UDC 547.759.07

79. Yoshio Ban and Takeshi Oishi : The Synthesis of 3-Spiro-oxindole Derivatives. I. Syntheses of 1-Methyl-2′, 3′, 10′,10′*a*-tetrahydrospiro[indoline-3,1′(5′*H*)-pyrrolo[1,2-*b*]-isoquinoline]-2-one and its Homologs.*1

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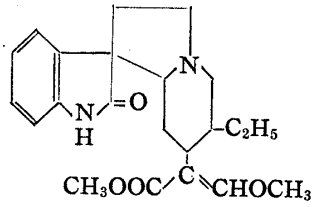
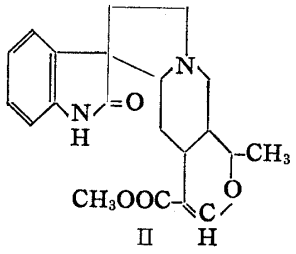
The oxindole alkaloids, such as rhynchophylline (I),[1,2] mitraphylline (II)[2,3] and uncarine (II),[2] are closely related to the true indole alkaloids on the biogenetic ground.



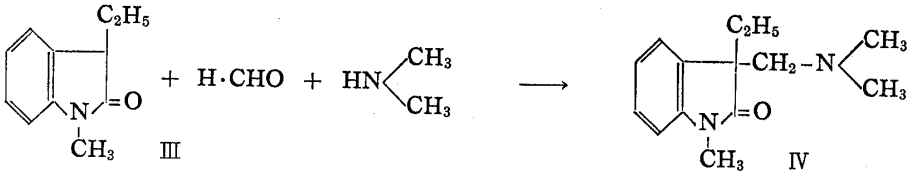
I



II

From this point of view, the oxidation-rearrangement carried out by van Tamelen[4] is of considerable interest, and it is also worth while to note Noland's suggestion[5] that in Woodward's scheme for the biogenesis of strychnine,[6] preliminary oxidation of the indole nucleus might serve to force the initial attack into the 3-position. Based upon the interest in the latter view and in attempts to imitate it in the laboratory as preliminary experiments for syntheses of the above alkaloids, 3-spiro-oxindole derivatives, XIV and XV, were synthesized by way of the intramoleclar Mannich reaction, followed by formation of so-called "berberine bridge."

Prior to the present work, Horning and Rutenberg[7] obtained the Mannich base (IV) by reacting formaline and dimethylamine with 1-methyl-3-ethyloxindole (III).



III IV

Also Harley-Mason and Ingleby[8] succeeded in condensation of benzaldehyde and 1-methyl-2-hydroxytryptamine hydrochloride (V) in the presence of sodium hydroxide to yield the product VI, which might be accepted as the intramolecular Mannich reaction.

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*1 The preliminary account of this work appeared in Chem. & Ind. (London), **1960**, 349.

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1) J.C. Seaton, L. Marion : Can. J. Chem. **35**, 1102 (1957).
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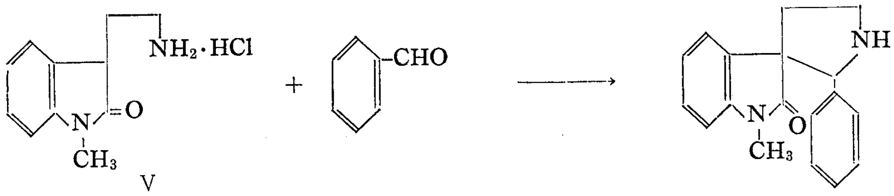
5) W.E. Noland, D.N. Robinson : Tetrahedron, **3**, 68 (1958).
6) R.B. Woodward : Nature, **162**, 155 (1948).
7) E.C. Horning, M.W. Rutenberg : J. Am. Chem. Soc., **72**, 3534 (1950).
8) J.Harley-Mason, R.F.J. Ingleby : J. Chem. Soc., 3639 (1958).



V VI

These syntheses suggested that 3-position of 3-monosubstituted oxindoles is so reactive as to be subject to this type of reaction.

Thus we attempted the extention of these methods, particularly applying the procedure of Harley-Mason to the syntheses of IX and X. A slightly alkaline solution of 1-methyl-2-hydroxytryptamine hydrochloride (V) and phenylacetaldehyde (VII)[9] was allowed to stand at room temperature for several days to afford a pale yellow oil IX in 80% yield, which was characterized as N-benzoate (m.p. 192~193°) and picrate (m.p. 220~221°). Prior to assignment of the structure (IX) to this product, two other possible structures (XVII and XVIII) had been taken into consideration and excluded by the following reasons: a) The product has an absorption of =NH (3320 cm^{-1}) in its infrared spectrum. b) When heated with 10% HCl for 1 hour, the starting material was recovered unchanged. c) It was indifferent to a solution of potassium permanganate in acetone. d) It was not oxidized with Tollens reagent.[10] e) It gave the benzoyl derivative (m.p. 192~193°) which has the absorption of >N-CO-Ph at 1625 cm^{-1}. If it had been 3-monosubstituted oxindole, on the above benzoylation reaction it would have given O-benzoyl derivative[11] (\N(H)^OCOPh) which might be expected to have the absorption at 1745 cm^{-1}.

In the case of substituting sodium phenylglycydate (XIX)[9] for phenylacetaldehyde (VII) in this reaction, the starting materials were recovered. And also an experiment using the solution of sodium acetate resulted in a lower yield of the objective compound. Thus this base (IX) was formylated to XI as a glassy substance, which without purification and characterization, was heated with phosphoric pentoxide in tetralin for cyclization: but the product was not isolated. To the solution of the crude cyclization product (to be mainly XII) in hydrochloric acid was added zinc and the mixture was heated for 1 hour. After standing, overnight the reaction mixture was treated in the usual manner to give the base XIII, colorless brilliant prisms, m.p. 180°, although in only 4% overall yield from IX.

On the other hand, Julian[12] obtained small colorless prisms, m.p. 182°, by palladium dehydrogenation of the base XV and described its structure as XVI, but later the same product was reinvestigated and revised to XIII by Belleau,[13] whose assignment was mainly based upon the facts which were: a) Dihydroisoquinoline involved in the structure XVI, is generally understood to be unstable, contrary to the stable nature of this product. b) The product does not reduce the Tollens reagent. c) Its ultraviolet absorption spectrum (Fig. 1. (3)) is similar to that of 3-alkyloxindole. d) When reduced with lithium aluminum hydride, it gave the compound which possesses the absorption spectrum being characteristic to that of indoline, and so on. These properties are in better agreement with the formula XIII rather than with XVI, and this assignment was

9) Y. Ban, T. Oishi: This Bulletin, **6**, 574 (1958).
10) K. Brunner: Monatsh. Chem., **17**, 479 (1896).
11) J.M. Bruce, F.K. Sutcliffe: J. Chem. Soc., **1957**, 4789.
12) P.L. Julian, A. Magnani, J. Pikle, W.J. Karpel: J. Am. Chem. Soc., **70**, 74 (1948); P.L. Julian, A. Magnani: *Ibid.*, **71**, 3207 (1949).
13) B. Belleau, Chem. & Ind. (London), **1955**, 229.

supported by Potts and Robinson[14] who referred to the dehydrogenation process (presumably XV→XVI→XIII) and developed the brilliant methoed of reductive cyclization for the yohimbine ring system.

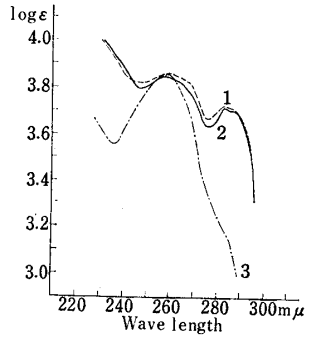


Fig. 1.
1 ---------- XIV (m.p. 179°)
2 ———— XIV (m.p. 123～124°)
3 —·—·—·— XIII

Therefore, in view of importance in confirming the structure of this product, a sample obtained by Julian's method, which was kindly supplied by Professor B. Belleau at our request, was directly compared with ours. The identity was proved by infrared spectra and mixed melting point determination, thereby conclusively establishing the structure XIII to the key intermediate in Julian's synthesis of the yohimbine ring system.[12]

Similarly, condensation of 1-methyl-2-hydroxytryptamine hydrochloride (V) with 3,4-dimethoxyphenylacetaldehyde (VIII)[9] gave the base X as a pale yellow oil which in turn, was converted by aqueous formaline and excess hydrochloric acid into the free base XIV, as small colorless prisms, m.p. 123～124°, recrystallized from hydrous ethanol. In the large scale experiments, however, carried out after the communication*1 had been published, the condensation always gave only one base, m.p. 179°, recrystallized from ethanol. The analytical data of both bases are in good agreement with the calculated value for the formula (XIV), and their ultraviolet absorption spectra are quite similar (see Fig. 1).

A slight discrepancy was observed in their infrared spectra, but it is not clear at present whether the existence of these two substances of the same composition is due to isomerism or to dimorphism. This problem will be investigated in the future.

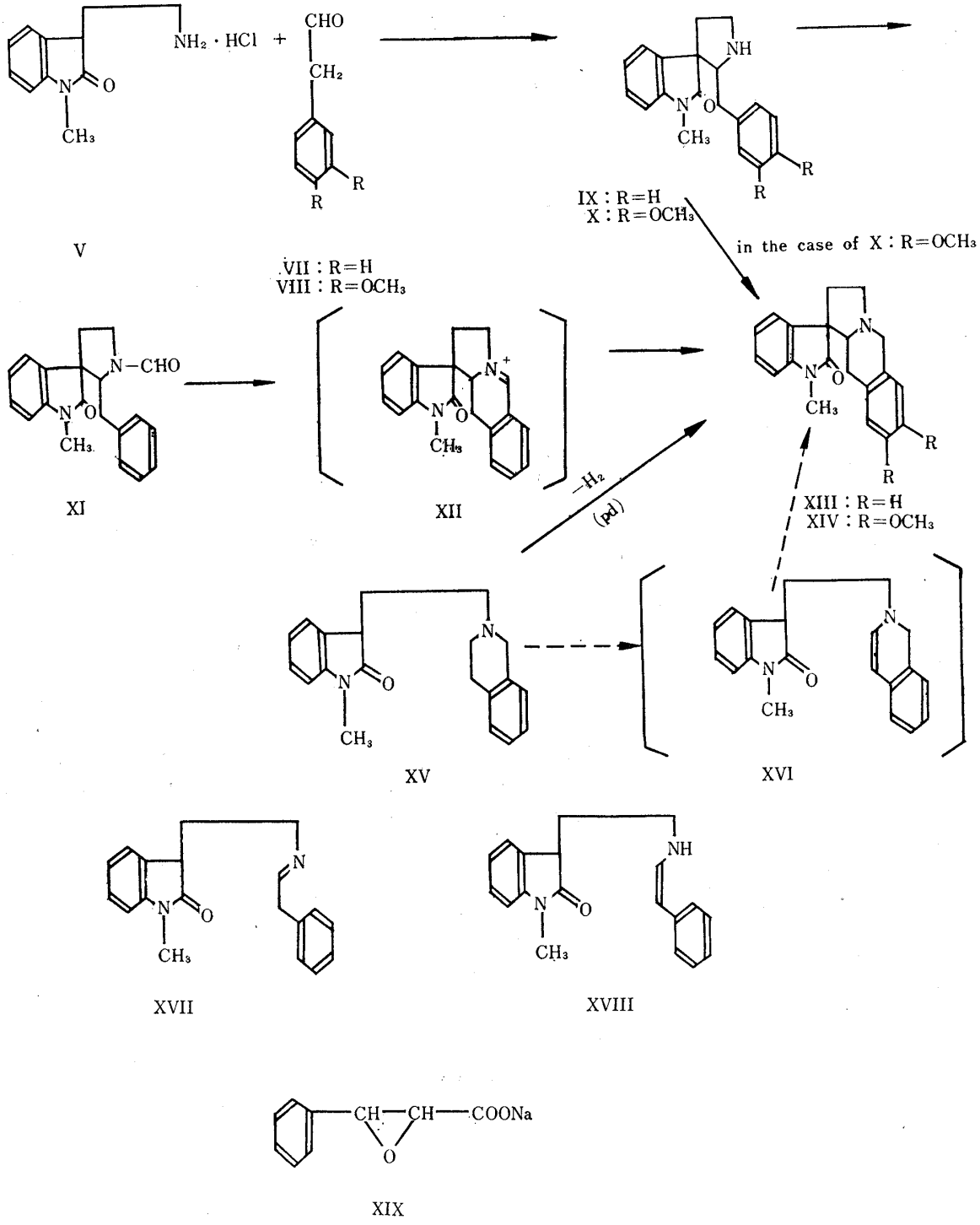
Thus, the product XIV might be a close relative of an important intermediate in Woodward's scheme for the biogenesis of strychnine.[6]

Experimental*3

1-Methyl-2′-benzylspiro[indoline-3,3′-pyrrolidine]-2-one (IX)——To a mixture of 1-methyl-2-hydroxytryptamine hydrochloride (2.5 g.), EtOH (10 cc.) and H_2O (8 cc.) was added 7.2 cc. of 2*N* NaOH; the mixture was cooled in an ice-bath and a solution of phenylacetaldehyde (1.33 g.) in EtOH (15 cc.) was added. After the whole mixture was allowed to stand at room temperature for three days, EtOH was evaporated *in vacuo* to give the aqueous suspension of oil, which was extracted with benzene. The benzene solution was extracted with 10% HCl five times (each time, 30 cc.) to take up the base in aqueous layer, which was washed with benzene, and treated with active charcoal. This solution was neutralized with K_2CO_3 under ice cooling, extracted with benzene and the benzene extract was dried over Na_2SO_4. The solvent was evaporated *in vacuo* to yield the pale yellow oil (2.52 g.). Yield, 78 %. Picrate, yellow prisms, m.p. 220～221°. *Anal.* Calcd. for $C_{25}H_{23}N_5O_8$: C, 57.58; H, 4.41; N, 13.43. Found : C, 57.42; H, H, 4.63; N, 13.45.

*3 A Koken model DS-301 spectrophotometer equipped with NaCl optics was used for the determination of infrared spectra, and samples were run as Nujol mulls or as KBr disks, unless otherwise stated. A Beckman Model DK-2 spectrophotometer was used for the determination of ultraviolet spectra. All melting points are uncorrected.

14) K. T. Potts, R. Robinson : J. Chem. Soc., **1955**, 2675.



1-Methyl-1′-benzoyl-2′-benzylspiro[indoline-3,3′-pyrrolidine]-2-one (N-Benzoylate of IX)——To a solution of the amine IX (0.5 g.) in 20 cc. of Et_2O was added 17 cc. of 5% KOH from a dropping funnel cooled by ice, to which mixture was added dropwise 1.5 g. of benzoyl chloride over a period of 30 min. under cooling by running water. Then, the whole was shaken for 30 min. and the Et_2O layer was separated. The Et_2O solution was extracted with 5% KOH to decompose the excess of benzoyl chloride, washed with water, and then with 10 % HCl to remove the unreacted base. In addition, the Et_2O solution was washed with $NaHCO_3$ solution and water, dried over Na_2SO_4, and the solvent was removed. To the residue was added benzene and then the benzene was removedafford to the pale yellow oil (0.70 g.), which was dried in a vacuum desiccator overnight. The oil solidified upon trituration with a small amount of EtOH, and the whole was kept in an ice-box for 4 hr. After filtration, the solid was recrystallized from EtOH to yield 0.53 g. (79.1 %) of white plates, m.p. 192～193°. *Anal.* Calcd. for

$C_{26}H_{24}N_2O_2$: C, 78.78; H, 6.06; N, 7.07. Found : C, 78.90; H, 6.00; N, 7.32. This was indifferent to the solution of $KMnO_4$ in Me_2CO.

1-Methyl-2′,3′,10′,10′a-tetrahydrospiro[indoline-3,1′(5′*H*)-pyrrolo[1,2-*b*]isoquinoline]-2-one (XIII)——A solution of 2.34 g. of the secondary amine IX in 0.7 cc. of formic acid, was heated for 1.5 hr. in an oil-bath kept at 200～205°. The excess formic acid and water was evaporated *in vacuo* to leave a hard glassy substance, which was dissolved in 47 cc. of tetralin under slight warming. To this solution was added 5.5 g. of P_2O_5 under ice-cooling, and the mixture was stirred and gradually heated in an oil bath. The whole was kept at 200°(bath temperature) for 10 min., when P_2O_5 became a black resin. Adding one mor eportion of 5.5 g. of P_2O_5 the mixture was kept at the same tempe rature for 10 min. more. After cooling, the whole was extracted with 100 cc. of water, separated, and the aqueous layer was extracted with Et_2O, then treated with active charcoal. After filtration, 12 g. of Zn and 40 cc. of conc. HCl were added to theforegoing aqueous solution, and the mixture was heated on a water bath for 1 hr., during which time the vigorous evolution of H_2 was observed. After standing at room temperature overnight, the solution became quite colorless. The excess Zn powder was filtered off, and washed well with hot water. To the combined filtrate was added the excess of conc. NH_4OH to separate the base, which was extracted with benzene; the benzene solution was washed with water, drie dover Na_2SO_4, and the benzene was removed to leave 0.3 g. of a yellow gum. To this residue was added Et_2O and the separated amorphous impurities were filtered off. The filtrate was concentrated, and allowed to stand in an ice-box overnight, while the white crystals deposited. This material was recrystallized from MeOH to yield 95 mg. of white prisms, m.p. 180°. Yield, 4% from IX. UV λ_{max}^{EtOH} : 254 mμ (log ε, 3.83) (see Fig. 1. (3)), IR ν_{max}^{Nujol} : 1715 cm^{-1} (=N-CO-). This compound wasi dentified with the sample obtained by Julian's method, by IR spectral comparison and mixed melting poin tdetermination.

1-Methyl-2′-(3,4-dimethoxybenzyl)spiro[indoline-3,3′pyrrolidine]-2-one (X)——This compound was readily synthesized by substituting 3,4-dimethoxyphenylacetaldehyde (VIII) for phenylacetaldehyde (VII) in the procedure descrided for synthesis of IX. Yield, 86.5%. Picrate, yellow prisms, m.p. 210～211°. *Anal.* Calcd. for $C_{27}H_{27}N_5O_{10}$: C, 55.76; H, 4.64; N, 12.04. Found : C, 55.54; H, 4.86; N, 11.84.

1-Methyl-7′,8′-dimethoxy-2′,3′,10′,10′a-tetrahydrospiro[indoline-3,1′(5′*H*)-pyrrolo[1,2-*b*]isoquinoline]-2-one (XIV)——To a solution of 0.5 g. of the foregoing secondary amine X in 2 cc. of 10% HCl, was added 1 cc. of 37% HCHO, and the whole mixture was allowed to stand for 2 bays. A part of the reaction mixture was made basic with 10% NaOH to separate white solid, which was dried in a desiccator, and dissolved in EtOH solution of HCl. On adding a small amount of Me_2CO to this solution, the white crystals deposited. After filtration, these were abbed to the above reaction mixture for stimulating separation of the product. Rubbed the wall of the vessel with a glass rod, white crystals deposited. Yield, 0.25 g. The hydrochloride was converted into the free base, which was recrystallized from aq. EtOH to afford small colorless prisms, m.p. 123～124°. *Anal.* Calcd. for $C_{22}H_{24}N_2O_3$: C, 72.52; H, 6.59; N, 7.69. Found : C, 72.14; H, 6.59; N, 7.38.

On the other hand, 2.8 cc. of 37% HCHO was added to a solution of 1.4 g. of the secondary amine X in 6 cc. of 10% HCl, and the whole was allowed to stand for 2 days, on which mixture was planted one grain of the foregoing crystalline hydrochloride to produce 1.1 g. (69.1%) of colorless prisms, m.p. 205～206°, recrystallized from EtOH. The hydrochloride was liberated to the free base XIV, which was recrystallized from EtOH to afford colorless prisms, m.p. 179°. *Anal.* Calcd. for $C_{22}H_{24}N_2O_3$: C, 72.52; H, 6.59; N, 7.69. Found : C, 72.26; H, 6.80; N, 7.79. Picrate, orange yellow prisms, m.p. 200°(decomp.). *Anal.* Calcd. for $C_{28}H_{27}N_5O_{10}$: C, 56.66; H, 4.55; N, 11.80. Found : C, 56.87; H, 4.51; N, 11.66.

The authors wish to express their deep gratitutde to Professor B. Belleau for kindly supplying a precious sample of 1-methyl-2′,3′,10′,10′a-tetrahydrospiro[indoline-3,1′(5′*H*)-pyrrolo[1,2-*b*]isoquinoline]-2-one (XIII), and to Professors S. Sugasawa and S. Yamada for their hearty encouragement throughout this work. Thanks are also due to Mr. K. Narita of the Central Analysis Room of this Institute for elemental analyses, and to the Minitstry of Education for Grant-in-Aid for Institutional Research (1960～1961) in aid of this work.

Summary

The syntheses of 1-methyl-2′,3′,10′,10′a-tetrahydrospiro[indoline-3,1′(5′*H*)-pyrrolo-[1,2-*b*]isoquinoline]-2-one (XIII) and its homologs were described. The compound XIII was identified with the dehydrogenation product of 1-methyl-2-hydroxy-3-[2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]indole (XV), which established Belleau's assignment to the key intermediate in Julian's synthesis of the yohimbine ring system.

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