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Studies on 1-Azabicyclo Compounds. XXVIII.[1] Synthesis of 1-Methyl-perhydroazocin-5-one from Pyrrolizidine

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Heating of pyrrolizidine N-oxide (V) with an aqueous solution of tartaric acid containing ferric nitrate gave $\Delta^{1(8)}$-dehydropyrrolizidine (VI), which, on treatment with water in the presence of methyl iodide, gave 1-methyl-perhydroazocin-5-one (IX).

Keywords——dehydropyrrolizidine; 1-methyl-perhydroazocin-5-one; enamine synthesis; ferric nitrate–tartaric acid; one step reaction; biogenetic mechanism; transannular interaction; IR

Although the protoberberine alkaloids have been shown to be the biogenetic precursor of the protopine alkaloids,[3] their biogenetic reactions are not fully clarified. On the basis of the fact that ten-membered ring amino ketone (III) was obtained by the reaction of $\Delta^{1(9a)}$-dehydroquinolizidine (II) derived from quinolizidine (I) with a combination of water and methyl iodide,[4] the biogenetic route of the formation of the protopine alkaloids from protoberberine alkaloids was inferred.

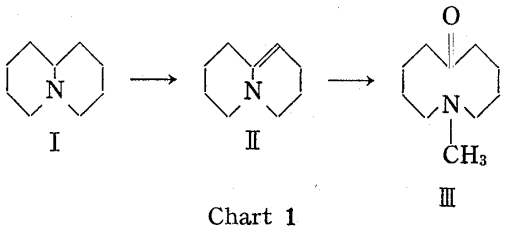

Chart 1

The senecio alkaloids, on the other hand, can conveniently be divided into pyrrolizidine- and otonecine[eight-membered ring amino ketone (IX) type]-group, the latter of which would be biogenetically derived from the former *via* the enamine. This paper describes the synthetic method which allow the formation of eight-membered ring amino ketone (IX) from pyrrolizidine (IV) *via* the enamine (VI).

It is well known that $\Delta^{1(9a)}$-dehydroquinolizidine (II) was obtained by oxidation of quinolizidine (I) with mercuric acetate in diluted acetic acid[5] or with N-bromosuccimide in aqueous dioxane.[6] Attempts to obtain $\Delta^{1(8)}$-dehydropyrrolizidine (VI) by oxidation of IV with the similar reagents were unsuccessfully carried out recovering only the starting materials. Treatment of IV with hydrogen peroxide gave the N-oxide (V) [picrate: mp 213—215° (dec.)], which, on warming in an aqueous solution of tartaric acid containing ferric nitrate, afforded the expected dehydropyrrolizidine (VI) in 20% yield. The perchlorate (VII), mp 208—210° (dec.), derived from VI was treated with potassium cyanide to yield 8-cyanopyrrolizidine (VIII) [infrared (IR) ν_{max}: 2200 cm^{-1}], which, on neutralization with perchloric acid followed by the recrystallization, reverted to VII. The infrared spectrum of VI showed a band at 1660 cm^{-1} owing to an enamine, while that of VII showed a band at 1700 cm^{-1} due to an iminium.

1) Part XXVII: Y. Arata, S. Yasuda, K. Tokuno, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), **24**, 1879 (1976).
2) Location: *3-Ho, Kanagawa-machi, Kanazawa 920-11, Japan.*
3) A.R. Battersby and J. Southgate, *J. Chem. Soc., Perkin I*, **1975**, 1147.
4) Y. Arata and Y. Oda, *Chem. Pharm. Bull.* (Tokyo), **21**, 752 (1973).
5) N.J. Leonard and D.F. Morrow, *J. Am. Chem. Soc.*, **80**, 371 (1957).
6) Y. Arata, T. Shioda, J. Yamada, and Y. Hayashi, *Yakugaku Zasshi*, **89**, 389 (1969).

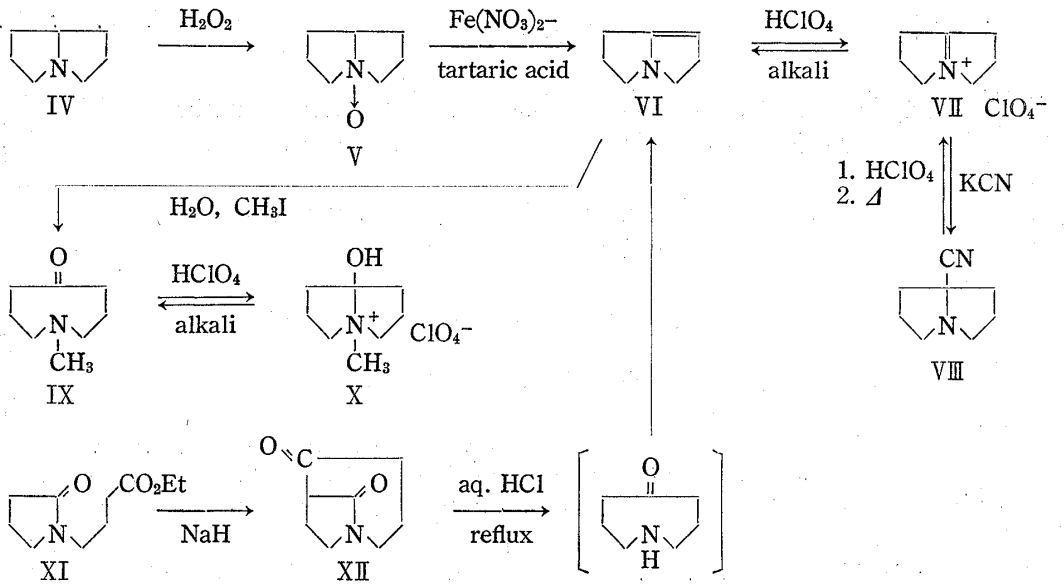

Chart 2

Alternatively, $\Delta^{1(8)}$-dehydropyrrolizidine (VI) was synthesized by acid-hydrolysis of the β-ketopyrrolidone (XII) [mass spectrum (MS) *m/e*: 153 (M^+)] obtained by the Dieckmann condensation of pyrrolidone N-butyric acid ester (XI). The compound VI derived from V was proved to be completely identical with the authentic specimen (VI) [perchlorate: mp 208—210° (dec.)] by infrared spectral comparison. Thus, the structure of VI was now confirmed to be correct.

Hereupon, the reaction of VI with methyl iodide in aqueous tetrahydrofuran was carried out in an ice chest under nitrogen atmosphere to give the expected amino ketone (IX)[7] in 22% yield. The infrared spectrum of IX indicated a band at 1660 cm^{-1} owing to a carbonyl band which was under transannular interaction[7] between N and $C_{C=O}$, while that of its perchlorate (X) indicated a band at 3250 cm^{-1} attributable to a hydroxyl group in transannular quaternary form, R–$\overset{|}{\underset{|}{N}}^+$–$\overset{|}{\underset{|}{C}}$–OH, but not a carbonyl band. A mechanism for the reaction of VI with methyl iodide producing IX might be postulated as follows: the enamine (VI) was precedently condensed with water throught the formation of the iminium type intermediate and the resulting product (XIII) further reacted with methyl iodide to afford 8-hydroxy-4-methyl-octahydropyrrolizidinium iodide (X′), which, on neutralization with alkali, yielded IX (Chart 3).

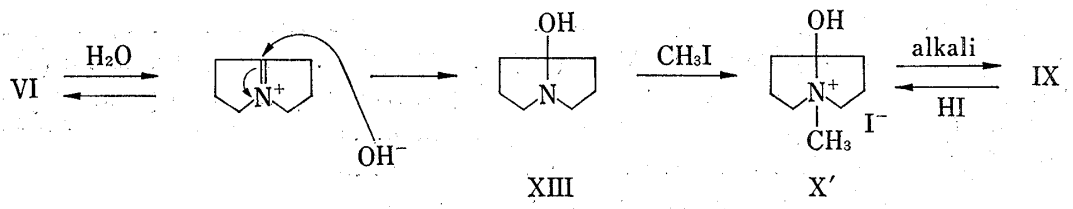

Chart 3

On the viewpoint of above experiment, it would be assumed that otonecine alkaloids are biogenetically derived from the pyrrolizidine alkaloids through their enamine derivatives producing along the pressumed route mentioned above, in which formaldehyde participates in place of methyl iodide.

7) N.J. Leonard, M. Ōki, and S. Chiavarelli, *J. Am. Chem. Soc.*, 77, 6234 (1955).

Experimental[8]

Pyrrolizidine-4-oxide (V)——To a solution of pyrrolizidine[9] (IV) (1.50 g, 16 mmol) in acetone (30 ml) was added a solution of 30% H_2O_2 (5 ml) in acetone (2 ml) under cooling. The reaction solution was kept standing in an ice chest for 5 days and then evaporated *in vacuo*. To the residue was added H_2O and the solution was washed with ether. The aqueous layer was evaporated *in vacuo* to dryness to give V (1.00 g, 61%) as hygroscopic scales. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 950 (N-oxide).

Picrate: Recrystallization from EtOH gave yellow needles, mp 213—215° (dec.). *Anal.* Calcd. for $C_{13}H_{16}NO_8$: C, 43.82; H, 4.52; N, 15.72. Found: C, 43.75; H, 4.51; N, 15.94.

$\Delta^{1(8)}$-Dehydropyrrolizidine (VI)——i) From N-Oxide (V): To a solution of a combination of ferric nitrate (4.0 g) and tartaric acid (10.0 g) in H_2O (30 ml) was added a solution of V (1.00 g, 8 mmol) in H_2O (5 ml) and the solution was heated at 80° for 2.5 hr with stirring in a stream of N_2 gas. Then, the solution was made alkaline with aq. NaOH and extracted with ether. The ether layer was dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled in a stream of N_2 gas to give a yellowish oil (VI) (0.17 g, 20%) which was unstable and turned reddish brown on standing, bp 85—90° (bath temp.)/22 mmHg. IR ν_{max}^{film} cm^{-1}: 1660 (enamine). The IR spectrum well matched that of the authentic sample derived from XII described below.

The Perchlorate (VII) of the Oil: Colorless scales, mp 208—210° (dec.) (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1700 (iminium). This sample was identical (by mixed melting-point test and IR spectrum) with the authentic specimen (VII) described below.

ii) From β-Ketopyrrolidone (XII): A solution of XII (2.50 g, 16 mmol) in 10% HCl (50 ml) was heated under reflux for 8 hr and then evaporated *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with ether. The ethereal phase was dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled in a stream of N_2 gas to give VI (0.67 g, 38%) as a pale yellow liquid, bp 85—90° (bath temp.)/22 mmHg. VI was unstable and turned reddish brown on standing. IR ν_{max}^{film} cm^{-1}: 1660 (enamine).

Perchlorate (VII): Recrystallization from EtOH gave colorless scales, mp 208—210° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1700 (iminium). *Anal.* Calcd. for $C_7H_{12}ClNO_4$: C, 40.10; H, 5.78; N, 6.68. Found: C, 40.34; H, 5.73; N, 6.70.

1-Azabicyclo[4.2.1]nonan-5,9-dione (XII)——To a suspension of NaH (50% in a mineral oil, 1.0 g) in anhyd. xylene (250 ml) was added dropwise a solution of XI (5.30 g, 27 mmol) in anhyd. xylene (50 ml) with stirring and the reaction mixture was refluxed for 8 hr. The excess hydride was decomposed with EtOH. To this was added H_2O and shaken. The aqueous layer separated was acidified with conc. HCl under cooling and then, the resultant solution was extracted with ether. The ether layer was washed with H_2O and dried over anhyd. Na_2SO_4, and evaporated leaving a colorless oil (XII) (1.20 g, 30%), bp 147—150°/2 mmHg. MS *m/e*: 153 (M^+). The ethanol solution of XII showed blue-violet with aq. $FeCl_3$.

8-Cyanopyrrolizidine (VIII)——To a solution of VII (0.50 g, 2 mmol) in water (10 ml) was added dropwise a solution of 5% KCN (4 ml) with stirring and the stirring was continued for 3 hr. Then, the solution was shaken with ether and the ether layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled in a stream of N_2 gas to give VIII (0.30 g, 92%) as a colorless oil, bp 145—150° (bath temp.)/19 mmHg. IR ν_{max}^{film} cm^{-1}: 2200 (C≡N).

Neutralization of VIII with 70% $HClO_4$ under cooling gave the perchlorate (VII) of VI, colorless scales of mp 208.5—210° (dec.) after recrystallization from EtOH. IR ν_{max}^{Nujol} cm^{-1}: 1700 (iminium). The IR spectrum of the perchlorate obtained here was completely coincident with that of authentic sample (VII).

1-Methyl-perhydroazocin-5-one (IX)——To a solution of VI (0.50 g, 3 mmol) in 70% aq. tetrahydrofuran (10 ml) was added methyl iodide (1 ml). The reaction solution was kept standing in an ice chest under nitrogen atmosphere for 4 days and then evaporated *in vacuo* to dryness. The residue was made alkaline with aq. NaOH and extracted with ether. The ethereal phase was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled in a stream of N_2 gas to give IX[7] (0.13 g, 20%) as a colorless liquid, bp 115—120° (bath temp.)/17 mmHg. IR ν_{max}^{film} cm^{-1}: 2800 (N–CH_3), 1660 (C=O).

Perchlorate (X): Recrystallization from EtOH–ether (1:1 v/v) gave colorless needles, mp 259—260° (dec.) (lit.[7] mp 260—261°). IR ν_{max}^{Nujol} cm^{-1}: 3250 (OH). *Anal.* Calcd. for $C_8H_{16}ClNO_5$: C, 39.75; H, 6.67; N, 5.79. Found: C, 39.82; H, 6.70; N, 5.80.

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8) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrophotometer. Mass spectrum was measured on a JEOL JMS D-100 spectrometer.

9) R. Adams, S. Miyano, and D. Fles, *J. Am. Chem. Soc.*, **82**, 1466 (1959).