(5.5 g.) in pure xylene (120 cc.) was mixed with freshly distilled $POCl_3$ (28 g.) and the whole was refluxed in an oil bath for 6 hrs., giving a light brown solution. Xylene and an excess of $POCl_3$ were removed *in vacuo* and the residue obtained was mixed with ice water containing some HCl. The mixture was once shaken with benzene and the benzene layer was extracted with dil. HCl, which was added to the original aq. acid layer and basified, separating an oily substance. The oil was taken up in benzene, washed and evaporated, leaving a faint brown vitreous substance, which gradually solidified on standing. Purified from petr. ether, it formed colorless prisms of m.p. 42~44°. Yield, 4.6 g. (88%). *Anal.* Calcd. for $C_{24}H_{39}O_2N$: C, 77.2; H, 10.4; N, 3.7. Found : C, 77.5; H, 10.6; N, 3.7

Picrate : Yellow needles (from EtOH), m.p. 142~143°. *Anal.* Calcd. for $C_{30}H_{42}O_9N_4$: C, 59.8; H, 7.0; N, 9.3. Found : C, 60.2; H, 7.1; N, 9.2. (cf. Tables VI, and XIV).

(4) **Dehydrogenation**

1-(Methyl-ethyl-amylmethyl)-6,7-dimethoxyisoquinoline (VIII : $R=CH_3$, $R'=C_2H_5$, $R''=C_5H_{11}$)—The dihydro base (3.5 g.), ethyl cinnamate (15 g.), and Pd-C (2.5 g. of 30%) were mixed and the whole was heated in an atmosphere of CO_2 in an oil bath kept at 280~290°. After 8 hrs.' heating the reaction mixture was dissolved in benzene, filtered from the catalyst, and the filtrate was extracted repeatedly with dil aq. HCl. The combined acid solution was basified and the oil separated was extracted with benzene, washed, and evaporated, leaving a colorless syrup, which dilstilled at 163~164° (0.02 mm.). Yield, 2.85 g. (81%).

Picrate : Yellow prisms (from EtOH) m.p. 141~142.5°. *Anal.* Calcd. for $C_{26}H_{32}O_9N_4$: C, 57.3; H, 5.9; N, 10.3. Found : C, 57.0; H, 5.9; N, 10.6. (cf. Tables VII, and XV).

Summary

A series of 1-*tert*-alkyl-6,7-dimethoxy-3,4-dihydroisoquinolines was synthesized in high yields by cyclizing N-(3,4-dimethoxyphenethyl)-2,2,2-trialkylacetamides with phosphoryl chloride. They were dehydrogenated over palladium-carbon only under strenuous conditions to furnish the corresponding isoquinolines. Their spasmolytic activity will be examined. A general procedure for the preparation of trialkylacetic acids of high purity was also described.

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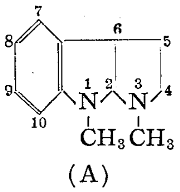
UDC 547.759.07

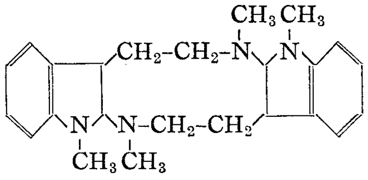
33. **Shigehiko Sugasawa and Masao Murayama** : Synthesis of *dl*-Esermethole.

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

For folicanthine, an alkaloid first isolated from the leaves of *Calycanthus floridus* L. and investigated by Eiter and Svierak,[1,2] two structural formulae (A) and (B) were proposed by Hodson and Smith,[3] of which the former (A) was considered more probable.[4]



(A)



(B)

Many years ago one of the present authors (S. S.) had attempted to synthesize *dl*-esermethole (IX) according to the following scheme :

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* Hongo, Tokyo (菅沢重彦, 村山正雄).

[1] K. Eiter, O. Svierak : Monatsh., **82**, 186 (1951).

[2] *Idem.* : *Ibid.*, **83**, 1453 (1952).

[3] H. F. Hodson, G. F. Smith : Chem. & Ind. (London), **28**, 740 (1956).

[4] Based on many experimental results Hodson and Smith later abandoned the formula (A) in favor of (B) (cf. J. Chem. Soc., **1957**, 1877).

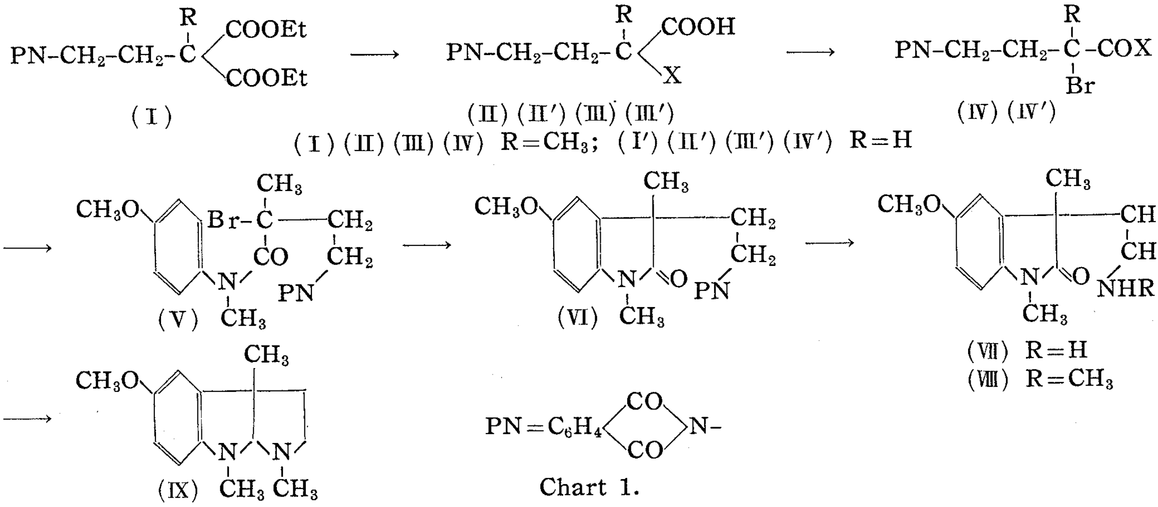

Chart 1.

While he was making efforts for the projected work there was published a paper on the synthesis of desoxyeseroline (compound A with an additional methyl group at 6-position) by Julian, *et al.*[5] and then successful syntheses of eserine by the same authors[6] and also independently by Hoshino, *et al.*[7] His effort towards the synthesis of *dl*-esermethole according to the above-mentioned scheme was thus abandoned.

Since the formula (A) proposed for folicanthine by Hodson can be regarded as 6-nordesoxyeseroline we again began the synthesise of the structure (A) according to the original scheme.

Thus diethyl (β-phthalimidoethyl)malonate (I′), prepared by the known method, was treated with conc. hydrochloric acid in acetic anhydride, when both ester groups were smoothly hydrolysed and the phthalimido group remained intact. (β-Phthalimidoethyl)-malonic acid (II′ : X=COOH) thus prepared suffered decarboxylation by heat, giving rise to γ-phthalimidobutyric acid (III′ : X=H), which was then converted to α-bromo-γ-phthalimidobutyryl chloride (IV′ : X=Cl) by the standard method.

The latter was now condensed with N-methylaniline to yield the corresponding anilide (X), which was then subjected to Stollé-type condensation to form the oxindole derivative (XI). Here again the phthalimido group was found indifferent towards the action of fused aluminum chloride. On being treated with hydrazine hydrate according to the method of Ing and Manske the phthalimido group was now removed readily from (XI) and N-methyl-3-(β-aminoethyl)oxindole (XII) was obtained.

For the preparation of (XII) another method was explored. When isatin and cyanoacetic acid were treated in the presence of ammonium acetate according to the Cope conditions, 3,3-bis(cyanomethyl)oxindole(XIII)was obtained as the sole product, but in the presence of pyridine in benzene solution they gave rise to oxindolylideneacetonitrile(XIV) in 29% yield. Inferior yield was obtained by piperidine. N-Methylisatin condesed with cyanoacetic acid in a like manner gave (1-methyloxindolylidene)acetonitrile (XV) in 20% yield as a mixture of two substances, while (XIV) was obtained in a single form of m.p. 194~195.5°. One of (XV) melted at 167~169° and the other at 155~157°. Both formed orange yellow needles and gave the same analytical values for C, H, and N, and their infrared spectra were also the same. When reduced with aluminum amalgam in wet dioxane they yielded one and the same N-methyl-3-cyanomethyloxindole (XVI). From these facts they can be regarded as *cis-trans* isomers around the semicyclic double bond.

Further reduction of (XVI) was carried out catalytically by hydrogen activated over

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[5] P. L. Julian, J. Pikl, D. Boggen : J. Am. Chem. Soc., **56**, 1797(1934).
[6] P. L. Julian, J. Pikl : *Ibid.*, **57**, 563, 755(1935).
[7] T. Hoshino, R. Kobayashi : Ann., **516**, 81(1935).

Adams' platinum catalyst, furnishing N-methyl-3-(β-aminoethyl)oxindole (XII), either in acetic acid or in acetic anhydride solution. That the acetylation did not occur during reduction in the latter solvent was rather remarkable. The identity of the amine (XII) now prepared with the one obtained via the alternative route was proved by direct comparison of their picrates and phthalimido derivatives.

For the purpose of cyclization (XII) was dissolved in absolute ethanol and treated with metallic sodium. On working up the reduction product there was obtained a colorless oil which distilled at 120~130°(bath temp.) under 1.5 mm. Hg. The examination of its infrared spectrum revealed that this compound has no $\nu_{C=O}$ absorption at 1695 cm^{-1} which is characteristic to the starting oxindole derivative (XII), but against our expectation this was found to be a primary amine, which gave mono- and di-picrates. The monopicrate forms orange yellow needles of m.p. 178~179° and the dipicrate deep red needles of m.p.167~168°. That it gives a red picrate, together with its ultraviolet spectrum showing λ_{max} 223 mμ ($\log \varepsilon_{max}$ 4.23) and λ_{max} 286 mμ ($\log \varepsilon_{max}$ 3.4) both in ethanol and 1% hydrochloric acid lends strong support for its being an indole derivative, and from the search of the literature it was found that this base is 1-methyltryptamine (XVII), as can be seen from Table I.

TABLE I.

	Our base	N-Methyltryptamine
Picrate, m.p. (°C)	178~179	179~180, 180~181
Hydrochloride, m.p. (°C)	199~201	199~202
Phthalimido derivative, m.p. (°C)	175~176	177

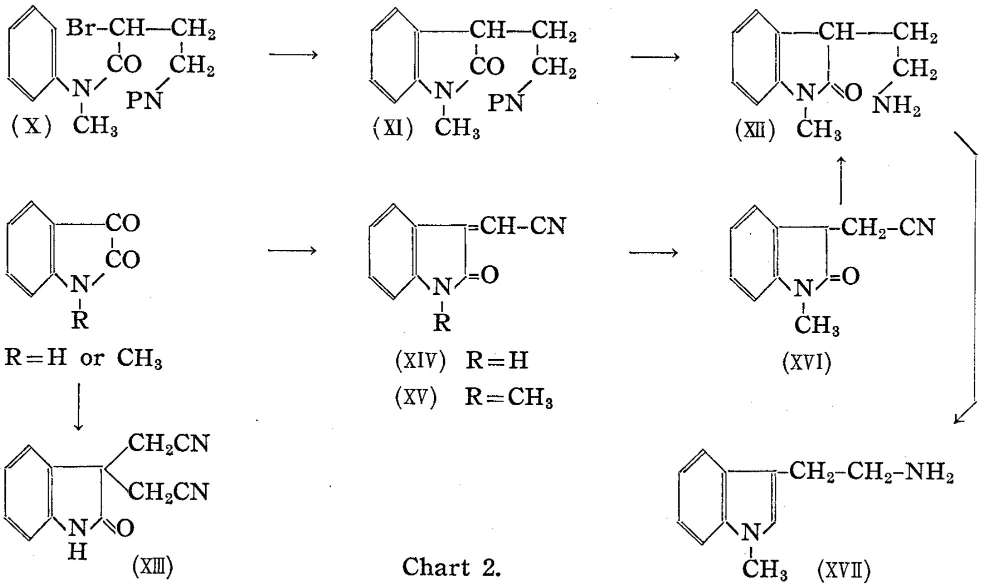

Chart 2.

Since the presence of an active hydrogen at 3-position in (XII) seemed to be responsible for this failure of cyclization, it appeared worth while to attempt again the synthesis of *dl*-esermethole according to the scheme as shown in Chart 1.

α-Methyl-α-bromo-γ-phthalimidobutyryl chloride (IV : X=Cl), prepared in a like manner, was condensed with N-methyl-*p*-anisidine and the corresponding anisidide (V) obtained was subjected to the modified Stollé cyclization in which $AlCl_3$: NaCl (5 : 1) mixture was used instead of aluminum chloride alone. The yield of 5-hydroxyoxindole derivative (IV : HO instead of CH_3O) was thus raised to 58% from 20% obtained under the standard Stollé conditions. The Stollé reaction product was methylated to yield (VI), from which phthalimido group was removed with hydrazine hydrate. The amine (VII) thus obtained was now monomethylated by Decker-Becker's method, yielding the base (VIII).

As is already known in the literature this base (VIII) underwent smooth cyclisation on being treated with metallic sodium in ethanolic solution, giving *dl*-esermethole (IX) in a good yield.[8] Though the picrate of our base melted somewhat higher (m.p. 162∼165°) than that prepared by Preobranzhenskii, *et al.*[9] (m.p. 150°), its infrared spectrum showed that absorptions for $\nu_{C=O}$ 1706 cm^{-1} and ν_{NH} 3320 cm^{-1}, which were characteristic to the starting oxindole derivative (VIII), had disappeared in (IX).

The authors' thanks are due to Mr. S. Ushioda for taking the infrared spectra reported in this paper.

Experimental

(β-Phthalimidoethyl)malonic Acid (II′: X=COOH)—Diethyl (β-phthalimidoethyl)malonate (11.6 g.) was dissolved in a mixture of 95 cc. of Ac_2O and 150 cc. of conc. HCl and the whole was refluxed for 2 hrs., resulting in a light brown solution. On evaporating *in vacuo* there remained a solid substance, which was recrystallised from hydr. EtOH, forming colorless dice of m.p. 145∼147°(decomp.). Yield, 9 g.(93%). It was remarkable that no decarboxylation occured while being refluxed. *Anal.* Calcd. for $C_{13}H_{11}O_6N$: C. 56.3; H, 4.0; N, 5.05. Found : C, 56.5; H, 4.1; N, 4.9.

β-Phthalimidobutyric Acid (III′ : X=H)—The malonic acid (II′ : 9 g.) was heated in an oil bath kept at 180∼190°, when strong effervescence was observed. After being heated for 20 mins. the residue was dissolved in $NaHCO_3$ solution, shaken once with benzene, and the aq. layer was acidified with HCl, separating an oily substance, which soon solidified on standing. Purified from benzene-petr. ether to colorless prisms of m.p. 115∼116.5°. Yield, 5.7 g.(75%). *Anal.* Calcd. for $C_{12}H_{11}O_4N$: C, 61.8; H, 4.75; N, 27.4. Found : C, 62.2; H, 4.8; N, 27.3.

α-Bromo-γ-phthalimidobutyric Acid (IV′ : X=OH)—The foregoing acid (III′ : 5.7 g.) was warmed with purified $SOCl_2$(10 cc.) on a steam bath for 2 hrs., until evolution of HCl-gas almost subsided. Br_2 (4.3 g.) was now added dropwise during 6 hrs. and then excess of $SOCl_2$ was distilled off. The residue was poured into cold water, giving a solid substance after some time. Purified from benzene or hydr. EtOH, this formed colorless needles of m.p. 153∼155°. Yield, 6.8 g.(89%). *Anal.* Calcd. for $C_{12}H_{10}O_4NBr$: C, 42.9; H, 3.2; N, 4.8; Br, 25.6. Found : C, 42.65; H, 3.0; N, 4.9; Br, 25.2.

N-Methyl-α-bromo-γ-phthalimidobutyranilide (X)—The acid (IV′ : X=OH 6.1 g.) was heated with $SOCl_2$(7 g.) on a water bath for 2 hrs. and then excess of $SOCl_2$ was distilled off as completely as possible with the aid of added benzene. Crude chloride (IV′ : X=Cl) was now dissolved in 10 cc. of pure benzene, which solution was then added to methylaniline (4.6 g.) in 20 cc. of pure benzene, while the latter was cooled and stirred. After 2 hrs.' stirring at room temperature, the whole was heated on a steam bath for 30 mins. On cooling the reaction mixture was repeatedly washed with water and from the benzene layer the solvent was removed *in vacuo*, leaving a yellowish brown syrup, which solidified on standing. Purified from benzene-petr. ether, it formed colorless prisms of m.p. 135∼136°. Yield, 6.5 g.(83%). *Anal.* Calcd. for $C_{19}H_{17}O_3N_2Br$: C, 56.8; H, 4.2; N, 7.0; Br, 19.9. Found : C, 57.0; H, 4.1; N, 7.3; Br, 20.4.

1-Methyl-3-(β-phthalimidoethyl)oxindole (XI)—The anilide (X : 1 g.) was mixed intimately with powdered $AlCl_3$ (3 g.) and the mixture was heated in an oil bath kept at 180∼200° for 30 mins. with stirring; evolution of HBr was observed. The reaction mixture was decomposed with cold dil. HCl, giving a white solid, which was washed with dil. HCl and then with water. The product was now dissolved in benzene, which solution was dried and filtered through an alumina column. From the faint yellow filtrate benzene was evaporated, leaving a crystalline solid, which was purified from benzene-petr. ether, forming colorless prisms of m.p. 150∼151.5°. Yield, 0.55 g.(69%). *Anal.* Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.2; H, 5.0; N, 15.0. Found : C, 71.5; H, 4.9; N, 15.1.

1-Methyl-3-(β-aminoethyl)oxindole (XII)—The foregoing compound (XI : 6 g.) and hydrazine hydrate (2 g.) were dissolved in 50 cc. of EtOH and the mixture was refluxed on a steam bath, separating a white solid after some time, which filled the solution. After heating for 15 mins. HCl (conc. HCl 30 cc.+H_2O 30 cc.) was added and the whole was again refluxed on a steam bath for 1 hr. EtOH was now distilled off and the residue was basified, separating an oily substance, which was taken up in benzene, washed, and evaporated. The residue distilled at 147∼149°(3 mm.), forming a colorless oil, which gradually became reddish purple on exposure to air. Yield, 3 g.(82%).

Picrate : Yellow scales (from EtOH), m.p. 190∼191°(decomp.). *Anal.* Calcd. for $C_{17}H_{17}O_8N_5$: C, 48.7; H, 4.1; N, 8.75. Found : C, 48.6; H, 4.1; N, 8.3.

3,3-Bis(cyanomethyl)oxindole (XIII)—A mixture of isatin(10 g.), cyanoacetic acid(5.8 g.), and $AcONH_4$ (0.2 g.) was added to benzene (10 cc.) and the whole was heated in an oil bath at 160°, until no more water distilled azeotropically with benzene. A dark resinous product obtained was dissolved in a

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[8] J. Harley-Mason and A.H. Jackson (J. Chem. Soc., **1957**, 3651) recently described an elegant synthesis of eserine.

[9] M.N. Kolosov, L.I. Metreveli, N.A. Preobrazhenskii : Zhur. Obsh. Khim., **23**, 2027(1953).

large amount of EtOH and treated repeatedly with decolorizing charcoal, giving a faint yellow ethanolic solution. On evaporating EtOH there was obtained a colorless solid, which was purified from EtOH to colorless prisms of m.p. 202~203°(decolorising). Yield, 1.25 g. *Anal.* Calcd. for $C_{12}H_9ON_3$: C, 68.2; H, 4.3; N, 19.9. Found : C, 68.1; H, 3.9; N, 19.8.

Oxindolylideneacetonitrile (XIV)—A mixture of isatin (2 g.) and cyanoacetic acid (1.3 g.) was dissolved in a mixture of 10 cc. of benzene and 8 cc. of pyridine. The whole, after being stirred for 1 hr. at room temp., was gradually heated on a water bath, when the color of the solution changed to deep red and evolution of CO_2 was observed. After being heated for 2 hrs. at 80° the reaction mixture was poured into a large amount of water. The supernatant benzene layer was washed thoroughly with water, dried, and evaporated, leaving a dark brown resinous substance. This was dissolved in a small amount of hot EtOH and cooled, separating orange-yellow crystals, which were purified further from EtOH. Orange colored needles of m.p. 194~195.5°. Yield, 0.65 g.(29%). *Anal.* Calcd. for $C_{10}H_6ON$: C, 70.6; H, 3.55; N, 16.5. Found : C, 70.7; H, 3.2; N, 16.5.

(1-Methyloxindolylidene)acetonitrile (XV)—N-Methylisatin (60 g.) and cyanoacetic acid (39 g.) were dissolved in a mixture of benzene (300 cc.) and pyridine (90 cc.), giving a clear solution, which became turbid and after some time solid substance began to separate out when stirred at room temperature. After being allowed to stand overnight, the whole was heated at 60°, when the precipitate disappeared, giving a clear red solution. Evolution of CO_2 was observed when the temperature was raised to 70~75°. After its cessation the whole was further heated at 80° for 30 mins. and then worked up as before. Yield of orange red crystalline solid of m.p. 141~145° was 16.5 g. On repeating the purification from EtOH there was obtained orange-red needles of m.p. 155~157°(12 g.) and from its mother liquor there separated another orange-red needles of m.p. 167~169°(2 g.). When admixed they melted over a range of 141~145° *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.7; H, 4.4; N, 15.2. Found (for compound of m.p. 155~157°) : C, 71.4; H, 4.1; N, 15.1. Found (for compound of m.p. 167~169°) : C, 71.8; H, 4.1; N, 14.85.

1-Methyl-3-cyanomethyloxindole (XVI)—The afore-mentioned compound of m.p. 155~157°(4 g.) was dissolved in 80 cc. of dioxane to which a little H_2O was added. Al-amalgam prepared from 4 g. of thin Al pieces was added to this solution in two portions while being stirred and the mixture was stirred further at 25~30° for 4 hrs., giving a colorless slurry. From the filtrate the solvent was removed and the residue was dissolved in benzene, washed, dried, and evaporated, leaving a syrup of $b.p_{2.5}$ 156~159°, which soon solidified. Purified from EtOH, it formed colorless prisms of m.p. 84~85°. Yield, 2.8 g. (70%).

From the compound of m.p. 167~169° a substance of m.p. 83~85° was obtained on being reduced in a like manner and was proved to be identical with the one obtained above by mixed melting point test. *Anal.* Calcd. for $C_{11}H_{10}ON_2$: C, 70.95; H, 5.4; N, 15.05. Found : C, 71.1; H, 5.65; N, 15.0.

1-Methyl-3-(β-aminoethyl)oxindole (XII)—The compound (XVI : 0.5 g.) in glacial AcOH (20 cc.) was reduced over Adams' Pt-catalyst as usual. From the reduction mixture AcOH was removed and the residue was dissolved in H_2O. An oil, separated from the aq. solution on being basified, was taken up in benzene, washed, dried, and evaporated, leaving an oily residue which distilled at 147~149° (2 mm.), forming a colorless oil. Yield, 0.45 g.(88%). On exposure to air the color gradually changes to reddish purple.

Picrate : Yellow scales (from EtOH), m.p. 190~191°(decomp.). *Anal.* Calcd. for $C_{17}H_{17}O_8N_5$: C, 48.7; H, 4.1; N, 16.7. Found : C, 48.7; H, 4.3; N, 16.8.

Phthalimido Derivative (XI)—The free base (XII : 0.2 g.) and phthalic anhydride (0.195 g.) were heated in xylene to give 0.25 g. of the phthalimido derivative (XI) as colorless prisms (from benzene-petr. ether), m.p. 150~151°, which was not depressed on admixture with the one of the same m.p. prepared by an alternative method. *Anal.* Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.2; H, 5.0; N, 8.75. Found: C, 71.0; H, 4.85; N, 8.9.

1-Methyltryptamine (XVII)—The afore-mentioned amine (XII : 1 g.) in dehyd. EtOH (65 cc.) was heated to boiling and to this solution was added Na (5 g.) in small pieces during 1.5 hrs. Color of the solution changed from blue to green and then became colorless. Water (50 cc.) was now added and EtOH was removed by distillation. The remaining oil was taken up in benzene, washed, and evaporated, leaving an oil, which distilled at 120~130°(bath temp.) under 1.5 mm. Yield, 0.8 g.(85%) of colorless oil.

Monopicrate : Orange-yellow prisms (from EtOH), m.p. 178~179°. *Anal.* Calcd. for $C_{17}H_{17}O_7N_5$: C, 50.6; H, 4.25; N, 17.4. Found : C, 50.6; H, 4.7; N, 17.3.

Dipicrate : Deep red needles (from EtOH), m.p. 167~168°. *Anal.* Calcd. for $C_{23}H_{20}O_7N_8$: C, 43.7; H, 3.2; N, 17.7. Found : C, 43.8; H, 3.0; N, 17.9.

Phthalimido derivative : Colorless crystals (form EtOH), m.p. 175~176°. *Anal.* Calcd. for $C_{19}H_{16}O_2N_2$: C, 75.0; H, 5.3; N, 9.2. Found : C, 75.2; H, 5.5; N, 9.0.

α-Bromo-α-methyl-γ-phthalimidobutyric acid (IV : X=OH)—Prepared in a like manner as (IV' : X=OH). Colorless prisms (from hydr. EtOH), m.p. 164~165°. *Anal.* Calcd. for $C_{13}H_{12}O_4NBr$: C, 47.9; H, 3.7; N, 4.3; Br, 24.5. Found : C, 48.2; H, 3.6; N, 3.9; Br, 24.9.

N-Methyl-α-bromo-α-methyl-γ-phthalimidobutyr-*p*-anisidide (V)—The foregoing acid (IV : 19 g.) was converted to its chloride by heating with $SOCl_2$ and then condensed with N-methyl-*p*-anisidine (18 g.) as usual. The anisidide formed colorless prisms of m.p. 122~124.5° from benzene-ligroine. Yield, 24 g.(90%). *Anal.* Calcd. for $C_{21}H_{21}O_4N_2Br$: C, 56.6; H, 4.7; N, 6.3; Br, 18.0. Found : C, 56.2; H, 4.9; N, 6.1; Br, 18.3.

5-Hydroxy-1,3-dimethyl-3-(β-phthalimidoethyl)oxindole (VI : HO instead of CH_3O)—A mixture of $AlCl_3$(40 g.) and NaCl (8 g.) was heated at 145~150° in an oil bath and to this melt was added 14 g. of finely powdered (V) in small portions during 30 mins. The product was poured into a mortar while hot and then powdered. This powder was then added in small portions into cold dil. HCl, separating a yellowish precipitate, which was collected on a filter and washed. When purified from EtOH this formed colorless prisms of m.p. 227~229°. Yield, 6.35.(58%). *Anal.* Calcd. for $C_{20}H_{18}O_4N_2$: C, 68.6; H, 5.2; N, 8.0. Found : C, 68.9; H, 5.0; N, 7.65.

5-Methoxy-1,3-dimethyl-3-(β-phthalimidoethyl)oxindole (VI)—The above-mentioned compound (6.2 g.) in 50 cc. of MeOH was added with 150 cc. benzene solution of CH_2N_2, which was generated from 15 g. of nitrosomethylurea. The mixture was allowed to stand in an ice chest overnight and then was shaken with NaOH solution. Benzene was now evaporated, leaving yellowish green syrup, which soon solidified on cooling. This was purified from benzene-petr. ether, forming faint yellowish green plates of m.p. 106~108°.[10] Yield, 5.8 g.(90%). *Anal.* Calcd. for $C_{21}H_{20}O_4N_2$: C, 69.2; H, 5.5; N, 7.7. Found : C, 69.5; H, 5.6; N, 7.5.

5-Methoxy-1,3-dimethyl-3-(β-aminoethyl)oxindole (VII)—The compound (VI : 5.7 g.) was treated with hydrazine hydrate (1 g.) in 17 cc. of EtOH as usual. The product was obtained as a colorless oil of b.p$_{2.5}$ 161~163°. Yield, 2.7 g.(74%).

Picrate : Yellow needles (from EtOH), m.p. 167~168°.[11] *Anal.* Calcd. for $C_{19}H_{21}O_9N_5$: C, 49.2; H, 4.6; N, 15.1. Found : C, 49.7; H, 4.8; N, 15.2.

Picrolonate : Faint yellow needles (from EtOH), m.p. 250°(decomp.), as was already given by previous authors.

When the free base (VII : 0.5 g.) was treated with a mixture of formic acid (0.6 g. of 80%) and HCHO (0.55 g. of 35%) according to the method of Eschweiler, 5-methoxy-1,3-dimethyl-3-(β-dimethylaminoethyl)oxindole was obtained as a faint brown syrup in good yield, which was characterized as a methopicrate of yellow leaflets, m.p. 194~195°, as is already known in the literature. *Anal.* Calcd. for $C_{22}H_{27}O_9N_5$: C, 52.3; H, 5.4; N, 13.9. Found : C, 52.5; H, 5.4; N, 13.7.

5-Methoxy-1,3-dimethyl-3-(β-methylaminoethyl)oxindole (VIII)—The amine (VII : 2 g.) was mixed with freshly purified benzaldehyde (0.95 g.) resulting in evolution of heat and separation of water. After being left standing for 2 hrs. at room temp. the mixture was heated on a steam bath for 30 mins. The product was dissolved in benzene, washed, dried, and evaporated, leaving 2.7 g. of a faint yellow oil. The Schiff base thus prepared was mixed with MeI (1.5 g.) and the mixture was heated in a sealed tube at 100° for 3 hrs. The product was dissolved in EtOH and evaporated, when an excess of MeI was also removed. The residue was covered with ether and decomposed by shaking vigorously with dil. HCl. The aq. layer was basified, separating an oily substance, which was taken up in benzene, washed, dried, and evaporated. The residue distilled at 153~156°(2.5 mm.) as a colorless oil. Yield, 1.5 g.(75%).

Picrate : Yellow prisms (from EtOH), m.p. 175~176.5°. *Anal.* Calcd. for $C_{20}H_{23}O_9N_5$: C, 50.3; H, 4.9; N, 14.7. Found : C, 50.25; H, 5.0; N, 14.7.

***dl*-Esermethole (IX)**—The foregoing base (VIII : 0.5 g.) in dehyd. EtOH (50 cc.) was boiled on a steam bath and to this solution was now added 2 g. of Na in small pieces during 2 hrs. To the reduction product H_2O was added and EtOH was evaporated *in vacuo*, separating a brownish oil, which was taken up in benzene and worked up as usual. Almost colorless oil of b.p$_2$ 128~130°(bath temp.) was obtained in a yield of 0.4 g.(85%).

Picrate : Orange-yellow dice (from EtOH), m.p. 162~163°. *Anal.* Calcd. for $C_{20}H_{23}O_7N_5$: C, 53.9; H, 5.2; N, 15.7. Found : C, 54.0; H, 5.05; N, 16.0.

Summary

N-Methyl-α-bromo-γ-phthalimidobutyranilide (X) was treated with fused aluminum chloride according to the method of Stollé, giving the corresponding oxindole derivative (XI), from which the phthalimido group was removed smoothly by Ing's method. When the amine (XII) thus prepared was treated with metallic sodium 1-methyltryptamine was

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[10] This compound had been prepared by R. Robinson and F. E. King by a different method and recorded as m.p. 108~109°.

[11] m.p. 161~162° according to the above authors.

produced in a fair yield as the sole isolable product and the expected cyclized product, *dl*-nordesoxyeseroline (A), once supposed as folicanthine, was not traced in the reduction product. However, when 1,3-dimethyl-3-(β-methylaminoethyl)oxindole (VIII), prepared in a silmilar manner as (XI), was subjected to the same reduction, there was obtained *dl*-esermethole (IX), which had already been prepared by Preobrazhenskii, *et al.* a few years ago by a different method. The presence or absence of a hydrogen atom at 3-position of oxindole derivatives was thus shown to be a decisive factor for the course of their reduction.

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34. **Shigehiko Sugasawa and Masao Murayama :** Synthesis of Homoesermethole.

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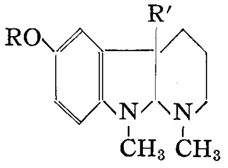
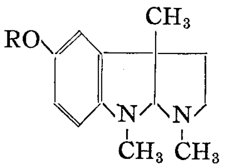
The structure (I) was first proposed as the skeleton of eserine by Polonovski, *et al.*,[1] which was later revised to (II) by Barger, *et al.*[2] based on the suggestion of Sir Robert Robinson. We have for some years been interested in the synthesis of a compound of the structure (I), but from the result published in the preceding paper it appears impossible to build up this compound according to the principle described there, so we decided to synthesize its methylated product, *dl*-homoesermethole (III), and this objective was attained exactly in the same manner as was described in the foregoing paper.



(I) R′=H, (III) R′=CH_3



(II)

A search of literature revealed that the compound (III) had already been prepared by Preobrazhenskii, *et al.*[3] a few years ago by a different and more attractive method. We traced their procedure and found that both final products were one and the same.

γ-Phthalimidopropyl bromide was prepared according to Drake's method, in which we used methyl ethyl ketone as a solvent instead of acetone and the yield of the product was thus raised to 80%. The bromide was now condensed with sodium compound of diethyl methylmalonate in boiling benzene to furnish diethyl α-methyl-α-(γ-phthalimidopropyl)malonate (IV) in 88% yield after 60 hrs.' reaction time. The ester groups of the latter were hydrolysed with conc. hydrochloric acid in boiling acetic anhydride, yielding α-methyl-α-(γ-phthalimidopropyl)malonic acid (V), which was then decomposed by heat to α-methyl-δ-phthalimidovaleric acid (VI).

α-Bromo-α-methyl-δ-phthalimidovaleryl chloride (VII : X = Cl) prepared from the foregoing acid by the standard method was condensed with *p*-anisidine and the resultant anisidide (VIII) was subjected to the Stollé reaction.

5-Hydroxy-1,3-dimethyl-3-(γ-phthalimidopropyl)oxindole obtained was now methylated to give (IX), from which phthalimido group could be readily removed according to

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[1] M. Polonovski, M. Polonvski : Compt. rend., **178**, 2028(1924).

[2] E. Stedman, G. Barger : J. Chem. Soc., **127**, 247(1925).

[3] M.N. Kolosov, L.I. Metreveli, N.A. Preobrazhenskii : Zhur. Obshchei. Khim., **23**, 2027(1953).