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 Stenhause*³ during the 18th Century. Its structure was determined by Clemo and his co-workers,*³ and the alkaloid was synthesized by Clemo and others,*³ Leonard and Beyler,*⁶ Galinovsky and Kainz,*⁵ and by Sorm and Keil.*⁶ By the determination of its steric structure*⁴ 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.

![Diagram](chart.png)

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*⁴ Included in Japanese Pharmacopoeiae Ed. VII.
3) G. R. Clemo, R. Raper, W. S. Short: Ibid., 1949, 663.
5) F. Galinovsky, G. Kainz: Monatsch., 80, 112 (1949).
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 compound 69 (III), 17-substituted compound 69 (IV), 6,11-disubstituted compound 69 (V), and the 5-substituted compound, α- or β-diplospartyrine 69 (VI).

These derivatives were synthesized from the oxidation products of I such as 17-oxosparteine, 17-hydroxysparteine (VII), 4(10)-dehydrosparteinum ion (VIII), and 4(10),11(10)-didehydrosparteinum dion.

Oxidation of sparteine with mercuric acetate results in the attack on the transquinolizidine ring to form VII and its treatment with alkali gives 4'-dehydrosparteine (V), 6. Since K takes the cyclic enamine form, its 5-position is expected to be active to electrophilic reagents. In recent years, Birkofer and others' obtained 2-benzylidene-cyclopentanone in 84% yield by the reaction of benzaldehyde with the enamine, N-(4'-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 di perchlorate (X) of m.p. 267~270°, UV \( \lambda_{\text{max}}^{\text{BCH}} : 321.2\text{ m}\mu \) (log ε 4.32). The ultraviolet absorption proved the presence of \( \text{C}_9\text{H}_8\text{CH}=\text{C}=\text{N} \) 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' reported the formation of VII by the condensation of VIII and IX at pH 8, during structural elucidation of VIII. 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 VIII. These workers had also obtained 1-methyl-3-benzylidene-1-piperidonium salt by the condensation of N-methyl-1-piperidinium salt and benzaldehyde at pH 7. From these evidences, the di perchlorate of VIII and benzaldehyde,

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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-$\delta^{(4)}$-dehydrosparteinium salt did not materialize. Therefore, X was reduced with sodium borohydride to 5-benzylidenesparteine (X) 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.

The reaction of nitrosyl chloride with the enamine (X) gave 5-hydroximinosparteinium chloride (XIII), UV $\lambda_{	ext{max}}$ : 260.5 nm (log $\varepsilon$ 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 ($\nu_{C=O}$), 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 substitution 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-$\delta^{(4)}$-dehydrosparteinium Diperchlorate (X)—a) Method: A mixture of 1.0 g. of $\delta^{(4)}$-dehydrosparteine$^{11}$ (X), 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 H₂O. This solution was basified with 10% NaOH and extracted three times with CHCl₃. To the separated CHCl₃ layer, 60% HClO₄ was added and CHCl₃ was evaporated under a reduced pressure. The solidified residue was recrystallized from 60% EtOH to 300 mg. (13%) of colorless needles, m.p. 267~270°. Anal. Calcd. for C₉H₇O₇N₃Cl₂: C, 50.71; H, 5.80; N, 5.38. Found: C, 51.27; H, 6.41; N, 5.85. UV λmax: 321.2 mλ (log ε 4.32).

b) Method: A mixture of 4.0 g. of 4'-dehydrosparteinum diperchlorate (II), 4 ml. H₂O, 4 g. Be₂H₂ and 4 drops of piperidine was heated on a water bath at 80~90° for 3 h. When cooled, unreacted Be₂H₂ 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. 267~270°, undepressed on admixture with the crystals obtained from method (a).

5-Benzylidenesparteine Perchlorate (XI)—A mixture of 2.0 g. of X, 50 ml. H₂O, 6 ml. of 10% NaOH, and 20 ml. of CHCl₃ was stirred at room temperature, 0.5 g. of NaBH₄ was added in small portions, and the mixture was stirred for 1 h. After allowing this reaction mixture to stand overnight at room temperature, the CHCl₃ layer was separated, the residual solution was extracted twice with CHCl₃, and the combined CHCl₃ extract was evaporated under a reduced pressure. The residual oil was dissolved in EtOH and addition of 60% HClO₄ produced crystals which were recrystallized from 60% EtOH to 1.5 g. (94%) of colorless crystals, m.p. 185~190°. Anal. Calcd. for C₁₂H₁₂O₅N₃Cl: C, 62.46; H, 7.39; N, 6.92. Found: C, 62.44; H, 7.22; N, 6.95. UV λmax: 242.3 mλ (log ε 4.08).

Attempted Oxidative Cleavage of XI—A mixture of 300 mg. of XI, 30 ml. of MeOH, and 15 ml. of C₆H₆Cl₃ was chilled with dry ice and about 4 times the theoretical amount of O₃ was passed through this solution. After addition of (C₆H₅)₃P, the mixture was allowed to stand for 5 min. 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% HClO₄. Its melting point of 267~270° showed no depression on admixture with X and its UV spectrum also agreed with that of X.

b) Oxone 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 Cr₂O₃ was dissolved in 20 ml. of H₂O 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 CHCl₃. After dehydration, CHCl₃ was evaporated under a reduced pressure, the oily residue was dissolved in a small quantity of EtOH and addition of 60% HClO₄ effected crystallization. The product, m.p. 267~270°, showed no depression of melting point on admixture with X.

5-Hydroximinosparteine (XIII)—A suspension of 8 g. of the diperchlorate of XI 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 45~50° and excess of C₂H₂ONO was passed through the solution with stirring. EtOH was evaporated under a reduced pressure, the oily residue was basified with 10% NaOH, and CHCl₃ was added. The mixture was stirred at room temperature, 3.0 g. of NaBH₄ was added with stirring, and the mixture was stirred for further 4 h. The CHCl₃ layer was separated, the mother liquor was extracted once with CHCl₃, and the solvent was evaporated from the combined CHCl₃ extract. The crystals thereby obtained were recrystallized from EtOH to colorless crystals, m.p. 175~178°. Yield, 3.0 g. (61%). Anal. Calcd. for C₁₂H₁₂O₇N₃: C, 68.50; H, 9.58; N, 15.98. Found: C, 68.14; H, 9.51; N, 15.68. Diperchlorate: m.p. 227~230°. Anal. Calcd. for C₁₂H₁₂O₅N₃Cl₂: C, 38.83; H, 5.87; N, 9.06. Found: C, 38.73; H, 6.01; N, 8.59.

The CHCl₃ layer before reduction with NaBH₄ was evaporated under a reduced pressure, leaving an oil. UV λmax: 260.5 mλ (log ε 5.13 (HON=C-C≡N=)).

b) NOC₁ was passed through a solution of 2.5 g. of the cyclic amine (K) dissolved in 50 ml. of ether, with ice cooling, and the crystals that separated out were collected. The crystals were dissolved in H₂O, basified with 10% NaOH, and extracted with three portions of ether. After dehydration of the ether extract, 60% HClO₄ was added and the crystals that separated out were recrystallized from H₂O to crystals melting at 238~239°, undepressed on admixture with XI. Recovery of XI, 500 mg. (11.5%).
The mother liquor left after extraction with ether was added with CHCl₃, 300 mg. of NaBH₄ was added with stirring, and the mixture was treated as in the above method (a). Crystals of m.p. 175~178° were obtained in 14.5% (400 mg.) yield. This product showed no depression of melting point on admixture with the crystals of m.p. 175~178° obtained from method (a).

5-Oxosparteine (II)—A mixture of 2.0 g. of the perchorlate 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

solution was extracted with 3 portions of ether and 60% HClO₄ 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 C₇H₇O₇N₂Cl: C, 51.77; H, 7.24; N, 8.05. Found: C, 51.31; H, 7.23; N, 8.24. IR cm⁻¹: 1701 (νC=O), 2817, 2717 (trans-quinonilidizine).

Formation of the Oxime (XIII) from II—A mixture of 1 g. of the perchlorate of II, 0.6 g. of NH₄OH·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 CHCl₃ 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% HClO₄ 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 spartine perchlorate.

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Summary

As the starting material for the synthesis of spartine derivatives, 5-oxospartine (II) was synthesized. Condensation of δ⁵-dehydrosartine (X) or δ⁴⁰-dehydrosartineion (XII) and benzaldehyde gave 5-benzylidene-δ⁴⁰-dehydrosartineion (X) which was reduced to 5-benzylidenespartine (XII), and its oxidative cleave should have provided II but the objective was not attained. 5-Hydroximinospartineion was obtained by the condensation of X and nitrosyl chloride or XII and ethyl nitrate, this spartineion was reduced to 5-hydroximinospartine (XIII), and its treatment with pyruvic acid gave the objective II. II has the same configuration as that of spartine.

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