12. Shigehiko Sugasawa and Tōzō Fujii: Studies on the Synthesis of Emetine. I. A Synthesis of 1-(N-Benzyl-2-oxo-5-ethyl-4-piperidylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. (Preliminary Experiments to the Synthesis of Emetine).

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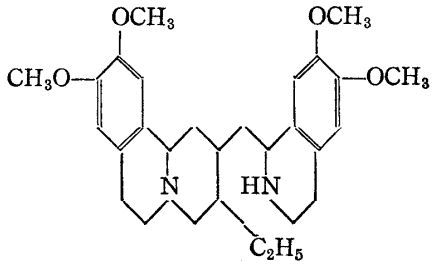
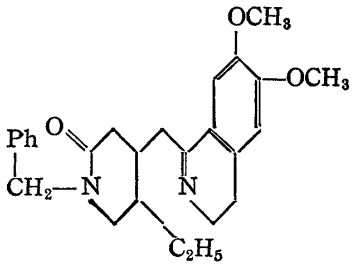
In 1948, Robinson[1] put forward a new emetine formula (A), chiefly based upon the experimental data obtained by other workers and at the same time applying the theory of Woodward fission, incorporating his general ideas of biogenesis of natural products. Later, his formula was substantially supported by Openshaw *et al.*,[2] who succeeded in synthesizing *rac*-rubremetinium salt, which was found to have the same structure as the one derived from natural emetine by the known method. Preobrazhenskii *et al.*[3] also claimed to have synthesized an optically active compound having the structure (A), which was proved to be identical with the natural alkaloid.

Our pursuit along this line was initiated towards the middle of 1952, and after numbers of fruitless efforts, we at last found a new route, through which the synthesis of emetine now appeared to be feasible. In this paper we are describing a synthesis of a complicated isoquinoline derivative mentioned in the title, the compound (B), as preliminaries to the synthesis of emetine.



(A)



(B) Ph=C_6H_5

When benzylamine and ethylmalonic acid were cross-condensed with formaldehyde under the Mannich conditions,[4] there was obtained (benzylaminomethyl)ethylmalonic acid (I) in an excellent yield, no trace of tertiary amine, which can be expected from (I) by further Mannich condensation, was detected in the reaction product, probably because the compound (I) is so sparingly soluble, that it immediately separates out as soon as it is formed. Decarboxylation of the compound (I) was best effected by boiling with dilute hydrochloric acid, furnishing α-(N-benzylaminomethyl)butyric acid (II) in a good yield, which was esterified as usual, thus giving the compound (III).

When this amino-ester (III) was acylated with the chloride of ethyl hydrogen malonate, there was produced N-ethoxycarbonylaceto derivative (IV) of (III) in a good yield. This compound (IV) underwent smooth cyclization under Dieckmann conditions, yielding the compound (V) again in an excellent yield, which readily suffered ketonic fission to give N-benzyl-2,4-dioxo-5-ethylpiperidine (VI). The latter dissolved in caustic alkali. The N-aceto derivative (IV′) of (III) was also prepared to reach the compound (VI) in a simpler fashion, but cyclization of (IV′) to (VI) could not be realized under various working conditions so far tried.

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1) Robert Robinson: Nature, **162**, 524(1948).
2) Buttersby, Openshaw, Wood: J. Chem. Soc., **1953**, 2463.
3) C. A., **47**, 5949(1953), and preceding papers.
4) Mannich, Ganz: Ber., **55**, 3486(1922).

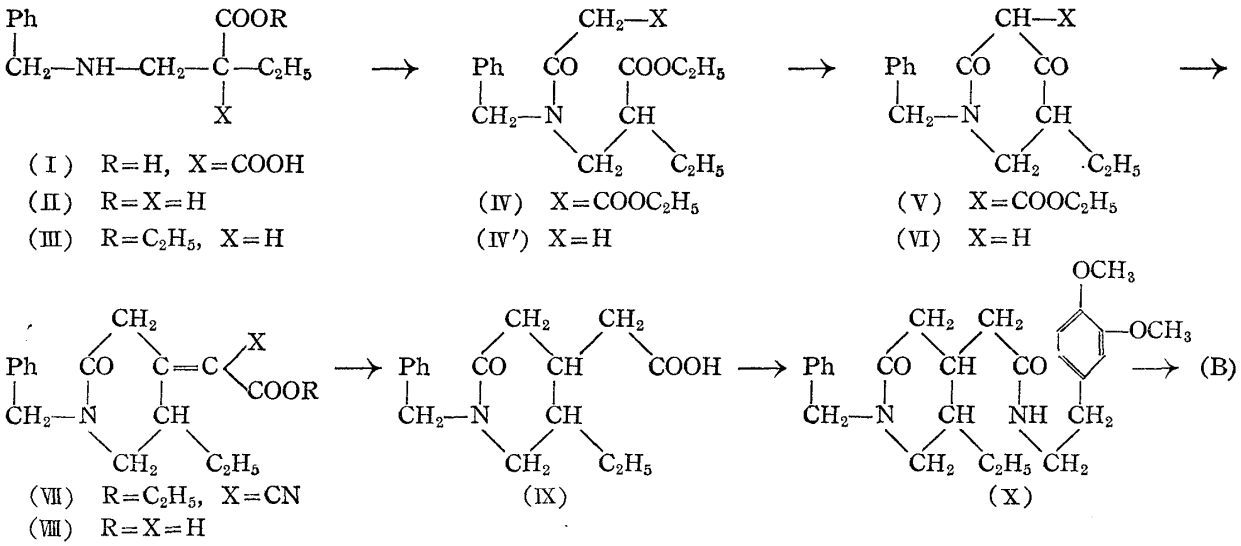
As can be judged from its solubility in caustic soda, this compound (VI) exists in enolized form and probably owing to this property it did not respond to either Dutt, Knoevenagel, or Reformatsky reaction, by means of which the introduction of $-CH_2-COOH$ chain at 4-position appeared feasible, but recovering the starting material (VI) in each case. The condensation with ethyl cyanoacetate under the Cope conditions was, however, successful, thus furnishing cyanoacrylic ester (VII) as caramel-like solid, which however was not obtained in a pure state.

The cyano group in (VII) was now esterified and without isolating the product, it was directly hydrolyzed and decarboxylated with boiling hydrochloric acid, thence acrylic acid derivative (VIII) was obtained in a crystalline form. Though the yield was by no means good (ca. 30% as the crude product), enough material was collected for the next step. The latter was then hydrogenated catalytically, absorbing one mole of hydrogen smoothly, to yield the saturated acid (IX) as colorless viscous syrup, a little portion of which solidified after being kept for a few months in a vacuum desiccator. When purified, this was separated into two forms. The one is colorless pillars of m.p. 105~106° and the other is colorless syrup, which resisted all efforts to make it crystallize.

The main portion of the diastereoisomeric mixture of (IX) was directly converted into its chloride by means of freshly purified thionyl chloride and the chloride was condensed with homoveratrylamine under the Schotten-Baumann conditions, when the amide (X) was produced, which was not induced to crystallize. So this was directly cyclized and the final product (B) was obtained as an uncrystallizable syrup.[5] Among its various derivatives the picrolonate was found to be suitable for characterization.

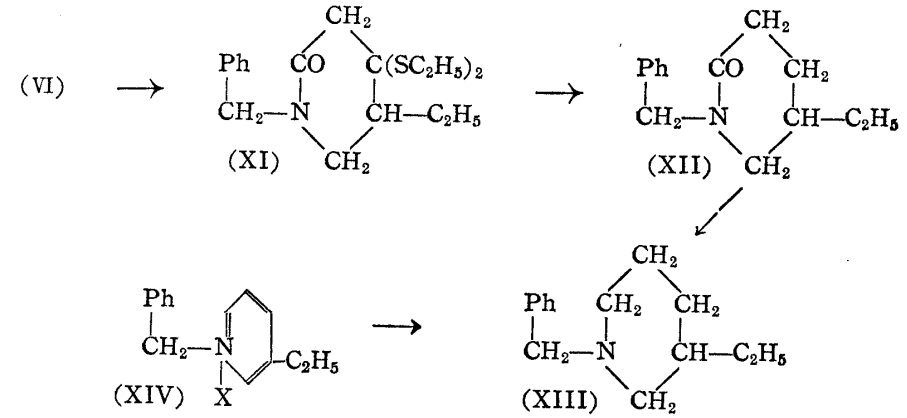
The crude picrolonate was prepared in ethanolic solution, separating as fluffy, orange yellow solid, which was purified from hot ethanol. On cooling there separated first the more sparingly soluble salt, forming orange yellow amorphous powder (decolorizing at 144°, shrinking at 150°, and melting at 200~203° with effervescence), which could not be induced into a crystalline form by further purification and did not give satisfactory analysis. When the first ethanolic mother liquor was evaporated to a small volume at room temperature there separated the second salt as yellow crystalline solid of m.p. 201~208°, which was raised to 213~215° by repeated purification from ethanol, forming fluffy, pale yellow needles, which analyzed correctly as (B) picrolonate.

The following chart illustrates the process of the present synthesis :



5) Acyl benzylamide does not cyclize to form isoindole-type of compounds. cf. Malan, Robinson : J. Chem. Soc., **1927**, 2653.

Since the compound (VI) forms the important key intermediate in the present synthesis, its structure was made beyond doubt. Bis(ethylthio) compound (XI) of (VI) was prepared and the latter was submitted to desulfurization according to the method of Wolfrom and Karabinos,[6] furnishing 2-piperidone derivative (XII), which was then reduced with lithium aluminum hydride in ethereal solution. N-Benzyl-3-ethylpiperidine (XIII) thus obtained was proved to be identical with the authentic (XIII), prepared by reducing N-benzyl-3-ethylpyridinium chloride (XIV), by direct comparison.



The synthesis of emetine now appears feasible through either one of the following two routes :

1) By substituting homoveratrylamine for benzylamine in the original Mannich condensation.

2) By removing the benzyl group from either (IX) or (B) in order to introduce the homoveratryl group in its stead.

Pursuit along these two lines are now under progress and the results will be published in due course.

The authors are grateful to the Ministry of Education for the Science Research Fund supplied to them during the years of 1953 and 1954 in aid of the present research work and their thanks are also due to the members of the Analysis Room of this Institute and those of the Tokyo Research Laboratories of Gohei Tanabe & Co., for microanalytical data.

Experimental

(Benzylaminomethyl)ethylmalonic Acid (I)—An aq. EtOH solution of ethylmalonic acid (1.95 g., 1.5 mole ratio in a mixture of 11 cc. water and 5 cc. EtOH) and benzylamine (1.1 g., 1 mole ratio), was added with 30% HCHO (1 g) separating colorless plate-shaped solid after some time. After standing at room temperature for 24 hrs., this was filtered, washed with water and EtOH, and dried in a vacuum desiccator. Yield, 2.3 g. of (I), m.p. 154~155°(decomp.). From the filtrate some more was recovered on standing. Total yield, 89% based on the amine used. For purification, this was dissolved in *N* NaOH solution, filtered, and the filtrate was acidified with AcOH, separating colorless prisms, m.p. 154.5~155° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.1; H, 6.8; N, 5.6. Found : C, 62.3; H, 7.0; N, 5.65.

This compound gives positive Liebermann test for secondary amines, and dissolves in acid and alkali as well. Sparingly soluble in water, EtOH, and general organic solvents in the cold.

α-Benzylaminomethylbutyric Acid (II)—Decarboxylation of the foregoing malonic acid derivative can be carried out by heating with dimethylaniline, but was best effected by boiling with HCl. Thus (I : 13 g.) in HCl (130 cc. of 20%) was refluxed for 5~6 hrs. at 135~140°(oil bath temp.) until the cessation of CO_2 evolution. Water and HCl were now evaporated under 70° *in vacuo*, leaving colorless hard syrup, which solidified on being kept in a desiccator overnight; yield, nearly quantitative. Repeatedly purified from EtOH, forming colorless minute plates, m.p. 188~189°. *Anal.* Calcd. for $C_{12}H_{17}O_2N \cdot HCl$:. C, 59.1; H, 7.4; N, 5.75. Found : C, 59.4; H, 7.1; N, 5.6.

Free amino acid : Colorless needles from EtOH-AcOEt (1:2), m.p. 165~166°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.5; H, 8.3; N, 6.8. Found : C, 69.4; H, 8.6; N, 7.1.

6) J. Am. Chem. Soc., **66**, 909(1944).

Ethyl ester (III) : The foregoing crude hydrochloride (prepared from 13 g. of (I)) in 150 cc. abs. EtOH was refluxed on a steam bath, dry HCl gas was passed through this solution for 3~4 hrs., and then worked up as usual. The ester distilled at 141~143°(5 mm. Hg); yield, 10.3 g. or 84.6%. Clear colorless liquid of characteristic odor. For analysis, it was redistilled, b.$p_{5.5}$ 147°. *Anal.* Calcd. for $C_{14}H_{21}O_2N$: C_2H_5O, 19.15. Found : C_2H_5O, 19.2.

Picrolonate : Yellow needles from EtOH, m.p. 170.5~171.5°. *Anal.* Calcd. for $C_{24}H_{29}O_7N_5$: C, 57.7; H, 5.9; N, 14.0. Found : C, 57.55; H, 6.2; N, 13.9.

Ethyl α-(N-Ethoxycarbonylacetobenzylaminomethyl)butyrate (IV)—A benzene solution of the foregoing ester (24 g. in 50 cc. of the solvent) was added dropwise with the chloride (23.4 g. in 50 cc. of benzene) of ethyl hydrogen malonate and at the same time keeping the solution always faintly basic with 10% Na_2CO_3 solution (140 cc.), with cooling and stirring. After all were added, the mixture was agitated for further 2 hrs. and the benzene layer was then separated, washed with dil. HCl, followed by water, dried, and evaporated *in vacuo*, leaving colorless viscous oil having an ester-like odor, which responded to sodium nitroprusside showing the presence of an active methylene group. Since its distillation was attended with some decomposition even in a high vacuum, it was directly used in the next step. Yield, nearly quantitative.

N-Benzyl-2,4-dioxo-3-ethoxycarbonyl-5-ethylpiperidine(V)—Na dust (1 g.) was suspended in pure xylene (25 cc.) and to this mixture was added dropwise a xylene solution of the above-mentioned ester (15 g. in 35 cc. xylene). After the vigorous evolution of H_2 became gentle, the whole was heated gently in an oil bath. At about 60~70°, H_2 evolution subsided and at 105~110° the reaction mixture became turbid. The temperature was now raised to 140~150° and kept there for about 4 hrs. (all Na disappeared after about 2 hrs.' heating). On cooling, the supernatant xylene layer was decanted from the solid and was repeatedly shaken with small portions of water. The solid residue was now dissolved in the combined aqueous washings and this solution was filtered through a wet filter, after being once shaken with ether. The filtrate was acidified with HCl under good cooling, separating an oily layer, which was taken up in benzene, washed, dried, and then evaporated *in vacuo*, leaving yellowish brown fluorescent syrup, soluble in Na_2CO_3 and NaOH solution. It gives brilliant red coloration with $FeCl_3$. Yield, 12 g. or 92%. When reacted with phenylhydrazine it gave white crystalline solid of m.p. 202~204° which is either the phenylhydrazone or the pyrazolone derivative.

Ethyl α-(N-Acetobenzylaminomethyl)butyrate (VI′)—This was prepared by acetylating (III) with either AcCl or Ac_2O as usual. The amide (IV′) forms a colorless syrup of b.$p_{0.06}$ 161~162°, having a faint agreeable odor. Yield, 95.1%. Redistilled for analysis, b.$p_{0.03}$ 150~151°. *Anal.* Calcd. for $C_{16}H_{23}O_3N$: N, 5.05; C_2H_5O, 16.25. Found : N, 4.9; C_2H_5O, 17.1.

N-Benzyl-2,4-dioxo-5-ethylpiperidine (VI)—The foregoing keto-ester (14.28 g.) was mixed with aq. HCl (45 cc. of 6.7%) and the mixture was refluxed in an oil bath, when the evolution of CO_2 became vigorous at about 90° and subsided on heating at 130~140°(oil bath temp.) for ca. 3 hrs. On cooling, the substance, which no longer gave the $FeCl_3$ color test, that separated was taken up in benzene, washed with dil. $NaHCO_3$, and then with sat. NaCl solutions. After being dried over Na_2SO_4, the solvent was evaporated *in vacuo*, leaving 9.18 g. (or 84.3%) of the crude (VI) as brown, fluorescent viscous syrup, which distilled at 180~181°(0.05 mm. Hg), forming nearly colorless viscous syrup and leaving much residue, which was probably produced through intermolecular self-condensation.[7] The distillation was thus attended with much loss of substance, so the crude product was directly used in the next step. The purity of the crude (VI) was judged as more than 80% through test by the Girard-P reagent and also through the quantity of the semicarbazone and the phenylhydrazone formed, which also served for the characterization of (VI).

(VI) dissolves in NaOH solution but is sparingly so in Na_2CO_3 solution. It dissolves in common organic solvents except light petroleum hydrocarbons. Forms crystalline $NaHSO_3$ addition product.

Phenylhydrazone : Fluffy needles from EtOH, m.p. 199~201°(decomp.), with previous sintering at 192°. *Anal.* Calcd. for $C_{20}H_{23}ON_3$: C, 74.7; H, 7.2; N, 13.1. Found : C, 74.7; H, 6.95; N, 13.3.

Semicarbazone : Colorless minute needles from EtOH, m.p. 190~191°.

Ethyl (N-Benzyl-2-oxo-5-ethyl-4-piperidylidene)cyanoacetate (VII)—The crude (VI) (12.4 g.), ethyl cyanoacetate (6.2 g.), glacial AcOH (2.8 g.), dried $AcONH_4$ (1.0 g.), and a few drops of piperidine were mixed and the whole was boiled with toluene (50 cc.) in an apparatus provided with a device to continuously remove the water formed. 2.2 cc. of water was collected after being boiled for 14 hrs. in an oil bath kept at 140~150°. Another batch of a mixture of glacial AcOH (1.4 g.), $AcONH_4$ (0.5 g.), and a few drops of piperidine was added and the whole was again refluxed for additional 17.5 hrs. until no more water distilled over (about 1 cc. of water was collected). On cooling, the clear reddish reaction product was washed 3 times with sat. NaCl solution. The combined salt solution was shaken with benzene, which was mixed with the original toluene layer, dried, and evaporated *in vacuo*, leaving viscous reddish oily substance. The latter was now dissolved in about 90 cc.

7) cf. Sugasawa, Oka : This Bulletin, 2, 87(1954).

of benzene, which was shaken 3 times with 10% NaOH solution to remove the unreacted (VI). During this procedure, there separated dark reddish oily substance on the bottom. The benzene layer was washed with water and the washing was combined with the original NaOH layer containing reddish oil. This was then salted out with NaCl and repeatedly extracted with AcOEt, dried, and evaporated *in vacuo*, leaving brown caramel-like solid (14.6 g. or 83.4%) of m.p. 124~127°, which is insoluble in ether and ligroine. Though soluble in benzene, it separates out on adding NaOH solution. It also dissolves readily in AcOEt, $CHCl_3$, EtOH, and acetone. This substance is probably represented by formula (VII), but could not be obtained in a pure state and so was used directly in the next step.

(N-Benzyl-2-oxo-5-ethyl-4-piperidylidene)acetic Acid (VIII)—The above-mentioned substance (7 g.) was dissolved in 40 cc. of abs. EtOH and the solution was saturated with dry HCl-gas without cooling, separating some white solid (NH_4Cl). The whole was then refluxed on a steam bath until the separation of NH_4Cl was no longer recognized, during which time dry HCl gas was passed through. HCl (30 cc. of 10%) was now added and the mixture was refluxed in an oil bath, evolving CO_2, which almost subsided after about 7 hrs. On evaporating *in vacuo*, there remained a faint yellow hard syrup, which was dissolved in AcOEt. This solution was then extracted repeatedly with sat. $NaHCO_3$ solution, the combined extract was filtered through a wet filter, and the filtrate was acidified with conc. HCl to Congo red. White solid separated after some time, which was collected on a filter after being kept standing overnight and dried in a vacuum desiccator, giving 1.7 g. (or 29%) of faint yellow needles, m.p. 115~117°.

On evaporating AcOEt layer, there was recovered 3.7 g. of non-acidic substance, from which additonal 0.3 g. of (VIII) was obtained on treating as above, making the total yield of 2.0 g. or 34%. (VIII) is readily soluble in EtOH, acetone, and AcOEt, but sparingly so in cold ether. Purified from hot water, forming colorless needles, m.p. 126~127°(slight effervescence). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.3; H, 7.0; N, 5.1; COOH, 16.5. Found: C, 70.2, 70.45; H, 7.3, 6.9; N, 5.4; COOH, 18.1.

N-Benzyl-2-oxo-5-ethyl-4-piperidylacetic Acid (IX)—The foregoing acid was hydrogenatd catalytically over Adams' Pt in EtOH solution, one mole equivalent of H_2 being smoothly absorbed, giving colorless syrup in quantitative yield. On keeping in a desiccator for a long time (ca. 3 months), this substance solidified to colorless leaflet-like solid, which melted over a range of 45~66°. When purified from benzene-hexane mixture it formed colorless pillars, m.p. 105~106°. *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.8; H, 7.7; N, 5.1. Found: C, 69.4; H, 7.7; N, 4.9.

From the mother liquor was obtained colorless syrup, from which no more crystalline substance was obtained.

N-Benzyl-2-oxo-5-ethyl-4-piperidylaceto-(β-3,4-dimethoxyphenyl)ethylamide (X)—The acid (IX: 0.86 g. of diastereoisomeric mixture) was treated with freshly purified $SOCl_2$ (0.45 g.) at about 60~70° until gas evolution became gentle (ca. 1.5 hrs.). After being heated on a boiling water bath for additional 30 mins., 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 (15 cc.) and used in the next step.

Homoveratrylamine (1.8 g.), dissolved in 15 cc. pure benzene, was added dropwise to the above obtained benzene solution of the acid chloride with shaking and cooling, giving orange yellow clear solution, from which the amine·HCl began to separate after some time. The whole was now kept standing overnight and then washed several times with dil. HCl, followed by water, 10% Na_2CO_3 solution, and at last with sat. NaCl solution, dried, and evaporated, leaving reddish brown viscous syrup, which was not induced to crystallize and was worked up directly. Yield, 1.15 g. or 83.9%, based on the acid (IX) used.

1-(N-Benzyl-2-oxo-5-ethyl-4-piperidylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (B)—The foregoing amide (X: 1.15 g.), dissolved in 12 cc. of pure benzene, was mixed with $POCl_3$ (3.5 cc.) and the whole was gently refluxed on a steam bath for about 3 hrs., separating a dark-colored viscous substance on the bottom. Petroleum ether (60 cc.) was then added and the mixture was left standing overnight. The supernatant layer was decanted and the residue was dissolved in 10% HCl and worked up as usual, leaving the crude (B) as reddish brown hard syrup (0.81 g. or 73.4%), which was characterized as the picrolonate.

Picrolonate: The crude (B) (0.3 g.) was dissloved in EtOH (3 cc.) and added with sat. EtOH solution of picrolonic acid (0.21 g. in 21 cc. EtOH), separating yellow orange fluffy solid immediately. A few hrs. later, the precipitate was collected on a filter, washed, and dried, weighing 0.25 g. This formed yellowish brown powder, which decolorized at 144°, shrunk at 150°, and decomposed at 200~203°, with previous liquefaction. When purified from EtOH, there separated orange yellow amorphous powder of m.p. 156~158°(sint. at about 150°), which however did not give satisfactory analysis.

EtOH mother liquor was concentrated *in vacuo* to a small volume (ca. 2 cc.) at room temp. and left standing, when yellow granular crystalline solid of m.p. 201~208° separated, which amounted to ca. 0.1 g. Repeatedly recrystallized from EtOH, forming pale yellow fluffy needles of m.p. 213~215°. *Anal.* Calcd. for $C_{26}H_{32}O_3N_2 \cdot C_{10}H_8O_5N_4$: C, 63.1; H, 5.9; N, 12.3. Found: C, 63.0; H, 5.7; N, 12.2.

N-Benzyl-4-bis(ethylthio)-5-ethyl-2-piperidone (XI)—The compound (VI : 3.5 g.) was mixed with anhyd. Na_2SO_4 (1.0 g.) and freshly fused $ZnCl_2$ (1.0 g.) and the whole was added dropwise into EtSH (3.5 cc.) with ice cooling. The mixture was stoppered in a bottle and kept at room temp. for about 90 hrs. with occasional shaking. The viscous content was poured into ice water (ca. 20 cc.) and yellowish brown oil that separated was taken up in benzene, washed with dil. NaOH solution to remove the unreacted EtSH and (VI), and then with sat. NaCl solution, dried, and evaporated. A brown, viscous oily substance having a peculiar odor was obtained (3.6 g. or 70.8%), which was directly reduced.

N-Benzyl-5-ethyl-2-piperidone (XII)—The crude substance (XI : 3.42 g.) in EtOH (340 cc. of 70%) was treated with Raney Ni[8](25 g.) under reflux for 5.5 hrs. and then filtered from the catalyst, which was washed with EtOH. All EtOH solutions were combined and concentrated *in vacuo* to a small volume (ca. 10 cc.). Faint yellow oil separated was taken up in benzene, washed with sat. NaCl solution, dried, and evaporated. The faint yellow oily residue was distilled *in vacuo*, giving a colorless fraction of $b.p_{5.5}$ 170~172°, which was redistilled at 161~162°(3 mm. Hg) for analysis. Yield, 1.95 g. or 88.6%. *Anal.* Calcd. for $C_{14}H_{18}ON$: C, 77.4; H, 8.8; N, 6.45. Found : C, 74.2; H, 9.1; N, 6.1. The extremely low C value may be due to the contamination of some perhydrogenated impurity of uncertain nature.

N-Benzyl-3-ethylpiperidine (XIII)—i) From N-benzyl-3-ethylpyridinium chloride (XIV) : The compound (XIV) was prepared from 3-ethylpyridine and benzyl chloride as usual in a good yield. It forms very faint yellow viscous syrup and was characterized as its picrate, which forms yellowish orange needles of m.p. 99~101° from EtOH. *Anal.* Calcd. for $C_{14}H_{16}N \cdot C_6H_2O_7N_3$: C, 56.3; H, 4.3; N, 13.1. Found : C, 56.3; H, 4.4; N, 13.2.

The pyridinium chloride (XIV) was smoothly reduced over Adams' Pt in EtOH, giving (XIII) as colorless liquid of disagreeable basic odor in an excellent yield; $b.p_6$ 109~113°. Characterized as the picrate, which forms brilliant yellow prisms from EtOH, m.p. 139~140°. *Anal.* Calcd. for $C_{14}H_{21}N \cdot C_6H_3O_7N_3$: C, 55.55; H, 5.6; N, 13.0. Found : C, 55.7; H, 5.6; N, 12.8.

The picrolonate was also obtained as well-defined yellow orange rhombic plates from EtOH, m.p. 131~132°. *Anal.* Calcd. for $C_{14}H_{21}N \cdot C_{10}H_8O_5N_4$: C, 61.65; H, 6.25; N, 15.0. Found : C, 61.2; H, 6.2; N, 14.8.

ii) From (XII) : Powdered $LiAlH_4$ (0.4 g.), suspended in 100 cc. of abs. ether, was added dropwise to the ethereal solution of (XII : 1.9 g. in 50 cc. of the solvent) with ice cooling and stirring. The mixture was then refluxed gently for 13 hrs., when another portion of 0.4 g. of $LiAlH_4$-powder was added, and again refluxed for additional 17 hrs., separating much of the white addition product. Hydrous ether and cold water were then added with ice cooling and stirring to decompose unreacted $LiAlH_4$ and the addition product as well. The supernatant ethereal layer was separated and the aqueous layer was acidified with HCl to give a clear solution, which was then strongly basified with an excess of NaOH solution, filtered from some undissolved matters, which were washed with ether. The alkaline filtrate was extracted with the combined ethereal washing, which was then added to the original ethereal layer, dried, and evaporated. The residual yellowish brown oil was distilled, coming over at 113~116° (7.5 mm. Hg) as colorless liquid having a basic odor. Yield, 1.45 g. or 81.5%. The picrate forms brilliant yellow orange prisms, m.p. 138~139°, and the picrolonate comes as yellowish orange plates, m.p. 130~131°. These salts were found to be respectively identical with the ones obtained above by admixture.

Summary

A synthesis of 1-(N-benzyl-2-oxo-5-ethyl-4-piperidylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (B) was described as preliminaries to the synthesis of emetine. Benzylamine, formaldehyde, and ethylmalonic acid were the starting materials. The structure of the key intermediate, N-benzyl-2,4-dioxo-5-ethylpiperidine (VI) was proved beyond doubt. The condensation of this ketone with ethyl cyanoacetate under the Cope conditions offered some difficulty and this stage was the only drawback in this synthesis.

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8) Prepared from Raney Ni alloy according to Org. Syntheses, **21**, 15, but heated 1 hr. only at the bath temperature of 53~55°.