[Chem. Pharm. Bull. 13(7) 775～785 (1965)]
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102. **Yoshio Ban and Masanao Terashima** : Studies on the Structure of (+)-Rubremetinium Cation. A New Synthesis of C-Bisnorrubremetinium Cation and its Model Compound.[*1]

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Emetine (I), a principal alkaloid of *Uragoga ipecacuanha* BAILL., is dehydrogenated with a variety of mild acidic oxidizing agents such as ferric chloride,1) iodine,2) bromine3) and mercuric acetate4) to afford rubremetinium salt, which is a salt of an optically active quaternary base, crystallizing in beautiful orange-red needles. In regard to the structure of rubremetinium salt, the formula Ⅱ ($C_{29}H_{33}O_4N_2X$) was proposed by Battersby, Openshaw and Wood5) who claimed that the following characteristics of this salt could be well explained by this formula : (i) The orange-red color of the salt. (ii) One of the two nitrogen atoms is quaternary and the other nonbasic. (iii) The similar salt being obtained from emetamine (I′) is different from this salt. (iv) The hydrogenation of rubremetinium salt gave the dihydro-derivative, which was oxidized with mercuric acetate to recover the original salt. The existence of pyrrole nucleus in the molecule of rubremetinium salt, is suggested by the positive Ehrlich reaction of the crude zinc reduction product of the salt. Contradictory to this proposal, the formula (Ⅲ, $C_{29}H_{31}O_4N_2X$) was preferred by Tietz and McEwen6) who referred to it as Woodward's formulation, which was mainly based on the investigation of the reduction product and the stable character of the salt. They assumed that the stable character could not be expected by the formula (Ⅱ), since Ⅱ contains two orthodihydropyridine rings which should be quite unstable.[*3] In this formula (Ⅲ) containing no asymmetric center, the optical activity of the salt is to be explained by nonplanarity of the molecule which is due to the intramolecular steric hindrance at the positions marked with an asterisk.[*4]

As for the reductions of rubremetine under various conditions which were carried out independently by three groups,6～8) the experimental results were contradictory each other, hence any definite conclusion could not be reached. In 1955 Openshaw9) claimed the correctness of formula (Ⅱ) by providing further supporting data. He quoted

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[*1] Preliminary communications of this paper have been published, Y. Ban and M. Terashima : Tetrahedron Letters, No. 22, 796 (1961); A. Brossi, M. Gereke, A.R. Battersby, J.C. Turner, Y. Ban, M. Terashima : Experientia, in press.

[*2] Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 寺島正直).

[*3] It is shown that several compounds containing two orthodihydropyridine rings synthesized in this laboratory are susceptible to mercuric acetate oxidations. Y. Ban, M. Nakagawa : This Bulletin, to be published.

[*4] The specific rotation of rubremetinium chloride (Ⅱ, X=Cl) was measured by H.T. Openshaw to be $[\alpha]_D^{15}$ +52.0°, $[\alpha]_{5461}^{15}$ +25.4° (c=0.4, water). See reference 8.

1) F.H. Carr, F.L. Pyman : J. Chem. Soc., **1914**, 1591.
2) *a*) P. Karrer: Chem. Ber., **49**, 2057 (1916). *b*) F.L. Pyman: J. Chem. Soc., **1917**, 419; *Ibid.*, **1918**, 222.
3) H. Staub : Helv. Chim. Acta, **10**, 826 (1927).
4) *a*) A.R. Battersby, H.T. Openshaw : J. Chem. Soc., **1962**, 567, 59; *b*) A. Brossi, O. Schnider : Helv. Chim. Acta, **45**, 1899 (1962).
5) A.R. Battersby, H.T. Openshaw, H.C.S. Wood : Experientia, **5**, 114 (1949).
6) R.F. Tietz, W.E. McEwen : J. Am. Chem. Soc., **75**, 4945 (1953); Cf. R.N. Hazlett, W.E. McEwen : *Ibid.*, **73**, 2578 (1951).
7) P. Karrer, O. Ruttner : Helv. Chim. Acta, **33**, 291 (1950).
8) H.T. Openshaw, H.C.S. Wood : J. Chem. Soc., **1952**, 391.
9) H.T. Openshaw : Chemical Society Special Publication No. 3, p. 28.

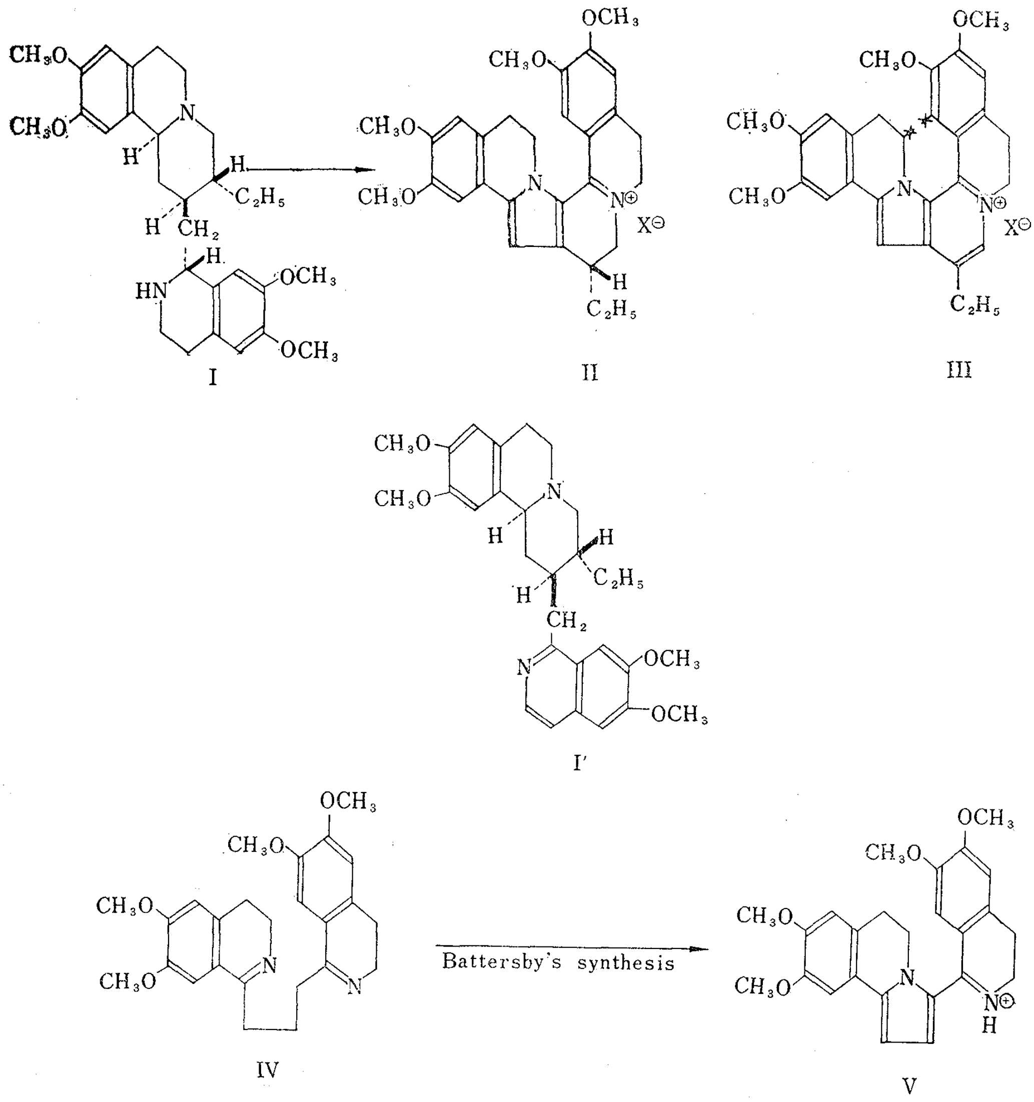

Chart 1.

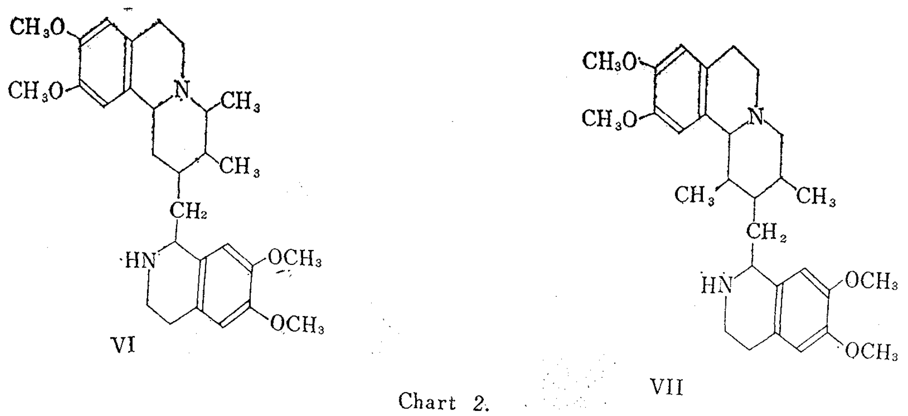

Chart 2.

the Battersby synthesis of the model compound (Ⅴ) which had been obtained through mercuric acetate oxidation of Ⅳ. The compound (Ⅴ) which contains the same chromophore as Ⅱ has been reported to possess an identical absorption spectrum in comparison with that of rubremetinium bromide, but the details seem not to have yet been published.

On the other hand, Preobrazhenskii[10] synthesized emetine homologs, Ⅵ and Ⅶ, the former of which was oxidized with bromine or iodine to afford the material containing the identical ultraviolet spectrum with that of rubremetine, but the latter gave nothing like the above by the similar oxidation. This experiment confirmed the necessity of non-substitution at C-1 position of emetine for production of rubremetinium cation. Accordingly, although several structures had been suggested for the rubremetinium cation, the alternative structures, Ⅱ and Ⅲ, which seem compatible with the characteristics of the salt, remained to be determined.

Meanwhile, the total syntheses of this compound have been already achieved by several groups,[11] but every known synthesis involved the oxidation process at the final

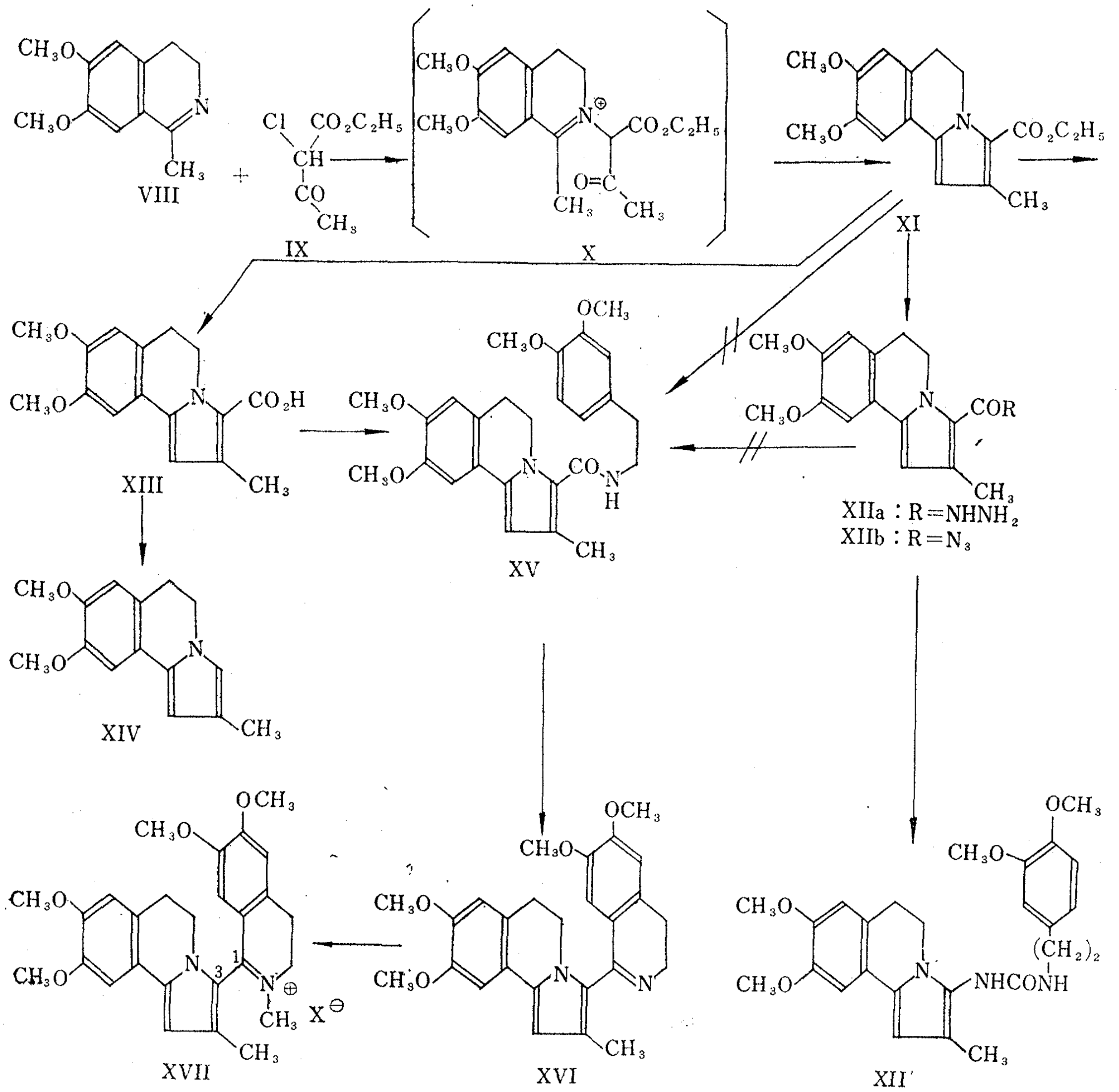

Chart 3.

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10) P. B. Evstigneeva, N. M. Kashnikova, M. S. Bainova, N. A. Preobrazhenskii : Zh. Obshchei Khim., 28, 1184 (1958).

11) *a*) A. R. Battersby, H. T. Openshaw : Experientia, **6**, 387 (1950); A. R. Battersby, H. T. Openshaw, H. C. S. Wood : J. Chem. Soc., **1953**, 2463. *b*) R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova, N. A. Preobrazhenskii : Dok. Akad. Nauk SSSR, **75**, 539 (1950); Chem. Abstr., **45**, 7577 (1951); Zh. Obshchei Khim. (J. Gen. Chem. U. S. S. R.), **22**, 1467 (1952); Chem. Abstr., **47**, 5949 (1953). *c*) S. Sugasawa, Y. Ban : Proc. Japan Acad., **31**, 31 (1955); This Balletin, **3**, 53 (1955); T. Fujii : This Bulletin, **6**, 591 (1958). *d*) M. Pailer, G. Beier : Monatsh. Chem., **88**, 830 (1957).

step, which did not give the accurate number of hydrogen atoms eliminated from the penultimate product and also gave no definite evidence about the existence of a pyrrole ring. This is the reason why none of the above syntheses established its structure. In this paper, we wish to report the detail of a new synthesis of C-bisnorrubremetinium salt and its relative compound containing the same chromophore as that of the formula (Ⅱ), which did not involve *any oxidation process.* This result, combined with the nuclear magnetic resonance data, confirmatively supported the correctness of the formula (Ⅱ) for rubremetinium cation.

The condensation of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (Ⅷ) with ethyl 2-chloroacetoacetate (Ⅸ) was carried out by heating in absolute ethanol to afford the pyrrocoline derivative (Ⅺ) in a good yield. This type of condensation is known in the literature,12) and in most cases the intermediate (cf. X) is usually isolated and converted into the pyrrocoline derivative on treatment of it in alkaline medium. Nevertheless, in the present case, the pyrrocoline derivative was obtained directly from the compound (Ⅷ), without isolation of any type of intermediate (cf. X), even though other solvents were used (for instance, benzene). The ester function in Ⅺ is considered to be rather unreactive since the condensation of Ⅺ with 3,4-dimethoxyphenethylamine was attempted in vain to get the amide (XV). The ester was also stable towards aqueous hydrazine and the corresponding hydrazide (Ⅻa) could only be prepared when anhydrous hydrazine was employed. The attempt of converting the above hydrazide (Ⅻa) to the amide (XV) through the condensation of the corresponding azide (Ⅻb) with 3,4-dimethoxyphenethylamine were unsuccessful, affording colorless needles, m.p. 195.5 ~197°, which was assumed to be Ⅻ′ according to its infrared (3324, 1638 cm^{-1} (NHCONH)) and ultraviolet spectra. Subsequently, the ester (Ⅺ) was hydrolyzed with ethanolic potassium hydroxide solution and the resulting potassium salt of the acid was carefully neutralized with an equivalent quantity of acetic acid under ice-cooling to yield the free acid (XⅢ). This acid (XⅢ) was rather unstable, because even when it was treated with the excess of acetic acid under ice-cooling, decarboxylation gradually proceeded to afford XIV, or when heated in a neutral medium such as benzene, a quantitative yield of XIV resulted.

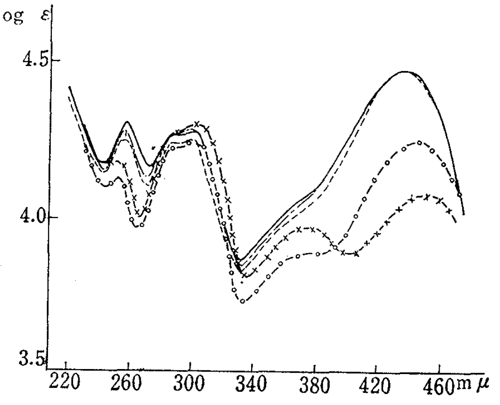

Fig.1. Ultraviolet Absorption Spectra

(1) —○— XVI in N/100 HCl
(2) —×— XVII in EtOH
(3) ——— (+)-Rubremetinium bromide in H_2O (A. R. Battersby)5)
(4) ----- C-Bisnorrubremetinium bromide in H_2O (M. Kirisawa)18)
(6) —·— C-Bisnorrubremetinium bromide in H_2O(present synthesis)

Consequently, the conversion of XⅢ into XV required a careful treatment in order to avoid the decarboxylation, and after a number of fruitless experiments, the condensation of XⅢ with 3,4-dimethoxyphenethylamine was conducted in the presence of dicyclohexylcarbodiimide (DCC) to yield XV, although in a low yield. The ultraviolet spectrum of XV is in accordance with the summation of those of Ⅻa and 3,4-dimethoxyphenethylamine. The structure of XV is further supported by its satisfactory elemental analyses and its infrared spectrum, $\nu_{\max}^{\text{Nujol}}$ 3314 (NH), 1620 cm^{-1} (CO-NH).

The amide (XV) was cyclized with phosphorus pentoxide in toluene to afford XVI, which in turn, was heated with dimethyl sulfate in benzene to give the quaternary base (XVⅡ).

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12) Cf. J. Thesing: Chem. Ber., **91**, 1546 (1958); A. E. Tschitschibabin: Ber., **60**, 1607 (1927).

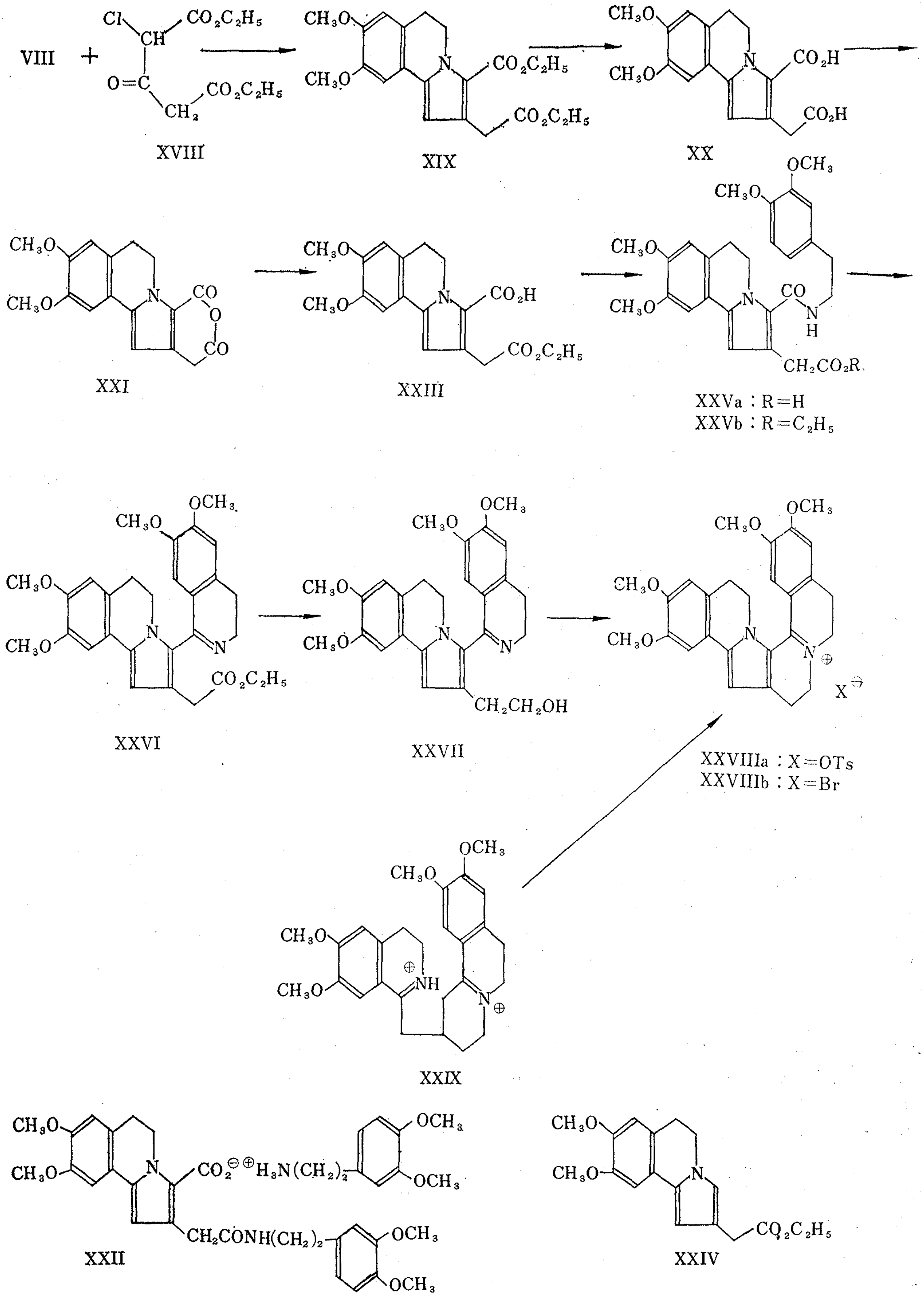
VIII
XVIII
XIX
XX
XXI
XXIII
XXVa : R=H
XXVb : R=C2H5
XXVI
XXVII
XXVIIIa : X=OTs
XXVIIIb : X=Br
XXIX
XXII
XXIV

Chart 4.

The ultraviolet and visible absorptions of XVI in $N/100$ HCl and XVII in a neutral medium are shown as curves (1) and (2) in Fig. 1, respectively.

Although XVI·hydrochloride and XVII possess the similar chromophore, the light absorptions are considerably different, particularly in the visible region, which is presumably dependent upon the non-planarity of the latter molecule. The steric requirements of the methyl group at β-position of pyrrole ring and the N-methyl substituent of the dihydroisoquinoline part in XVII seems not to permit the free rotation around the axis $C_{(3)}$-$C_{(1)}$, but with the former compound (XVI·hydrochloride), steric hindrance only exists to a small extent. The observed similarity of the absorption curves (1) and (2) in comparison with that of (3) is in support of structure (II) for (+)-rubremetinium cation, but it is felt, that the existing differences do not allow to rule out structure (III) rigidly.

Thus, a new synthesis of bisnorrubremetinium salt (XXVIII) was attempted with success, substituting XVIII for IX in the above synthesis. A 2:1 molar mixture of VIII and XVIII was refluxed in ethanol to afford the diester (XIX). The partial hydrolysis of the diester (XIX) to get a half ester acid was attempted but it resulted in failure. For instance, XIX was treated with 1/2 equivalent quantity of ethanolic potassium hydroxide solution to give a mixture of XIX and XX. The hydrolysis of XIX with the barium hydroxide solution gave XX, and in any case a half ester acid was not obtained. Thus, the diester (XIX) was hydrolyzed with 10% ethanolic potassium hydroxide solution to afford the diacid (XX), which is rather stable, compared to the acid (XIII). Namely, the diacid (XX) is only decomposed very gradually in the presence of the excess of acetic acid. In a neutral medium, as for instance boiling xylene, the acid (XX) is almost perfectly stable. Only a very small amount of the decarboxylated material (XIV) was detected from the xylene layer. An attempt to obtain a monosalt of the diacid (XX) was unsuccessful. Subsequently, the acid (XX) was treated with DCC in chloroform to afford the anhydride (XXI), which was contaminated with dicyclohexylurea produced as a by-product. Even after repeated recrystallizations, the obtained material was still contaminated with the above by-product judging from the infrared spectrum, and accordingly this method was given up. Finally, the diacid (XX) was treated with acetic anhydride in benzene to afford the anhydride (XXI) (IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1766, 1720 (CO-O-CO)) in a good yield.

This anhydride (XXI) was reacted with 3,4-dimethoxyphenethylamine with an aim to get the amide (XXVa) to afford the material, m.p. 143° (decomp.), which was assigned to XXII, not XXVa, since its ultraviolet spectrum is in good agreement with the summation of those of XIX and 2 moles of veratryl residues. Furthermore, this assignment was supported by the absorption at $\nu_{\max}^{\text{Nujol}}$ cm^{-1} 3330 (NH) and 1623 (CONH) in its infrared spectrum.

According to this result, the anhydride (XXI) was warmed with pyridine-ethanol to yield the half-ester (XXIII), m.p. 148°, IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} 1736 (COOEt), 1646 (COOH), whose ultraviolet absorption at $\lambda_{\max}^{95\%\text{EtOH}}$ 321 mμ shifted hypsochromically into 295 mμ by heating it to the decomposition point. This shift could be accepted as the elimination of the carboxyl group at an α-position of the pyrrole nucleus.

A small amount of the crystals obtained from the mother liquor of XXIII, was also deduced by its light absorptions (UV $\lambda_{\max}^{95\%\text{EtOH}}$ mμ: 295 and IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1718 (COOEt)), to be XXIV.

To a solution of the half-ester (XXIII) in chloroform was added 1/2 mole equivalent of DCC. After the reaction, there was added 1/2 mole equivalent of 3,4-dimethoxyphenethylamine. The operation of adding the reagents was repeated twice to afford the amide (XXVb) in a better yield, compared to the previous case (XV).

The amide (XXVb) was cyclized with phosphorus pentoxide in toluene to afford the base (XXVI) whose ultraviolet spectra in both acidic and alkaline media are in good agreement with those of XVI. The base (XXVI) was refluxed with lithium aluminum hydride in tetrahydrofuran-ether to afford XXVII, during which time a pale yellow color of the initial mixture was changed to a blue-green. On cooling after the reaction, the color was changed back to the initial pale yellow.

The ultraviolet stectrum of this product (XXVII) was in accordance with that of the starting material. Thus, to a solution of XXVII in anhyd. benzene was added a benzene solution of tosyl chloride and the whole mixture was kept at room temperature. In 10~15 min. orange red crystals began to deposit and were collected after completion of precipitation.

Unexpectedly, the ultraviolet and visible absorption spectra of this material in either a crude or a pure state were in good agreement with that of (+)-rubremetinium cation obtained from the natural (−)-emetine, which made it clear, that the initially formed tosylate cyclized spontaneously. These conversion of XXVII to XXVIIIa proceeded smoothly and no phenomena such as the evolution of gas or the change of the crystal form was observed which could have been indicative of a dehydrogenation process.

The tosylate (XXVIIIa) was converted in the usual manner into the corresponding bromide (XXVIIIb), orange red needles, m.p. 215° (lit. m.p. 236~237° as the trihydrate,[13] m.p. 215°[14]), whose ultraviolet and visible spectra were the same in both crude and pure state, which demonstrated that the conversion process had not been accompanied by any change of the structure.

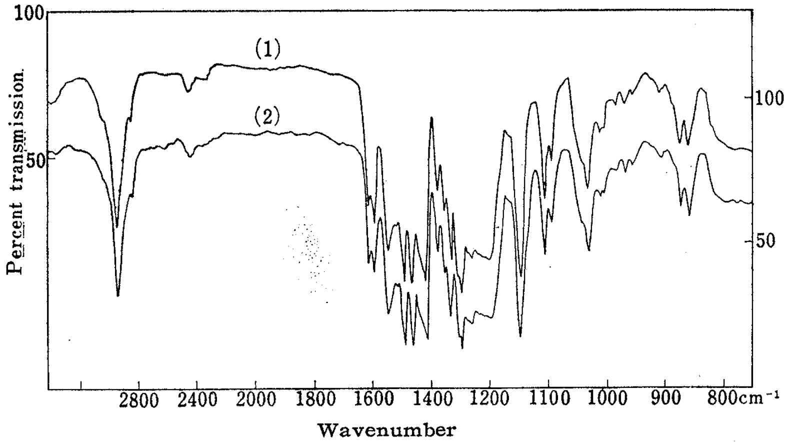

Fig. 2. Infrared Absorption Spectra (in $CHCl_3$)

(1) Bisnorrubremetinium bromide (Kirisawa)
(2) Bisnorrubremetinium bromide (XXVIIIb)(the present synthesis)

The infrared spectrum ((1) of Fig. 2) of this bromide (XXVIIIb) was identical with that of C-bisnorrubremetinium bromide ((2) of Fig. 2) kindly supplied by Professors Sugasawa and Kirisawa who obtained their product by mercuric acetate oxidation of XXIX.[13] The absorption spectra (curves (4) and (5) of Fig. 1) of the bromide (XXVIIIb) are in accordance with that of rubremetinium cation, showing that both compounds have the same chromophore.

Since it could be generally accepted that dehydrogenation does not occur at the final step of the present synthesis of XXVIIIa and XXVIIIb, the formula (II) is confirmatively supported.

This conclusion was further confirmed by the determination of the nuclear magnetic resonance spectrum of (+)-rubremetinium bromide.

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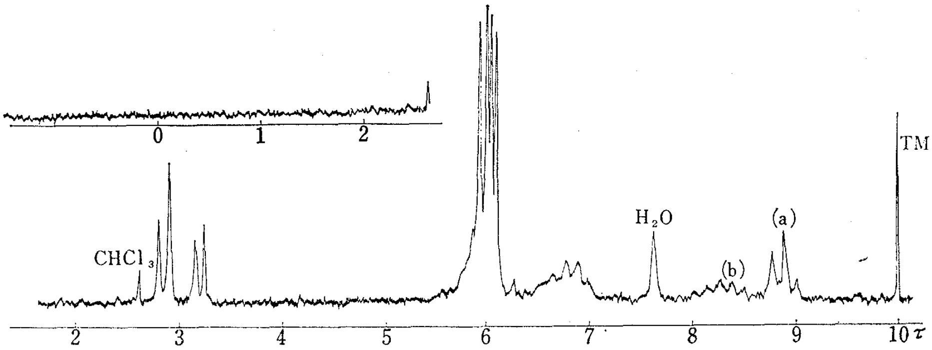
13) M. Kirisawa : This Bulletin, **7**, 38 (1959).
14) M. Pailer, H. Strohmayer : Monatsh. Chem., **83**, 1198 (1952).

As is shown in Fig. 3, there is observed a broad multiplet centered at 8.34 τ which is due to methylene protons of the ethyl side chain. The position and multiplicity of this signal demonstrate that the ethyl group could be attached to a carbon atom bearing at least one proton. And the positions (3.24, 3.15, 2.90, and 2.80 τ) and the numbers (ca. 5) of the aromatic protons are compatible with the Battersby's formula (II) for rubremetine, but imcompatible with the alternative formula (III).



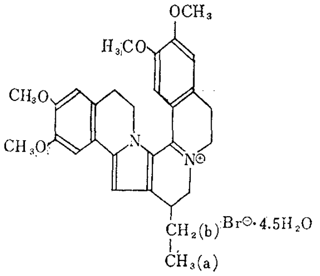


Fig. 3. Nuclear Magnetic Resonance Spectrum of (+)-Rubremetinium Bromide (60 Mc. in $CDCl_3$)

As a conclusion, (+)-rubremetinium cation should be represented by the formula (II) in terms of the absolute configuration, which is derived from the established absolute stereochemistry of (−)-emetine (I).[15]

Experimental

Ethyl 2-Methyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (XI)——To a solution of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (4 g.) in abs. ethanol (15 ml.) was added ethyl chloroacetoacetate (1.6 g.). The whole solution was refluxed for 2 hr. and then allowed to stand at room temperature overnight. The ethanol was removed *in vacuo* to leave a red brownish resin, which was triturated with benzene. The precipitated hydrochloride of the isoquinoline (VIII) was filtered off, the filtrate (the benzene layer) was washed with 10% acetic acid, satd. $NaHCO_3$ and with H_2O. The benzene extract was dried (K_2CO_3), and evaporated to afford the residual gum, which was treated with a small amount of abs. EtOH to give pale yellow pillars, m.p. 89~92°, yield 2.9 g. (94%). The Ehrlich reaction was negative at room temperature, but positive (pale blue) on warming. Recrystallization from aq. EtOH gave colorless needles, m.p. 91~92°. UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ mμ (log ε): 336 (4.47), 324 (4.49). $\lambda_{\min}^{95\%\ \mathrm{EtOH}}$ mμ (log ε): 272 (3.46). IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1664 (COOEt). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.57; H, 6.66; N, 4.44. Found: C, 68.82; H, 6.56; N, 4.57.

2-Methyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid hydrazide (XIIa)——The mixture of the foregoing ester (XI; 1.3 g.) and 100% $NH_2 \cdot NH_2$ (2.5 g.) was heated in an oil-bath kept

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[15] E. E. van Tamelen, J. B. Hester: J. Am. Chem. Soc., **81**, 507 (1959); E. E. van Tamelen, P. E. Aldrich, J. B. Hester: *Ibid.*, **81**, 6214 (1959); A. R. Battersby, S. Garratt: Proc. Chem. Soc., **1959**, 86; A. R. Battersby, R. Binsks, T. P. Edwards: *Ibid.*, **1960**, 3474; A. R. Battersby, S. W. Breuer: Abstracts A, IUPAC XIXth International Congress of Pure and Applied Chemistry, p. 159 (1963, London); Y. Ban, M. Terashima, O. Yonemitsu: Chem. & Ind. (London), **1959**, 569; M. Terashima: This Bulletin, 8, 517 (1960).

at 150° for 10 hr. On cooling, water was added to the reaction mixture to separate the crystalline hydrazide which was collected by filtration. Recrystallization from EtOH afforded colorless prisms, m.p. 197~199°. *Anal.* Calcd. for $C_{16}H_{19}O_3N_3$: C, 63.78; H, 6.31; N, 13.95. Found : C, 63.44; H, 6.27; N, 13.70.

2-Methyl-3-[3-(3, 4-dimethoxyphenethyl)ureido]-8, 9-dimethoxy-5, 6-dihydropyrrolo[2, 1-*a*]isoquinoline (XII′)——The above hydrazide (0.50 g.) was dissolved in 15% AcOH (50 ml.) by warming to give a pale blue solution, to which was added 80 ml. of ether. To the whole solution was added under ice-cooling an aqueous solution (20 ml.) of $NaNO_2$ (0.125 g.). The ether layer was separated and the aqueous layer was extracted with two portions (each 20 ml.) of ether. The combined extract was washed with H_2O, satd. $NaHCO_3$ sol., again with H_2O and dried ($MgSO_4$). A solution of 3,4-dimethoxyphenethylamine (0.5 g.) in abs. ether (20 ml.) was added under ice-cooling to the foregoing azide (Ⅻb) solution. The ether was removed by distillation, during which time abs. benzene was added. The benzene solution was refluxed for 3 hr. and cooled. The whole solution was washed with 5% HCl, H_2O, 10% Na_2CO_3, again with H_2O and dried ($MgSO_4$). The solvent was removed to afford an amorphous solid which was recrystallized from EtOH to give small colorless needles, m.p. 195.5~197°. Yield, 0.22 g. Positive (blue purple at room temperature) in the Ehrlich reaction. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3324, 1638 (NHCONH). *Anal.* Calcd. for $C_{26}H_{31}O_5N_3$: N, 9.03. Found : N, 8.94.

2-Methyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid (XIII)——The foregoing ester (Ⅺ; 1.00 g.) was dissolved in 10% ethanolic KOH solution was refluxed for 3 hr. and was allowed to stand at room temperature overnight. The potassium salt was precipitated, filtered, washed with EtOH and dried. Yield, 1.1 g. (the theoretical amount 1.03 g.). Colorless small leaves. This salt (1.1 g.) was dissolved in H_2O (20 ml.) by warming, to which solution was added under ice-cooling a mixture of acetic acid (0.18 g.) and water (5 ml.). The whole solution was left in a refrigerater overnight. The pale blue precipitate (m.p. 160~162° (decomp.)) was collected and dried. Yield, 0.87 g. (97%). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1627 (COOH).

2-Methyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (XIV)——A solution of the foregoing acid (XIII; 40 mg.) in benzene (10 ml.) was refluxed for 3 hr. On cooling, the reaction mixture was filtered to remove the insoluble impurity, and the benzene of the filtrate was removed *in vacuo* to yield colorless crystals. The crude product was recrystallized from hexane to afford colorless prisms, m.p. 110~110.5°. Yield 33.5 mg. (99%). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ mμ (log ε) : 313 (4.18), 298 (4.22). $\lambda_{\min}^{95\%\ \text{EtOH}}$ mμ (log ε) : 262 (3.49). *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.07; H, 6.99; N, 5.76. Found : C, 73.97; H, 6.92; N, 5.69.

N-(3,4-Dimethoxyphenethyl)-2-methyl-8,9-dimethoxy-5,6-dihydropyrrolo[2, 1-*a*]isoquinoline-3-carboxamide (XV)——To a solution of the acid (XIII; 1.64 g.) and 3,4-dimethoxyphenethylamine (1.05 g.) in chloroform (30 ml.) was added dicyclohexylcarbodiimide (3 g.). The whole mixture was allowed to stand at room temperature for 3 days. The precipitated urea was filtered off and to the filtrate was added 5% AcOH to decompose the excess of DCC, converting it into dicyclohexylurea, which was filtered off. The $CHCl_3$ layer of the filtrate was washed with 5% AcOH, H_2O, 10% NaOH solution, again with H_2O and dried (K_2CO_3). The $CHCl_3$ was removed *in vacuo* to leave a brownish resin, to which was added dry ether. The whole mixture was allowed to stand at room temperature, when crystals gradually deposited, filtered, washed with a small amount of dry ether, and dried. Yield, 1.10 g., m.p. 158~167°, Recrystallization from abs. ethanol (35 ml.) afforded pale pink needles, m.p. 171~173°. Yield, 0.60 g. (23%). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε) : 333 (4.46), 322 (4.52). $\lambda_{\min}^{\text{EtOH}}$ mμ (log ε) : 268 (3.77). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3314 (NH), 1620 (CONH). *Anal.* Calcd. for $C_{26}H_{33}O_5N_2$: C, 69.33; H, 6.66; N. 6.22. Found : C, 68.72; H, 6.43; N, 6.25.

2-Methyl-3-(6,7-dimethoxy-3,4-dihydro-1-isoquinolinyl)-8,9-dimethoxy-5,6-dihydropyrrolo [2,1-*a*] isoquinoline (XVI)——A solution of the foregoing amide (XV; 200 mg.) in dry toluene (20 ml.) was refluxed, and 2 g. of P_2O_5 was added in three portions every half an hour. The whole mixture was stirred and refluxed for 2 hr., cooled, to which was added H_2O (50 ml.) under ice-cooling, then 10% HCl (15 ml.) was added on slightly warming to dissolve a small amount of suspended solid. On cooling, the aqueous layer was separated, and the supernatant layer was extracted with 5% HCl. The combined aqueous solution was filtered, the filtrate was rendered alkaline with solid K_2CO_3 to liberate the oil which was taken up in ethyl acetate. The extract was washed with satd. NaCl solution, dried (K_2CO_3), and the solvent was evaporated to leave the solid, which was recrystallized from abs. MeOH to afford pale yellow prisms, m.p. 164°. Yield, 89 mg. (46%). Further recrystallization from benzene : petr. ether afforded pale yellow prisms, m.p. 165~167°. UV (See Fig. 1.). *Anal.* Calcd. for $C_{26}H_{28}O_4N_2$: N, 6.48. Found : N, 6.48.

2-Methyl-3-(6, 7-dimethoxy-3,4-dihydroisoquinolyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline Methosulfate (XVII, X=$MeSO_4^-$)——To a solution of the foregoing base (XVI; 100 mg.) in dry benzene (15 ml.) was added a solution of Me_2SO_4 (29 mg., freshly distilled, equiv. quantity) in dry benzene (5 ml.), and the whole mixture was refluxed on a steam bath for 2 hr., during which time red crystals deposited and collected. Recrystallization from EtOH-benzene gave red prisms, m.p. 176~178°. Yield 127 mg. (nearly quantitative). UV (Fig. 1). *Anal.* Calcd. for $C_{28}H_{34}O_8N_2S$: C, 60.21; H, 6.02; N, 5.02. Found : C, 59.70; H, 6.18; N, 5.04.

Ethyl 3-Ethoxycarbonyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-acetate (XIX)——To a solution of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (Ⅷ, 27.80 g.) in abs. ethanol (150 ml.) was added under ice-cooling a solution of diethyl 2-chloro-3-oxopentanedioate (XVIII; b.p$_{12}$ 146.5~147.5°; 16.07 g.) in abs. ethanol (50 ml.), and the whole solution was gently refluxed for 30 min. The color of the reaction mixture gradually turned ruby red. The ethanol was removed *in vacuo* to leave a dark red resin, to which was added 100 ml. of absolute benzene to separate the hydrochloride of the starting material (VIII). After filtration, the benzene solution was washed with 10% AcOH, satd. $NaHCO_3$ sol., and H_2O, and dried (K_2CO_3) and the solvent was removed. The residual red brownish gum (20.7 g.) was dissolved in a hexane : ethanol (1:2) mixture, from which on standing the crystal deposited in 54% (14.2 g.) yield. On recrystallization from a hexane-ethanol (1:2) mixture afforded colorless prisms, m.p. 95~97°. UV λ_{max}^{EtOH} mμ (log ε) : 333 (4.45), 324 (4.47). λ_{min}^{EtOH} mμ (log ε) : 276 (3.56). IR ν_{max}^{Nujol} cm^{-1} : 1735 (aliphatic ester), 1682 (aromatic ester). *Anal.* Calcd. for $C_{21}H_{25}O_6N$: C, 65.12; H, 6.46; N, 3.62. Found; C, 65.16; H, 6.26; N, 3.78.

3-Carboxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-acetic Acid (XX)——To a solution of the ester (11.5 g.) in abs. ethanol (100 ml.) was added 100 ml. of 10% EtOH-KOH and the whole mixture was gently refluxed for 1 hr. On cooling, the precipitated K-salt collected on a filter, washed with abs. EtOH, and dried. Colorless prisms. Yield, 10.94 g. (91%). This K-salt was dissolved in water (35 ml.), to which solution was added AcOH (prepared from glac. AcOH (3.21 g.) and H_2O (25 ml.)) under ice-cooling. Soon after the addition of the acid, colorless crystals began to deposit, and the whole was kept in a refrigerator for 3 hr. The crystals were collected, and dried *in vacuo* to yield 7.7 g. (81%) of XX as pale blue crystals, m.p. 160~161° (decomp.), which were used for the next reaction without further purification.

Decarboxylation of XX——A suspension of the foregoing acid (XX) in 4 ml. of xylene was refluxed in an oil bath kept at 205° under a stream of N_2 for 1.5 hr. Upon cooling, the insoluble material was collected, which was identified with the starting material by mixed melting point determination and IR comparison. The yield of recovery was nearly quantitative. The xylene layer was once filtered and concentrated to dryness under diminished pressure to afford a very small amount of pink gum which solidified (m.p. 100~103°) on short standing. One recrystallization from hexane gave pale pink prisms, m.p. 110~111°, whose infrared spectrum was identical with that of XIV.

3-Carboxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-acetic Acid Cyclicanhydride (XXI)——A suspension of the acid (XX; 7.63 g.) in dry benzene (70 ml.) and acetic anhydride (70 ml.) was refluxed on a water bath for 20 min., during which time the crystalline form of the suspended material clearly changed, but did not dissolve in the solvent. Upon cooling, the crystals were collected, washed with dry benzene and dried. Yield, 6.55 g. (90.6%). Pale yellow needles, m.p. 215~216° (decomp.). IR ν_{max}^{Nujol} cm^{-1} : 1720 (O–CO–O).

The Reaction between the Acid anhydride (XXI) and 3,4-Dimethoxyphenethylamine——A mixture of the acid anhydride (XXI, 40 mg.), $CHCl_3$ (5 ml.) and 3,4-dimethoxyphenethylamine (23.3 mg.) was refluxed for 1.5 hr. The $CHCl_3$ was removed *in vacuo* to leave the residue which was recrystallized from dry benzene to afford 50 mg. of colorless small needles, m.p. 142~143° (decomp.), UV λ_{max}^{EtOH} mμ (log ε) : 318 (4.47), 287 (4.17). IR ν_{max}^{Nujol} cm^{-1} : 3330 (NH), 1623 (CONH). These data are compatible with the structure of XXII.

Ethyl 3-Carboxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-acetate (XXIII)——A solution of the acid anhydride (XXI; 6.05 g.) in pyridine-ethanol (1:1; 120 ml.) was gently refluxed for 15 min. and the mixture was allowed to stand at room temperature overnight. The solvent was removed *in vacuo* at 40° (bath temperature) to leave a brownish resin, to which was added dry ether (20 ml.). There gradually deposited the crystals which were collected on a filter and dried. Yield, 5.5 g. (79.3%), m.p. 143° (decomp.). Recrystallization from abs. ethanol gave pale pink needles, m.p. 148° (decomp.). UV λ_{max}^{EtOH} mμ (log ε) : 331 (4.42), 321 (4.45). λ_{min}^{EtOH} mμ (log ε) : 270 (3.64). IR ν_{max}^{Nujol} cm^{-1} : 1736 (ester), 1646 (carboxylic acid). *Anal.* Calcd. for $C_{19}H_{21}O_6N$: C, 63.51; H, 5.85; N, 3.90. Found : C, 63.92; H, 5.98; N, 3.97.

The above ether filtrate was concentrated to dryness under a diminished pressure to afford yellow brownish prisms, which could not be purified. UV λ_{max}^{EtOH} mμ : 295. IR ν_{max}^{Nujol} cm^{-1} : 1718 (ester).

Ethyl 3-[(3,4-Dimethoxyphenethyl)carbamoyl]-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-acetate (XXVb)——To a solution of the acid (XXIII; 2.52 g.) in $CHCl_3$ (25 ml.) was added a solution of DCC (1.00 g., 0.55 molar equivalent) in $CHCl_3$ (5 ml.), and the whole mixture was allowed to stand at room temperature for 24 hr., to which was added a solution of 3,4-dimethoxyphenethylamine (0.62 g., 0.5 molar equivalent) in $CHCl_3$ (4 ml.). The mixture was allowed to stand at room temperature for further 15 hr. Again, a $CHCl_3$ (5 ml.) solution of DCC (1.00 g.) was added to the mixture, left 24 hr., 3,4-dimethoxyphenethylamine (0.62 g.) in $CHCl_3$ was added, which was left for 15 hr. The separated urea was filtered off, the filtrate was concentrated, to which residue was added AcOEt (70 ml.). The separated urea was again filtered off, the AcOEt layer was washed with 10% acetic acid, saturated $NaHCO_3$ solution and with water, then dried over K_2CO_3. The solvent was removed to yield the red brownish gum which was dissolved in ethanol (12 ml.) by warming. Upon cooling, there deposited crystals which were collected on a filter, washed with EtOH and dried. The crude product (2.416 g. Yield; (66%). m.p. 130°) was recrystallized from a mixture of hexane and ethanol to give the amide (XXVb), colorless needles, m.p. 132°.

UV λ_{max}^{EtOH} mμ (log ε) : 318 (4.45). λ_{min}^{EtOH} mμ (log ε) : 266 (3.78). IR ν_{max}^{Nujol} cm^{-1} : 3331 (NH), 1697 (COOEt), 1640 (CONH). *Anal.* Calcd. for $C_{29}H_{34}O_7N_2$: C, 66.67; H, 6.51; N, 5.36. Found : C, 66.47; H, 6.36; N, 5.74.

Ethyl 3-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-acetate (XXVI)——The foregoing amide (XXVb; 1.00 g.) was dissolved in abs. toluene (30 ml.) by warming and the solution was stirred and refluxed with 5 g. of P_2O_5 which was added in three portions every one hour. The mixture was kept at 125~130° under stirring for additional two hours. After the reaction, water (20 ml.) was added under ice-cooling, followed by another addition of a mixture of ethyl acetate (20 ml.) and water (80 ml.). The precipitated solid was collected on a filter and washed with water. A suspension of this material in water was rendered alkaline with satd. sodium bicarbonate solution, extracted with ethyl acetate, and the extract was worked up in the usual way and dried over K_2CO_3. The aqueous layer of the filtrate which was obtained by filtration of the precipitated material, was basified with solid K_2CO_3, extracted with AcOEt and the extract, after a usual worked-up, was combined with the foregoing extract. The ethyl acetate was removed *in vacuo* to afford a dark-red gum which was dissolved in EtOH. On standing, there deposited 455 mg. of pale yellow prisms, m.p. 134°, in 47.2% yield. Recrystallization from EtOH gave pale yellow prisms, m.p. 136°. *Anal.* Calcd. for $C_{29}H_{32}O_6N_2$: C, 69.03; H, 6.39; N, 5.55. Found : C, 68.70; H, 6.51; N, 5.69.

3-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-ethanol (XXVII)——To a solution of the foregoing ester (XXVI; 400 mg.) in a mixture of absolute tetrahydrofran (20 ml.) and ether (30 ml.), was added 59.7 mg. of $LiAlH_4$ in one portion under ice-cooling. The mixture was stirred and refluxed in a water bath kept at 73° for 3 hr., during which time the color of the reaction mixture changed from pale yellow to greenish and to deep green in 1.5 hr. after the start of reaction. The green color returned to pale yellow on cooling, and 10 ml. of tetrahydrofuran containing water (162 ml.) was added to the reaction mixture, which was allowed at room temperature overnight. The supernatant layer was separated, dried over K_2CO_3 and the solvent was removed to leave the yellow residue which was recrystallized from AcOEt to afford 243.0 mg. (66%) of pale yellowish needles, m.p. 163~164°. UV $\lambda_{max}^{0.01N\,HCl}$ mμ (log ε) : 440 (4.24), 300 (4.27), 293 (4.27), 255 (4.18); $\lambda_{min}^{0.01N\,HCl}$ mμ (log ε) : 334 (3.77). 266 (4.04), 244 (4.14). *Anal.* Calcd. for $C_{27}H_{30}O_5N_2$: C, 70.11; H, 6.54; N, 6.06. Found : C, 70.09; H, 6.59; N, 6.12.

Bisnorrubremetinium Salts (XXVIII)——To a solution of the foregoing alcohol (XXVII; 255 mg.) in abs. benzene (20 ml.), was added a solution of *p*-toluenesulfonyl chloride (105 mg., equivalent quantity) in abs. benzene (5 ml.) and the whole mixture was allowed to stand at room temperature overnight. In ten or fifteen min. after standing, orange red small needles began to deposit. After completion of precipitation, the separated crystals were collected on a filter and dried under reduced pressure, which had m.p. 190~193° (after sintered at 186°). Yield, 329 mg. (97%). Recrystallization from water gave orange yellow needles, m.p. 192~194° (afrer drying over P_2O_5 at 95° under 3 mm. Hg for 15 hr.). UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 435 (4.48), 300 (4.29), 285 (4.28), 255 (4.28). $\lambda_{min}^{H_2O}$ mμ (log ε) : 332 (3.84), 270 (4.13), 244 (4.15). *Anal.* Calcd. for $C_{34}H_{36}O_7N_2S \cdot 2H_2O$: C, 62.58; H, 6.13; N, 4.29. Found : C, 62.23; H, 6.57; N, 4.50. The foregoing tosylate (XXVIIIa; 200 mg.) was dissolved in water (30 ml.) by heating, and to the resulting hot solution was added a solution of KBr (58.2 mg., 1.5 mole equiv.) in water (5 ml.), which was kept on warming for a while. On cooling, orange red needles deposited, which were collected on a filter and dried under reduced pressure, having m.p. 212~214°. Yield, 160 mg. (quantitative). Recrystallizations from 4% potassium bromide solution (30 ml.) and then from water gave orange yellow needles, m.p. 215° (afrer drying over P_2O_5 at 95° under the reduced pressure of 3 mm. Hg for 15 hr.). The UV and IR spectra are shown in Figs. 1 and 2. *Anal.* Calcd. for $C_{27}H_{29}O_4N_2Br \cdot 2\frac{1}{2}H_2O$: C, 56.84; H, 5.96; N, 4.91. Found: C, 56.81; H, 6.03; N, 4.69.

The infrared spectrum of this bromide was identified with that of C-bisnorrubremetinium bromide kindly supplied by Professor Sugasawa and Kirisawa (See Fig. 2).

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Summary

With an aim of determining the structure of rubremetinium cation, C-bisnorrubremetinium salts and their relative compounds were synthesized without any oxidation step, which indicated that the formula (II) is correct for rubremetinium cation in terms of absolute configuration. This assignment was supported by nuclear magnetic resonance data of this salt.

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