Utilization of Protopine and Related Alkaloids. I.
Ring Closure of Anhydroprotopine

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When anhydroprotopine was treated with dilute hydrochloric acid, it gave the different compounds from the "Perkin's compound". Their structures were identified to contain the spiro-type skeleton by the nuclear magnetic resonance spectroscopy, and two of them (VI and VII) were assigned to be the stereoisomers by the successive reactions and also physico-chemical investigation.

We have recently described the isolation of three nematocidal alkaloids, sanguinarine, chelerythrine, and bocconine, from Bocconia cordata, whose structures contain benzo[c]-phenanthridine skeleton. These alkaloids are the minor constituents and the major ones are protopine and α-allocryptopine which are biologically inactive and contain ten membered ring system.

In the interests of utilization of these biologically inactive alkaloids, attempts to convert protopine to sanguinarine have been carried out in our laboratory.

In 1916, Perkin presented the enormous papers concerning the chemistry of cryptopine, a close relative of protopine. According to his paper, anhydrocryptopine (I) derived from cryptopine yielded two isomeric hydroxysoanhydrodihydrocryptopine (II) by treatment with dilute hydrochloric acid and the formation mechanism of II was roughly proposed without the evidences for the structure of the products as shown in Chart 1.

![Diagram](attachment:image)

On the other hand, it seems rather likely to us that the route-(a) and/or route-(b) (Chart 2) will be involved in the formation of II to yield the different ring systems from the

1) Location: Shiba-shirokane, Minato-ku, Tokyo.
"Perkin's compound". If the route-(a) is involved, a magnificent intermediate for the benzo[c]phenanthridine derivative would be expected. Accordingly, we reinvestigated the products obtaining from protopine via Perkin's procedure.

![Chemical structures](image)

Chart 2

![Chemical structures](image)

Chart 3

As shown in Chart 3, protopine (III) gives isoprotopine chloride (IV) with phosphorous chloride, which is converted to anhydroprototopine (V) by Hofmann degradation.

When V was treated with dilute hydrochloric acid, three following bases were obtained: VI, mp 209—209.5°, C_{30}H_{19}O_{6}N; VII, mp 216—217°, C_{28}H_{16}O_{6}N; VIII, mp 147—148°, C_{29}H_{17}O_{4}N. Both VI and VII show no doublet methyl signals in the nuclear magnetic resonance (NMR) spectra. This result indicates that Perkin's proposal should be surely excluded in the formation of VI and VII. The infrared (IR) spectra of VI and VII (in Nujol) show the absorption band at around 3340 cm^{-1} corresponding to –OH and the NMR spectra also show the presence of –OH at 7.60 and 7.95 τ, respectively, which disappear by the addition of deuterium oxide. As shown in Fig. 1 and 2, and Table I, VI and VII show the signals at 4.96 (t) (1H), and 4.85 (q) τ (1H), respectively, corresponding to –CH_{3}–CH–OH which shift ca. 1.1 ppm for lower field on acetylation.

Further, the fact that VI and VII are easily oxidized to the same ketone (IX) with active manganese oxide shows the presence of Ar–CH–CH_{3}– in its molecule. Also VI exhibits two OH AB-type quartets at 5.98 (d), 6.54 (d) (J=17), and 6.93 (d), 7.52 (d) τ (J=16 cps), and an
A₂X–type at 7.90 (d) and 4.96 (t) \( J = 6 \) cps, while VII exhibits two AB–type quartets at 6.08 (d), 6.51 (d) \( J = 17 \), and 6.81 (d), 7.13 (d) \( J = 16 \) cps, and an ABX–type at 7.41 (q) \( J = 14 \) and \( J = 7 \), 8.37 (q) \( J = 14 \) and \( J = 3 \) and 4.85 (q) \( J = 7 \) and 3 cps. From the NMR data mentioned above, the route–(a) is excluded in the ring formation. Both VI and VII have the same ring system via the route–(b) and are presumably the isomers of C–OH configuration of five membered ring.

As shown in Chart 4, VI and VII are dehydrated to yield VIII with concentrated hydrochloric acid, whose IR and NMR spectra show no longer –OH. The NMR spectrum of VIII exhibits two AB–type quartets at 5.90 (d), 6.32 (d) \( J = 17 \) and 6.79 (d), 7.37 (d) \( J = 15.6 \) cps, and two olefinic protons at 3.34 (d) and 3.74 \( J = 6 \) cps. The compound (VIII) catalytically absorbs one mole equivalent of hydrogen to yield X, in whose NMR spectrum two olefinic protons disappear. Consequently, VIII has the same ring system with VI and VII. The methiodide of VIII offers an orange base (XI) by Hofmann degradation, whose ultraviolet absorption (UV) spectrum shows an absorption band at \( \lambda_{\text{max}} \) 361 \( \mu \) (log \( \varepsilon = 4.6 \)) corresponding to 1–benzylideneindenes.⁵ This result exclusively provides the evidence for the structure of VIII. Judging from the facts that VI and VII are the major products and

VIII is the minor (see experimental), and that VIII is not hydrated with dilute hydrochloric acid to yield VI and VII. VIII is presumably formed through VI and VII during the reaction.

Configuration of C₃'-OH of VI and VII:
On comparison with the NMR spectra of VI and VII, N-methyl of VI appears at lower field than that of VII, and C₄-H₂ and C₃'-H of VI appear at upper field than those of VII. From the dipole contribution and the magnetic anisotropy of C-OH and C=N, C₃'-OH probably orientates cis to C₄'-N in VI and trans in VII. The fact that the IR spectrum of VI exhibits the absorption band at 3600 cm⁻¹, which is invariable with the change of concentration (in CCl₄) to show the presence of intramolecular hydrogen bond (Fig. 3), also supports the above deduction.

The assignment of C₄'-H₂ is slightly complicated. Rosen, et al.⁶ successfully identified the configuration of substituted indanes by means of the measurement of the vicinal coupling constants. That is, the application of the principle of the Karplus equation for the dihedral

angles involved generally provides $J_{\text{cis}} > J_{\text{trans}}$ in the ethane fragment of cyclopentene. Due to this generalization, one proton of VII appearing at 8.37 ($J_{\text{vicinal}} = 3$) corresponds to Hb and another at 7.41 $\tau$ ($J_{\text{vicinal}} = 7$ cps) corresponds to Hα (Chart 5).

This assignment reveals that $C_3'$-OH shields $C_2'$-Hα ($\text{cis}$ to OH) and conversely, $C_1'$-N deshields $C_2'$-Hα ($\text{cis}$ to N). On the other hand, two protons of VI overlap at 7.90 $\tau$. It is reasonably deduced that in VI the contradiction of the paramagnetic anisotropy of $C_1'$-N for Hα by the diamagnetic anisotropy of $C_3'$-OH, and the release of the diamagnetic anisotropy of $C_3'$-OH from Hα result in making Hα and Hβ magnetically nearly equivalent. This deduction is actually supported by the triplet of $C_4''$-H in VI.

Unfortunately, we could not find out the compound which was formed via the six-membered ring formation. However, it seems to be still remained the adequate choice of the condensation reagents for us to study further.

**Experimental**

Melting points were determined on a micro hot-stage and were uncorrected. Ultraviolet spectra were measured with a Hitachi EPS-2U and infrared spectra with a Jasco Model IR-S. Intramolecular hydrogen bond was measured with a Perkin-Elmer 221 spectrophotometer. Nuclear magnetic resonance spectra were measured in CDC13 with a Hitachi Perkin-Elmer (H-60) at 60 MHz, and a Varian Associates (HA-100) recording spectrometer at 100 MHz. Chemical shifts are given in $\tau$ values, using tetramethylsilane as internal reference.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1'-3'-hydroxy-5',6'-methylenedioxyindane (VI) and (VII) — A mixture of anhydroyprotopine (V)7 (8.0 g) and 10% HCl (80 ml) was heated for 20 min on a boiling water bath. The crystals began to separate from the clear solution 5 min later. After cooling, the solid was collected and made alkaline with ammonia to extract with AcOEt. The solid residue was washed with ether to afford the mixture of VI and VII (5.6 g)8 which were sparingly soluble in ether and the ether solution contained VIII as the major product. A mixture of VI and VII (1.0 g) was dissolved in AcOEt (30 ml) and passed through silica gel column (100 g), followed by elution with benzene-AcOEt (1:1). The first fraction afforded VI (111 mg) which was recrystallized from AcOEt-ether to give colorless prisms, mp 209—209.5 $^\circ$. TLC<sup>9</sup>: Rf 0.53. Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>NO<sub>4</sub>: C, 67.97; H, 5.42; N, 3.96. Found: C, 68.03; H, 5.36; N, 4.16.

The second afforded a mixture of VI and VII (593 mg). The third afforded VII (304 mg) which was recrystallized from AcOEt-ether to give colorless prisms, mp 216—217 $^\circ$. TLC: Rf 0.36. Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>NO<sub>4</sub>: C, 67.97; H, 5.42; N, 3.96. Found: C, 67.60; H, 5.48; N, 4.20.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1'-5',6'-methylenedioxyindane (VIII) — a) The above mentioned ether solution gave a solid residue (ca. 1.5 g). By the chromatography separation over Al<sub>2</sub>O<sub>3</sub> (80 g) using benzene as eluent VIII was obtained from the first fraction, which was recrystallized from n-hexane-benzene to yield colorless rosettes, mp 147—148 $^\circ$. TLC: Rf 0.95. Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>NO<sub>4</sub>: C, 71.62; H, 5.11; N, 4.17. Found: C, 71.65; H, 5.11; N, 4.20.

Methodide: Yellow granules, mp 230 $^\circ$. Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>NO<sub>4</sub>: C, 52.83; H, 4.22; N, 2.93. Found: C, 52.66; H, 4.55; N, 2.73. HCl-salt: Colorless granules, mp 260—262 $^\circ$. Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>NO<sub>4</sub>•HCl•1/2H<sub>2</sub>O: C, 63.83; H, 4.95; N, 3.72. Found: C, 63.99; H, 4.79; N, 3.61.

b) A mixture of the equivalent amounts of VI and VII (109 mg) was added to a solution of conc. HCl (1 ml) and DMSO (4 ml) and the solution was heated for 1 hr on a boiling water bath. After cooling, the reaction mixture was made alkaline with ammonia to extract with benzene. The solid residue was chromatographed on Al<sub>2</sub>O<sub>3</sub> (12 g) using benzene as eluent to afford colorless rosettes (51 mg), mp 145—146 $^\circ$, from the first fraction which was identified with VIII through the melting point on admixture. The second fraction, which was successively eluted with AcOEt, gave the unreacted starting material (52 mg), and the TLC of this fraction showed the presence of almost all amounts of VI and VII.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1'-5',6'-methylenedioxyindane-3-one (IX) — To the solution of a mixture of the equivalent amounts of VI and VII (100 mg) in benzene (30 ml) was added MnO<sub>2</sub> (350 mg) and the solution was stirred at 70—80 $^\circ$ for several hours until the starting materials completely disappeared on TLC.

After cooling, the reaction mixture was filtered and evaporated under reduced pressure. The residue was passed through silica gel column (10 g) and the benzene-CH<sub>2</sub>Cl<sub>2</sub> (2:1)
fraction gave colorless prisms (70 mg), mp 253—255°, after recrystallization from n-hexane—AcOEt. IR ν^\text{max}_{\text{cm}^{-1}} 1694 (\text{C=O}). \textit{Anal.} Calcd. for C_{26}H_{27}O_{3}N: C, 68.37; H, 4.84; N, 3.98. Found: C, 68.48; H, 4.80; N, 3.76.

\textbf{N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1'-5',6'-methylenedioxyindane (X)—}

The hydrochloride of VIII (196 mg) was hydrogenated over previously reduced PtO_{2} (100 mg) in MeOH (30 ml) to absorb one mole equivalent of hydrogen within 20 min. The filtered solution was evaporated \textit{in vacuo}, and the residue was made alkaline with ammonia to extract with AcOEt. The residue, in which no starting material was contained on TLC, was passed through silica gel column (18 g) and eluted with benzene to yield colorless prisms (63 mg), mp 138—139°, after recrystallization from n-hexane—ether. \textit{Anal.} Calcd. for C_{26}H_{27}O_{3}N: C, 71.21; H, 5.63; N, 4.17. Found: C, 71.41; H, 5.44; N, 4.20.

\textbf{1-(2'-Dimethylaminomethyl-3',4'-methylenedioxybenzylidene)-5,6-methylenedioxyindene (XI)—A mixture of the methiodide of VIII (400 mg) and 25% KOH—MeOH (4 ml) was refluxed for 1 hr on water bath. The reaction mixture was evaporated \textit{in vacuo} and then water was added. The precipitate was extracted with ether. The residue (225 mg) was recrystallized from n-hexane to afford orange prisms (XI) (160 mg), mp 130°. UV λ^{\text{max}}_{\text{nm}} \mu (\log e): 259 (4.4), 268 (4.5), 308 (4.5), 361 (4.6). \textit{Anal.} Calcd. for C_{37}H_{26}O_{3}N: C, 72.20; H, 5.48; N, 4.00. Found: C, 72.33; H, 5.32; N, 3.75.}

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