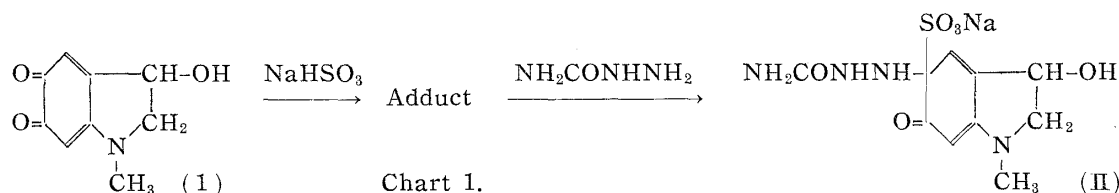


48. **Jun-ichi Iwao** : Studies on Adrenochrome Derivatives. VI.*
Solubilization of Adrenochrome Monosemicarbazone and its
Derivatives. (2). Synthesis and Structure of Sodium 1-Methyl-
5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-Sulfonate.

(Osaka Research Laboratory, Gohei Tanabe & Co., Ltd.**)

The 4- β -hydroxyethylsemicarbazones described in the preceding paper* were 3.5 times more soluble in water than adrenochrome monosemicarbazone but this degree of solubility is still not satisfactory. In order to obtain a more soluble compound, addition of sodium hydrogen sulfite to $>C=N-$ group in 5- and $>C=O$ group in 6-positions of adrenochrome monosemicarbazone was attempted. It was thereby learned that, although the reaction of the two substances by warming on a water bath by the usual method sometimes resulted in decomposition and resinification to form a brown precipitate, reaction of the two by warming at around 30° for a long period afforded yellowish orange needle crystals which were fairly soluble in water. This compound was tentatively designated AC-17*** for the sake of convenience.

During the course of the present work, Belgian Patent No. 510,295 published a process for the manufacture of water-soluble adrenochrome derivatives. This patent, as shown in Chart 1, calls for the reaction of sodium hydrogen sulfite and adrenochrome (I) and, without isolating the compound thereby formed, semicarbazide is added to the



mixture to obtain sodium 1-methyl-3-hydroxy-5-semicarbazido-6-oxo-2,3,5,6-tetrahydroindole 5-sulfonate (II). This differs from the writer's method and, although (II) is described as pale greenish yellow crystals decomposing at over 330° and as giving pale brown solution, reexamination of this process gave colorless crystals which formed a colorless aqueous solution. AC-17 comes as yellowish orange needles melting at 227~228° with decomposition and its aqueous solution is also yellowish orange. Examination of its ultraviolet and infrared spectra clearly indicated it to be a new compound. Moreover, its solubility in water is 15 mg./cc. at 0° and 50 mg./cc. at 35°, which is about 50 times that (0.3 mg./cc.) of adrenochrome monosemicarbazone, compared at 0°. This makes it possible to manufacture preparations of high concentrations easily. The analytical values of AC-17 corresponds to $C_{10}H_{17}O_8N_4NaS$. Its infrared spectrum exhibits its specific absorption (in Nujol) at 5.89 and 6.04 μ ($>C=O$) and at 8.50 and 9.58 μ (SO_3^-) (Fig. 2), and its ultraviolet spectrum (Fig. 3) shows $\lambda_{max}^{H_2O(pH 2.2)}$ 360 $m\mu$ ($\log \epsilon$ 5.40) and $\lambda_{max}^{H_2O(pH 11.4)}$ 435 $m\mu$ ($\log \epsilon$ 5.31). The compound is labile in alkaline solution and decomposes on standing in alkaline medium, separating a brown, resinous substance.

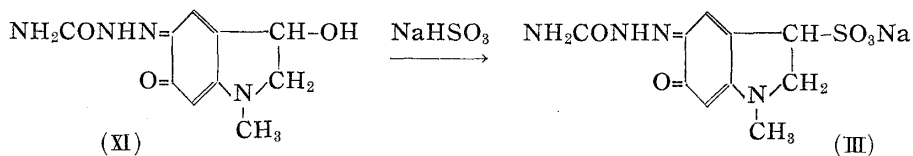
For the reasons listed below, the structure of this AC-17 was confirmed to be sodium 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-sulfonate (III).

1) When 10% hydrochloric acid is added to a concentrated aqueous solution of (III), a part undergoes decomposition with liberation of sulfur dioxide but the majority

* Part V : This Bulletin, 4, 247 (1956).

** Honjo-Kawasaki-cho, Ohyo-do-ku, Osaka (岩尾順一).

*** AC-17 is the abbreviation for adrenochrome derivative No. 17.



forms a yellow crystalline powder (IV) which colors at 130° and decomposes at 195°. The analytical values of (IV) correspond to $\text{C}_{10}\text{H}_{12}\text{O}_5\text{N}_4\text{S} \cdot 1\frac{1}{2}\text{H}_2\text{O}$. Potentiometric titration of (IV) consumes 1 mole of sodium hydroxide, $K = \text{ca. } 3.1 \times 10^{-4}$, indicating it to be a comparatively strong acid. When (IV) is suspended in water and sodium hydrogen carbonate is added, it converts to (III) with effervescence. Its neutralization with ammonia affords an ammonium salt. These properties of (III) agree well with those of sulfonic acids and it cannot be a hydrogen sulfite or an ester.

When a concentrated aqueous solution of (III) and that of the metal salts such as barium chloride, copper sulfate, or silver nitrate are brought together, exchange decomposition takes place, and sparingly soluble barium, copper, or silver salt of (III) precipitates out. These metal salts contain water of crystallization but, for example, heating of the silver salt for 24 hours at 103~105° liberates this water and the analytical values of the compound so obtained correspond to $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{AgS} \cdot \frac{1}{2}\text{H}_2\text{O}$ or $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{AgS}$. Although the analytical values of (III) were given as corresponding to $\text{C}_{10}\text{H}_{17}\text{O}_8\text{N}_4\text{NaS}$, the foregoing properties suggest that this should be corrected to $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{NaS} \cdot 3\text{H}_2\text{O}$. Compared to the composition of $\text{C}_{10}\text{H}_{12}\text{O}_3\text{N}_4$ for adrenochrome monosemicarbazone, this formula indicates that (III) had been formed by the dehydration reaction of adrenochrome monosemicarbazone and sodium hydrogen sulfite.

2) Possibility of sodium hydrogen sulfite reacting with adrenochrome monosemicarbazone are the addition reactions at 5-position with $>\text{C}=\text{N}-$ and at 6-position with $>\text{C}=\text{O}$, and a substitution reaction with $-\text{OH}$ at 3-position. The infrared spectrum of adrenochrome monosemicarbazone (Fig. 1) exhibits an absorption maxima (in Nujol) at 5.90 and 6.05 μ ($\text{C}=\text{O}$ of amide and ketone), and similar absorption maxima appear in that of (III) (Fig. 2) at 5.89 and 6.04 μ ($\text{C}=\text{O}$ of amide and ketone). This naturally suggests the presence of $>\text{C}=\text{O}$ at 6-position and addition of sodium hydrogen sulfite in this position cannot be accepted.

The ultraviolet absorption maxima of (III), as described earlier, shifts towards a longer wave length range in alkaline solution. The same shift is noted in that of

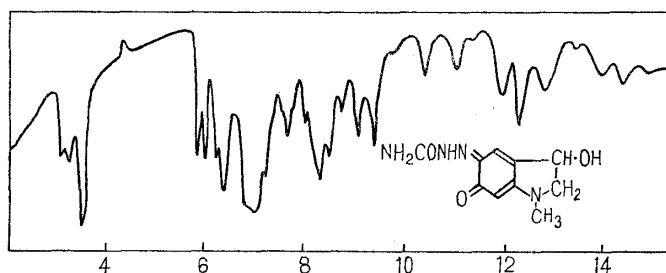


Fig. 1

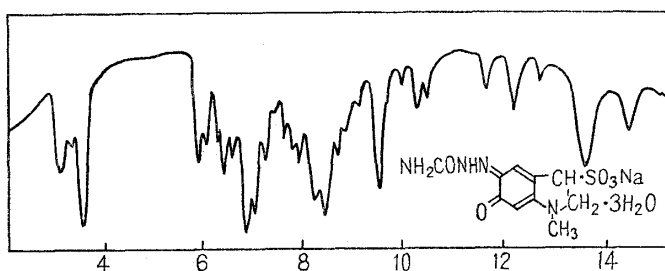
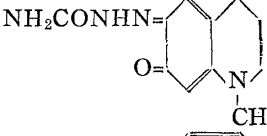
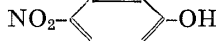


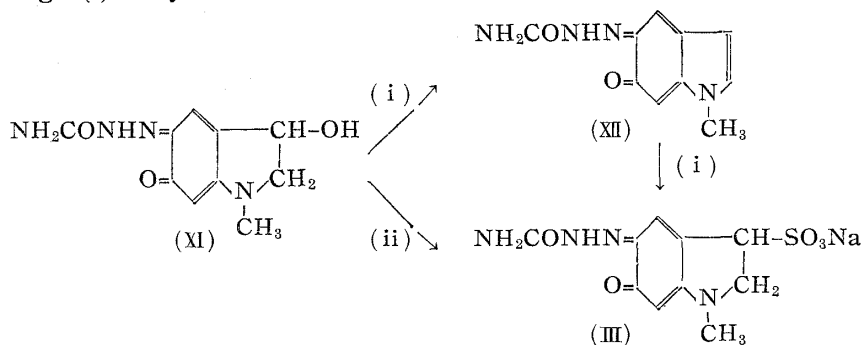
Fig. 2

TABLE I. Ultraviolet Absorption of Adrenochrome Derivatives

| General formula | | | | Acid solution | | | Alkaline solution | | |
|---|---------------------|-----------------------------------|------------------------------------|----------------------------|-----|----------------|----------------------------|------|----------------|
| Substituents | | | | λ_{max} (m μ) | pH | log ϵ | λ_{max} (m μ) | pH | log ϵ |
| R ₁ | R ₂ | R ₃ | R ₄ | | | | | | |
| NH ₂ CONHN= | -SO ₃ Na | H | CH ₃ | 360 | 2.2 | 5.40 | 435 | 11.4 | 5.31 |
| NH ₂ CONHN= | -OH | H | CH ₃ | 352 | 2.2 | 5.39 | 446 | 12.0 | 5.35 |
| HOCH ₂ CH ₂ NHCONHN= | -OH | H | CH ₃ | 360 | 2.6 | 5.38 | 455 | 11.4 | 5.37 |
| HOCH ₂ CH ₂ NHCONHN= | -OH | H | CH ₂ CH ₂ OH | 365 | 2.8 | 5.40 | 462 | 11.5 | 5.46 |
| NH ₂ CONHN= | -H | -COOC ₂ H ₅ | CH ₃ | 359 | 1.1 | 5.43 | 436 | 11.0 | 5.38 |
| O= | -OH | H | CH ₃ | 300 | 2.2 | | | | |
|  | | | | 365 | 2.2 | 5.24 | 460 | 11.4 | 5.26 |
|  | | | | 317 | 5.0 | | 407 | 9.0 | |

(VII) and (VIII) do not. When there is such a hydroxyl group present, reaction with the sulfite proceeds while the reaction does not proceed in its absence. If the sulfite were to have reacted in the position unaffected by the hydroxyl in (XI), then (VII) and (VIII) should also have produced the same reaction products. This clearly indicates that the presence or absence of a benzyl alcohol-type hydroxyl determines the progress of this reaction. The hypothesis that the reaction of (XI) and sodium hydrogen sulfite has resulted in the exchange reaction between -OH and -SO₃Na groups at 3-position is not contrary to explanations listed in the foregoing 1), 2), and 3).

4) Examples of the formation of R-SO₃Na by the exchange reaction of R-OH and NaHSO₃ are rather rare. In 1902, Baeyer and Villiger⁴⁾ prepared triphenylmethanesulfonic acid by reacting triphenylcarbinol and sodium hydrogen sulfite at room temperature for one month, and in 1904, Morthwurf⁵⁾ obtained tri-(*p*-tolyl)methanesulfonic acid by the reaction of tri-(*p*-tolyl)carbinol and sodium hydrogen sulfite at room temperature. These sulfonic acid compounds are reported as giving free acid and sparingly soluble calcium salt. Holmberg⁶⁾ reacted phenylmethylcarbinol or diphenylcarbinol with sodium hydrogen sulfite in a sealed tube, heating at 180°, and obtained the corresponding sulfonic acid derivatives. It is said that in the preparation of a sulfite pulp, exchange reaction occurs between OH of lignin and SO₃Na but this is still not certain yet. The formation of (III) by the dehydrative exchange reaction between adrenochrome monosemicarbazone and sodium hydrogen sulfite may have occurred through (i) dehydration of adrenochrome monosemicarbazone to form an



4) A. Baeyer, V. Villiger: Ber., **35**, 3016(1902).

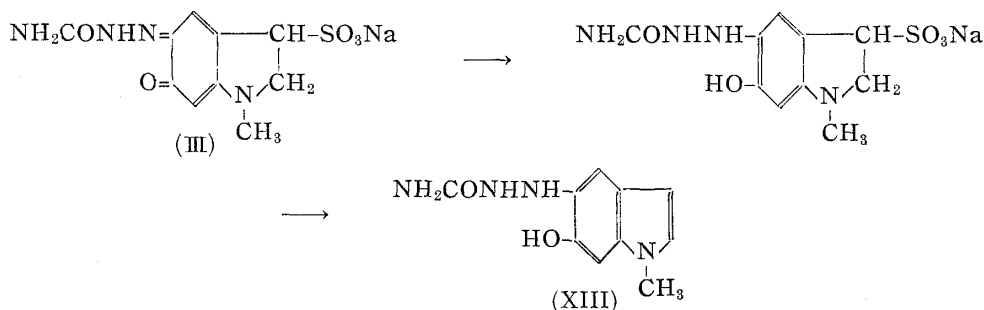
5) A. Morthwurf: *Ibid.*, **37**, 3158(1904).

6) B. Holmberg: Svensk. kem. Tid., **48**, 207(1936)(C. A., **31**, 2182(1937)).

unsaturated compound (XII) to which sodium hydrogen sulfite added, or (ii) through simple exchange reaction.

Reaction of the optically active (XI) ($[\alpha]_D^{25} +135^\circ$) and sodium hydrogen sulfite at around 30° for a long period of time afforded an optically active (III), $[\alpha]_D^{25} -16^\circ$ ($c=1.0, H_2O$). This fact seems to suggest that (III) was formed by (ii)-type reaction.

5) Catalytic reduction of (III) with palladium-carbon catalyst resulted in the absorption of one mole of hydrogen and greyish white microneedles, m.p. 205° (decomp.), were obtained. This compound does not contain sulfur atom, gives positive Ehrlich reaction, and its melting point and ultraviolet spectrum are identical with those of 1-methyl-5-semicarbazido-6-hydroxyindole (VIII). Addition of benzaldehyde to the mother liquor left after the removal of the catalyst and (XIII) afforded benzaldehyde-sodium hydrogen sulfite adduct, which clarified that the sodium hydrogen sulfite had liberated by reduction. If the structure of (III) were correct, it would form (XIII) by the reaction course similar to the catalytic reduction⁷⁾ of adrenochrome monosemicarbazone.



From the facts listed in the foregoing sections (1) to (5), the structure of AC-17 is determined as sodium 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-sulfonate. This compound possesses hemostatic action equal to or better than that of adrenochrome monosemicarbazone with an improved solubility in water that much is expected of its future development.

The writer takes this opportunity to express his deep gratitude to Prof. Shigehiko Sugawara of the University of Tokyo for his kind and unflinching guidance throughout the course of this work. He is also indebted to Mr. Shiro Tejima, Director of Preparations and Planning Section of this Company, Dr. Masao Fujisawa, Director of this Laboratory, Dr. Hikaru Ozawa, and Dr. Shunichi Yamada for their advices and encouragements, to Mr. Kōichi Tomino for technical help, to Mr. K. Kotera for infrared spectral measurements, to Dr. Y. Satoh and Mr. R. Shimizu for the measurement of physical constants, and to Mrs. F. Hisamichi and Mr. T. Yoda for microanalytical data.

Experimental

Sodium 1-Methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-Sulfonate (III)—To 120 cc. of water containing SO_2 gas (pH 1~1.2), 40 g. of adrenochrome monosemicarbazone (XI) and 40 g. of $NaHSO_3$ were added and the mixture was shaken in tightly stoppered bottle at about 30° . The reddish orange (X), which at first floated on the solution, changed to yellowish orange crystals towards the end of the reaction (after about 2 days) and became immovable. The crude crystals were collected and recrystallized from 120 cc. of water, affording 48.2 g. of pale yellowish orange microneedles, m.p. $227\sim 228^\circ$ (decomp.). Rf 0.08 by paper chromatography developed with H_2O : $AcOH:BuOH=5:1:4$ at 20° for 17 hrs. *Anal.* Calcd. for $C_{10}H_{11}O_5N_4NaS\cdot 3H_2O$: C, 31.92; H, 4.52; N, 14.89; Na, 6.12; S, 8.51. Found: C, 32.53; H, 4.77; N, 14.92; Na, 5.85; S, 8.52.

1-Methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-Sulfonic Acid (IV)—Addition of 10% HCl to a concentrated aqueous solution of (III) separated yellow crystalline powder, which was insoluble in EtOH and MeOH, but soluble in hot water with decomposition. It begins to color at 130° and decomposes at 195° . *Anal.* Calcd. for $C_{10}H_{12}O_5N_4S\cdot 1\frac{1}{2}H_2O$: C, 36.70; H, 4.59; N,

7) Part I. J. Iwao: This Bulletin, 4, 244 (1956).

17.13; S, 9.79. Found: C, 37.32; H, 4.24; N, 16.70; S, 9.74.

Various Metal Salts of 1-Methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-Sulfonic Acid (IV)—The metal salts formed by the following three methods are listed in Table II.

- Reaction of (XI) and metal hydrogen sulfite as for the synthesis of (III).
- Neutralization of (IV) with NH_3 aq. or NaHCO_3 .
- Warming a mixture of conc. aq. solution of (III) and that of various metal salts, and allowing the mixture to stand to precipitate the salt.

TABLE II.

| Metal | Method | Reagent | Product | | Analytical values |
|---------------|--------|---|----------------------|-----------------------|-------------------|
| | | | Crystal form | m.p.(decomp.) °C | |
| Na | a, b | NaHSO_3 | Orange needles | 227~228 | |
| Ca | c | CaCl_2 | Red prisms | No decompn. below 270 | 1 |
| Ba | c | BaCl_2 | Yellow prisms | // | |
| Cu | c | CuSO_4 | Brown needles | // | |
| Co | c | CoSO_4 | Red brown prisms | // | |
| Zn | c | ZnSO_4 | Orange prisms | // | |
| K | a | KHSO_3 | // | 243 | 2 |
| NH_4 | b | NH_4OH | Orange red prisms | 223 | |
| Mg | c | MgSO_4 | Yellow prisms | 190 | |
| Al | c | AlCl_3 | Yellow orange prisms | 130 | |
| Ag | c | AgNO_3 | Red prisms | No decompn. below 270 | 3 |
| <i>Anal.</i> | (1) | Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{S}\cdot\frac{1}{2}\text{Ca}\cdot 8\text{H}_2\text{O}$: C, 30.69; H, 4.89; N, 14.34. Found: C, 31.23; H, 4.98; N, 14.00. | | | |
| | (2) | Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{KS}\cdot\text{H}_2\text{O}$: C, 33.58; H, 3.68; N, 15.73. Found: C, 33.77; H, 3.97; N, 15.37. | | | |
| | (3) | Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{AgS}\cdot\text{H}_2\text{O}$: C, 28.17; H, 3.31; N, 13.15; Ag, 25.40. Found: C, 28.17; H, 3.08; N, 12.50; Ag, 25.60. Sample dried at 103~105° for 24 hrs. Found: C, 29.23; H, 3.17; N, 13.27; Ag, 25.63. Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{AgS}\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 28.85; H, 2.89; N, 13.46; Ag, 25.96. Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_5\text{N}_4\text{AgS}$: C, 29.55; H, 2.73; N, 13.80; Ag, 26.53. | | | |

Sodium 1-Methyl-6-semicarbazono-7-oxo-1,2,3,4,6,7-hexahydroquinoline 4-Sulfonate (X)—A mixture of 0.9 g. of 1-methyl-4-hydroxy-6-semicarbazono-7-oxo-1,2,3,4,6,7-hexahydroquinoline, 0.9 g. of NaHSO_3 , and 30 cc. of water containing SO_2 gas was refluxed for 1 hr., the mixture was chilled, and unreacted material was recovered by filtration. The filtrate was evaporated to dryness under a reduced pressure, MeOH was added to the residue, and inorganic matter was filtered off. MeOH was evaporated from the filtrate, the residue was dissolved in water, and addition of acetone to this solution separated 0.4 g. of red crystals, which were recrystallized from a small amount of water. Red crystalline powder which colors at 160~170° and decomposes at 210°. *Anal.* Calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_5\text{N}_4\text{NaS}\cdot 4\text{H}_2\text{O}$: C, 32.35; H, 5.15; N, 13.75; S, 7.82. Found: C, 32.47; H, 5.14; N, 13.65; S, 7.75.

Catalytic Reduction of (III)—A suspension of 3 g. of (III) in 50 cc. MeOH, added with 1 g. of 5% Pd-C, was submitted to reduction at ordinary temperature and pressure and 1 mole of H_2 was absorbed during 7 hrs., during which the orange color was decolorized. The colorless solution contained some white crystals. The catalyst and the crystals were collected by suctional filtration, digested with warm MeOH, and MeOH was distilled off. The crude crystals (1.2 g.) thereby obtained were recrystallized from MeOH to greyish white needles, m.p. 205°(decomp.). The compound does not contain S and dissolves in NaOH with coloration. The properties and its ultra-violet spectrum were identical with 1-methyl-5-semicarbazido-6-hydroxyindole.

The same reduction carried out in aqueous solution, addition of BzH to the aqueous filtrate, evaporation of this to dryness under a reduced pressure, and removal of organic matter by the addition of EtOH afforded white powder. This powder dissolved in 10% HCl with evolution of SO_2 and liberation of BzH. This is therefore an adduct of BzH and NaHSO_3 .

Summary

In order to obtain water-soluble compound of adrenochrome monosemicarbazone (XI), reaction of (XI) and sodium hydrogen sulfite was carried out and a compound fairly well soluble in water was obtained. Its solubility is 15 mg./cc. at 0°, being about 50 times that of (XI). Detailed examinations of this substance indicated it to be sodium

1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-sulfonate (III). (III) converts to 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-sulfonic acid (IV) and forms metal salts with barium, copper, silver, and other metals. Catalytic reduction of (III) affords 1-methyl-5-semicarbazido-6-hydroxyindole (XII). 1-Methyl-4-hydroxy-6-semicarbazono-7-oxo-1,2,3,4,6,7-hexahydroquinoline also reacted with sodium hydrogen sulfite to form water-soluble sodium 1-methyl-6-semicarbazono-7-oxo-1,2,3,4,6,7-hexahydroquinoline 4-sulfonate (X).

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U.D.C. 547.836/7

49. Shigenobu Okuda : Über die Konstitution des Matrins. XXVI.¹⁾
Beiträge zur Konstitution des Dehydro- α -matrinidins.

(Pharmaz. Institut d. medizin. Fakultät d. Universität Tokyo*)

Für die Konstitution des Matrins wurde die Formel (I) bzw. (II) aufgestellt, von denen die Formel (I) phylogenetisch wahrscheinlicher gemacht wurde.²⁾ Die beiden Formeln wurden auf Grund der für das Dehydro- α -matrinidin aufgestellten Formel (III) bzw. (IV) abgeleitet.

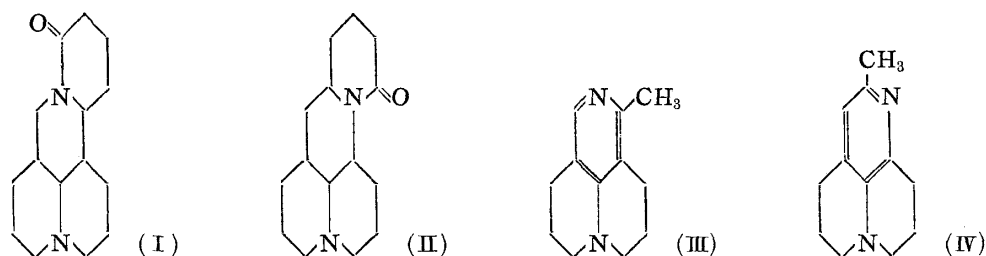
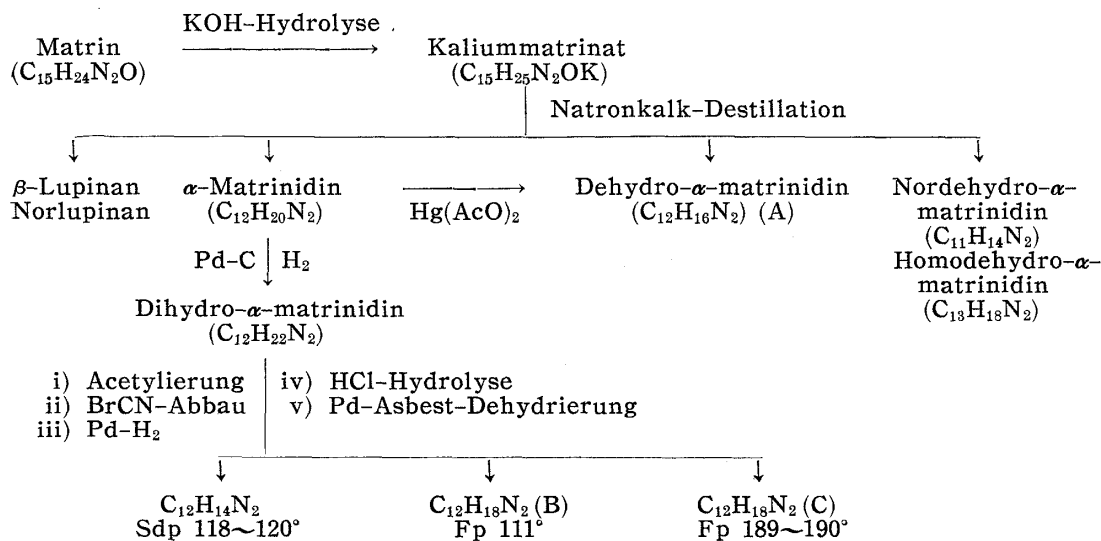


TABELLE I.³⁾



* Hongo, Tokyo (奥田重信).

1) Mitt. XXV. E. Ochiai, S. Okuda : Dieses Bulletin, 1, 266(1953).

2) K. Tsuda : J. Pharm. Soc. Japan, 56, 16(1936).

3) H. Kondo, E. Ochiai, K. Tsuda, S. Yoshida : *Ibid.*, 55, 483(1935).