UDC 547.836.7:547.94[582.736]

16. **Eiji Ochiai**[*1] **and Hitoshi Minato**[*2] : Synthesis of Matrine Derivatives. II.[1)] Studies on the Diazotization of Decarbonylmethylmatrinamine and the Ring-closure of Matrinic Acid Derivatives.

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H. Kondo and Ochiai[2)] reported that diazotization of decarbonylmethylmatrinamine[2),3)] (I) with silver nitrite in 10% hydrobromic acid yielded base-A, b.p$_4$ 140~142°, and base-B, b.p$_4$ 180~184°. Base-A was called decarbonylmatrinene and, by allowing to stand for 36 days, it was isomerized to base-A′, b.p$_{12}$ 168~169°. Base-B was a primary alcohol corresponding to (I), i.e. decarbonylmethylmatrinol (II). Although the values of the elemental analysis of base-A agreed with the empirical formula formed by subtracting one mole of water from that of base-B, base-A did not absorb hydrogen on catalytic hydrogenation over palladium in glacial acetic acid. Hence, the composition of base-A seemed rather questionable.

In this paper will be described the preparation of several derivatives of decarbonylmethylmatrinol (II) and experimental results on reinvestigation of the diazotization of (I).

When decarbonylmethylmatrinamine (I) was diazotized in 10% sulfuric acid with 1.1 or 7.5 equivalents of sodium nitrite in the usual manner, about 50% of the starting material was recovered and the remainder became resinous. Therefore, the method of H. Kondo and Ochiai[2)] was reinvestigated.

The carbonate[2)] of (I), m.p. 141°, in 10% hydrobromic acid was diazotized with silver nitrite or sodium nitrite. After the addition of a small amount of silver nitrite or a few drops of sodium nitrite solution with stirring at room temperature, the reaction mixture was positive to the color-test with zinc iodide-starch paper even after 45 minutes and it was realized that the consumption of nitrogen trioxide was very slow. When all the nitrite was added to this mixture and heated at 70~80°, some bubbles were observed (the color-test was still positive). Subsequently, this mixture was heated up to 100° until the bubbling stopped and the color-test for nitrogen trioxide became negative. Thus, a yellow oil, b.p$_7$ 185~200° (bath temp.), and a deep brown viscous oil containing halogen atom were obtained. As the former gave a monomethiodide, m.p. 222~223°, which was identical with that of base-B, it was found to be decarbonylmethylmatrinol (II).

The latter oil was dissolved in water, the solution was made alkaline with potassium hydroxide and potassium carbonate, and extracted with chloroform. A viscous oil containing halogen atom was recovered again; and therefore this oil should be the quaternary salt (III). By treatment of this quaternary salt with fresh silver oxide or Amberlite IRA-400, it was converted into a mixture of an amorphous solid and a viscous oil, which was negative to the Beilstein test for halogen atom, and vigorously decomposed with evolution of methanol to yield a yellow oil, b.p$_7$ 155~160° (bath temp.), when heated at 200~250° in an oil bath in reduced pressure. This yellow oil gave a monomethiodide, m.p. 233~234°. Therefore, it was elucidated that the Hofmann degradation product was (IV) and that the quaternary salt was (III). However, the bases-A and -A′ reported by H. Kondo and Ochiai were not obtained. Although it was rather curious that the consumption of nitrogen

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1) Part I : Yakugaku Zasshi, **73**, 914 (1953).

2) H. Kondo, E. Ochiai, Y. Nishimura : *Ibid.*, **48**, 1051 (1928).

3) E. Ochiai, K. Noda : *Ibid.*, **58**, 624 (1938).

trioxide was very slow and the evolution of nitrogen gas[*3] could not be confirmed as stated above, (II) and (III) were obtained as the product by diazotization of (I).

Then, the behavior of methylmatrinamine (XI), which may be prepared from methylmatrinol (V),[1] to diazotization was compared with that of decarbonylmethylmatrinamine (I).

Since it was shown in the preceding paper of this series that the application of thionyl chloride to (V) resulted in the formation of (VI), which yielded (VIII) via (VIIa) by treatment with alkali, (VI) was directly heated in methanol containing ca. 25% by weight of ammonia in a sealed tube and afforded (VIIa) as a major product and (XI) in ca. 10% yield. (VIIa) was also obtained alone by the reaction of (VI) with potassium phthalimide. As the starting material for preparation of (XI), (IX) was prepared by the application of benzyl chloride to (V) and methylmatrinamine (XI) was obtained through (X) in 33% yield. Methylmatrinamine (XI) was very similar to decarbonylmethylmatrinamine (I); (XI) gave a carbonate by the action of carbon dioxide in the air, and a hygroscopic picrate, hydriodide, hydrochloride and perchlorate, an amorphous mercuric chloride salt, an oily toluenesulfonamide, and a thiourea derivative, m.p. 122°.

As in the case of (I) stated above, the amine (XI) was diazotizated in 10% hydrobromic acid with heating, using silver nitrite to yield an oil, which gave a monomethiodide, m.p. 173~174°, and a viscous oil containing a halogen atom. The former was identified as methylmatrinol by comparison of its methiodide with that of (V). The oil was dissolved in water, made alkaline with potassium hydroxide, and extracted with chloroform, from which a viscous oil containing halogen atom was recovered. Therefore, this oil should be the quaternary salt (VIIb) as in the case of (I). Thus, the behavior of (XI) on diazotization was completely identical with that of (I).

Attempt was made to prepare several derivatives of matrinol (XIII), which may be obtained from matrinic acid[5] (XII). Reduction of (XII) with lithium aluminium hydride gave the corresponding primary alcohol, i.e. matrinol (XIII), m.p. 157~158°, in ca. 40% yield and matridine (VIII) in nearly equal amount. Tosylation of (XIII) was attempted by the application of tosyl chloride in pyridine, but the starting material was recovered on heating on a water bath for 1.5 hours, while matridine (VIII) was obtained on refluxing in an oil bath for

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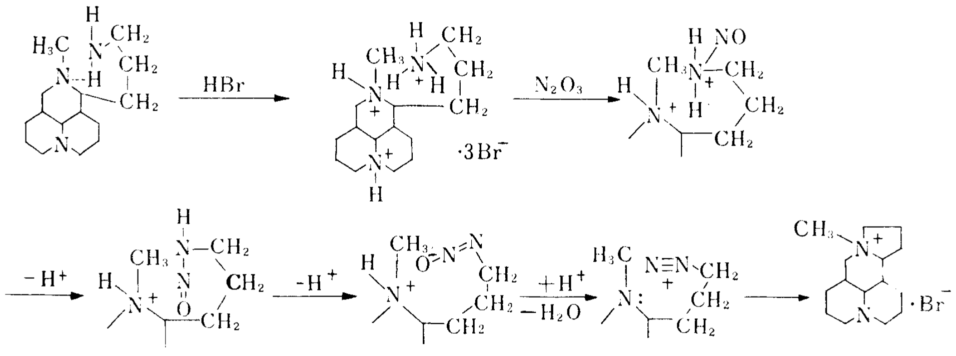
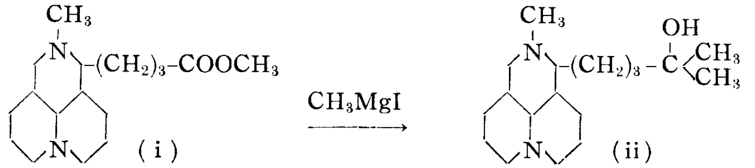
[*3] Since the primary amino group can be sterically very close to ring-N, the intermediate, diazonium salt may be stabilized by interaction between ring-N and the cation of the diazonium salt.



Moreover, H. Kondo and Ochiai[4] reported that methyl methylmatrinate (i) gave the corresponding tertiary alcohol (ii) by Grignard reaction of (i) with methyl iodide, but dehydration of (ii) was entirely unsuccessful.



4) H. Kondo, E. Ochiai, Y. Nishimura : Yakugaku Zasshi, **48**, 1043 (1928).

5) H. Kondo, S. Sato : *Ibid.*, **41**, 659 (1921).

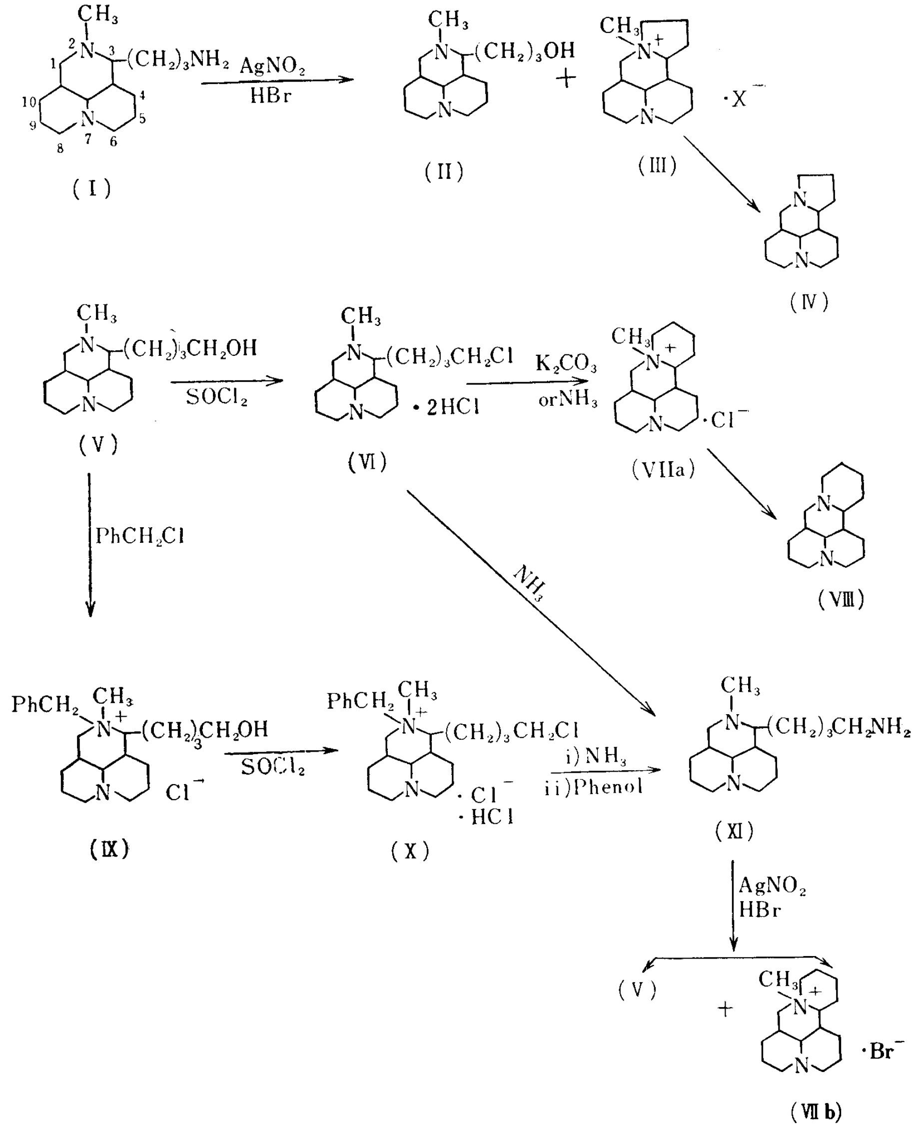


Chart 1.

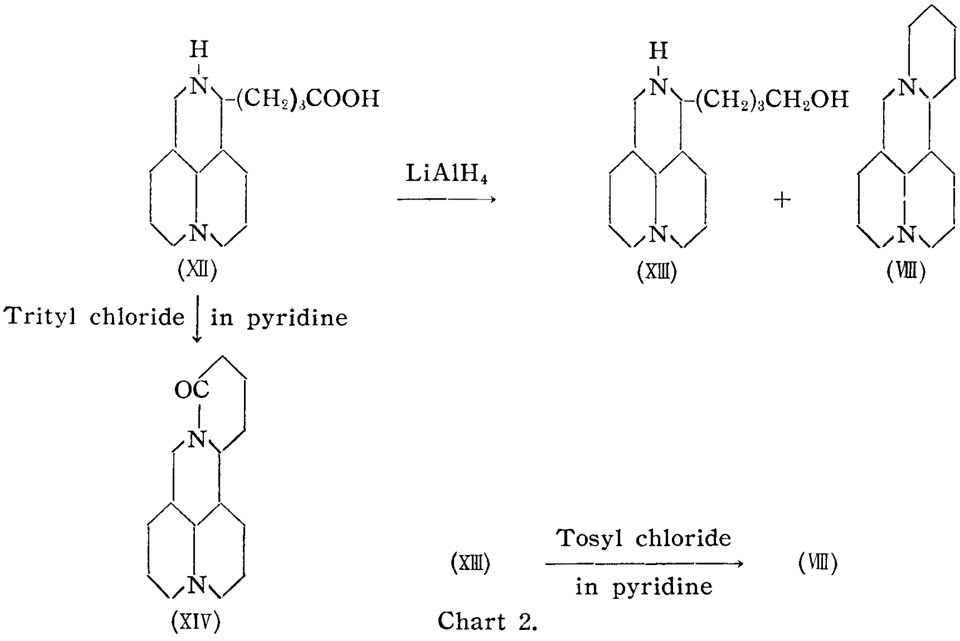


Chart 2.

2 hours. Protection of the secondary amino group of (XII) with trityl chloride gave matrine (XIV) quantitatively.

The easy ring-closure of these compounds to (IV), matridine (VIII), or matrine (XIV) may be explained by the fact that the terminal end of the side chain is sterically very close to the nitrogen atom in ring-C to form a hydrogen bond or zwitter ion as stated above.

Experimental

Diazotization of Decarbonylmethylmatrinamine (I) with $AgNO_2$—To a solution of 1.13 g. of the carbonate of (I) in 13 cc. of 10% HBr, 820 mg. (1.3 equiv.) of fresh $AgNO_2$ was added in small portions with stirring during 30 min. After the mixture was stirred at room temperature for an additional 2.5 hr., it was heated at 70~80° for 1 hr., during which time some effervescence was observed and the color-test with ZnI_2-starch paper was still positive. The temperature was elevated to 100°, when the bubbles stopped and the color-test became negative. After filtration, AgBr was washed thoroughly with hot water, the combined filtrate and washings was filtered through charcoal to remove colloidal silver, and evaporated *in vacuo*. The residue containing a foaming viscous oil (Beilstein's test, positive) was dissolved in water, made alkaline with K_2CO_3 and KOH, extracted with $CHCl_3$, and dried over anhyd. K_2CO_3. The residue obtained upon removal of the solvent was digested with Et_2O, and 200 mg. of a yellow oil (II), b.p$_7$ 185~200° (bath temp.), was obtained from the Et_2O extract. (II) gave a methiodide as colorless prisms, m.p. 222~223° (from Me_2CO), undepressed on admixture with that of base-B, m.p. 216~219°. *Anal.* Calcd. for $C_{15}H_{28}ON_2 \cdot CH_3I$: C, 48.73; H, 7.91; N, 7.11. Found : C, 48.98; H, 7.76; N, 7.66.

The Et_2O-insoluble fraction (Beilstein's test, positive) of the residue, the quaternary salt (III), was dissolved in 6 cc. of water and shaken with fresh Ag_2O, prepared from 2.8 g. of $AgNO_3$ and 700 mg. of NaOH, at room temperature for 5 hr. After filtration of the silver salt and sufficient washing with hot water, the combined filtrate and washings (negative to the color-test with a fluorescein paper for Br_2) was evaporated *in vacuo*. The residue consisting of a mixture of a dark-red viscous oil and an amorphous solid decomposed with evolution of MeOH on heating at 200~250° at 7 mm. Hg in an oil bath and yielded 400 mg. of a yellow oil (IV), b.p$_7$ 115~160° (bath temp.).
Methiodide : Colorless plates, m.p. 233~234° (from Me_2CO). *Anal.* Calcd. for $C_{14}H_{24}N_2 \cdot CH_3I$: C, 49.72; H, 7.46; N, 7.74. Found : C, 50.34; H, 7.44; N, 8.21.

Methylmatrinamine (XI)—A mixture of 600 mg. of methylmatrinol (V) and 800 mg. of BzCl in 5 cc. of MeOH was refluxed for 3.5 hr. The mixture was evaporated *in vacuo*, the residue was dissolved in water, and extracted with Et_2O to remove excess BzCl. The aqueous layer was made alkaline with K_2CO_3, extracted with $CHCl_3$, and the extract was dried over anhyd. K_2CO_3 and evaporated.

To a solution of the residual quaternary salt (IX) dissolved in 5 cc. of $CHCl_3$, a solution of 1 g. of $SOCl_2$ in 2 cc. of $CHCl_3$ was added dropwise with stirring in an ice bath. The mixture was evaporated *in vacuo*, and immediately dissolved in a solution of 20 cc. of 28% NH_4OH and 20 cc. of MeOH containing 25% by weight of NH_3. This mixture was heated in a sealed tube at 105~110° for 5 hr. and then evaporated *in vacuo*. The orange solid residue was dissolved in 5 cc. of phenol, refluxed for 3 hr., and then dissolved in Et_2O. The Et_2O solution was extracted with 10% HCl, the acid layer was made alkaline with K_2CO_3 and KOH, and extracted with Et_2O. The extract was washed with water, dried over anhyd. K_2CO_3, and Et_2O was evaporated to leave 520 mg. of an orange-red oil. This oil was distilled at 205-210°/6 mm. Hg (bath temp.) to yield 200 mg. of a pale yellow oil (XI) (yield, 33.3%). (XI) was positive to isonitrile test for the primary amine and gave an amorphous carbonate with CO_2, an amorphous $HgCl_2$ salt, and a hygroscopic picrate, hydriodide, hydrochloride, and perchlorate. Its acylation was attempted by application of tosyl chloride and Ac_2O, but acylated compound was not obtained in a crystalline state. The treatment of (XI) with NH_4CNS gave a thiourea derivative as colorless prisms, m.p. 122°.

Diazotization of Methylmatrinamine (XI) with $AgNO_2$—A solution of 100 mg. of methylmatrinamine (XI) in 1.5 cc. of 10% HBr was diazotized with 80 mg. of $AgNO_2$, as in the case of (I). The behavior of (XI) on diazotization was completely identical with that of (I). Thus, (XI) gave 50 mg. of a quaternary salt (VIIb) and 50 mg. of an orange oil (V) which gave a methiodide as colorless needles, m.p. 173~174° (from Me_2CO-AcOEt), undepressed on admixture with that of (V).

Reduction of Matrinic Acid (XII) with $LiAlH_4$—To a solution of 950 mg. of $LiAlH_4$ in 40 cc. of dehyd. tetrahydrofuran, a suspension of 1.3 g. of matrinic acid in 40 cc. of dehyd. tetrahydrofuran was added dropwise with stirring at 50~65° during 1 hr. and the mixture was refluxed with stirring for an additional 1 hr. This mixture was decomposed by the addition of 10% HCl in an ice bath and then stirred for 20 min. at room temperature. The mixture was steam-distilled to remove tetrahydrofuran, made alkaline with K_2CO_3, and extracted with AcOEt. The extract was dried over anhyd. K_2CO_3 and crystalline residue obtained upon removal of the solvent was digested with petr. ether. The material insoluble in petr. ether was recrystallized from Me_2CO to colorless needles (XIII), m.p. 157~158°; yield, 400 mg. (40%). *Anal.* Calcd. for $C_{15}H_{28}ON_2$: C, 71.38; H, 11.18; N, 11.10. Found : C, 71.17; H, 11.01; N, 11.33.

Hydrochloride : Colorless cubic crystals, m.p. 237~239° (decomp.) (from MeOH-Me_2CO). *Anal.* Calcd. for $C_{15}H_{28}ON_2 \cdot HCl$: C, 62.39; H, 10.04; N, 9.72. Found : C, 62.30; H, 9.99; N, 9.80.

Urethanurea derivative : Colorless needles, m.p. 147° (decomp.) (from AcOEt-petr. ether). *Anal.* Calcd. for $C_{29}H_{38}O_3N_4$: C, 70.99; H, 7.81; N, 11.42. Found : C, 71.27; H, 7.83; N, 11.30.

From the petr. ether extract of the above, 40 mg. of colorless needles, m.p. 53~54°, was obtained, which was found to be matridine (VIII) by mixed m.p. of 54~57°.

Reaction of Matrinic Acid (XII) with Trityl Chloride—A mixture of 130 mg. of matrinic acid (XII) and 300 mg. (2.2 equiv.) of trityl chloride in 4 cc. of pyridine was heated in a water bath for 1.25 hr. This mixture was evaporated *in vacuo* and digested with Et_2O. The Et_2O-insoluble residue was dissolved in water, the solution was acidified with 10% HCl, and extracted with $CHCl_3$. The aqueous layer was made alkaline with K_2CO_3, extracted with Et_2O, washed with water, and dried over anhyd. K_2CO_3. The residue obtained upon removal of the solvent was crystallized with the addition of petr. ether to 130 mg. of colorless prisms, m.p. 74~76°, which was found to be matrine (XIV) by mixed m.p. of 74~75° and elemental analysis. *Anal.* Calcd. for $C_{15}H_{24}ON_2$: N, 11.28. Found : N, 11.37.

Reaction of Matrinol (XIII) with Tosyl Chloride—A mixture of 130 mg. of matrinol and 220 mg. (1.1 equiv.) of tosyl chloride in 2 cc. of pyridine was refluxed in an oil bath for 4 hr. This mixture was evaporated *in vacuo*, dissolved in ice-water, and extracted with Et_2O. The extract was washed with water, dried over anhyd. K_2CO_3, and 70 mg. of an orange oil was obtained upon removal of the solvent. This oil was dissolved in petr. ether and filtered through a column of alumina. From the filtrate, colorless needles, m.p. 56~59°, were obtained, whose m.p. was undepressed on admixture with matridine (VIII).

Summary

Diazotization of decarbonylmethylmatrinamine (I) with silver nitrite in 10% hydrobromic acid yielded decarbonylmethylmatrinol (II) and the quaternary salt (III). Tosylation of matrinol (XIII) gave matridine (VIII), and reaction of (XIII) with trityl chloride gave matrine (XIV) quantitatively. The facile ring-closure of these compounds may be explained by the fact that the terminal end of the side chain is sterically very close to the nitrogen atom in ring-C.

(Received May 10, 1960)