermore, the quaternary salt (XLVII),[19] the starting material for (XLIV), was resistant to catalytic reduction as in the case of (III) and finally homologous compound (XLVIII) obtained by Robinson and Sugasawa[20] furnished an indole derivative even in the atmosphere of hydrogen in the presence of Adams' platinum catalyst.


(XLVII)


(XLVIII)

The authors are indebted to Messrs. G. Chihara and K. Tanikawa for the measurement of infrared spectra. Microanalyses were carried out by the members of the analysis room of this Faculty, Tokyo Research Laboratory of Tanabe Seiyaku Co., Ltd., Osaka Research Laboratory of Fujisawa Co., Ltd., and Tokyo College of Pharmacy, to all of whom the authors' thanks are due.

## Experimental[21]

**2-(2-Quinolyl)indole (XIII)**—A mixture of methyl 2-quinolyl ketone (26.4 g.), phenylhydrazine (16.9 g.), and one drop of glacial AcOH in EtOH (150 cc.) was refluxed for 2 hr. On cooling, faint yellow needles of phenylhydrazone of the ketone was obtained, which was purified from EtOH, forming yellow needles of m.p. 154° as described by Kaufmann and Kunkler.[11] Yield, 39.1 g. or 97%. The finely powdered foregoing phenylhydrazone (39 g.) was mixed with polyphosphoric acid (PPA) (100 g.) and the resulting dark red mixture was heated in an oil bath. At 120~130° the mixture became homogeneous, giving a viscous liquid, and at about 135° an exothermic reaction started. The flask was taken out of the oil bath to allow the reaction to proceed spontaneously. The internal temperature rose to 210° within 5 min. After cooling, ca. 400 cc. of $H_2O$ was added, separating phosphate of (XIII) as a yellow solid, which was collected, washed with water, and decom-

17) S. Sugasawa, K. Kodama, H. Inagaki: Chem. Ber., **74**, 456(1941); cf. *Ibid.*, **73**, 782(1940); **72**, 980 (1939); **71**, 1860(1938).
18) E. Ochiai, S. Suzuki: This Bulletin, **5**, 405(1957).
19) K. Kakemi: Yakugaku Zasshi, **60**, 2(1940).
20) R. Robinson, S. Sugasawa: J. Chem. Soc., **1932**, 789.
21) All m.p.s are uncorrected.

posed with NaOH solution, giving a brown solid. The free base was taken up in benzene (ca. 15. L.), washed with water, dried ($K_2CO_3$), and purified through $Al_2O_3$ column. On distilling off the benzene, there remained a faintly yellow crystals, which were purified from benzene, forming colorless needles of m.p. 200~201°. Yield, 30.0 g. or 90%. *Anal.* Calcd. for $C_{17}H_{12}N_2$ : C, 83,58; H, 4.95; N, 11.47. Found : C, 83.85; H, 4.67; N, 11.23.

Picrate : Yellow needles of m.p. 213~214°(decomp.) from EtOH. *Anal.* Calcd. for $C_{17}H_{12}N_2 \cdot C_6H_3O_7N_3$ : C, 58.35; H, 3.19; N, 14.80. Found : C, 58.13; H, 3.36; N, 14.88.

**2-(2-Quinolyl)-3-diethylaminomethylindole (XV)**—To a cold mixture of aq. $Et_2NH$ (14 g. of 50%) and glacial AcOH (11.5 g.), HCHO solution(8 g. of 35%) and finely powdered 2-(2-quinolyl)indole(17.3 g.) were added. The whole was warmed at 50° on a water bath for 20 hr. with stirring, giving a dark red homogeneous solution. Any unreacted starting material was filtered off and the filtrate was poured into 15% NaOH solution (250 cc.) with cooling, separating a faint yellow solid, which melted at 50~60°. This base was taken up in benzene, washed with water, dried ($K_2CO_3$), and the solvent was evaporated, leaving 21.3 g. (89%) of a vitreous substance, which could not be induced to crystallize and so was characterized as the picrate which formed well defined yellow pillars of m.p. 183~184°(decomp.) from EtOH. *Anal.* Calcd. for $C_{22}H_{23}N_3 \cdot C_6H_3O_7N_3$ : N, 15.1. Found : N, 15.0. The methiodide was also obtained in crystalline state.

**2-(2-Quinolyl)-3-diethylaminomethylindole Methiodide (XVII)**—The foregoing base (20 g.) was dissolved in a mixture of benzene (150 cc.) and AcOH (4 g.),[22] and a sufficient amount of EtOH was added to make the solution clear. To this solution was now added MeI (9.0 g.) and the whole was kept standing at room temperature for 4 days, separating some yellow crystals. These were collected on a filter, washed with benzene, and then recrystallized from hydr. EtOH, forming faint yellow plates of m.p. 202~205°(decomp.). Yield, 11.75 g. To the filtrate was added a little more MeI (1 g.) and the mixture was allowed to stand at room temperature for a week, giving same crystals (7.6 g.). Total yield, 17.4 g. or 65%. *Anal.* Calcd. for $C_{23}H_{26}N_3I$ : C, 58.59; H, 5.56; N, 8.91. Found : C, 58.30; H, 5,08; N, 9.22.

**2-(2-Quinolyl)-2-(3-indolyl)acetonitrile (XIX)**—The above-mentioned methiodide (5.8 g.) in EtOH (65 cc.) was mixed with an excess of NaCN (1.5 g.) dissolved in $H_2O$ (25 cc.) and the mixture was refluxed in an oil bath (110°). After about 30 min.'s refluxing, colorless needles began to separate out. Heating was continued for 3 hr. and on cooling, the crystalline solid was collected, washed with $H_2O$, and dried. Yield of the crude nitrile amounted to 3.4 g. (nearly quantitative). Recrystallized from benzene-EtOH, this formed colorless needles of m.p. 197~198°. *Anal.* Calcd. for $C_{19}H_{13}N_3$ : C, 80.54; H, 4.63; N, 14.83. Found : C. 80.16; H, 4.19; N, 14.59.

**2-(2-Quinolyl)-2-(3-indolyl)acetic Acid(XXI)**—The nitrile (XIX) (3.0 g.)was hydrolysed with an excess of boiling KOH solution(15 g. KOH in 50 cc. EtOH and 12 cc. $H_2O$). After 15 hr.'s heating, the reaction mixture was concentrated *in vacuo* and then salted out with $K_2CO_3$, giving K-salt of the acid as a brown solid. The solid was collected, dissolved in hot water (50 cc.), and filtered through a wet filter. The filtrate was acidified with AcOH, forming bulky yellow precipitate, which was collected and washed with water. Yield, 3.0 g. or 94% of the crude acid. When purified from dil. AcOH, this formed yellow granules of m.p. 217~218°(decomp.). *Anal.* Calcd. for $C_{19}H_{14}O_2N_2$ : C, 75.48; H, 4.67; N, 9.27. Found : C, 75.19; H, 4.58; N, 8.81.

**Ethyl 2-(2-Quinolyl)-2-(3-indolyl)acetate (XXIII)**—To a cold mixture of anhyd. EtOH (35 cc.) and conc. $H_2SO_4$ (15 cc.) 3 g. of finely powdered (XXI) was added. The whole was warmed at 80° for 3 hr. and then heated at 100° for additional 7 hr. under gentle refluxing. When cool, the reaction mixture was poured into ice water (ca. 100 g.), basified with 10% $NH_4OH$, and the base that separated out was extracted thoroughly with benzene-$Et_2O$. The benzene-$Et_2O$ solution was washed, dried over $K_2CO_3$, and evaporated. There remained 2.5 g. of brown crude ester, which was dissolved in benzene, purified through $Al_2O_3$ column, and the solvent was removed from the filtrate. The residue was recrystallized from benzene-EtOH, forming colorless pillars of m.p. 162°. Yield, 2.2 g. or 67%. *Anal.* Calcd. for $C_{21}H_{18}O_2N_2$ : C, 76.34; H, 5.49; N, 8.48. Found : C, 76.08; H, 5.29; N, 8.50.

**2-(2-Quinolyl)-3-(2-hydroxyethyl)indole (XXV)**—A solution of the foregoing ester (2.2 g.) in anhyd. tetrahydrofuran (30 cc.) was added during 10 min. to a suspension of $LiAlH_4$ (0.5 g.) in anhyd. tetrahydrofuran (30 cc.) with cooling and stirring, separating a yellow solid. After being stirred for 3 hr. under ice cooling, water (1.5 cc.) in tetrahydrofuran (5 cc.) was added to decompose the unreacted $LiAlH_4$ and the whole was refluxed on a water bath for 30 min. The reaction mixture was filtered while hot and the yellow residue was washed with $CHCl_3$ containing EtOH until the filtrate became colorless. The solvent was evaporated from the filtrate to dryness *in vacuo* and the residue was thoroughly extracted with a mixture of anhyd. tetrahydrofuran-benzene (2:1), giving a faint yellow solution. The solution was filtered, concentrated *in vacuo*, and allowed to stand overnight at room temperature, depositing pale yellow crystals, which was purified from

22) C. Schöpf, J. Thesing : Z. angew. Chem., **63**, 377(1951).

EtOH, forming colorless micropillars of m.p. 226°. Yield, 1.47 g. (96%). *Anal.* Calcd. for $C_{19}H_{16}ON_2$: C, 79.33; H, 5.59; N, 9.72. Found: C, 79.14; H, 5.39; N, 9.25.

**8,9-Dihydro-14*H*-benz[*f*]indolo[2,3-*a*]quinolizinium Bromide (III)**—To a suspension of the foregoing alcohol (500 mg.) in dehyd. $CHCl_3$ (30 cc.), $PBr_3$ (500 mg.) in $CHCl_3$ (15 cc.) was added to give a clear orange-red solution. The mixture was refluxed gently in an oil bath for 5 hr., until the evolution of HBr had ceased. The mixture was cooled, the yellow crystalline solid that separated was collected on a filter, washed with benzene, and then recrystallized from EtOH, forming orange red elongated plates of m.p. 308~311°(decomp.). Yield, 480 mg. (62%). *Anal.* Calcd. for $C_{19}H_{15}N_2Br$: C, 64.95; H, 4.30; N, 7.97. Found: C, 64.61; H, 4.09; N, 7.89. U.V. (a) In acid and neutral soln. $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 231(4.33), 250(4.22), 309(4.24), 435(4.33); $\lambda_{min}$ 244(4.20), 273(3.63), 343(3.50), (b) In alkaline soln. (0.01*N* KOH). $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 256(4.27), 300(3.88), 324(3.41), 468(4,16); $\lambda_{min}$ 241 (4.26), 292(3.88), 307(3.85), 388(3.47).

The O-picrate forms orange plates of m.p. 275~277°(decomp.) from EtOH. *Anal.* Calcd. for $C_{19}H_{15}N_2 \cdot C_6H_2O_7N_3$: N, 14.02. Found: N, 14.35.

**1,2,8,9-Tetrahydro-14*H*,14b*H*-benz[*f*]indolo[2,3-*a*]quinolizine (XXXVII)**—To the orange solution of the foregoing bromide (200 mg.) in hydr. EtOH (40 cc.), $NaBH_4$(100 mg.) in EtOH (10 cc.) was added, an immediate vigorous evolution of $H_2$ set in, and the whole became pale yellow. After the evolution of $H_2$ subsided, Raney Ni (0.3 g.) in EtOH (10 cc.) was added to the solution and again a strong effervescence of $H_2$ took place. The mixture was shaken in $H_2$ atmosphere at 50° for 7 hr., giving a colorless solution. The catalyst was removed by filtration and the filtrate was concentrated in $CO_2$ atmosphere of low pressure. The excess of $NaBH_4$ was decomposed by adding 10% HCl, the resultant acid solution was basified with 10% NaOH, and extracted repeatedly with benzene-$CHCl_3$. The extract was washed with water, dried over anhyd. $Na_2SO_4$, and the sovlent was removed in $CO_2$ atmosphere of low pressure, leaving a faintly brownish vitreous substance (120 mg. or 72%). This substance was so susceptible to air oxidation, forming a red resinous product, that it was dissolved in a small amount of EtOH and the whole was allowed to stand in $CO_2$ atmosphere in an ice box for 2 days. Although utmost care was taken for the treatment of this substance, majority of it turned into a reddish resinous product, from which a small amount of crystalline solid was obtained. This was collected and purified from hydr. EtOH, affording almost colorless (slightly pinky) plates of m.p. 173~175°. Yield, 37.5 mg. (20%). *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 82.95; H, 64.7; N, 10.19. U.V. $\lambda_{max}^{95\%EtOH}$ mμ(log ε): 252(3.98); $\lambda^{shoulder}$ 284(3.76); $\lambda_{min}$ 244(3.97).

**2-(1-Isoquinolyl)indole (XIV)**—The phenylhydrazone of methyl 1-isoquinolyl ketone was prepared in 94% yield as described above and formed yellow pillars of m.p. 166~167° from EtOH as is given in the literature.[11] This (6.5 g.) was mixed with PPA (30 g.) and the mixture was heated at 180° for 5 min. The product was worked up and purified as before and the indole formed colorless hexagonal plates of m.p. 150~151°. Yield, 4.3 g.(90%). *Anal.* Calcd. for $C_{17}H_{12}N_2$: C, 83,58; H, 4.95; N, 11.47. Found: C, 83.36; H, 5.03; N, 11.14.

**2-(1-Isoquinolyl)-3-diethylaminomethylindole (XVI)**—The mixture of aq. $Et_2NH$ (5.6 g. of 50%), glacial AcOH (4.8 g.), HCHO solution (3.2 g. of 35%), and 2-(1-isoquinolyl)indole (7.2 g.) was warmed at 50° for 18 hr. with stirring. On working up the reaction product as described for (XV), a crude base melting at 80~105° was obtained. Yield, 9.5 g.(96%). This could not be induced to crystallize and so was characterized as a picrate, which separated as yellow needles of m.p. 213~214°(decomp.) from EtOH. *Anal.* Calcd. for $C_{17}H_{12}N_2 \cdot C_6H_3O_7N_3$: C, 58.35; H, 3.19; N, 14.80. Found: C, 58.13; H, 3.36; N, 14.88.

**2-(1-Isoquinolyl)-3-diethylaminomethylindole Methiodide (XVIII)**—To a solution of the crude Mannich base (XVI) (11 g.) in benzene (35 cc.), MeI (4.8 g.) was added and the mixture was allowed to stand at room temperature for 24 hr., affording bulky yellow precipitate. This was collected and dried on a porcelain plate. Yield, 14.6 g.(88%). This crude methiodide (m.p. 183~193°) was too hygroscopic for further purification and was characterized as the O-picrate of orange microcrystals, m.p. 199°(decomp.), from EtOH. *Anal.* Calcd. for $C_{23}H_{26}N_3 \cdot C_6H_2O_7N_3$: C, 60.71; H, 4.93; N, 14.63. Found: C, 60.76; H, 5.26; N, 14.60.

**2-(1-Isoquinolyl)-2-(3-indolyl)acetonitrile (XX)**—A mixture of the foregoing methiodide (7 g.) and NaCN (2.5 g.) in 50% EtOH (110 cc.) was gently refluxed in an oil bath for 5 hr. The reaction mixture was concentrated *in vacuo* to a small volume to separate a brownish oily product. This was taken up in benzene, washed with $H_2O$, dried ($K_2CO_3$), and the solvent was removed *in vacuo*, leaving a brownish vitreous substance. Yield, 4.1 g.(97%) of the crude nitrile, which could not be induced to crystallize and was characterized as the picrate, which formed well defined orange microneedles of m.p. 246°(decomp.) from EtOH-benzene. *Anal.* Calcd. for $C_{19}H_{13}N_3 \cdot C_6H_3O_7N_3$: C, 58.60; H, 3.15; N, 16.41. Found: C, 58.78; H, 3.52; N, 16.54.

**2-(1-Isoquinolyl)-2-(3-indolyl)acetic acid (XXII)**—The nitrile (XX) (5.5 g.) was hydrolysed with a boiling KOH solution (20 g. KOH in 120 cc. of 80% EtOH) for 15 hr. and the product was worked up as above, affording the free acid as yellow pillars of m.p. 201~203°(decomp.) from hydr. MeOH.

Yield, 5.0 g.(85%). *Anal.* Calcd. for $C_{19}H_{14}O_2N_2$ : C, 75.48; H, 4.67; N, 9.27. Found : C, 75.48; H, 4.40; N, 8.80.

**Ethyl 2-(1-Isoquinolyl)-2-(3-indolyl)acetate (XXIV)**—The foregoing acid was esterified by the standard method and the resultant ester (XXIV) was recrystallized from EtOH-petr. ether, affording colorless tetrahedral crystals with one mole of ethanol of crystallization. Yield, 1.35 g.(54%). *Anal.* Calcd. for $C_{21}H_{18}O_2N_2 \cdot C_2H_6O$ : C, 73.34; H, 6.43; N, 7.44. Found : C, 73.02; H, 6.06; N, 7.68.

**2-(1-Isoquinolyl)-3-(2-hydroxyethyl)indole (XXVI)**—A solution of the ester (XXIV) (0.23 g.) in anhyd. tetrahydrofuran (15 cc.) was added dropwise to a stirred solution of $LiAlH_4$(0.25 g.) in anhyd. tetrahydrofuran (15 cc.) at below −5°. On working up as in the case of (XXV), the alcohol (XXVI) was obtained as colorless minute octahedral crystals of m.p. 182~183° from a small amount of benzene. Yield, 0.15 g.(75%). *Anal.* Calcd. for $C_{19}H_{16}ON_2$ : C, 79.14; H, 5.59; N, 9.72. Found : C, 79.2; H, 5.40; N, 9.65.

**8,9-Dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizinium Bromide (IV)**—The alcohol (XXVI) (320 mg.) in anhyd. $CHCl_3$(15 cc.) was added to $CHCl_3$ solution of $PBr_3$(350 mg. in 5 cc. of $CHCl_3$), separating a yellowish solid. After about 7 hr.'s refluxing in an oil bath, the mixture was cooled and the resultant solid was collected on a sintered glass filter. This was washed with benzene and recrystallized from EtOH, forming brilliant orange-red leaflets of m.p. 318~320°(decomp.). Yield, 360 mg.(92%). *Anal.* Calcd. for $C_{19}H_{15}N_2Br$ : C, 64.95; H, 4.30; N, 7.97. Found : C, 65.34; H, 4.75; N, 8.00.

**5,6,8,9-Tetrahydro-14*H*,14b*H*-benz[*a*]indolo[3,2-*h*]quinolizine (XXXVIII)**—When the bromide (IV) (100 mg.) in 15 cc. of 80% EtOH was cautiously treated with 100 mg. of powdered $NaBH_4$, there occurred a vigorous effervescence and orange color of the solution faded. The colorless solution was then refluxed for 1 hr. and diluted with $H_2O$ (4 cc.), separating colorless crystals, which were collected and purified from hydr. EtOH, forming completely colorless pillars of m.p. 97~99°. Yield, 55.9 mg.(63%). *Anal.* Calcd. for $C_{19}H_{18}N_2 \cdot C_2H_6O$ : C, 78.71; H, 7.55; N, 8.74. Found : C, 78.59; H, 7.05; N, 8,71. U.V. $\lambda_{max}^{95\%EtOH}$ mμ (log ε) : 282(3.99); $\lambda_{min}$ 250(3.63).

Methiodide : Colorless plates from MeOH, m.p. 263~264°(decomp.). *Anal.* Calcd. for $C_{20}H_{21}N_2I$: N, 6.74. Found : N, 6.24

**2-(2-Quinolyl)indole Methosulfate**—2-(2-Quinolyl)indole (580 mg.) in xylene (20 cc.) was mixed with freshly purified $Me_2SO_4$(1 g.) and the whole was refluxed in an oil bath for 3 hr., separating a viscous oily substance. The xylene layer was decanted, the residue was washed with benzene, dried in a vacuum desiccator, and treated with a small amount of MeOH, affording a crystalline solid. When purified from MeOH, this formed yellow plates of m.p. 278~279°(decomp.). Yield, 360 mg. *Anal.* Calcd. for $C_{19}H_{18}O_4N_2S$ : C, 61.60; H, 4.90; N, 7.57. Found : C, 61.30; H, 5.17; N, 7.51. U.V. (a) In acid and neutral soln. : $\lambda_{max}^{95\%EtOH}$ mμ (log ε) : 323(3.94), 389(3.90); $\lambda_{shoulder}$ 278(3.96); $\lambda_{min}$ 297(3.72), 360(3.88). (b) In alkaline soln. (0.01*N* KOH) : $\lambda_{max}^{95\%EtOH}$ mμ (log ε) : 294 (4.07), 433(3.94); $\lambda_{min}$ 268(3.89), 299(4.06), 350(3.39).

**1-Methyl-2-(2-indolyl)-1,2,3,4-tetrahydroquinoline (XXXIII)**—The above-mentioned methosulfate (300 mg.) in EtOH (20 cc. of 95%) was reduced catalytically with $H_2$ activated over Adams' Pt. In 3 hr. theoretical amount of $H_2$ was consumed, giving an almost colorless solution (slightly blue). The filtrate from the catalyst was concentrated *in vacuo* to ca. 10 cc. and basified with 10% $Na_2CO_3$, separating a crystalline solid. This was collected, dissolved in benzene, purified through a column of silica gel-$Na_2SO_4$(1:10) to effect decolorization, and was recrystallized from MeOH, forming colorless plates of m.p. 202~204°. Yield, 170 mg. *Anal.* Calcd. for $C_{18}H_{18}N_2$ : C, 82.40; H, 6.92; N, 10.68. Found. C, 81.96; H, 6.57; N, 11.05. U.V. $\lambda_{max}^{95\%EtOH}$ mμ (log ε) : 247(4.27), 281(4.09), 288(4.06); $\lambda_{min}$ 257(4.23), 274(4.19), 285(4.05).

**2-(1-Isoquinolyl)indole Methiodide**—A mixture of 2-(1-isoquinolyl)indole (2.2 g.) and MeI (1.5 g.) in acetone (20 cc.) was heated in a sealed tube at 100° for 5 hr. Evaporation of the solvent left a brown vitreous substance. Yield, 3.2 g. This did not crystallize in spite of various attempts and was characterized as a picrate. The methopicrate forms yellow minute needles of m.p. 216~217° (decomp.) from EtOH. *Anal.* Calcd. for $C_{18}H_{15}N_2 \cdot C_6H_2O_7N_3$ : C, 59.14; H, 3.52; N, 14.37. Found : C, 59.58; H,3. 77; N, 14.08. U.V. (crude methiodide). (a) In acid and neutral soln. : $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 393(3.86); $\lambda_{shoulder}$ 260 (4.36), 352 (3.79); $\lambda_{min}$ 305 (3.43). (b) In alkaline soln. (0.01 *N*KOH) : $\lambda_{max}^{95\%EtOH}$ mμ (log ε) : 284(4.01), 292(4.01), 435(3.63); $\lambda_{shoulder}$ 305(3.91); $\lambda_{min}$ 261(3.72), 289(3.99), 370(3.31).

**1-(2-Indolyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (XXXIV)**— The foregoing methiodide (3 g.) in hydr. EtOH (30 cc.) was converted into the corresponding methochloride by the usual method and was subjected to catalytic reduction in the presence of $PtO_2$. The catalyst was separated by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in a mixture of acetone and EtOH (1:1) and allowed to stand in an ice box for a day, separating a white crystalline soild. It was recrystallized from EtOH, forming colorless minute crystals of m.p. 209~210°(decomp.). Yield, 1.1 g. *Anal.* Calcd. for $C_{18}H_{19}N_2Cl$ : C, 72.35; H, 6.07; N, 9.36. Found : C, 72.52; H, 6.21; N, 9.05. U.V. $\lambda_{max}^{95\%EtOH}$ mμ (log ε) : 271(3.99); $\lambda_{min}$ 244(3.55).

**2-(4-Quinolyl)indole (XXXII)**—The phenylhydrazone (1.14 g.) of methyl 4-quinolyl ketone[11] was

mixed with P.P.A. (6 g.) and the mixture was heated at 180° for 5 min. The product was worked up as for (XIV), and was purified from EtOH, giving colorless plates of m.p. 142~143°. Yield, 0.56 g. *Anal.* Calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.12; H, 5.29; N, 11.65.

Picrate: Orange minute pillars, m.p. 246~247° (decomp.). *Anal.* Calcd. for $C_{17}H_{12}N_2 \cdot C_6H_3O_7N_3$: C, 58.35; H, 3.19; N, 14.80. Found: C, 57.88; H, 3.43; N, 14.66.

**2-(4-Quinolyl)indole Methiodide**—The above-mentioned 2-(4-quinolyl)indole (XXXII) (0.48 g.) was dissolved in an excess of MeI and the whole was allowed to stand overnight at room temperature, separating a bulky orange-red precipitate. The excess of MeI was evaporated, the residue was washed with benzene, and recrystallized from MeOH, affording wooly orange needles of m.p. 242~243° (decomp.). Yield, 0.45 g. *Anal.* Calcd. for $C_{18}H_{15}N_2I$: C, 55.97; H, 3.91; N, 7.26. Found: C, 56.24; H, 4.20; N, 7.46. U.V. (a) In acid and neutral soln.: U.V. $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 327(3.70), 435 (4.37); $\lambda_{shoulder}$ 260(4.06), 314(3.59); $\lambda_{min}$ 303(3.43), 342(3.48). (b) In alkaline soln. (0.01*N* KOH): $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 292(3.97), 470(3.74); $\lambda_{min}$ 287(3.95), 376(3.24).

## Summary

The synthesis of β-carboline derivative reported in the preceding paper[9] was now successfully extended to include the syntheses of two new salts of pentacyclic β-carbolinium derivatives (III and IV), which formed the anhydronium bases (XXVIII and XXIX) by the agency of alkali. The reduction of (III) to the corresponding tetrahydro base (XXXVII) was only possible with sodium borohydride, directly followed by catalytic reduction over Raney nickel catalyst, while the tetrahydro base (XXXVIII) of (IV) could be obtained with an excess of sodium borohydride in boiling hydrous ethanol in one step. The stability of (XXXVII) and (XXXVIII) in the air was compared with that of tetrahydrodibenzoquinolizines.

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## 79. Koiti Kimura,[*1] Kazuko Yamauchi,[*2] and Shigeaki Kuwano[*2]: Studies on Tannins. VIII.[1] Effect of Tannins and Related Compounds on Cysteine Desulfhydrase Activity of *Escherichia coli*.

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In the preceding report[2] of this series an investigation was made on the inhibitory action of tannins and related compounds towards the production of diamines by *Escherichia coli*. The present paper deals with the effect of these compounds on the enzymatic formation of hydrogen sulfide from cysteine. This investigation was primarily undertaken with the object of comparing the effects of the same series of compounds on the two different enzymes requiring the same coenzyme. It is well known that pyridoxal phosphate is the common cofactor for the enzyme systems responsible for the diamine formation (amino acid decarboxylases) and for the hydrogen sulfide liberation (cysteine desulfhydrase).

The formation of hydrogen sulfide by the action of microörganisms occurs in the large intestine and this causes some injurious effects on the host organism. Therefore, it was also hoped that such an investigation might shed some light on the mechanism of pharmacological and even medicinal action of tannins.

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1) Part VII: Yakugaku Zasshi, **78**, 327(1958).
2) K. Kimura, S. Kuwano, H. Hikino: *Ibid.*, **78**, 236(1958).