UDC 547.836.3

117. **Tozo Fujii**: A Synthesis of *dl*-Rubremetinium Bromide.**

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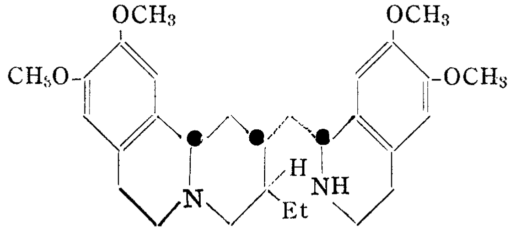
The Robinson formula[1] of the alkaloid emetine has been well established.[2] Since the presentation of this formula in 1948, number of papers concerning the synthesis of emetine and allied compounds have been published, among which that of Preobrazhenskii, *et al.*[3] will be mentioned here, because they reported the successful synthesis of a compound identical with the natural alkaloid. Of late, Battersby, *et al.*[4] and van Tamelen, *et al.*[5] studied its stereochemistry and put forward the following expression (I) as indicating its configuration.



(I)

The effort to synthesize a compound having the structure of emetine in this laboratory was initiated in 1952 and Sugasawa and Fujii,[6] the present author, in their preliminary work succeeded in synthesizing the compound (IV) starting from benzylamine, formaldehyde, and ethylmalonic acid as is depicted in Chart 1.

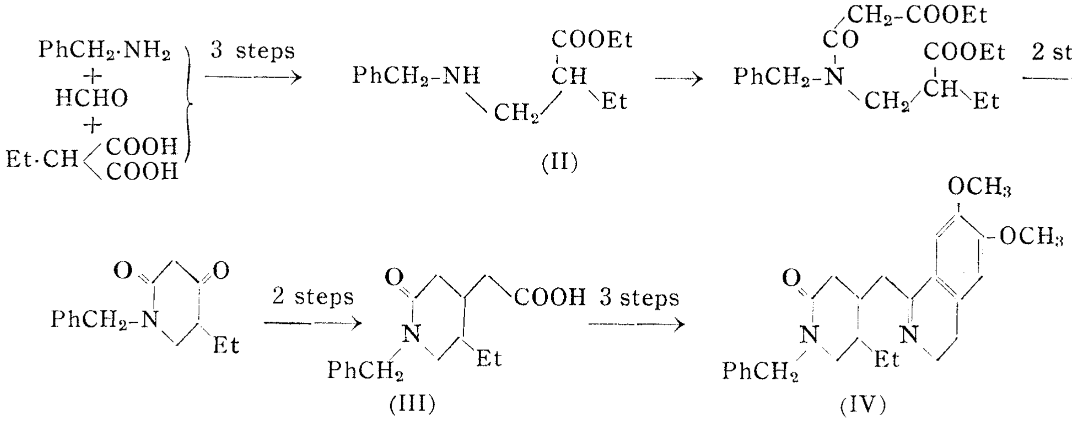


Chart 1.

On that occasion they expressed the view that their objective would be achieved (i) if one uses 3,4-dimethoxyphenethylamine in place of benzylamine in the above scheme, or (ii) if debenzylation was effected at any one stage between (II) and (IV), and then intro-

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* Hongo, Tokyo (藤井澄三).

** This paper constitutes Part III of "Studies on the Synthesis of Emetine" by S. Sugasawa. Part II: This Bulletin, **3**, 53(1955).

[1] R. Robinson: Nature, **162**, 524(1948).

[2] 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; N. A. Preobrazhenskii, *et al.*: C.A., **45**, 7577 (1951); **46**, 8130 (1952); **47**, 5949(1953).

[3] N. A. Preobrazhenskii, *et al.*: *loc. cit.*

[4] A. R. Battersby, *et al.*: Chem. & Ind. (London), **1957**, 983.

[5] E. E. van Tamelen, P. E. Aldrich, J. B. Hester Jr.: J. Am. Chem. Soc., **79**, 4817(1957).

[6] S. Sugasawa, T. Fujii: This Bulletin, **3**, 47(1955).

duce 3,4-dimethoxyphenethyl group instead of benzyl group, and so on.

Ban⁷⁾ worked according to the first scheme and succeeded in obtaining the final product, but unfortunately, many of the intermediate compounds were not obtained crystalline and hence the final product was inevitably a mixture of diastereoracemates and he could not succeed in isolating any one of the isomers in crystalline condition. However, the fact that the expected chemical structure existed in the oily substance was provided by the formation of *dl*-rubremetinium bromide, the well-defined crystalline compound, from this oil by the known dehydrogenation process.

The second route was adopted by the present writer and it was decided to carry out the debenzylation of (III) in Chart 1⁸⁾ because one (IIIa) of its racemates has been obtained in crystalline condition.

At the first step, however, a great difficulty was encountered. Only in meager examples it has been shown in the literature that N-benzyl-acylamide-type of compounds withstand catalytic hydrogenation and the starting compounds are usually recovered. In coincidence with this fact, (III) resisted obstinately to all attempts for debenzylation through hydrogenolysis over palladium catalyst, even under pressure and heat. It was also found that the lactam ring of (III) could not be cleaved either by acids or alkalis to form the corresponding N-benzylamino acid, from which the benzyl group should be removable by hydrogenolysis.

In the mean time, Sugasawa and Fujii⁹⁾ discovered that the benzyl group on the amide-type nitrogen, including lactams, could be removed smoothly by means of metallic sodium in liquid ammonia, yielding debenzylated amides and toluene. When this debenzylation technique was applied to (III), which was a mixture of two diastereoracemates, the debenzylation proceeded smoothly and 2-oxo-5-ethyl-4-piperidineacetic acid (V) was obtained in a yield of 65.8%, which was separated into approximately equal proportions of (Va) of m.p. 147~149° and (Vb) of m.p. 205~207°, which ratio roughly corresponded to that of (IIIa) and (IIIb) in (III). A separate debenzylation experiment with (IIIa) mainly gave (Va) and a small amount of (Vb),¹⁰⁾ and it was revealed that (IIIa) corresponds to (Va). The debenzylation of (IIIb) similarly gave (Vb) contaminated with some (Va).

The structure of (V) was proved as follows: When diethyl 3-(1-cyanopropyl)glutarate¹¹⁾ (VI), which was one of the starting materials in the Preobrazhenskii's synthesis of emetine, was reduced at 125~130° and 130 atm. pressure over Raney nickel catalyst in ethanol according to the Soviet authors, there was obtained a solid product,¹²⁾ which was separated into two components in roughly 3:2 ratio by alumina chromatography. The former was a solid of m.p. 93~94° and was proved to be identical through direct comparison with the ester (VIIa) derived from (Va). The latter remained oily. When, however, these were hydrolyzed, they both gave single crystalline acid of m.p. 147~149° and of m.p. 205~207°, respectively, which were identical with (Va) and (Vb).

The introduction of 3,4-dimethoxyphenethyl group to 2-piperidone to form 1-(3,4-dimethoxyphenethyl)-2-piperidone (VIII) was now studied as a model and it was found that when potassium salt of 2-piperidone, prepared by refluxing the latter with potassium dust in xylene, was heated with 3,4-dimethoxyphenethyl bromide in the presence of copper powder for 20 hours, (VIII) was obtained in a yield of 25.5%. Its structure was proved by

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7) Y. Ban: This Bulletin, **3**, 53(1955).

8) Prior to the debenzylation attempt, condensation of ammonia, formaldehyde, and ethylmalonic acid was studied to produce 2-(aminomethyl)butyric acid, but the reaction failed to give any definite compound under a variety of working conditions so far tried.

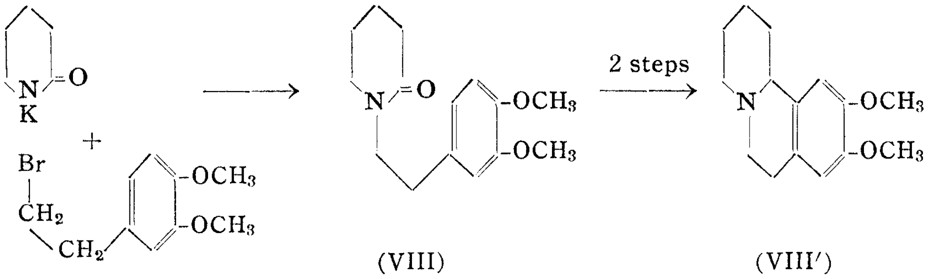
9) S. Sugasawa, T. Fujii: This Bulletin, **6**, 587(1958).

10) Whether this formation was due to a small contamination of (IIIb) in (IIIa) or due to the rearrangement occurring during the debenzylation process is not clear.

11) The writer is grateful to Mr. T. Kutsuma for a donation of this compound.

12) This is recorded as an oil of b.p$_{0.32}$ 180~185° by the Soviet workers.

converting it to the benzoquinolizine derivative (VIII′) by the known method,[17] and was identified with an authentic specimen.[13]



This alkylation technique was now extended to the ester (VIIa) of m.p. 93∼94°, prepared from (Va) by the conventional esterification. When the product was hydrolyzed, (IXa) was obtained in a yield of 17.1% with simultaneous recovery of (VIIa) in 54.2% yield.

To secure enough material for further study, the ester (VII), prepared by esterifying the mixture of (Va) and (Vb), was treated with 3,4-dimethoxyphenethyl bromide as above and hydrolyzed. The crude acid thus obtained was now converted to the chloride and coupled with 3,4-dimethoxyphenethylamine to yield the amide (X) as a reddish brown syrup. Since this could not be induced to crystallize this was cyclized with phosphoryl chloride and worked up as usual. The product (XI) again remained oily as in the case described by Ban. Hence this was converted to the crystallizable *dl*-rubremetinium salt (*dl*-XII), the technique often adopted by previous workers[14] in similar cases. Thus the chloride (XI: X=Cl) of the cyclized product was treated with mercuric acetate in dilute acetic acid, when orange red minute needles were obtained. The latter was converted to the corresponding bromide (*dl*-XII: X=Br), the ultraviolet and infrared absorption spectra of which were respectively identical with those of an authentic specimen of *d*-rubremetinium bromide (*d*-XII: X=Br), prepared from *l*-emetine (I) according to the method of Battersby, *et al.*[15] (Figs. 1 and 2).

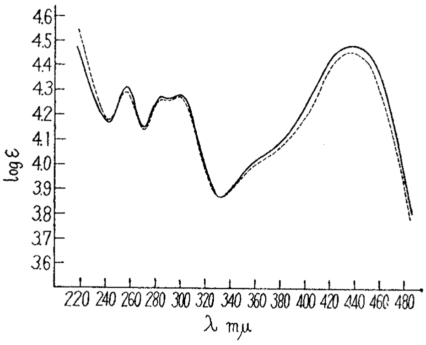


Fig. 1.
Ultraviolet Absorption Spectra (in H_2O)
—— *d*-Rubremetinium bromide (c=2.139×10^{-5} *M*)
---- *dl*-Rubremetinium bromide (c=2.022×10^{-5} *M*)

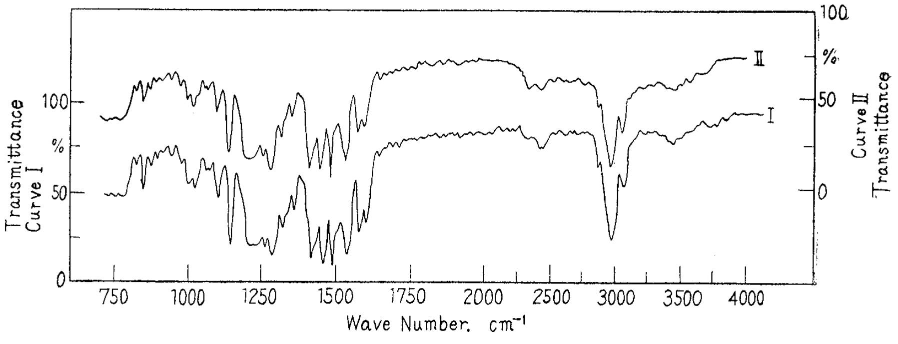


Fig. 2.
Infrared Absorption Spectra (in $CHCl_3$)
I: *d*-Rubremetinium bromide
II: *dl*-Rubremetinium bromide

A new approach to the synthesis of emetine was thus provided. For the total synthesis of this alkaloid the stereochemical study of the two intermediate crystalline acids (Va and b) became desirable. The infrared spectra of (Va and b) and (VIIa and b), and pKa values of (Va and b), which are recorded in the experimental section, did not furnish sufficient data with which the stereochemistry of these two acids could be discussed.

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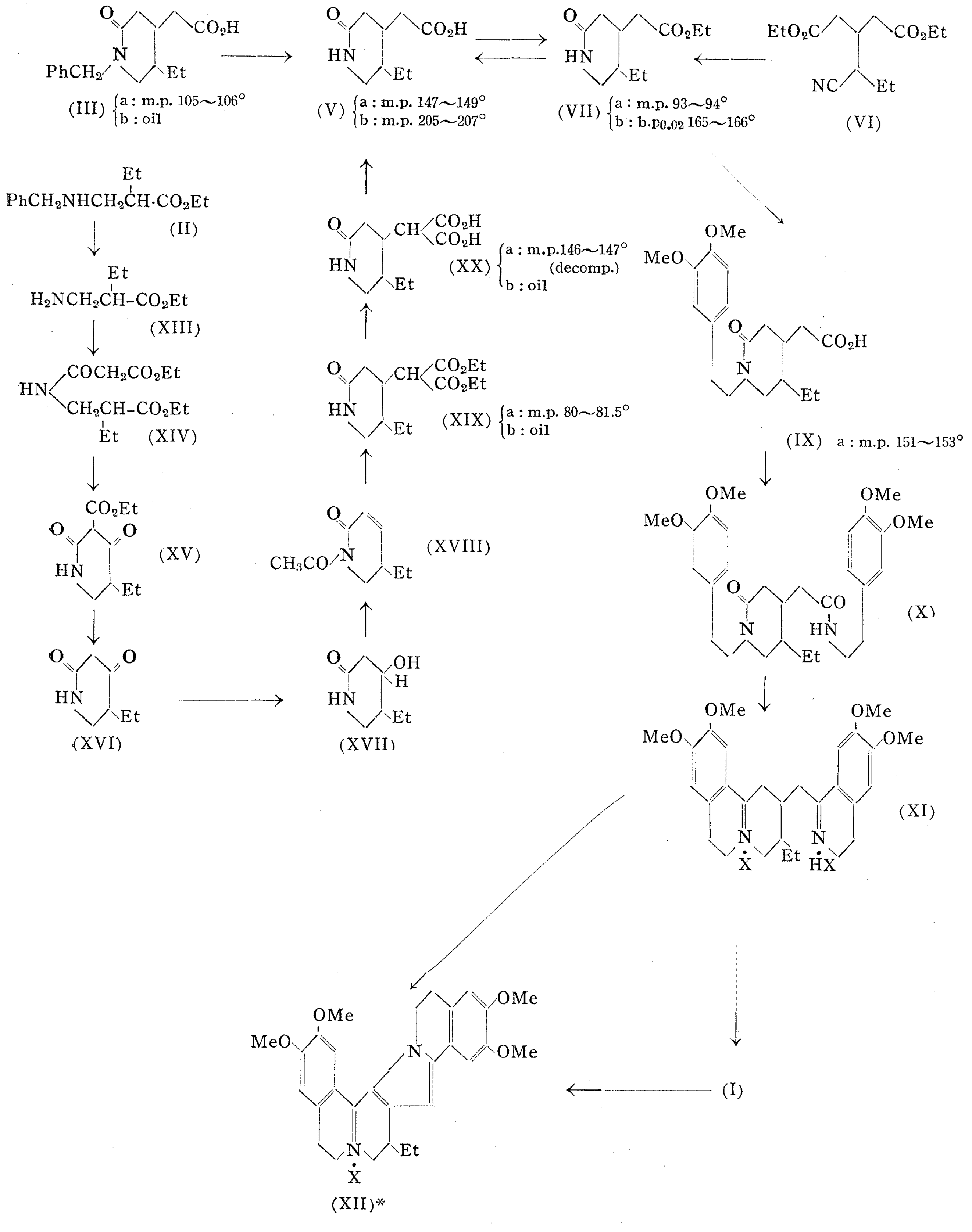
13) R. Child, F. L. Pyman: J. Chem. Soc., **1931**, 36.
14) cf. footnote 2; Y. Ban: *loc. cit.*; M. Pailer, G. Beier: Monatsh., **88**, 830(1957).
15) A. R. Battersby, H. T. Openshaw: J. Chem. Soc., **1949**, S67.



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* The structure of rubremetinium salt is not yet rigidly established. The formula (XII) proposed by Battersby, *et al.* (Experientia, **5**, 114 (1949)) was adopted here.

In the course of their work concerning the synthesis of α-dihydrokainic acid, Ueyanagi, *et al.*(16) obtained two forms of 2-oxo-5-isopropyl-4-piperidinemalonate (XIX: *iso*-Pr for Et) in roughly 20:1 ratio through Michael-type condensation of diethyl malonate with 1-acetyl-5-isopropyl-5,6-dihydro-2(1*H*)-pyridone (XVIII: *iso*-Pr for Et) and assigned the *trans*-configuration to the main product from the steric requirement of the isopropyl group at 5-position.

Based on this fact, ethyl 2-(benzylaminomethyl)butyrate (II) was debenzylated by hydrogenolysis to yield ethyl 2-(aminomethyl)butyrate (XIII), from which ethyl 2,4-dioxo-5-ethyl-3-piperidinecarboxylate (XV) was prepared via (XIV). The ketonic fission of (XV) was achieved by boiling with 10% acetic acid, yielding 2,4-dioxo-5-ethylpiperidine (XVI) of m.p. 72~74° in 94.7% yield. The latter absorbed one molar equivalent of hydrogen activated over Adams' platinum catalyst in ethanolic solution to furnish the corresponding alcohol (XVII), which was directly dehydrated by boiling with acetic anhydride. 1-Acetyl-5-ethyl-5,6-dihydro-2(1*H*)-pyridone (XVIII) thus formed was now reacted with diethyl malonate in the presence of sodium ethoxide, when diethyl 2-oxo-5-ethyl-4-piperidinemalonate (XIX) was obtained as an oil of b.p$_{0.05}$ 180~193° in a yield of 62.7%. On standing, this oil partially solidified and by triturating with cold ether this was separated into two components; the one was a crystalline solid (XIXa) of m.p. 80~81.5°, and the other was an oil (XIXb), the proportion of which was roughly 14:10. This means that the steric requirement of ethyl group is not so pronounced as that of isopropyl group and thus stereochemical assignment of (XIXa and b) through these data appeared to be impossible.

From (XIXa) the malonic acid (XXa) of m.p. 146~147°(decomp.) was obtained, but the malonic acid (XXb) from (XIXb) was an oily substance. When (XXa and b) were respectively decarboxylated by heating at 175~180° for 30 minutes, there was obtained a mixture of two acids of m.p. 147~149° and 205~207° in both cases, which were found to be respectively identical with (Va) and (Vb). In view of the fact that (Va) and (Vb) are interconvertible through heat, the above-mentioned phenomena could be ascribed to an equilibrium between (Va) and (Vb) induced by heat treatment. This conversion could also be effected by boiling in 20% hydrochloric acid.

The present attempt for stereochemical assignment of (Va) and (Vb) has so far been unsuccessful, but the present experiment afforded a strong support to the plane structure of these acids (Va and b). The work is being continued.

Grateful acknowledgement is offered to Professor S. Sugasawa for his interest and encouragement throughout this work. Thanks are also due to Dr. G. Fukuchi of Sankyo Co. Ltd. for a donation of *l*-emetine. The author wishes to thank Messrs. E. Ohki, N. Ikekawa, and K. Tanigawa for spectral data and to Mr. A. Hanaki for pKa measurement, and also thanks the members of Analysis Room of this Faculty, of Research Laboratory of Tanabe Seiyaku & Co., and of Women's Dept., Tokyo College of Pharmacy, for elemental analyses. Some of the materials used in this work were prepared by Mr. M. Tashiro, whose unwearying technical assistance is highly appreciated.

Experimental

2-Oxo-5-ethyl-4-piperidineacetic Acid (Va and Vb)—i) The diastereoisomeric mixture of 1-benzyl-2-oxo-5-ethyl-4-piperidineacetic acid (IIIa+IIIb: 17.6 g., 0.064 mole) was dissolved in ca. 300 cc. of liq. NH_3 and to this solution was added with stirring metallic Na (4.5 g., 0.196 atom), cut into small pieces, in small portions during 1.5 hrs. at the boiling point of liq. NH_3. The digestion of Na occurred smoothly and the solution became turbid. Toward the end of the reaction the blue-violet coloration maintained continuously. Then the solution was evaporated at room temp., leaving a white powdery solid with an odor of toluene. On addition of ice water to this powder slowly, an oily substance separated out, which was collected in ether. The ethereal solution was washed with H_2O, dried, and

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16) J. Ueyanagi, *et al.*: Yakugaku Zasshi, **77**, 603(1957).

17) S. Sugasawa, *et al.*: *Ibid.*, **59**, 247(1939); **71**, 1341(1951); This Bulletin, **6**, 359(1958).

distilled fractionally, giving toluene (2.8 g. or 47.5%) as a fraction of b.p. 108~110°. UV $\lambda_{\max}^{95\%\text{EtOH}}$ mμ (log ε): 255.5, 262, 268.5 (2.21, 2.32, 2.24).

The clear, light yellow, aqueous solution was then made slightly acidic to Congo red with conc. HCl under cooling, separating a small amount of light yellow oil, which was extracted twice with benzene without delay. From this benzene solution, after being dried and evaporated, unreacted (III) (1.5 g. or 8.5%) was recovered. After extraction with benzene, the aqueous solution soon became turbid and there separated colorless needles and prisms, which were collected on a filter after being kept standing overnight in an ice chamber, washed with a little ice water, and dried in a vacuum desiccator, giving 5.1 g. (or 43.2%) of diastereoisomeric mixture of (V), m.p. 145~190°.

The diastereoisomeric mixture of (V) (1.0 g.) thus obtained was dissolved in boiling EtOH (15 cc.) and left standing at room temp., when the more sparingly soluble colorless prisms (540 mg.) of m.p. 190~195° separated, which was purified once from EtOH (15 cc.), forming colorless prisms (370 mg.) of m.p. 200~202°. Repeated recrystallization from EtOH gave (Vb) as colorless prisms of m.p. 205~207°. *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.1; H, 8.05; N, 7.4. pKa values: pK_1, 4.87; pK_2, 9.71. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3271, 3185(NH).

When the first EtOH mother liquor, which was left after filtration of the crystals of m.p. 190~195°, was concentrated to a small volume and left standing, there separated the second isomer (Va) (360 mg.) as white fluffy needles of m.p. 145~147°, which was raised to 147~149° by repeated purification from EtOH, forming white fluffy needles. *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.7; H, 8.3; N, 7.3. pKa values: pK_1, 4.94; pK_2, 9.81. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3290, 3235(NH).

The above-mentioned aq. mother liquor, which was obtained by filtering the mixture of (Va) and (Vb), was evaporated *in vacuo* to dryness, leaving a mixture of NaCl and yellowish brown hard syrup. This residue was dried in a vacuum desiccator, 12.5% ethanolic HCl (70 cc.) was added, the mixture was refluxed on a steam bath for 3 hrs., and worked up as described in the later section on (VII). The mixture of (VIIa) and (VIIb), $b.p_{0.02}$ 153~155°, thus obtained solidified on standing and amounted to 3.06 g. (or 22.6% from (III)). When this was purified from hexane, there separated (VIIa) (1.5 g.) of m.p. 93~94°, and impure (VIIb) contaminated with (VIIa) was recovered from hexane mother liquor. On being hydrolyzed, as will be described in section (iv), they furnished (Va) and (Vb), respectively. The total yield of (Va) was slightly higher than that of (Vb).

ii) (IIIa) (3.3 g.), m.p. 105~106°, which was obtained in a yield of 44.6% from the crude (III) by repeated recrystallization from a mixture of benzene and hexane (1:2), was submitted to the debenzylation reaction as described above. The ratio of formation of (Va) and (Vb) was about 10:1.

iii) When (IIIb) (5.5 g.), which was obtained in a yield of 50% from the crude (III) by evaporation of the mother liquor of (IIIa), was worked up as above, (Va) and (Vb) were obtained in a ratio of about 8:11.

iv) To (VIIa) (410 mg.) dissolved in 2.5 cc. of EtOH, 50% KOH (300 mg.) was added, the whole was refluxed on a steam bath for 2 hrs., and then evaporated *in vacuo*. The faint yellow viscous syrupy residue, K-salt of (Va), was dissolved in 1.5~2.0 cc. of H_2O, acidified to Congo red with conc. HCl under cooling, separating colorless needles after some time, which was collected on a filter, washed with a small volume of ice-cold H_2O, and dried in a vacuum desiccator, giving (Va) (270 mg. or 75.8%) of m.p. 147~149°. This acid was found by admixture to be identical with the one obtained above.

v) 300 mg. of (Va) or (Vb) in 3 cc. of conc. HCl was refluxed in an oil bath at 130~140° for 20 hrs. After evaporating *in vacuo*, the residue was triturated with 3~5 cc. of H_2O and the whole was kept standing, separating colorless prisms and needles, from which (Va) and (Vb) were obtained by working up as above. These acids were found by admixture to be respectively identical with the ones obtained above.

vi) (Va) (200 mg.) was heated in an oil bath at 175~180° for 30 mins., forming slightly brown transparent syrup, which solidified on cooling and showed m.p. 135~185°. There was no loss in weight. By repeated recrystallization from EtOH this was separated into (Va) of m.p. 147~149° and (Vb) of m.p. 205~207°. They were identified by admixture with the authentic specimens.

When (Vb) (200 mg.) was heated in an oil bath at 180~190° for ca. 15 mins. a liquefaction of (Vb) occurred. After heating for further 30 mins. a brown hard syrup was obtained, which turned to a light brown solid of m.p. 140~175° on cooling. There was no loss in weight. By repeated recrystallization as described above, (Va) and (Vb) were obtained and respectively identified with the ones obtained above by admixture.

vii) From (XX) by decarboxylation: (XXa) (150 mg.) was heated in an oil bath, when the evolution of CO_2 became evident at the decomposition point. After being heated at 175~180° for 30 mins. a slightly brown transparent syrup (120 mg.) was obtained, which solidified on cooling and melted at 135~185°. By fractional recrystallization from EtOH as described above, (Va) and (Vb) were obtained and respectively identified with the authentic samples by admixture. Also the crude (XXb), a mixture of KCl and a yellow syrup, was heated as above, forming a mixture of KCl and a black brown syrup, which solidified on addition of a little H_2O. This was collected on a filter, dissolved in EtOH (charcoal), and the filtrate was concentrated to a small volume, separating white prisms of (Vb). From the mother liquor of (Vb), white needles (Va) were obtained and these were identified as above.

Ethyl 2-Oxo-5-ethyl-4-piperidineacetate (VIIa and VIIb)—i) The solution of (Va) (700 mg.) in 10 cc. of 12.5% ethanolic HCl was refluxed on a steam bath for 3 hrs. and evaporated, leaving a faint yellow transparent viscous syrup. This residue was diluted with H_2O, basified with 10% Na_2CO_3, salted out with K_2CO_3, and extracted with benzene. The benzene extract was dried and evaporated *in vacuo*, leaving 670 mg. (or 83.2%) of white crystals, m.p. 80~90°. Purified from hot hexane to form white pillars (VIIa) of m.p. 93~94°. *Anal.* Calcd. for $C_{11}H_{19}O_3N$: C, 61.9; H, 9.0; N, 6.6. Found: C, 61.8; H, 9.05; N, 6.3. IR ν_{max}^{Nujol} cm^{-1}: 3185(NH), 1725(COOEt), 1670(CONH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3402, 3204 (NH), 1722 (COOEt), 1658 (CONH). From the hexane mother liquor further crop of (VIIa) was obtained on evaporating *in vacuo*.

ii) The solution of (Vb) (1.00 g.) in 12.5% ethanolic HCl (15 cc.) was treated as described above and evaporated *in vacuo*, leaving white crystals (perhaps lactam ester hydrochloride ?), which was worked up as above. The benzene extract was evaporated *in vacuo*, leaving 1.07 g. of a fairly viscous colorless transparent oil which distilled at 165~166°/0.02 mm. Hg to give 950 mg. (or 82.6%) of a colorless oil (VIIb). On being kept standing the oil turned to a jelly. *Anal.* Calcd. for $C_{11}H_{19}O_3N$: N, 6.6. Found: N, 6.3. IR $\nu_{max}^{Capil.}$ cm^{-1}: 3200(NH), 1730(COOEt), 1667-1655-1637 (broad, CONH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3393, 3197(NH), 1715(COOEt), 1650(CONH). The IR absorption spectrum of (VIIb) in $CHCl_3$ was slightly different from that of (VIIa).

iii) Diethyl 3-(1-cyanopropyl)glutarate3) (VI), b.p$_1$ 132° (1.10 g.), Raney Ni (1 g.), EtOH (35 cc.), and H_2 (93 atom/cm^2) was heated in an autoclave and began to shake at 100°, and the reduction was allowed to proceed at 125~130° for 3 hrs., then worked up as usual. The residual 910 mg. of a brownish purple viscous oil thus obtained solidified on standing. A 700-mg. portion of this crude (VII) was dissolved in benzene and purified through an Al_2O_3 (5.0 g.) column. From the first 50 cc. of eluate, 590 mg. of light yellow crystals was obtained on evaporating *in vacuo*, which was recrystallized four times from hexane, forming white pillars (VIIa) (320 mg.) of m.p. 93~94°. This ester was found to be identical with the one obtained by the esterification of (Va) described above, and when hydrolyzed according to (V)-(iv) method, (Va) was obtained in a yield of 64.7%, which was also found to be identical with the one obtained by debenzylation method described above.

On evaporating the next 100 cc. of benzene eluate, 30 mg. of a faint yellow oil (VIIb) was obtained, to which was combined the yellowish brown oily residue (VIIb) (170 mg.) obtained from the first hexane-mother liquor of (VIIa) on evaporating *in vacuo*. On being hydrolyzed according to the method described in (V)-(iv), this mixture gave white prisms (Vb) of m.p. 205~207°, which was proved to be identical with the one obtained by the debenzylation method as described above.

The 2nd to 4th hexane-mother liquors of (VIIa) were combined and evaporated to give a mixture of light yellow oil (VIIb) and white crystals (VIIa), which amounted to 100 mg.

1-(3,4-Dimethoxyphenethyl)-2-oxo-5-ethyl-4-piperidineacetic Acid (IX)—K dust (320 mg.) was suspended in pure xylene (15 cc.) and to this mixture was added dropwise a xylene solution of the above-mentioned lactam ester (VIIa) (1.92 g. in 25 cc. of pure xylene) at room temp. All the K disappeared with evolution of H_2 after about 1 hr.'s standing. To the faint yellow solution thus obtained was added dropwise a solution of 3,4-dimethoxyphenethyl bromide (2.21 g.) in pure xylene (20 cc.) and then Cu dust (120 mg.), and the whole was heated in an oil bath at 160~170° for 33 hrs. On cooling, KBr separated and Cu dust were filtered off, and washed with benzene. The filtrate and washings were combined, washed with H_2O (the washings were acid to litmus), dried, and then evaporated *in vacuo*, leaving 3.14 g. of a brown oil. To this were added EtOH (30 cc.) and 50% KOH (1.32 g.), this solution was refluxed on a steam bath for 2 hrs., and then evaporated *in vacuo*. To the residue thus obtained was added H_2O and an oil that separated was extracted repeatedly with ether. From the ether layer, 3,4-dimethoxystyrene and 3,4-dimethoxyphenethyl alcohol were obtained.

When the brownish orange aqueous layer (ca. 60 cc.) was acidified to Congo red with 10% HCl after being treated with charcoal, it became turbid and there separated a brownish yellow oil, which was extracted with AcOEt, washed repeatedly with H_2O, dried, and then evaporated *in vacuo*, leaving a light yellow solid (540 mg. or 17.1% from (VIIa)). This crude (IXa) was dissolved in saturated aq. $NaHCO_3$, then acidified with 10% HCl, and kept standing, separating white dices, which were collected on a filter, washed with H_2O, and then purified from EtOH, forming white dices (IXa) of m.p. 151~153°. *Anal.* Calcd. for $C_{19}H_{27}O_5N$: C, 65.3; H, 7.8; N, 4.0. Found: C, 65.1; H, 7.7; N, 4.2. IR $\nu_{max.}^{Nujol}$ 1707 cm^{-1}(COOH). There was no band corresponding to NH.

The aqueous layer of AcOEt-extraction and H_2O washings were combined and evaporated *in vacuo* to dryness, leaving a mixture of KCl and a brownish yellow hard syrup, which was dried in a vacuum desiccator and esterified with 40 cc. of 12.2% ethanolic HCl as described in (VII)-(i), recovering 1.04 g. (or 54.2%) of crude crystals (m.p. 78~87°) of the starting ester (VIIa), which was purified from hexane, forming white pillars of pure (VIIa).

When benzene was used in place of xylene as a solvent in this reaction, the yield of (IX) increased somewhat. The diastereoisomeric mixture of (VIIa) and (VIIb) was reacted with 3,4-dimethoxyphenethyl bromide as above but the resultant crude (IX) was a brownish yellow, hard syrup, which was not induced to crystallize.

The solution of the crude (IXa, b) (240 mg.) thus obtained in 12.2% ethanolic HCl (20 cc.) was refluxed on a steam bath for 2.5 hrs. and evaporated *in vacuo*, leaving a light yellow viscous syrup, to which was added aq. 10% Na_2CO_3 and benzene, and mixed thoroughly. The separated benzene layer was washed with ca. 3% NaOH, then with H_2O, dried, and evaporated *in vacuo*, leaving 170 mg. of a light yellow viscous syrup, the crude ethyl 1-(3,4-dimethoxyphenethyl)-2-oxo-5-ethyl-4-piperidineacetate. IR $\nu_{max}^{capil.}$ cm^{-1}: 1726 (COOEt), 1639 (CON<).

N,1-Bis(3,4-dimethoxyphenethyl)-2-oxo-5-ethyl-4-piperidineacetamide (X)—To the acid (IX) (1.00 g. of the diastereoisomeric mixture) was added freshly purified $SOCl_2$ (0.52 g.) with ice cooling. After being kept at room temp. for 20 mins., this mixture was heated in a water bath at 65~70° for 1 hr., and at 90~95° for 15 mins, when evolution of gas became gentle. The dark brown reaction product was dissolved in pure benzene, giving a clear solution. The solvent and the excess of $SOCl_2$ were removed *in vacuo*, leaving a dark brown viscous syrup, which was again dissolved in pure benzene (30 cc.) and used in the next step.

To a solution of 3,4-dimethoxyphenethylamine (1.7 g.) in pure benzene (30 cc.), the benzene solution of the acid chloride obtained above was added dropwise with stirring and cooling, giving an orange-yellow clear solution, from which the amine-hydrochloride began to separate after some time. The whole was now kept standing overnight and then diluted with AcOEt, washed with dil. HCl, followed by H_2O, 10% Na_2CO_3 solution, and at last with H_2O, dried, and evaporated, leaving a reddish brown vitreous syrup (X), which was not induced to crystallize and was used directly in the next cyclization step. Yield, 1.26 g. or 85.7%, based on the acid (IX) used.

2-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolyl)methyl-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium Chloride Hydrochloride (XI: X=Cl).—The foregoing amide (X) (1.24 g.) was mixed with $POCl_3$ (7 cc.) and the whole was gently refluxed in an oil bath at 125~130° for 1 hr. After evaporating the excess of $POCl_3$, the dark brown viscous residue obtained was extracted with warm H_2O. The orange-yellow H_2O solution thus obtained was washed with AcOEt and benzene, treated with charcoal, and concentrated to ca. 30 cc. *in vacuo*. To this solution was added an excess of KI, separating a yellowish brown syrup, which was taken up in $CHCl_3$, dried, and evaporated. The residual yellowish brown caramel-like iodide hydriodide (XI: X=I) (1.10 g. or 62.1%) was converted as usual into the corresponding chloride hydrochloride (XI: X=Cl), which formed a yellowish brown caramel-like solid (820 mg. or nearly quantitative, based on the iodide hydroiodide).

Rubremetinium Bromide (XII)—i) The above-mentioned chloride hydrochloride (XI: 430 mg.) was dehydrogenated according to the report of Ban7) (in which Battersby and Openshaw's method15) had been applied). The orange-red needles of *dl*-rubremetinium chloride thus obtained amounted to 120 mg. after drying in an evacuated (2 mm. Hg) desiccator at room temp. overnight, and melted at 115~117° with effervescence. The whole chloride was dissolved in 25 cc. of H_2O, filtered to remove a trace of insoluble materials, and to this orange-red, clear filtrate KBr (500 mg.) was added while being heated on a steam bath, the solution becoming turbid. After heating for some time, this solution was filtered to remove a trace of insoluble material, then cooled, and separated orange-red needles were purified three times from hot water, forming orange-red micro-needles of *dl*-rubremetinium bromide (*dl*-XII). Air-dried, it melted at 115~120° with effervescence. When dried at 100° for 16 hrs. over P_2O_5 *in vacuo* (3 mm. Hg), it sintered at 160~180° and melted around 195~210° with gentle decomposition. *Anal.* Calcd. for $C_{29}H_{33}O_4N_2Br \cdot 2H_2O$: C, 59.1; H, 6.3; N, 4.75. Found: C, 59.3, 58.75; H, 5.9, 6.2; N, 4.85.

The IR and UV absorption spectra of *dl*-rubremetinium bromide thus obtained were respectively well superimposable with those of *d*-rubremetinium bromide described below (Figs. 1 and 2).

ii) *d*-Rubremetinium bromide (*d*-XII) was prepared from natural emetine hydrochloride according to the method of Battersby and Openshaw.15) Air-dried bromide melted at 115~117° with effervescence. When dried at 100° for 16 hrs. over P_2O_5 *in vacuo* (3 mm. Hg), it sintered at 160~180° and melted around 195~210° with gentle decomposition. *Anal.* Calcd. for $C_{29}H_{33}O_4N_2Br \cdot 2H_2O$: C, 59.1; H, 6.3; N, 4.75. Found: C, 58.9; H, 6.6; N, 4.8.

1-(3,4-Dimethoxyphenethyl)-2-piperidone (VIII)—K dust (0.95 g.) was suspended in pure xylene (5 cc.) and to this mixture was added dropwise a xylene solution of 2-piperidone (2.4 g. in 15 cc. pure xylene) at room temp. The exothermic reaction ensued with evolution of H_2, while white K-salt separated. After being kept standing at room temp. for 30 mins., the whole was refluxed in an oil bath at 150~160° for 30 mins. and then cooled. To this mixture was added dropwise a solution of 3,4-dimethoxyphenethyl bromide (7.05 g.) in pure xylene (15 cc.) and then Cu dust (0.2 g.), and the whole was refluxed in an oil bath at 155~165° for 20 hrs. After cool, separated KBr and Cu dust were filtered off, and washed with benzene, AcOEt, and H_2O. The filtrate and the organic washings were combined and extracted several times with 20% HCl and then with conc. HCl. The light brown aqueous layer thus obtained was basified with anhyd. Na_2CO_3 under ice-cooling, separating a brown oil, which was taken up in AcOEt, washed with H_2O, dried, and evaporated *in vacuo*, leaving a brown viscous oil (3.17 g). This was subjected to distillation *in vacuo* to give a colorless viscous oil (VIII) of $b.p_{0.01}$ 190°, in a yield of 1.63 g. or 25.5%.

For the purpose of proving the structure of (VIII), this sample (1.63 g.) was mixed with pure toluene (16 cc.) and $POCl_3$ (5 cc.), and the mixture was refluxed in an oil bath at 130° for 1.5 hrs., separating a reddish orange oily substance on the bottom. Petr. ether (ca. 70 cc.) was then added and the mixture was left standing overnight. The supernatant layer was decanted, the residue was dissolved in H_2O, and treated with charcoal, giving a faint yellow solution of quaternary chloride, from which 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium picrate was obtained as yellow scales of m.p. 185~186° from EtOH, identical with an authentic sample[13] by admixture.

The above-obtained quaternary salt solution was smoothly hydrogenated catalytically over Adams' Pt under ordinary pressure, and furnished crude 9,10-dimethoxy-1, 2, 3, 4, 6, 7-hexahydro-11*bH*-benzo-[*a*]quinolizine (VIII') as light yellow crystals, from which were obtained the picrate as yellow pillars of m.p. 171~172° from EtOH, and perchlorate as white pillars of m.p. 183~185° from H_2O. They were found to be respectively identical with authentic samples[13] by admixture.

Ethyl 2-(Aminomethyl)butyrate (XIII)—Ethyl 2-(benzylaminomethyl)butyrate[6] (II) (6.1 g) was hydrogenated catalytically over 10% Pd-C (0.6g.) in EtOH (60 cc.) solution at 60~65° under atmospheric pressure, 660 cc. of H_2 being smoothly absorbed in ca. 1.5 hrs. (required, 580 cc.). This hydrogenation did not proceed at room temp. After removing the catalyst, the colorless filtrate with an odor of toluene was fractionally distilled. (XIII) was obtained as a colorless liquid of $b.p_{31}$ 95~96° in a yield of 3.3 g. or 87.8%.

For characterization, (XIII) was dissolved in 10 volumes of conc. HCl, the solution was heated on a steam bath for 2 hrs., evaporated *in vacuo*, leaving the crude 2-aminomethylbutyric acid hydrochloride, which was treated with BzCl and 5% NaOH solution as usual, forming 2-(benzamidomethyl)butyric acid as colorless pillars of m.p. 140~141° from hot H_2O. *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.1; H, 6.8; N, 6.3. Found: C, 65.1; H, 6.6; N, 6.15.

Ethyl 2-(Ethoxycarbonylacetamidomethyl)butyrate (XIV)—To a solution of the foregoing amino-ester (XIII: 48.0 g.) in benzene (100 cc.) was added dropwise a solution of ethoxycarbonylacetyl chloride (56.8 g) in pure benzene (80 cc.) with cooling and stirring, keeping the solution always slightly basic by adding aq. 10% Na_2CO_3 (250 cc). After all were added during 1 hr., the mixture was agitated for further 2 hrs. and the benzene layer was then separated, washed successively with H_2O, 10% HCl, and H_2O, dried, and evaporated *in vacuo*, leaving a colorless oil (XIV) having an ester-like odor, which responded to sodium nitroprusside showing the presence of an active methylene group. Yield, 84.6 g or 98.6%. (XIV) was directly used in the next step.

Ethyl 2,4-Dioxo-5-ethyl-3-piperidinecarboxylate (XV)—NaH (0.7 g) was suspended in pure toluene (20 cc.) and to this mixture, a toluene solution of above-mentioned ester (XIV) (3.62 g. in 30 cc. toluene) was added dropwise at room temp. After evolution of H_2 became gentle, the whole was heated in an oil bath, separating the Na-salt at about 100°. The temp. was now raised to 125~130° and kept there for 4 hrs. When cool, H_2O was added to the reaction mixture to dissolve the Na-salt, the separated toluene layer was washed several times with small portions of H_2O, and the washings were combined with the aqueous layer. After washing with benzene, this orange yellow aqueous solution was acidified with 10% HCl, separating a yellow oil, which was extracted with benzene, dried, and evaporated *in vacuo*, leaving an orange yellow viscous oil (XV). The oil solidified on standing to form plates of m.p. 54~65°, soluble in Na_2CO_3 and NaOH solution. Yield, 1.73 g. or 57.7%. (XV) gives purplish red coloration with $FeCl_3$ in EtOH. For characterization the phenylhydrazone was prepared as usual. It formed white needles of m.p. 176~177° (decomp.) from 50% EtOH. *Anal.* Calcd. for $C_{16}H_{21}O_3N_3$: C, 63.35; H, 7.0; N, 13.85. Found: C, 63.5; H, 6.7; N, 13.9.

2,4-Dioxo-5-ethylpiperidine (XVI)—The foregoing keto-ester (XV: 11.8 g.) was mixed with 10% AcOH (50 cc.) and the mixture was refluxed in an oil bath, when the evolution of H_2 became vigorous at about 85° and subsided on heating at 125~130° (oil bath temp.) for 40 minutes. When cool, the light yellow turbid solution was neutralized with Na_2CO_3, salted out with NaCl, and extracted with AcOEt. AcOEt layer was dried and evaporated *in vacuo*, leaving 7.4 g. (or 94.7%) of (XVI) as a yellow viscous oil which solidified on standing. (XVI) distilled at 156~157°/1 mm. Hg and became a white solid of m.p. 69~71°, which was recrystallized from benzene-hexane to form white prisms of m.p. 72~74°. *Anal.* Calcd. for $C_7H_{11}O_2N$: C, 59.55; H, 7.85; N, 9.9. Found: C, 59.2; H, 7.8; N, 9.9. IR ν_{max}^{Nujol} cm^{-1}: 3238 (NH), 1716, 1700 (CO), 1675, 1669, 1652, 1646 (CONH, chelated CO?).

(XVI) is soluble in 10% NaOH solution and showed light brown coloration with $FeCl_3$ in EtOH, but not very distinct. A prolonged heating of (XVI) during distillation caused a great loss. 2,4-Dinitrophenylhydrazone: Orange yellow minute prisms from EtOH, m.p. 217° (decomp.). *Anal.* Calcd. for $C_{13}H_{15}O_5N_5$: C, 48.6; H, 4.7; N, 21.8. Found: C, 48.7; H, 4.7; N, 21.5.

4-Hydroxy-5-ethyl-2-piperidone (XVII)—The distilled lactam-ketone (XVI: 2.11 g.) was dissolved in 40 cc. of EtOH and hydrogenated catalytically over Adams' Pt (200 mg.) at 45° under ordinary pressure, one molar equivalent of H_2 being absorbed and giving a faint yellow turbid jelly (XVII) in a yield of 2.18 g. IR $\nu_{max}^{Capil.}$: Very broad band centered at 3327 cm^{-1} (OH, NH), 1653 cm^{-1} (CONH). The bands at 1700 and 1716 cm^{-1} present in (XVI) had disappeared. The crude (XVII) was used directly in the next step.

1-Acetyl-5-ethyl-5,6-dihydro-2(1*H*)-pyridone (XVIII)—The crude (XVII: 2.15 g.) was mixed with Ac_2O (15 cc.) and the mixture was refluxed in an oil bath at 160~170° for 4.5 hrs. When cooled, the excess of Ac_2O was removed by distillation *in vacuo* and the residual oil was distilled under reduced pressure, forming a colorless liquid (XVIII) of $b.p_{36}$ 155~158° in a yield of 2.09 g. or 83.3%. Redistilled for analysis, $b.p_{32}$ 155~156°. *Anal.* Calcd. for $C_9H_{13}O_2N$: C, 64,65; H, 7.8; N, 8.4. Found: C, 64.4; H, 7.7; N, 8.3. IR $\nu_{max}^{Capil.}$ cm^{-1}: 1685(CH_3CONCO), 1626(-C=C-).

Diethyl 2-Oxo-5-ethyl-4-piperidinemalonate (XIX)—To a solution of Na (0.40 g.) in dehyd. EtOH (10 cc.) was added dropwise diethyl malonate (3.60 g.) in dehyd. EtOH (2 cc.) with stirring. A solution of the dihydropyridone (XVIII: 1.87 g.) in dehyd. EtOH (2 cc.) was added dropwise to the cooled, above-obtained solution within 40° (internal temp.) and the whole was then warmed on a steam bath at 50~60° for 1 hr. with stirring. When cool, the faint pink reaction mixture was poured into ice water which contained 1.2 cc. of AcOH, and then EtOH was removed *in vacuo*, separating an oil. The oil was taken up in benzene, which was washed with satd. $NaHCO_3$ solution, followed by H_2O, dried, and evaporated *in vacuo* to leave a light yellowish brown oil (3.40 g.). When this oil was distilled fractionally, diethyl malonate of $b.p_{18}$ 93~94° was recovered as a forerun and then a faint yellow viscous oil (XIX) of $b.p_{0.06}$ 180~197° was obtained in a yield of 2.00 g. or 62.7% based on (XVIII) used. Redistilled for analysis, $b.p_{0.05}$ 180~193°. *Anal.* Calcd. for $C_{14}H_{23}O_5N$: N, 4.9. Found: N, 4.7. IR $\nu_{max}^{Capil.}$ cm^{-1}: 3215(NH), 1738,1727 (COOEt), 1672(CONH).

On being kept standing for ca. 2 weeks, the distilled (XIX) (1.39 g.) partially solidified, which was washed with three 3-cc. portions of cold dehyd. ether to form (XIXa) as white prisms of m.p. 78~81°, amounting to 440 mg. The ether washings were combined and concentrated to ca. 2 cc., separating further 360 mg. of white prisms (XIXa), m.p. 78~81°. The total yield of (XIXa) was 800 mg., and when it was purified from hexane-ether (3:1), it formed white prisms of m.p. 80~81.5°. *Anal.* Calcd. for $C_{14}H_{23}O_5N$: C, 58.9; H, 8.1; N, 4.9. Found: C, 58.7; H, 7.9; N, 4.9. IR ν_{max}^{Nujol} cm^{-1}: 3219(NH), 1743, 1731 (COOEt), 1674(CONH).

On evaporating the ethereal mother liquor, the crude (XIXb) (580 mg.) was obtained as a light brown fluorescent syrup.

2-Oxo-5-ethyl-4-piperidinemalonic Acid (XX)—i) The mixture of above-mentioned ester (XIXa) (400 mg.), EtOH (5 cc.), and 50% KOH (370 mg.) was refluxed on a steam bath for 2 hrs., separating a colorless oil. When EtOH was removed *in vacuo* a colorless caramel-like solid was obtained, which was dissolved in ca. 1 cc. of H_2O to form a clear solution. This aqueous solution was acidified to Congo red with conc. HCl under cooling and the separated colorless crystals were collected on a filter, washed with a small volume of ice-cold H_2O, and then dried in a vacuum desiccator, giving 290 mg. of the crude (XXa), m.p. 140~141° (decomp.). When purified from hot H_2O, it formed colorless prisms (XXa) of m.p. 146~147° (decomp.) (m.p. 151~152° (decomp.) by rapid heating). *Anal.* Calcd. for $C_{10}H_{15}O_5N$: N, 6.1. Found: N, 6.0.

On heating in a capillary, (XXa) liquefied and decomposed. The residue solidified to colorless needles on cooling and melted at ca. 145° (perhaps (Va)). Decarboxylation of (XXa) was already decreased in (V)-(vii).

ii) The crude (XIXb: 580 mg.) was also hydrolysed as described above, but the carboxylic acid corresponding to (XXb) separated as a light yellow syrup, which could not be induced to solidify. Therefore the whole was evaporated *in vacuo* to dryness to yield a mixture of KCl and a light yellow syrup, which was directly decarboxylated to a mixture of (Va) and (Vb), as was described in (V)-(vii) (p. 596).

Summary

1-Benzyl-2-oxo-5-ethyl-4-piperidineacetic acid (III) was debenzylated by metallic sodium in liquid ammonia and the product was alkylated with 3,4-dimethoxyphenethyl bromide to yield N-(3,4-dimethoxyphenethyl)-lactam derivative (IX). The chloride of the latter was coupled with 3,4-dimethoxyphenethylamine and the resultant oily amide (X) was cyclized to give dehydroemetine (XI), which was also obtained as a syrup. For characterization the latter was converted to the crystallizable *dl*-rubremetinium bromide (XII), the ultraviolet and infrared absorption spectra of which were respectively identical with those of the authentic sample of *d*-salt. Aiming at the total synthesis of emetine the stereochemical assignment of two forms (Va and b) of (V) was attempted, but so far was unsuccessful.

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〔Added in proof〕 After this paper was submitted for publication, the communications of M. Barash and J. M. Osbond (Chem. & Ind. (London), **1958**, 490) and of A. Brossi, A. Cohen, J. M. Osbond, Pl. A. Plattner, O. Schnider, and J. C. Wickens (*ibid.*, **1958**, 491) became available in our Library. The former authors describe the synthesis of emetine and its stereoisomers, and the latter, stereochemistry of emetine.

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118. **Shigehiko Sugasawa and Hisayuki Matsuo**: A Modified Emde Degradation. Reductive Cleavage of Quaternary Ammonium Salts by Raney Nickel.†

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An important rôle of Emde degradation[1] in alkaloid chemistry and allied fields is well known. Thus the cleavage of C-N linkage of even those quaternary ammonium salts, which are resistant to Hofmann degradation, can in many cases be achieved by heating them with 5% sodium amalgam in aqueous solution, hence under a strong alkaline working condition. In order to avoid working in alkaline medium Emde[2] carried out the cleavage through catalytic hydrogenation in the presence of platinum oxide or palladium on barium sulfate. Emmert[3] used electrolytic reduction for the same purpose and zinc-copper couple in amyl alcohol was used by Kishi.[4] However, none of these modified methods is so widely used as the original Emde method.

It was in 1942 when Papa, *et al.*[5] introduced a combination of aqueous sodium hydroxide solution and Raney nickel alloy as a strong reduction agent for organic compounds. Thus by this means aryl ketones gave arylmethylenes, aliphatic carbonyl compounds yielded the corresponding alcohols, and isolated ethylenes and acetylenes were reduced to the saturated compounds. The efficacy of this combination can be attributed to the nascent hydrogen, which is activated over nickel catalyst formed.

We now applied the Papa type of reduction method to various quaternary ammonium salts with the expectation that the Emde type of cleavage would be possible under milder working conditions and in simpler manipulation than the conventional Emde method, and so far our preliminary experiments, which will be described in this paper, are concerned the cleavage was effected usually with better yield of the products and in shorter working time than the original method.

As open-chain model compounds phenethyl-(I), benzyl-(II), phenyl-(III), and 2-biphenyltrimethylammonium (IV) salts were chosen. The compound was mixed with aqueous sodium hydroxide solution (15~20%) and to the resultant alkaline solution of ammonium compound 1.5~2.5 times the required amount of 50% Raney nickel alloy was added in small portions with stirring and cooling to keep the temperature of the reaction mixture within 25° as was required for the preparation of Raney nickel W-2.[6] The evolution of trimethylamine, which was collected in hydrochloric acid and characterized, became evident as soon

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† cf. S. Sugasawa, H. Matsuo: This Bulletin, **4**, 142(1956).

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[6] R. Mozingo: Org. Syntheses, **21**, 15(1941).