13. **Yoshio Ban**: Studies on the Synthesis of Emetine. II.[1] Synthesis of Rubremetinium Bromide.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**)

In the preceding paper,[1] Sugasawa and Fujii described the synthesis of 1-(N-benzyl-2-oxo-5-ethyl-4-piperidylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (compound B in the preceding paper) as preliminaries to the synthsis of emetine, and they expressed their view that synthesis of emetine would probably be achieved by substituting homoveratrylamine for benzylamine at the first stage of their synthesis.

Based upon this idea the synthesis of emetine was now investigated, but unfortunately, differing from their case, most of the intermediates were not obtained crystalline in the present synthesis, thus rendering the final decision of the formation of emetine impossible. So it was decided to oxidize the penultimate compound, which may be called *rac*-tetradehydroemetinium salt (XII), when scarlet crystalline solid was produced, which was proved to be structurally identical with the natural rubremetinium salt by direct comparison of their ultraviolet and infrared absorption spectra.

Thus, it was proved that the synthesis of *rac*-emetine was virtually effected by the present method and further effort will be focussed upon the isolation of *rac*-emetine in substance.

The synthesis of rubremetinium salt (I) is not without precedent. After having proved the correctness of the Robinson formula of emetine by studying its Hofmann degradation reactions,[2] Openshaw *et al.*[3] made a preliminary report of their successful synthesis of rubremetinium bromide, which result was later described in detail with some supplemental experiments.[4] During the years of 1951~1953, Preobrazhenskii *et al.*[5] also claimed to have succeeded in synthesizing rubremetinium salt, *rac*-emetine, and also *l*-emetine.

The present synthesis started from β-(3,4-dimethoxyphenyl)-ethylamine (referred to as homoveratrylamine hereafter), ethyl malonic acid, and formaldehyde, which formed N-homoveratrylaminomethylethylmalonic acid (II) in an excellent yield. Decarboxylation of the latter was best effected by boiling with 60% acetic acid and after evaporating to dryness (III being formed), the residue was esterified with ethanol and dry hydrogen chloride. The ester (IV) thus obtained was then ethoxycarbonylacetylated to yield the amide (V), which was then cyclized under the Dieckmann conditions, furnishing a fluorescent syrup (VI), which gave brilliant red ferric chloride test. When (V) was cyclized by heating with phosphoryl chloride, there was produced an isoquinoline derivative (V′) of m.p. 78~79°, which had already been synthesized by Openshaw *et al.*[4] by a different method as an intermediate in their synthesis of rubremetinium salt. Judging from the melting point of (V′) (76~77° accoding to them) there is hardly any doubt of its identity.

The ketonic fission of (VI) could be carried out by boiling either with 6.7% hydrochloric acid or 10% acetic acid. The time required was longer by the latter acid, but this was found preferable, because the former acid sometimes caused the fission of the

* Hongo, Tokyo (伴 義雄).

1) Part I: This Bulletin, **3**, 47(1955).
2) Battersby, Openshaw: Experientia, **5**, 398(1949); J. Chem. Soc., **1949**, 3207, S59, S67; Nocross, Openshaw: J. Chem. Soc., **1949**, 1174.
3) Battersby, Openshaw: Experientia, **6**, 387(1950).
4) Battersby, Openshaw: J. Chem. Soc., **1953**, 2463.
5) Preobrazhenskii, *et al.*: C. A., **45**, 7577(1951); **46**, 8117, 8130(1952); **47**, 5949(1953).

lactam ring also, with simultaneous loss of carbon dioxide, giving a basic substance.

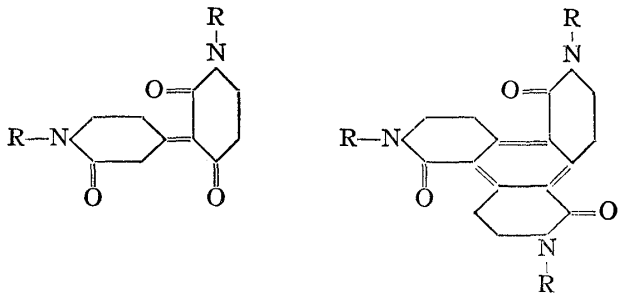
The crude ketone (VII) thus obtained was brown, slightly fluorescent viscous oil, dissolved in caustic soda solution and was characterized as its phenylhydrazone and semicarbazone. At variance with N-benzyl-2,4-dioxopiperidine,[6] which soon underwent bimolecular condensation at ordinary temperature and trimolecular condensation at higher temperature, this ketone (VII) was found to be quite stable, probably because of the deactivating influence of the ethyl group upon the adjacent ketonic function.

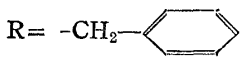
In order to effect the isoquinoline cyclization at this stage, this ketone (VII) was treated with ethyleneglycol in the presence of *p*-toluenesulfonic acid, yielding the corresponding ethyleneketal (VII') in a good yield, but the latter compound was found not stable enough toward phosphoryl chloride in boiling benzene, thus the expected isoquinoline base was not obtained. The ketone also did not behave as ordinary ketones towards the Reformatsky and Rupe reactions, probably due to its highly enolyzed nature; the starting ketone being recovered.

The ketone was then condensed with ethyl cyanoacetate, giving the condensation product (VIII) as a caramel-like solid. Though the crude yield attained was as high as 80% of the theoretical, it could not be induced to crystallize and so was directly esterified followed by hydrolysis and decarboxylation to give the acrylic acid (IX). The latter formed hard brown syrup and dissolved in a bicarbonate solution, from which flocculent solid separated on being acidified, which soon turned resinous. Since the purification of (IX) thus appeared difficult, it was hydrogenated catalytically over the Adams platinum. After about a half of the necessary amount of hydrogen was absorbed, the reduction became sluggish and so was revived by adding a new batch of the same catalyst, thus about 80% of the required amount of hydrogen was fixed at 45°. The saturated acid (X) was again a syrup, which resisted all efforts to induce it to crystallize and so was directly treated with thionyl chloride, giving the correponding syrupy chloride, which was then condensed with homoveratrylamine. The amide (XI) was obtained as a clear brown, viscous syrup, which was submitted to the action of phosphoryl chloride. The double cyclization appeared to proceed smoothly, yielding the salt (XII : X=Cl), of which the corresponding iodide-hydriodide separated as yellowish brown solid.

Since none of the intermediates from (VII) to (XII) was obtained crystalline, a rigid structural proof of the latter was desirable. This compound (XII) corresponds to tetradehydroemetinium salt, which is supposed to be the intermediate of rubremetinium salt from emetine, hence its conversion into the latter salt was attempted. Thus when (XII) was treated with mercuric acetate in dilute acetic acid, there was produced orange red well-defined needle-shaped crystals, the chloride of which behaved just like the natural rubremetinium chloride. The correspoding bromide was also prepared and compared directly with the bromide prepared from natural emetine. When air-dried, both speci-

6) Sugasawa, Oka : This Bulletin, **2**, 87(1954). Bi- and tri-molecular condensation products are well-defined solid, probably having the following structures, respectively.





mens melted at 115~120°, and after dried at 95° for 10 hours over calcium chloride *in vacuo*, the synthetic product contained 4.5 moles of water of crystallization and melted at about 185° after sintering towards 120°. By further drying at 98° for 14 hours *in vacuo*, it lost 1 mole of water of crystallization and sintered at 160° and then melted at 180~185° with decomposition, turning to a reddish liquid.

According to Pyman, rubremetinium bromide from natural emetine melts at 115~120° when air-dried and contains 6 moles of the water of crystallization, and a specimen dried at 100° *in vacuo* sinters at 160~180° and melts at 195~200°, decomposing gradually. The bromide prepared from natural emetine in my hands and dried at 98° for 14 hours *in vacuo* over phosphorus pentoxide behaved quite similarly with the synthetic sample, sintering at about 115° and turning into a reddish liquid at 180~185°, but differing from the latter, it contained 4.5 moles of the water of crystallization.

The more rigorous proof of their structural identity was provided by their ultraviolet and infrared spectra, as shown in Figs. 1 and 2.

The accompanying chart delineates the course of the present synthesis.

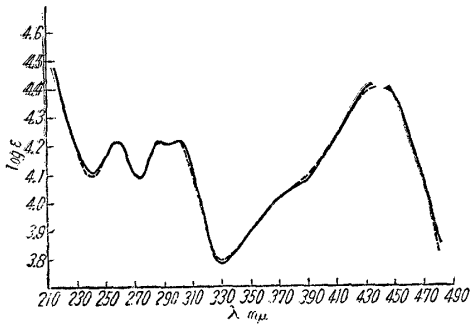


Fig. 1. Ultraviolet Absorption Spectra (in water)
—— Natural rubremetinium bromide
------ Synthetic rubremetinium bromide

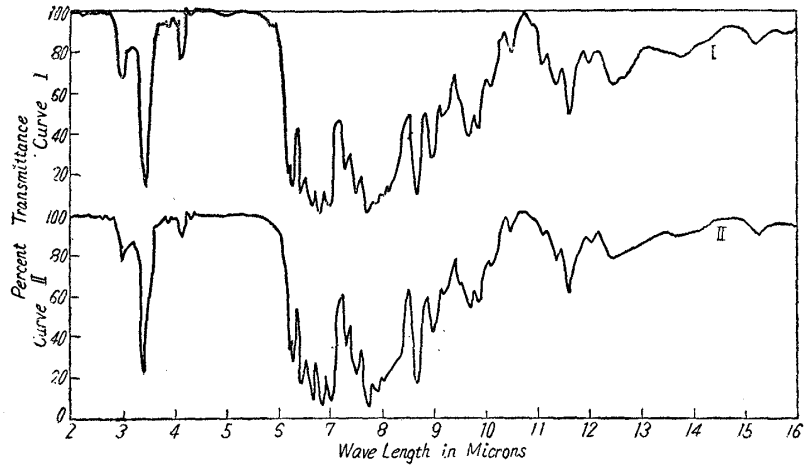


Fig. 2. Infrared Absorption (in chloroform)

I. Natural rubremetinium bromide

II. Synthetic rubremetinium bromide

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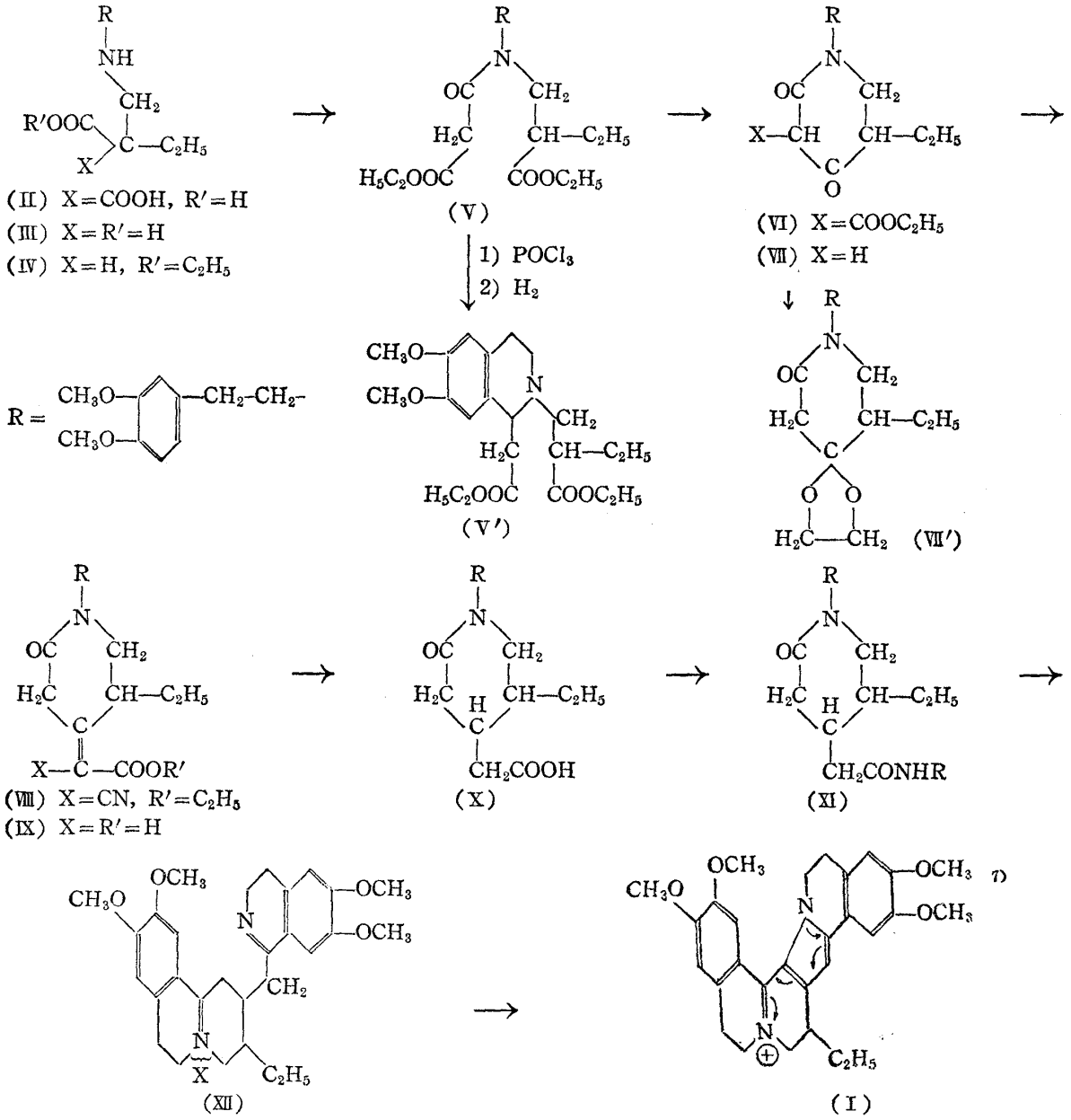
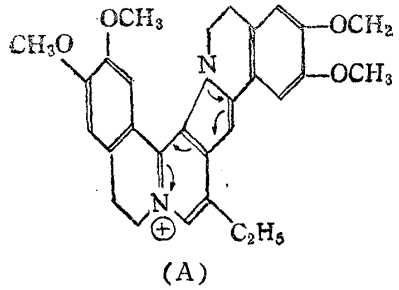
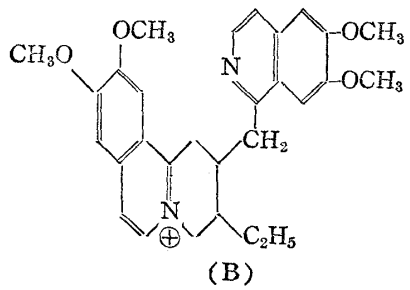


7) The structure of rubremetinium salt is not yet rigidly established. Openshaw[4] proposed formula (I) for this compound, in which + center resonates between the two nitrogen atoms causing deep coloration of this substance as in the case of the well-known cyanine dyes. Woodward's formula (A) requires $C_{29}H_{31}O_4N_2X$ instead of $C_{29}H_{33}O_4N_2X$ as is usually accepted for rubremetinium salt, while that of Karrer (B) has the fundamental difficulty in explaining the non-basicity of both nitrogen atoms in this compound. These are the reasons why the formula (I) of Openshaw was adopted here.


(A)


(B)

Experimental

(Homoveratrylaminomethyl)ethylmalonic Acid (II)—Homoveratrylamine (17 g.) and ethylmalonic acid (18.6 g.) were dissolved in hyd. EtOH (50 cc. EtOH and 105 cc. water) and to this solution was added 9.4 g. of 30% HCHO, separating a white crystalline solid after some time. After standing overnight in an ice chest, the solid was collected on a filter and washed with water and then with MeOH. This acid (II) melts at 164.5°(decomp.) and was pure enough for the next step. Yield, 27.6 g. or 93%. Purified by dissolving in dil. NH_4OH, filtered, and then acidified with AcOH, separating in colorless plates of m.p. 166°(decomp.). The Liebermann test, positive. Sparingly soluble in water and common organic solvents in the cold. *Anal.* Calcd. for $C_{16}H_{23}O_6N$: C, 59.1; H, 7.1; N, 4.3. Found: C, 58.8; H, 7.6; N, 4.25.

Ethyl α-Homoveratrylaminomethylbutyrate (IV)—The malonic acid (II : 20 g.) in 200 cc. of 60% AcOH was heated in an oil bath at 160° for 7 hrs., until the evolution of CO_2 ceased. AcOH was evaporated *in vacuo*, leaving a faint yellow syrup, which, after being dried in a vacuum desiccator overnight, was dissolved in 140 cc. of abs. EtOH and the solution was saturated with dry HCl gas at a room temp. The mixture was then warmed on a steam bath at 80° for 2.5 hrs. without introducing HCl gas any more. EtOH was then evaporated *in vacuo*, and the residue was dissolved in water, once shaken with ether, and then basified with Na_2CO_3 solution, separating an oily ester, which was taken up in benzene, washed with satd. NaCl solution, dried, and evaporated. The residue distilled at 160~165°(0.02 mm. Hg), forming colorless viscous oil, which gave a positive Liebermann test. Yield, 12.3 g. or 65%.

Picrate : Yellow minute rhombic plates, m.p. 129~130.5°, from EtOH. *Anal.* Calcd. for $C_{23}H_{30}O_{11}N_4$: C, 51.3; H, 5.6; N, 10.4. Found : C, 51.0; H, 5.7; N, 10.8.

Ethyl α-(N-Ethoxycarbonylacetohomoveratrylaminomethyl)butyrate (V)—The foregoing ester (12.3 g.) in 40 cc. of benzene was acylated with the chloride of ethyl hydrogen malonate (9 g. in 40 cc. of benzene) under the Schotten-Baumann conditions, using 10% Na_2CO_3 solution. Worked up as usual, a light yellow syrup was obtained which was directly used in the next step. Yield, 15.5 g. or 89.4%.

2-(2-Ethoxycarbonylbutyl)-1-ethoxycarbonylmethyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (V′)—This compound was prepared with the purpose of proving the structure of (V). The latter (V : 4.2 g.) in 24 cc. of pure benzene was refluxed gently with $POCl_3$ (12.6 g.) for 1.5 hrs. On cooling, much petroleum ether was added, causing a reddish brown syrup to separate, which was dissolved in 25 cc. of EtOH, acidified with 5 cc. AcOH, and reduced catalytically over the Adams Pt, absorbing about 1 molar portion of H_2 (240 cc.). The product was isolated as usual, yielding ca. 1 g. of a yellowish syrup, which was covered with hexane and kept in an ice chest, forming a crystalline solid in a low yield. Separates as colorless needles from hexane, m.p. 78~79°. Openshaw gave m.p. 76~77° for this compound. *Anal.* Calcd. for $C_{22}H_{33}O_6N$: C, 64.7; H, 8.15; N, 3.45. Found: C, 64.7, H, 8.1; N, 3.4.

1-Homoveratryl-2, 4-dioxo-3-ethoxycarbonyl-5-ethylpiperidine (VI)—The ester (V : 10.95 g.) in 20 cc. of pure xylene was poured into a suspension of Na dust (0.6 g.) in 20 cc. of xylene. On warming the mixture at 50~60°, the reaction started with evolution of H_2, which became gentle after some time. The temp. was now raised to 100~110°, thence a vigorous reaction set in again and all the Na disappeared after about 20 mins.' heating. The whole was boiled gently for additional 2 hrs., when the mixture separated into two layers, of which the Na-salt of the reaction product formed the lower layer. On cooling, the upper layer was decanted and washed with water. The bottom layer was now dissolved in this aqueous washing, once shaken with ether, and then acidified with HCl with cooling, separating an oily substance. The latter was collected in benzene and worked up as usual, furnishing a yellowish brown fluorescent syrup, which gave a scarlet $FeCl_3$ test. Yield, 8.65 g. or 88.8%. This was submitted to ketonic fission.

1-Homoveratryl-2, 4-dioxo-5-ethylpiperidine (VII)—A mixture of the crude keto-ester (4.75 g.) and 30 cc. of 6.7% HCl was heated in an oil bath. At about 80°, CO_2 began to evolve and became vigorous at 90°. The reaction was completed by refluxing the mixture for 1.5 hrs. (oil bath temp., 110~120°). On cooling, the resultant ketone was taken up in benzene, which solution was successively washed with $NaHCO_3$ solution and water, dried, and evaporated, leaving 3.9 g. of a slightly fluorescent brownish viscous syrup. The kotonic fission was also carried out advantageously by boiling with 10% AcOH for 3 hrs. in place of HCl. This ketone dissolved in NaOH solution, but scarcely in $NaHCO_3$ solution.

Phenylhydrazone : Pale yellow needles from EtOH, m.p. 169°(decomp.). *Anal.* Calcd. for $C_{23}H_{29}O_3N_3$: C, 69.9; H, 7.3; N, 10.6. Found : C, 69.9; H, 7.6; N, 10.5.

Semicarbazone : Colorless needles, m.p. 169°, from EtOH. *Anal.* Calcd. for $C_{18}H_{26}O_4N_4$: C, 59.7; H, 7.2; N, 15.5. Found : C, 60.2; H, 6.9; N, 15.3.

1-Homoveratryl-2-oxo-4-ethylenedioxy-5-ethylpiperidine (VII′)—The ketone (VII : 4.2 g.), ethyleneglycol (0.95 g.), toluene-*p*-sulfonic acid (0.2 g.), and abs. benzene (15 cc.) were boiled in an oil bath (110~120°) in a Cope apparatus until no more water distilled over (ca. 5 hrs.). On cooling, the

reaction mixture was shaken twice with dil. NaOH solution to remove the unreacted ketone and *p*-toluenesulfonic acid, washed with H_2O, dried, and evaporated, leaving 3.25 g. of an oily residue, which distilled at 275~280°(bath temp., 0.07 mm. Hg). *Anal.* Calcd. for $C_{19}H_{27}O_5N$: C, 65.3; H, 7.8; Found : C, 65.0; H, 7.7.

Ethyl 1-Homoveratryl-2-oxo-5-ethyl-4-piperidylidene-α-cyanoacetate (VIII)—A mixture of the ketone (VII : 14.5 g.), ethyl cyanoacetate (4.2 g.), glacial AcOH (2.46 g.), $AcONH_4$ (0.9 g.), and abs. toluene (30 cc.) was boiled in a Cope apparatus for 7 hrs., separating ca. 1.5 cc. of water. Another batch of the same amount of AcOH and $AcONH_4$ was added and the mixture was boiled for another 7 hrs. Toluene was now evaporated and the residue was dissolved in benzene, which solution was shaken with 10% NaOH solution, separating a heavy syrupy precipitate. The supernatant benzene layer was shaken 3 times more with 10% NaOH solution, each time separating some more heavy syrup. The combined syrupy residue was then dissolved in $CHCl_3$, washed with satd. NaCl solution, dried, and evaporated *in vacuo*, leaving a brown caramel-like solid. Yield, 15 g. or 79%. Since this substance could not be purified, it was directly used in the next step.

1-Homoveratryl-2-oxo-5-ethyl-4-piperidylideneacetic Acid (IX)—The foregoing ester (5 g.) was dissolved in a mixture of 37 cc. abs. EtOH and 0.37 g. H_2O. Dry HCl gas was now passed through this solution until saturation. The whole was now refluxed on a steam bath for 2 hrs., during which time dry HCl gas was introduced, separating NH_4Cl as a white solid. After being left standing overnight, EtOH was removed *in vacuo*, and the residue was added with HCl (50 cc. of 20%) and some AcOH to give a homogeneous solution, and the whole was refluxed for 8 hrs., giving off CO_2. On cooling, the solvents and HCl were removed *in vacuo* and the residue was taken up in AcOEt, which solution was repeatedly extracted with 10% Na_2CO_3 solution. The combined brownish Na_2CO_3 solution was filtered through a wet filter and the filtrate was acidified with conc. HCl with cooling. Fluffy substance separated was now taken up in AcOEt, washed, dried, and evaporated, leaving a syrupy residue. The residue was dissolved in EtOH, treated with charcoal, and the solvent was removed *in vacuo*, giving 1.85 g. of a hard brown syrup (46%), which was dissolved again in $NaHCO_3$ solution and acidified, separating a fluffy solid. All efforts to induce this substance and its derivatives to crystallize ended fruitless and so it was directly used in the following step.

1-Homoveratryl-2-oxo-5-ethyl-4-piperidylacetic Acid (X)—The acid (IX : 0.85 g.) in EtOH was reduced catalytically over the Adams Pt, 45 cc. of H_2 being absorbed in ca. 5 hrs. (required, 52 cc.). The product (0.85 g.) was obtained as a faint yellow syrup, which again resisted all efforts to crystallize.

1-Homoveratryl-2-oxo-5-ethyl-4-piperidylacetohomoveratrylamide (XI)—The foregoing acid (0.85 g.) in 5 cc. $CHCl_3$ was treated with $SOCl_2$ (1 g.) dissolved in 5 cc. $CHCl_3$. After being gently refluxed on a water bath, the solvent was removed *in vacuo* together with the excess of $SOCl_2$, furnishing a syrupy residue, which was dissolved in $CHCl_3$ and reacted with homoveratrylamine (2 g. in 5 cc. $CHCl_3$) with ice cooling and stirring. After standing overnight, the reaction product was washed successively with 10% Na_2CO_3 solution, 10% HCl, and water, dried, and evaporated. The yellow syrupy residue (1.25 g.), which gave a negative Beilstein test, was directly used in the next step.

9,10,1″,2″-Tetradehydroemetinium Chloride (XII)—The foregoing amide (1.25 g.) was dissolved in pure toluene (5 cc.) and the mixture was refluxed with 6.5 cc. of $POCl_3$ for 1.5 hrs. After evaporating toluene and the excess of $POCl_3$, the residue obtained was washed with ether and then dissolved in 10% HCl, added with a little EtOH, treated with charcoal, and evaporated. The residue was then dissolved in water containing a little EtOH, and to this solution was added KI, separating the iodide-hydriodide as yellowish brown amorphous solid, which was taken up in $CHCl_3$, dried, and evaporated. The residual salt was converted into the corresponding chloride-hydrochloride as usual, which formed a reddish syrup (540 mg.).

Rubremetinium Bromide (I)—Oppenshaw's method was applied to the afore-said salt. A solution of this salt (540 mg.) in 5.4 cc. H_2O, containing 110 mg. of anhyd. AcOK was warmed on a steam bath and to this solution was added a solution of $(AcO)_2Hg$ (1.4 g.) in a mixture of 6.5 cc. H_2O and 0.43 g. AcOH, separating AcOHg immediately. The whole was refluxed in an oil bath (125°) for 1 hr. On cooling, the solid was filtered and successively washed with H_2O, EtOH, and acetone, and the combined washings was evaporated *in vacuo*. The residue obtained was added to the original filtrate and the mixture was again refluxed with 0.65 g. of $(AcO)_2Hg$ for 2 hrs. Through this hot solution, H_2S stream was passed until saturation and HgS filtered off. HgS was treated with a boiling mixture of 100 cc. EtOH and acetone, filtered, and the filtrated was combined with the original filtrate. The solution was now boiled with charcoal and filtered through a wet filter, giving a clear orange red solution, which was concentrated *in vacuo* to ca. 20 cc. A few drops of conc. HCl were added to this solution, rapidly separating orange red needle crystals, which were filtered after being kept in an ice chest over night.

Rubremetinium chloride thus prepared melted at about 120° with effervescence. It dissolves in H_2O, giving a clear yellow solution, but is sparingly soluble in dil. HCl, thus behaving quite like rubremetinium chloride from emetine. The correspoding bromide was prepared by conversion with KBr

and was purified once from 10% KBr solution and twice from water, forming orange red needles, identical with the natural salt in appearance. Air-dried, it melted at 115~120° with decomposition. When dried at 95° for 10 hrs. over $CaCl_2$ *in vacuo*, it sintered at 120° and then gradually liquefied to a red syrup at about 185° with decompositon. *Anal.* Calcd. for $C_{29}H_{33}O_4N_2Br \cdot 4.5\,H_2O$: C, 54.9; H, 6.7; N, 4.4. Found : C, 54.8; H, 6.6; N, 4.9.

When this was further dried at 98° for 14 hrs. on P_2O_5 *in vacuo*, it lost 1 mole of H_2O of crystallization and sintered at about 165° and melted towards 180~185° with decomposition, giving a red liquid. *Anal.* Calcd. for $C_{29}H_{33}O_4N_2Br \cdot 3.5\,H_2O$: C, 54.5; H, 6.5; N, 4.5; (4.5~3.5) H_2O, 2.8. Found : C, 54.8; H, 6.25; N, 4.0; H_2O, 3.1.

For comparison, the authentic rubremetinium bromide was prepared from natural emetine, which, when purified from H_2O, formed orange red needles. When dried at 98° for 14 hrs. *in vacuo*, it melted at 180~185° with decomposition after sintering at 115°, which analyzed for a hydrated salt with 4.5 moles of H_2O of crystallization. *Anal.* Calcd. for $C_{29}H_{33}O_4NBr \cdot 4.5\,H_2O$: C, 54.9; H, 6.7; N, 4.4. Found : C, 55.15; H, 6.6; N, 4.4.

Summary

Synthesis of *rac*-emetine was attempted on the working basis described in the preceding paper,[1] starting from homoveratrylamine, formaldehyde, and ethylmalonic acid. Distinct from the former case, most of the important intermediates were not obtained in a crystalline state, rendering the structure of the ultimate compound ambiguous. When however the penultimate compound, tetradehydroemetinium salt (XII) was submitted to dehydrogenation by means of mercuric acetate, there was obtained *rac*-rubremetinium bromide (I) in beautifully crystallized state. Structural identity of this salt with the one prepared from natural emetine was established through the direct comparison of their ultraviolet and infrared spectra. Evidence was thus provided for the correctness of this route for the synthesis of emetine.

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