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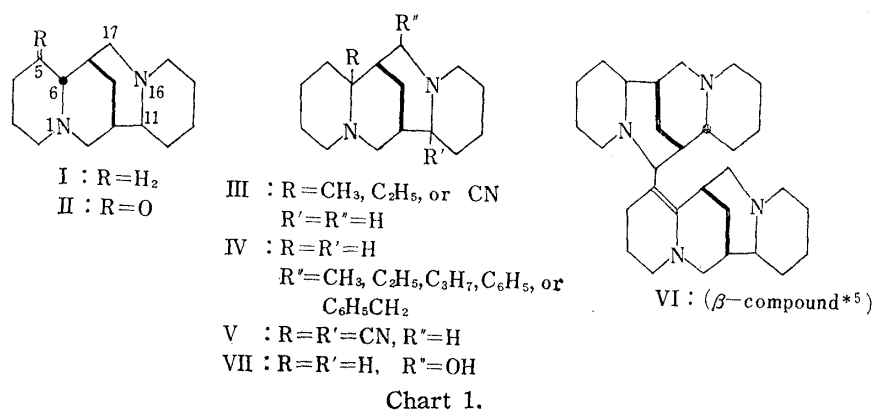
23. Kazuro Sugimoto,*¹ Nori Sunakawa,*¹ and Sadao Ohki*² :
Nitrogen-containing Heterocyclic Compounds derived
from Sparteine.*³ I. Synthesis of 5-Oxosparteine.

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Sparteine (I) is the alkaloid of *Cytisus scoparius* and *Lupinus luteus*, isolated by Stenhouse¹⁾ during the 18th Century. Its structure was determined by Clemo and his co-workers,²⁾ and the alkaloid was synthesized by Clemo and others,³⁾ Leonard and Beyler,⁴⁾ Galinovsky and Kainz,⁵⁾ and by Šorm and Keil.⁶⁾ By the determination of its steric structure⁴⁾ and absolute configuration,⁷⁾ chemical problems connected with sparteine seem to have been settled.

The present series of this work was investigated in order to derive natural sparteine to other lupin series alkaloids and other substances having pharmacological activity.

Sparteine (I) is comparatively easily isolated from the foregoing plants and a considerable quantity of I is used as the uterus contracting agent*⁴ so that it is one of the alkaloids that is easily available. Utilization of I as a starting material for synthesis includes (a) preparation of derivatives having the C₁₅-ring structure present in I, and (b) conversion of the ring structure of I to form other kinds of nitrogen-containing heterocyclic compounds. The preceding paper of this series*³ had shown that the uterus-contracting activity of I is mainly due to its fundamental structure of quinolizidine ring. Consequently, derivatives of (a) and (b) types still retaining one quinolizidine ring would be expected to have sparteine-like uterus contracting activity. If a nitrogen-containing heterocyclic compounds with a new skeleton can be obtained by the (b) method, different kind of pharmacological action may be expected.



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*³ This constitutes Part XIV of a series entitled "Synthesis of Quinolizine Derivatives" by Sadao Ohki. Part XIII : This Bulletin, 10, 1250 (1962).

*⁴ Included in Japanese Pharmacopoeiae Ed. VII.

1) J. Stenhouse : Ann., 78, 1 (1851).

2) G.R. Clemo, W. McG. Morgan, R. Raper : J. Chem. Soc., 1936, 1025.

3) G.R. Clemo, R. Raper, W.S. Short : Ibid., 1949, 663.

4) N.J. Leonard, R.E. Beyler : J. Am. Chem. Soc., 72, 1316 (1950).

5) F. Galinovsky, G. Kainz : Monatsh., 80, 112 (1949).

6) F. Šorm, B. Keil : Collection Czechoslov. Chem. Commun., 13, 544 (1948).

7) S. Okuda, K. Tsuda, H. Kataoka : Chem. Ind. (London), 1961, 1115; This Bulletin, 13, 491 (1965).

In the present work, 5-oxosparteine (II) was synthesized and there is a possibility that II may prove to be a good starting material for the synthesis of a variety of sparteine derivatives.

Compounds derived directly from I are not many, among which may be cited the 6-substituted compound⁸⁾ (III), 17-substituted compound⁹⁾ (IV), 6,11-disubstituted compound⁸⁾ (V), and the 5-substituted compound, α - or β -diplospartyrine¹⁰⁾ (VI).

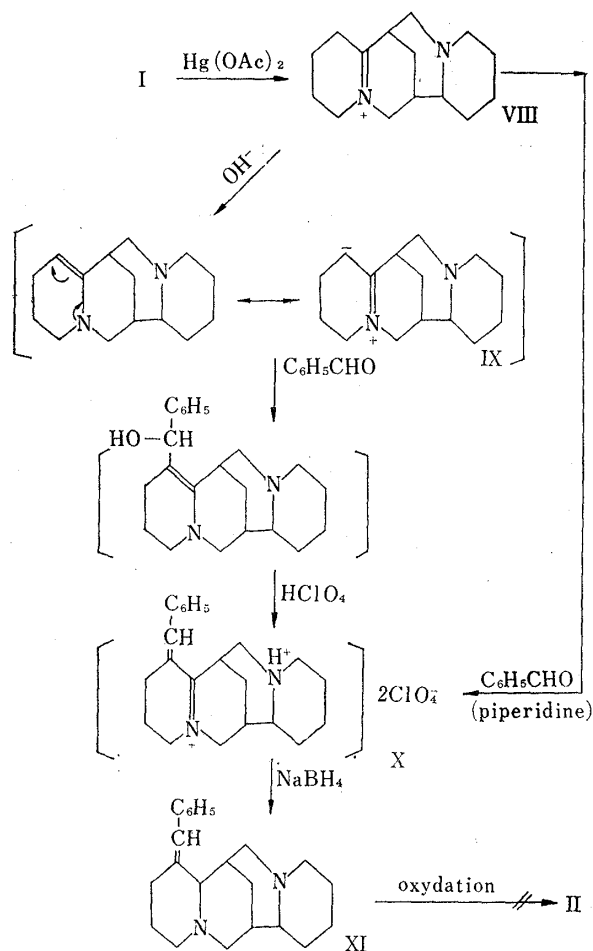


Chart 2.

These derivatives were synthesized from the oxidation products of I such as 17-oxosparteine, 17-hydroxysparteine (VII), $\Delta^{1(6)}$ -dehydrosparteinium ion (VIII), and $\Delta^{1(6),11(16)}$ -didehydrosparteinium diion.

Oxidation of sparteine with mercuric acetate results in the attack on the *trans*-quinolizidine ring to form VIII and its treatment with alkali gives Δ^5 -dehydrosparteine (K).^{8,11)} Since K takes the cyclic enamine form, its 5-position is expected to be active to electrophilic reagents. In recent years, Birkofer and others¹²⁾ obtained 2-benzylidenecyclopentanone in 84% yield by the reaction of benzaldehyde with the enamine, N-(Δ^1 -cyclopentyl)-morpholine. Based on this report, reaction of K with benzaldehyde was attempted. A mixture of these two compounds in benzene was refluxed for 4 hours and the product was purified as the diperchlorate (X) of m.p. 267~270°, UV $\lambda_{\text{max}}^{\text{EtOH}}$: 321.2 m μ (log ϵ 4.32). The ultra-violet absorption proved the presence of $\text{C}_6\text{H}_5\text{CH}=\text{C}-\text{C}=\text{N}^+$ by substitution with the benzylidene group.

The yield of X from this reaction was only 13% and, therefore, examinations were made on some other reaction conditions. Some time ago, Schöpf and others^{13,14)} reported the formation of VI by the condensation of VII and VIII at pH 8, during structural elucidation of VI. It is considered that, in this reaction, the 5-position of VIII, adjacent to immonium ion, had become an active methylene and underwent aldol-type condensation with VII. These workers had also obtained 1-methyl-3-benzylidene-1-piperidenium salt by the condensation of N-methyl-1-piperidenium salt and benzaldehyde at pH 7.¹⁵⁾ From these evidences, the diperchlorate of VIII and benzaldehyde,

*5 The α and β compounds are stereoisomers.

- 8) N. J. Leonard, P. D. Thomas, V. W. Gash: J. Am. Chem. Soc., **77**, 1552 (1955).
- 9) M. Rink, K. Grabowski: Naturwissenschaften, **42**, 460 (1955).
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- 12) L. Birkofer, S. M. Kim, H. D. Engels: Chem. Ber., **95**, 1495 (1962).
- 13) C. Schöpf, K. Keller: Naturwissenschaften, **43**, 325 (1956).
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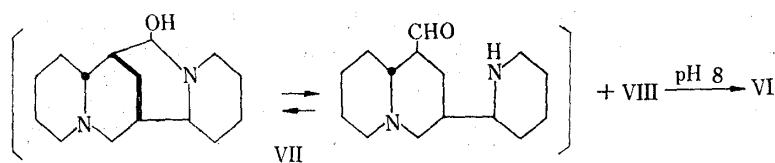


Chart 3.

in the presence of a small amount of piperidine, were warmed on a water bath to effect similar condensation, and X was obtained in 73% yield.

Oxidation of X to 5-oxo- $\Delta^{1(6)}$ -dehydrosparteinium salt did not materialize. Therefore, X was reduced with sodium borohydride to 5-benzylidenesparteine (XI) and fission of benzylidene was attempted with various oxidation agents such as ozone, permanganate, and chromic acid but the objective II was not obtained, either recovering the starting material or forming dehydrosparteinium ion (X). Formation of X by ozonolysis was totally unexpected.

Having failed to obtain II by the foregoing route, the following process was tried.

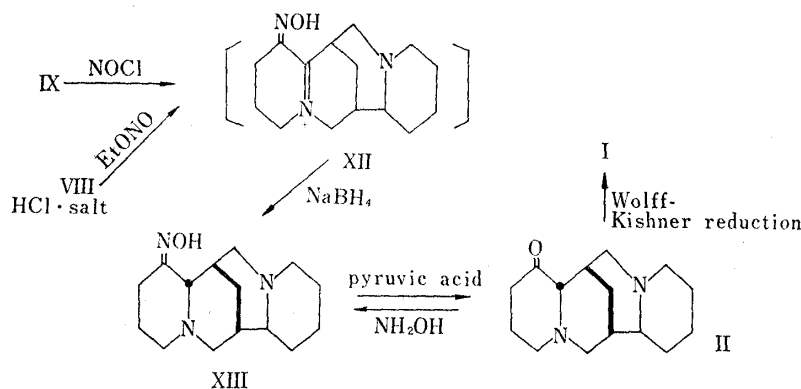


Chart 4.

The reaction of nitrosyl chloride with the enamine (X) gave 5-hydroximinosparteinium chloride (XII), UV $\lambda_{\text{max}}^{\text{EtOH}}$: 260.5 μ ($\log \epsilon$ 5.13), which was reduced, without isolation, with sodium borohydride to 5-hydroximinosparteine (XIII) in 14.3% yield calculated from X. XIII was also obtained on warming the dichloride of VIII and ethyl nitrite in ethanol solution at 45~55° and reduction of the product with sodium borohydride. This reaction utilizes the reactivity of the methylene at 5-position and its yield of 61% is better than that from the former method. XIII melts at 175~178°.

Hydrolysis of XIII with 20% sulfuric acid gave the objective II but a better yield of 75.5% was obtained by warming with pyruvic acid. II exhibited absorptions in the infrared region at 1701 ($\nu_{\text{C=O}}$), 2817, and 2717 cm^{-1} (*trans*-quinolizidine). Its unity was confirmed through gas and thin-layer chromatography. The perchlorate of II came as colorless plates of m.p. 204~208°. II reverted to XIII on reaction with hydroxylamine. Wolff-Kishner reduction of II gave sparteine. This fact proves that the configuration of II is the same as that of sparteine.

The successful formation of II in a comparatively good yield indicated that a substituent can be introduced into the 1-position of the quinolizidine ring by the enamine reaction of the dehydroquinolizidine-type compounds and the reaction of dehydroquinolizinium ions with active methylene.

Experimental

5-Benzylidene- $\Delta^{1(6)}$ -dehydrosparteinium Diperchlorate (X)—a) Method: A mixture of 1.0 g. of Δ^5 -dehydrosparteine¹¹⁾ (K), 4 g. of benzaldehyde, and 20 ml. of benzene was refluxed for 4 hr. After

cool, the reaction mixture was extracted with 10% HCl, the acid extract was evaporated to dryness under a reduced pressure, and the residual oil was dissolved in a small quantity of H_2O . This solution was basified with 10% NaOH and extracted three times with CHCl_3 . To the separated CHCl_3 layer, 60% HClO_4 was added and CHCl_3 was evaporated under a reduced pressure. The solidified residue was recrystallized from 60% EtOH to 300 mg. (13%) of colorless needles, m.p. $267\sim 270^\circ$. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{30}\text{O}_5\text{N}_2\text{Cl}_2$: C, 50.71; H, 5.80; N, 5.38. Found: C, 51.27; H, 6.41; N, 5.85. UV $\lambda_{\text{max}}^{\text{EtOH}}$: $321.2 \text{ m}\mu$ ($\log \epsilon 4.32$).

b) Method: A mixture of 4.0 g. of $\Delta^1(6)$ -dehydrosparteinium diperchlorate¹¹⁾ (VIII), 4 ml. H_2O , 4 g. BzH, and 4 drops of piperidine was heated on a water bath at $80\sim 90^\circ$ for 3 hr. When cooled, unreacted BzH was removed by extraction with ether, and the residue was allowed to stand. The crystallized residue was recrystallized from 60% EtOH to colorless needles of m.p. $267\sim 270^\circ$, undepressed on admixture with the crystals obtained from method (a).

5-Benzylidenesparteine Perchlorate (XI)—A mixture of 2.0 g. of X, 50 ml. H_2O , 6 ml. of 10% NaOH, and 20 ml. of CHCl_3 was stirred at room temperature, 0.5 g. of NaBH_4 was added in small portions, and the mixture was stirred for 1 hr. After allowing this reaction mixture to stand overnight at room temperature, the CHCl_3 layer was separated, the residual solution was extracted twice with CHCl_3 , and the combined CHCl_3 extract was evaporated under a reduced pressure. The residual oil was dissolved in EtOH and addition of 60% HClO_4 produced crystals which were recrystallized from 60% EtOH to 1.5 g. (94%) of colorless crystals, m.p. $185\sim 190^\circ$. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{31}\text{O}_4\text{N}_4\text{Cl}$: C, 62.46; H, 7.39; N, 6.62. Found: C, 62.44; H, 7.22; N, 6.95. UV $\lambda_{\text{max}}^{\text{EtOH}}$: $242.3 \text{ m}\mu$ ($\log \epsilon 4.08$).

Attempted Oxidative Cleavage of XI—a) A mixture of 300 mg. of XI, 30 ml. of MeOH, and 15 ml. of $\text{C}_2\text{H}_4\text{Cl}_2$ was chilled with dry ice and about 4 times the theoretical amount of O_3 was passed through this solution. After addition of $(\text{C}_2\text{H}_5\text{O})_3\text{P}$, the mixture was allowed to stand for 5 min.¹⁰⁾ and further overnight at room temperature. The solvent was evaporated under a reduced pressure and the residual oil crystallized on addition of ether and 60% HClO_4 . Its melting point of $267\sim 270^\circ$ showed no depression on admixture with X and its UV spectrum also agreed with that of X.

b) Ozone oxidation was carried out as above using the free base of XI and the starting material was recovered.

c) A solution of 0.8 g. of CrO_3 dissolved in 20 ml. of H_2O was added to 2.0 g. of XI in 10 ml. of AcOH and the mixture was warmed on a water bath for 3 min. AcOH was evaporated under a reduced pressure, the residual oil was basified with 10% NaOH, and extracted with three portions of CHCl_3 . After dehydration, CHCl_3 was evaporated under a reduced pressure, the oily residue was dissolved in a small quantity of EtOH and addition of 60% HClO_4 effected crystallization. The product, m.p. $267\sim 270^\circ$, showed no depression of melting point on admixture with X.

5-Hydroximinosparteine (XIII)—a) A suspension of 8 g. of the diperchlorate of VIII in a small amount of water was basified with 20% KOH and extracted with three portions of ether. The combined ether extract, after addition of 6 ml. of conc. HCl, was evaporated on a water bath and the oily residue was dissolved in 60 ml. of EtOH. The solution was warmed to $45\sim 55^\circ$ and excess of $\text{C}_2\text{H}_5\text{ONO}$ was passed through the solution with stirring. EtOH was evaporated under a reduced pressure, the oily residue was basified with 10% NaOH, and CHCl_3 was added. The mixture was stirred at room temperature, 3.0 g. of NaBH_4 was added with stirring, and the mixture was stirred for further 4 hr. The CHCl_3 layer was separated, the mother liquor was extracted once with CHCl_3 , and the solvent was evaporated from the combined CHCl_3 extract. The crystals thereby obtained were recrystallized from EtOH to colorless crystals, m.p. $175\sim 178^\circ$. Yield, 3.0 g. (61%). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{25}\text{ON}_3$: C, 68.50; H, 9.58; N, 15.98. Found: C, 68.14; H, 9.51; N, 15.68. Diperchlorate: m.p. $227\sim 230^\circ$. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{27}\text{O}_7\text{N}_3\text{Cl}_2$: C, 38.83; H, 5.87; N, 9.06. Found: C, 38.73; H, 6.01; N, 8.59.

The CHCl_3 layer before reduction with NaBH_4 was evaporated under a reduced pressure, leaving an oil. UV $\lambda_{\text{max}}^{\text{EtOH}}$: $260.5 \text{ m}\mu$ ($\log \epsilon 5.13$ ($\text{HON}=\overset{+}{\text{C}}-\overset{+}{\text{C}}=\text{N}=\text{N}$)).

b) NOCl was passed through a solution of 2.5 g. of the cyclic enamine (K) dissolved in 50 ml. of ether, with ice cooling, and the crystals that separated out were collected. The crystals were dissolved in H_2O , basified with 10% NaOH, and extracted with three portions of ether. After dehydration of the ether extract, 60% HClO_4 was added and the crystals that separated out were recrystallized from H_2O to crystals melting at $238\sim 239^\circ$, undepressed on admixture with VIII. Recovery of VIII, 500 mg. (11.5%).

The mother liquor left after extraction with ether was added with CHCl_3 , 300 mg. of NaBH_4 was added with stirring, and the mixture was treated as in the above method (a). Crystals of m.p. $175\sim 178^\circ$ were obtained in 14.3% (400 mg.) yield. This product showed no depression of melting point on admixture with the crystals of m.p. $175\sim 178^\circ$ obtained from method (a).

5-Oxosparteine (II)—A mixture of 2.0 g. of the perchlorate of II, 1 g. pyruvic acid, and 10 ml. of 6% AcOH was warmed on a water bath for 6 hr., allowed to cool, and basified with 20% KOH. This

16) W. S. Knowles, Q. E. Thompson: J. Org. Chem., 25, 1031 (1960).

solution was extracted with 3 portions of ether and 60% HClO_4 was added cautiously to the ether extract. The crystals that formed were recrystallized from 90% EtOH to 2.0 g. (75.5%) of colorless plates, m.p. 204~208°. *Anal.*. Calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_5\text{N}_2\text{Cl}$: C, 51.77; H, 7.24; N, 8.05. Found: C, 51.31; H, 7.23; N, 8.24. IR cm^{-1} : 1701 ($\nu_{\text{C=O}}$), 2817, 2717 (trans-quionlizidine).

Formation of the Oxime (XIII) from II—A mixture of 1 g. of the perchlorate of II, 0.6 g. of $\text{NH}_2\text{OH}\cdot\text{HCl}$, and 0.6 g. of AcONa in EtOH was refluxed for 5 hr., EtOH was evaporated, and the residue was neutralized with 10% NaOH. This was extracted with CHCl_3 which was dried and evaporated. Addition of EtOH to its residue produced crystals which were recrystallized from EtOH to 400 mg. (50.3%) of crystals, m.p. 173~177°, undepressed on admixture with XIII.

Reduction of II—A mixture of 0.6 g. of II, 0.6 g. of KOH and 1 ml. of hydrazine hydrate in 10 ml. of triethylene glycol was refluxed for 3 hr. at 120~130°, and the water formed and excess hydrazine were removed by distillation, and the temperature of solution was allowed to rise to 190~200° and heating was continued for 10 hr. After cooling, the product was extracted with ether and 60% HClO_4 was added cautiously to the ether extract. The crystals that formed were recrystallized from EtOH to 400 mg. (41.6%) of colorless crystals, m.p. 170~171°, undepressed on admixture with sparteine perchlorate.

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Summary

As the starting material for the synthesis of sparteine derivatives, 5-oxosparteine (II) was synthesized. Condensation of Δ^5 -dehydrosparteine (IX) or $\Delta^{1(6)}$ -dehydrosparteinium ion (VIII) and benzaldehyde gave 5-benzylidene- $\Delta^{1(6)}$ -dehydrosparteinium ion (X) which was reduced to 5-benzylidenesparteine (XI), and its oxidative cleave should have provided II but the objective was not attained. 5-Hydroximosparteinium ion was obtained by the condensation of IX and nitrosyl chloride or VIII and ethyl nitrite, this sparteinium ion was reduced to 5-hydroximosparteine (XIII), and its treatment with pyruvic acid gave the objective II. II has the same configuration as that of sparteine.

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