

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 similar 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.

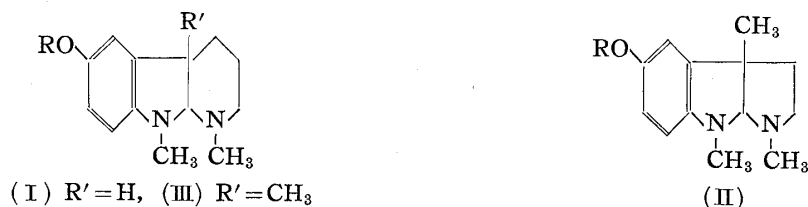
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34. Shigehiko Sugawara and Masao Murayama : Synthesis of Homoesermethole.

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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.



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 aniside (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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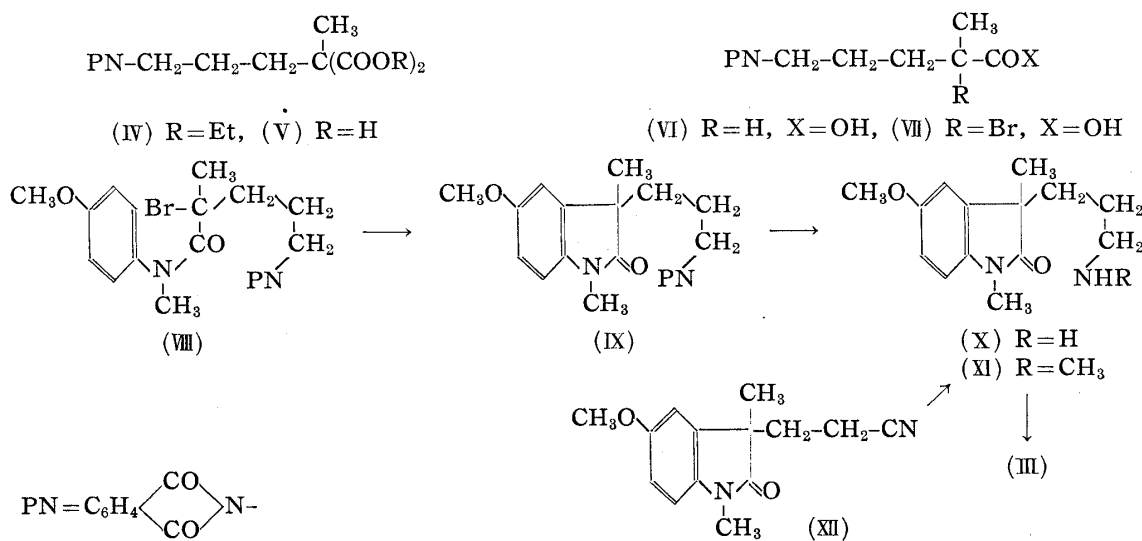
the method of Ing and Manske, furnishing 5-methoxy-1,3-dimethyl-3-(γ -aminopropyl)-oxindole (X).

The monomethyl derivative (XI) of the latter was prepared by two different routes. The one from (X) by Decker-Becker's method and the other by catalytically reducing 5-methoxy-1,3-dimethyl-3-(β -cyanoethyl)oxindole (XII), prepared according to the method of Preobrazhenskii, *et al.*,³⁾ over Raney nickel catalyst in the presence of methylamine. Both methods gave the same product.

The reductive cyclization of (XI) was executed by sodium in boiling ethanol solution, when the formation of *cis* and *trans* isomers of (III) was to be expected. The reduction product here obtained was 2.3 g. of a basic oil of b.p.₄ 160~161°, which soon solidified after distillation. This was purified from ethanol, furnishing 2.05 g. of colorless needles of m.p. 68.5~69.5° as a pure single substance, in which the absence of $\nu_{C=O}$ 1700 cm^{-1} and ν_{NH} 3353 cm^{-1} absorptions of (XI) was proved in its infrared spectrum.

On evaporating the mother liquor there remained a brown vitreous substance, which amounted to 220 mg. after being distilled at 156~160°(bath temp.) under 2 mm. Though this oil and also its derivative could not be induced to crystallize examination of its infrared spectrum showed a distinct $\nu_{C=O}$ and ν_{NH} absorptions of (XI) and by comparison with that of the starting oxindole derivative (XI), this oil was assumed to be impure (XI), which escaped reductive cyclization reaction to form the compound (III).

Thus the cyclization of (XI) by the above method was shown to have occurred almost, if not solely, in a single direction.



Experimental

Diethyl α -Methyl- α -(γ -phthalimidopropyl)malonate (IV)—To a suspension of Na-dust (4.2 g.) in dehyd. benzene (150 cc.) diethyl methylmalonate (33 g.) was added dropwise with stirring and the mixture was refluxed on a steam bath for 2 hrs., giving a white slurry. γ -Phthalimidopropyl bromide (45 g.) was now added and the whole was refluxed for 60 hrs. with stirring. Unreacted methylmalonate was steam-distilled together with benzene and the residue was taken up in benzene, washed, dried, and the solvent was removed. A colorless viscous oil of b.p.₂ 217~219° was obtained in a yield of 53 g.(88%). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_6\text{N}$: C, 63.1; H, 6.4; N, 3.9. Found C, 62.9; H, 6.6; N, 3.7.

α -Methyl- α -(γ -phthalimidopropyl)malonic Acid (V)—The above ester (IV : 30 g.) was added to a mixture of conc. HCl (400 g.) and Ac_2O (240 cc.), and the whole was refluxed for 2 hrs. On evaporating there was obtained white crystalline solid, which was washed with benzene and then purified from hydr. EtOH, forming colorless dice of m.p. 157°(decomp.). Yield, 18 g.(71%). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{15}\text{O}_6\text{N}$: C, 59.0; H, 4.95; N, 4.6. Found C, 59.3; H, 5.1; N, 4.3.

α -Methyl- δ -phthalimidovaleric Acid (VI)—The malonic acid (V : 18 g.) was heated at 180° for 30 mins., giving a brown melt with evolution of CO_2 . On cooling, the decomposition product was dissolved in NaHCO_3 solution and was treated with decolorising charcoal. The filtrate was acidified

with HCl and separated an oily layer, which solidified on standing. This was purified from benzene-petr. ether, forming colorless prisms of m.p. 108~109°. Yield, 12 g.(86%). *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.4; H, 5.8; N, 5.4. Found: C, 64.8; H, 5.95; N, 5.1.

α -Bromo- α -methyl- δ -phthalimidovaleric Acid (VII)—The foregoing acid (VI: 1 g.) was warmed with freshly purified $SOCl_2$ (2 g.) on a steam bath for 2 hrs. and to the reaction mixture was now added dropwise 0.65 g. of Br_2 . After removing the excess of $SOCl_2$ the yellowish brown oily residue was decomposed by warming with H_2O , separating crystalline solid, which came in colorless prisms of m.p. 133~134.5°, when purified from benzene-ligroine. Yield, 1.16 g.(89%). *Anal.* Calcd. for $C_{14}H_{14}O_4NBr$: C, 49.4; H, 4.1; N, 4.1; Br, 23.5. Found: C, 49.7; H, 4.2; N, 4.5; Br, 23.2.

N-Methyl- α -bromo- α -methyl- δ -phthalimidovaler-*p*-anisidide (VIII)—The acid (VII: 6.6 g.) was converted to its chloride (VIII: X=Cl) by treating with $SOCl_2$ (7 g.) for 2 hrs. The excess of $SOCl_2$ was removed by distillation with the aid of added benzene. The crude acid chloride thus obtained was now dissolved in 10 cc. of pure benzene and reacted with freshly purified *p*-anisidine as usual. The anisidide was obtained as colorless dice of m.p. 129~130° from benzene-ligroine. Yield, 8.9 g. or nearly quantitative. *Anal.* Calcd. for $C_{22}H_{28}O_4N_2Br$: C, 57.5; H, 5.0; N, 6.1; Br, 17.4. Found: C, 57.4; H, 5.0; N, 6.3; Br, 17.1.

5-Hydroxy-1,3-dimethyl-3-(γ -phthalimidopropyl)oxindole (IX: HO instead of CH_3O)—An intimate mixture of the foregoing anisidide (VIII: 3 g.) and $AlCl_3$ (8 g.) was fused by heating in an oil bath at 190~200° for 30 mins., giving a dark brown melt with evolution of HBr, which was poured into a mortar while hot and powdered. When decomposed with cold dil. HCl there was obtained a pale yellow precipitate, which was collected on a filter and washed with H_2O . Purified from EtOH with the aid of decolorising charcoal this was obtained as colorless pillars of m.p. 213~214°. Yield, 1.48 g.(62%). *Anal.* Calcd. for $C_{21}H_{20}O_4N_2$: C, 69.2; H, 5.5; N, 7.7. Found: C, 69.0; H, 5.3; N, 7.7.

5-Methoxy-1,3-dimethyl-3-(γ -phthalimidopropyl)oxindole (IX)—The above phenolic compound (0.5 g.) was suspended in MeOH (10 cc.) to which was now added ethereal solution of CH_2N_2 , generated from 2 g. of nitrosomethylurea. All solid substance went into solution, while evolution of N_2 was observed. The whole was allowed to stand for 2 days, the reaction mixture was washed with dil. NaOH solution and H_2O , and dried. The solvent was then evaporated and the residue was purified from EtOH, forming faint greenish yellow prisms of m.p. 121~122°. Yield, 0.49 g.(94%). *Anal.* Calcd. for $C_{22}H_{22}O_4N_2$: C, 69.8; H, 5.9; N, 7.4. Found: C, 69.9; H, 5.5; N, 7.1.

5-Methoxy-1,3-dimethyl-3-(γ -aminopropyl)oxindole (X)—From 0.5 g. of the foregoing compound (IX) phthalimido group was removed by treating with 0.1 g. of $NH_2NH_2 \cdot H_2O$ according to the standard method. The amine (X) was obtained as a colorless viscous syrup of b.p.₃ 183~185°. Yield, 0.27 g.(83%).

Picrate: Yellow dice (from EtOH), m.p. 185.5~187°. *Anal.* Calcd. for $C_{20}H_{23}O_9N_5$: C, 50.3; H, 4.9; N, 14.7. Found: C, 50.55; H, 4.6; N, 15.0.

5-Methoxy-1,3-dimethyl-3-(γ -methylaminopropyl)oxindole (XI)—i) A Schiff base was prepared from the foregoing compound (X: 6.3 g.) and benzaldehyde (2.7 g.) in 10 cc. of benzene. Yield, 8.1 g.(95%) of colorless prisms (purified from ligroine), m.p. 110~112°. *Anal.* Calcd. for $C_{21}H_{24}O_2N_2$: C, 75.0; H, 7.2; N, 8.3. Found C, 75.1; H, 7.4; N, 8.0.

This Schiff base (8 g.) was heated with CH_3I (4 g.) in a sealed tube at 100° for 4 hrs. and the product was worked up as usual. The methylated product was obtained as a colorless viscous oil of b.p.₃ 183~185°. Yield, 4.9 g.(89%).

Picrate: Yellow scales of m.p. 178~179.5°, when purified from EtOH. *Anal.* Calcd. for $C_{21}H_{25}O_9N_5$: C, 51.3; H, 5.1; N, 14.25. Found: C, 51.0; H, 4.9; N, 14.3.

ii) 5-Methoxy-1,3-dimethyl-3-(β -cyanoethyl)oxindole (XII: 3 g.), prepared after the method of Preobrazhenskii, *et al.*, was dissolved in 30 cc. of MeOH, which was previously saturated with CH_3NH_2 . This mixture was treated with H_2 at 100~115° under a pressure of 110 atm. in the presence of 3 g. of Raney Ni. After the absorption of H_2 was over the reduction product was worked up as usual and gave a viscous oil, which distilled at 168~170°(1 mm.), forming a faint yellow viscous syrup. Yield, 2.3 g.(91%). The picrate of this substance, yellow scales from EtOH, m.p. 179~180°, was not depressed on admixture with the specimen obtained above. *Anal.* Calcd. for $C_{21}H_{25}O_9N_5$: C, 51.3; H, 5.1; N, 14.25. Found: C, 51.55; H, 5.3; N, 14.0.

dl-Homoesermethole (III)—The foregoing compound (XI: 3 g.) in boiling dehyd. EtOH (400 cc.) was added with 17 g. of Na in small pieces during 1 hr. When reduction was over H_2O (150 cc.) was added and EtOH was evaporated *in vacuo*, separating an oily layer, which was taken up in benzene, washed, dried, and then the solvent was evaporated. The residue distilled at 160~161°(4 mm.), which soon solidified, yielding 2.3 g. of the crude substance. This was purified from EtOH, forming 2.05 g.(73%) of colorless needles of m.p. 68.5~69.5°. *Anal.* Calcd. for $C_{15}H_{22}ON_2$: C, 73.1; H, 9.0; N, 11.4. Found: C, 73.0; H, 8.8; N, 11.6.

From the mother liquor was obtained a brown syrup, which gave 0.22 g. of faint yellow vitreous substance of b.p.₂ 156~160°(bath temp.), which could not be induced to crystallize.

Picrate of (III): Orange-yellow prisms (from EtOH), m.p. 147~148°. *Anal.* Calcd. for $C_{21}H_{25}O_9N_5$:

C, 53.05; H, 5.3; N, 14.7. Found: C, 53.05; H, 5.1; N, 14.6.

Picolonate of (III): Faint yellow plates (from EtOH), m.p. 230°(decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_6N_6$: C, 58.8; H, 5.9; N, 16.5. Found: C, 58.7; H, 5.8; N, 16.5.

Summary

α -Bromo- α -methyl- δ -phthalimidovaler-*p*-anisidide (VIII) was fused with aluminum chloride according to Stollé to give 5-methoxy-1,3-dimethyl-3-(γ -phthalimidopropyl)oxindole (IX) after methylation. Phthalimido group could be readily removed from this compound by the standard method, furnishing 3-(γ -aminopropyl)oxindole derivative (X), which was then monomethylated to (XI). This compound could also be prepared advantageously by reducing 5-methoxy-1,3-dimethyl-3-(β -cyanoethyl)oxindole (XII) catalytically in the presence of methylamine. On being reduced with sodium in boiling ethanol the latter gave rise to a single *dl*-homoesermethole (III) in a fair yield, no isomeric base being detected in the reduction product.

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35. Osamu Tanaka: Metabolic Products of Fungi. XIV.¹⁾ The Structure of Skyrin. (3). On Pseudoskyrin.

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The structure of skyrin, an orange-red coloring matter which was isolated from various fungi,²⁻⁶⁾ was established as diemodin-(8,8')(I) by the synthesis of its 2,2'-dimethyl ether (II).^{4,5)} However, a peculiar nature of skyrin on which a short discussion was given in the previous paper³⁾ has remained for further studies.

Howard and Raistrick²⁾ described that on treatment with alcoholic sulfuric acid, hexaacetylskyrin was converted into yellow crystalline dialkylskyrin, whose properties, as were pointed out earlier,⁴⁾ especially the instability of these alkoxy groups to the action of cold aq. alkali, were not explained by the ordinary β -alkyl ether of polyhydroxybianthraquinone-(1,1'). It was found that on the action of diazomethane, skyrin yielded a genuine 2,2'-dimethyl ether (II), and it was suggested that the alkyl ether prepared by Howard and Raistrick would be the product of isomerization, for which a structural formula (VI) and (IX) was proposed.⁴⁾

Some further evidences for the isomerization of skyrin to establish the correctness of the proposed structure of dialkylpseudoskyrin have now been accumulated.

The isomerized alkyl ether of skyrin, which was named dialkylpseudoskyrin, was prepared directly from skyrin by the action of alcoholic sulfuric acid, and also by refluxing crude skyrin in alcohol. On boiling in glacial acetic acid for a short time, dialkylpseudoskyrin regenerated skyrin.

Dialkylpseudoskyrin gave tetraacetate (VII) (its infrared spectrum showed a phenolic acetate C=O band at 1772 cm^{-1} in chloroform), and tetrakis(ethyl carbonate) (VIII, XI). These derivatives as well as dialkylpseudoskyrin itself were readily hydrolyzed

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