On the Alkaloids of the Rhyzome of Nuphar japonicum D. C.

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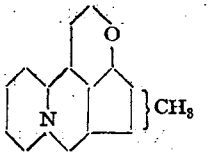
The second [1] and third parts [2] of the presentt thesis have already been completely reported in Journal of the Pharmaceutical Society of Japan. As for the first part, due to the limited space of the journal, only the abstract [3] was published and the experimentals had to be left out. These three parts are rearranged here with additional experimentals, which have not been made public so far.

J. Arima and T. Takahashi [4] found an alkaloid, nupharidin $C_{15}H_{23}O_2N$ (I) in the rhyzome of Nuphar japonicum which has been used as a material for some home medicines in Japan.

In that rhyzome too, we found the second alkaloid $C_{15}H_{23}ON$ (II) [b. p. 112 −5° (3mm.), picrate m. p. 153°, methyliodide m. p. 146°] which can be oxidized into nupharidin, a genalkaloid by H_2O_2. M. Kotake et al [5] obtained a base $C_{15}H_{25}ON$ by the reduction of nupharidin, giving it the name of desoxynupharidin. This second alkaloid was identified with desoxynupharidin by us. Kotake et al and we found respectively that desoxynupharidin has a double bond, an ether oxygen, and a ter. nitrogen. Kotake reported that Kawahonin $C_{15}H_{24}O$ obtained by exhaustive methylation of desoxynupharidin gave n-valeric acid, β-oxypropionic acid and $C_5H_{11}O_2 \cdot COOH$ by ozonization, in consequence of which he proposed a formula (i) for desoxynupharidin.



[i]

But we found several experimental data about desoxynupharidin which can not be explained by Kotake's formula.

We obtained dihydrodesoxynupharidin $C_{15}H_{25}ON$ (III) and tetrahydrodesoxynupharidin $C_{15}H_{27}ON$ (VI) by catalytic reduction of nupharidin with Pd, the latter being produced by the rapture of C-N bond. (This can be explained by the existence of an active hydrogen of Zerewitinoff and a secondary amino group in the molecule of (VI).)

$C_{15}H_{23}ON$ (II) ($\equiv N, =O, \urcorner_1$) —H→ $C_{15}H_{25}ON$ (III)

$C_{15}H_{27}ON$ (VI) ($=NH, =O, \urcorner_1$)

Now we experimented with three kinds of exhaustive methylation, i. e. (A) started with (III) through hydrogenation 2 or 3 times during the experiments, (B) started with (II) through no hydrogenation, (C) started with (III) through hydrogenation 2 times following Kotake's method:

(A) $C_{15}H_{25}ON$ (III) $\xrightarrow{CH_3I}$ $C_{15}H_{25}ON \cdot CH_3I$ (IV) $\xrightarrow{Ag_2O}$ $C_{15}H_{34}ON \cdot CH_3$ (V)

$\xrightarrow{H}$ $C_{15}H_{27}ON$ (VI) $\xrightarrow{CH_3I}$ $C_{15}H_{25}ON \cdot CH_3$ (VII) $\xrightarrow{CH_3I}$ $C_{15}H_{26}ON(CH_3)_2I$ (VIII)

$\xrightarrow{Ag_2O}$ $C_{15}H_{25}ON(CH_3)_2$ (IX) $\xrightarrow{H}$ $C_{15}H_{27}ON(CH_3)_2$ (X) $\xrightarrow{CH_3I}$ $C_{15}H_{27}ON(CH_3)_3I$

$\xrightarrow{Ag_2O}$ $C_{15}H_{26}O$ (XI) $\xrightarrow{H}$ $C_{15}H_{28}O$ (XII) $\xrightarrow{KMnO_4}$ CH_3COOH + $\begin{matrix}CH_2—COOH\\ |\\ CH_2—COOH\end{matrix}$

$\xrightarrow{O_3}$ $\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>\!CH\text{–}CH_2\text{–}COOH$ + $C_9H_{15}O\text{–}COOH$ (XIII)

$\xrightarrow{KMnO_4}$ $\begin{matrix}CH_2—CO\\ |\\ CH_2—CO\end{matrix}\!\!>\!O$

(B) $C_{15}H_{23}ON$ (II) $\xrightarrow{CH_3I}$ $C_{15}H_{23}ON \cdot CH_3I$ $\xrightarrow{Ag_2O}$ $C_{15}H_{22}ON \cdot CH_3$ (XIV) $\xrightarrow{CH_3I}$

$C_{15}H_{22}ON(CH_3)_2I$ (XV) $\xrightarrow{Ag_2O}$ $C_{15}H_{21}ON(CH_3)_2$ (XVI) $\xrightarrow{CH_3I}$ $C_{15}H_{21}ON(CH_3)_3I$ (XVII)

$\xrightarrow{Ag_2O}$ $C_{15}H_{20}O$ (XVIII) $\xrightarrow{KMnO_4}$ $\begin{matrix}CH_2—COOH\\ |\\ CH_2—COOH\end{matrix}$ + d-methylsuccinic acid

(C) $C_{15}H_{23}ON$ (II) $\xrightarrow{CH_3I}$ $C_{15}H_{23}ON \cdot CH_3I$ $\xrightarrow{Ag_2O}$ $C_{15}H_{22}ON \cdot CH_3$ (XIX) $\xrightarrow{H}$

$C_{15}H_{24}ON \cdot CH_3$ (XX) $\xrightarrow{CH_3I}$ $C_{15}H_{24}ON(CH_3)_2I$ (XXI) $\xrightarrow{Ag_2O}$ $C_{15}H_{23}ON(CH_3)_2$ (XXII)

$\xrightarrow{H}$ $C_{15}H_{25}ON(CH_3)_2$ (XXIII) $\xrightarrow{CH_3I}$ $C_{15}H_{25}ON(CH_3)_3I$ (XXIV) $\xrightarrow{Ag_2O}$

$C_{15}H_{24}O$ (XXV) $\xrightarrow{O_3}$ $H \cdot COOH$ + $\begin{matrix}CH_2—COOH\\ |\\ CH_2—COOH\end{matrix}$ + CH_3COOH + $\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>\!CH\text{–}CH_2\text{–}COOH$

+ an unknown acidic substance (XXVI)

(semicarbazone, m.p. 99-102°)

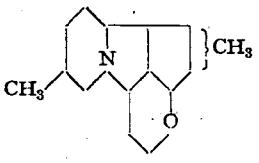
It is to be noticed that n-valeric acid has never been found in any one of the above 3 experiments performed by us but i-valeric acid has been produced.

By dehydrogenation of the mixture of dihydro- (III) and tetrahydrodesoxynupharidin (VI) by Pd, we obtained $C_{15}H_{23-25}N$ (XXVII) (b. p. 134-4° (22 mm.), picrolonate m. p. 116-3°) and $C_{15}H_{21-23}ON$ (XXVIII) (b. p. 145-6° (6mm.), picrolonate m. p. 114-6°), the latter can also be produced in addition to $C_{12}H_{24}$ (XXIX) when the mixture is heated with Se. Pyridin-2, 5-dicarboxilic acid was produced from (XXVII) or (XXVIII) by $KMnO_4$-oxidation.

The so-called C-methyl-titration by P. Karrer for desoxynupharidin (II), dihydrodesoxynupharidin (III) or methyliodide of N-methyltetrahydrodesoxynupharidin, gives about 2 mol. of acetic aeid. Hence the facts which can not be explained by Kotake's formula (i) are as follows:

(a) $C_{15}H_{26}O$ (XI) or $C_{15}H_{24}$ (XXV) gives isovaleric acid by oxidation.
(b) $C_{15}H_{26}O$ (XI) gives $C_9H_{15}O \cdot COOH$ (XIII) by oxidation.
(c) $C_{15}H_{23-5}N$ (XXVII) or $C_{15}H_{21-3}ON$ (XXVIII) gives pyridine-2, 5-dicarboxylic acid.
(d) $C_{15}H_{28}O$ (XXII) gives succinic acid by oxidation.
(e) The existence of 2 C-methyl groups in the molecule of desoxynupharidin, dihydrodesoxynupharidin of tetrahydrodesoxynupharidin.

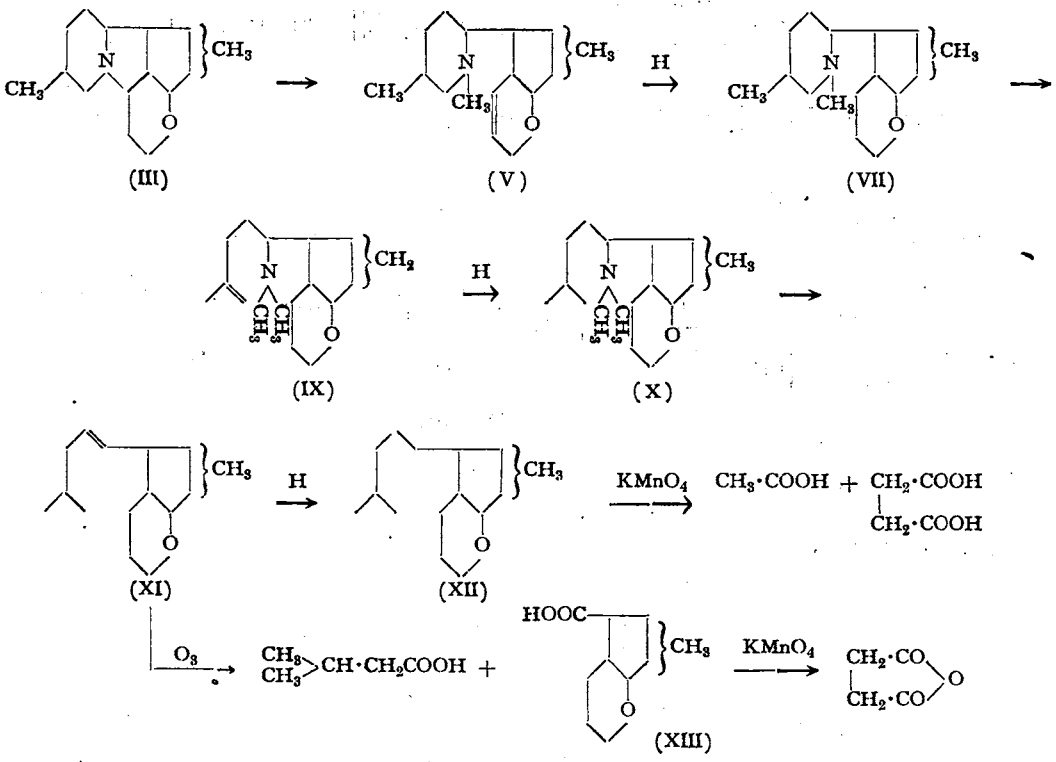
Therfore we propose the following formula (ii) for dihydrodesoxynupharidin.



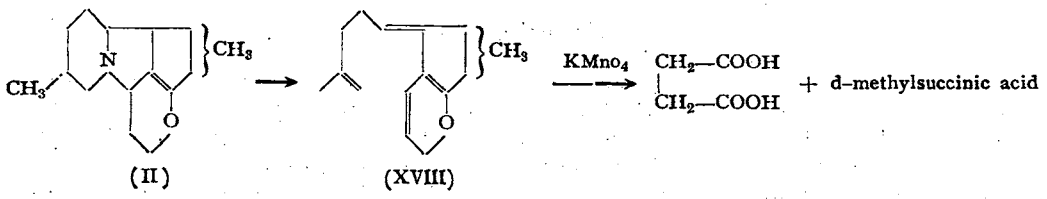
(ii)

Adopting this formula we can explain all the above experimental facts as follows:

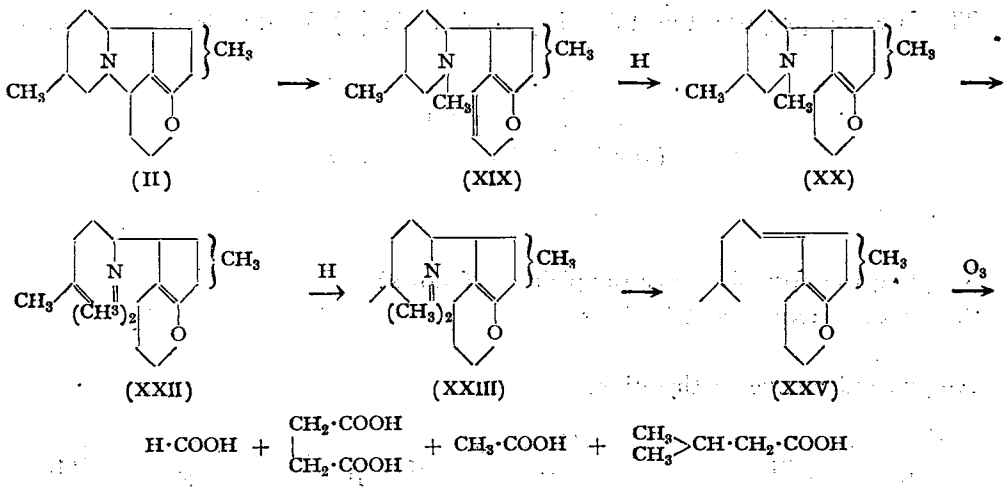
A-type exhaustive methylation.



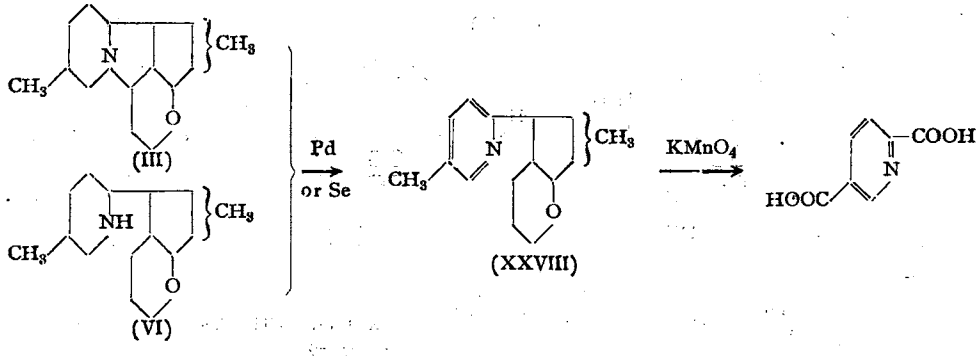
B-type exhaustive methylation.



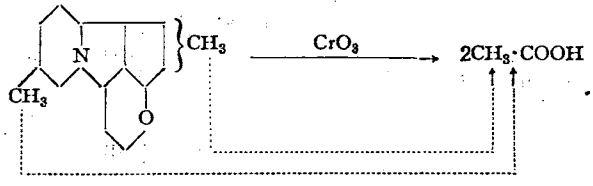
C-type exhaustive methylation.



Dehydration of (III) or (VI) by Pd or Se.



C–methyl–titration



Experimental

Nupharidin.....To the alcoholic solution in which the rhyzome was treated, was added 20% plumb acetate and the solution was separated from the deposit by the centrifugal machine. The addition of picric acid to the solution, acidified with sulfuric acid, filtered and neutralized with sodium carbonate resulted in the production of picrate. The raw base freed from picric acid was extracted with chloroform. After evaporation of the solvent, the residue was treated with ether, thus the unsolidified part was removedby the solvent. This solidified base was recrystallized from acetic acid. Prism. m. p. 222°. $[\alpha]_D^8$ (H_2O): + 14.48°.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.23; H, 9.30; N, 5.62.
Found: C, 72.53; H, 8.95; N, 5.76.

Picrate, recrystallized from alcohol: decomposition point 176°.

Anal. Calcd. for $C_{15}H_{23}O_2N \cdot C_6H_3O_7N_3$: C, 52.80; H, 5.48; N, 11.72.
Found: C, 52.68; H, 5.35; N, 11.99.

Hydrochloride, recrystallized from acetic ester containing ethanol: Plate. m. p. 262°.

Anal. Calcd. for $C_{15}H_{23}ON \cdot HCl$: C, 63.00; H, 8.47; N, 4.96.
Found: C, 62,89; H, 8.34; N, 5.23.

Desoxynupharidin. ……Desoxynupharidin picrate was obtained from the mother liquor when the raw nupharidin picrate was purified with ethanol. After being freed from picric acid, the base was distilled in vacuum, b. p. 112–5° (8mm.), m. p. 21–2°. $[\alpha]_D^{16}$ ($CHCl_3$): $-112.5°$ n_D^{15}: 1.5081. d^{15}: 1.0155. It decolorizes the solution of $KMnO_4$ in acetic acid and assumes brown color on standing.

Anal. Calcd. for $C_{15}H_{23}ON$: C, 77.19; H, 9.94; N, 6.01; mol. weight 233.2.
Found: C, 77.02; H, 9.76; N, 6.06; mol. weight 205.5. (titrated with N/10HCl)

Picrate, recrystallized from ethanol: Needle, m. p. 153°.

Anal. Calcd. for $C_{15}H_{23}CN \cdot C_6H_3O_4N_3$: C, 54.52; H, 5.67; N, 12.12.
Found: C, 54.76; H, 5.72; N, 12.24.

Hydrochloride, recrystallized from abs. ethanol: Plate. m. p. 262°.

Anal. Calcd. for $C_{15}H_{23}ON \cdot HCl$: C, 66.75; H, 8.97; N, 5.19; Cl, 13.15.
Found: C, 66.56; H, 8.98; N, 5.63; Cl, 13.17.

Methyliodide, recrystallized from aceton and acetic ester: Needle. m. p. 146°.

Anal. Calcd. for $C_{15}H_{23}ON \cdot CH_3I$: C, 51.13; H, 6.99; I, 33.84.
Found: C, 50.67; H, 6.66; I, 34.00.

Reduction of nupharidin by KI. …… 0.5g. of nupharidin was added to the mixture of 25cc. of saturated KI solution and 5cc. of 10% HCl solution, warmed on a water bath for 2 hours. After cooling, a brown substance was separated from the solution and then solidified. This solid was treated with 10% NaOH solution and the mixture was extracted by ether. After the evaporation of ether, the residue was changed into the picrate which after purification with abs. alcohol melted at 152° and produced no m. p. depression with nupharidin picrate.

Anal. Calcd. for $C_{15}H_{23}ON \cdot C_6H_3O_7N_3$: C, 54.52; H, 5.67; N, 12.12.
Found: C, 54.49; H, 5.36; N, 12.12.

Reduction of nupharidin by SO_2. ……The water solution of nupharidin was saturated with SO_2 gas, heated until the white precipitate which was formed was dissolved, and left for 3 days. After evaporation the residue was treated with 10% KOH and the mixture was extracted with ether. The base, obtained from the extract, gave a picrate, which after purification melted at 153° and produced no m. p. depression with desoxynupharidin picrate.

Catalytic reduction of nupharidin with Pd–C. …… After H_2 was passed through the mixture of 4cc. of 2% $PdCl_2$, 0.3g. of C and 20cc. of alcohol, 5g. of nupharidin dissolved in 30cc. of alcohol was added to it. The catalytic reduction was carried out at 8°C and about 1 mol. of H_2 was absorbed during 1.5 hours. The reaction puoduct was treated as usual and the obtained base was identified with nupharidin, using its picrate.

Oxidation of desoxynupharidin by H_2O_2. …… 1g. of desoxynupharidin was dissolved in the mixture of 5cc. of 30% H_2O_2 and 20cc. of acetone and left for 11 days. After evaporation in vacuum, the residue was extracted first with ether and then with chloroform. From the chloroform extract we obtained 0.75g. of crystal which after recrystallization from acetic ester produced no m. p. depression with nupharidin.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.23; H, 9.30; N, 5.62.
Found: C, 72.12; H, 9.08; N, 5.92.

Catalytic reduction of desoxynupharidin under the heat.……After the mixture of 30cc. of 2% $PdCl_2$, 3.5g. of C and 15cc. of acetic acid was saturated with H_2, 9.8g. of desoxynupharidin and 20cc.

of acetic acid were added to it. The reaction apparatus was heated by steam. 2.4 mole of H_2 were absorbed during 7 hours. After filtration the solvent was distilled, and the residue was treated with dil. Na_2CO_3. The mixture was extracted with ether. We obtained 9.8g. oil from the ether solution. This oil was divided into 2 parts by fractionating according to Klenk's method: b. p. 133–4° (4mm.) and b. p. 148° (3mm.).

Dihydrodesoxynupharidin (III). ……The above mentioned fraction of b. p. 133–4° (4mm.) was not changed by $KMnO_4$. $[\alpha]_D^{20}$ ($CHCl_3$): + 2.87°.

Anal. Calcd. for $C_{15}H_{24}ON$: C, 76.60; H, 10.72; N, 5.96.
Found: C, 76.26; H, 10.91; N, 5.88.

Tetrahydrodesoxynupharidin (VI). ……The fraction of b. p. 148° (3mm.) was not changed by $KMnO_4$ but showed deep blue color when treated with acetaldehyde and sodium nitroprusside. (sec. amine). $[\alpha]_D^{13}$ ($CHCl_3$): + 0.17°.

Anal. Calcd. for $C_{15}H_{27}ON$: C, 75.95; H, 11.48; N, 5.91
active hydrogen 0.425.
Found: C, 75.50; H, 11.85; N, 5.81
active hydrogen 0.459.

Acetylderivative of (VI). ……Colorless liquid of b. p. 191–4° (4mm.).

Anal. Calcd. for $C_{17}H_{29}O_2N$: N, 5.03.
Found: N, 05.02.

$C_{15}H_{23}ON \cdot CH_3$ (VII) and $C_{15}H_{26}ON(CH_3)_2I$ (VIII). ……The reduction product of desoxynupharidin by Pd–C under the heat was dissolved in acetone, mixed with CH_3I, warmed for 2 hours and left overinght, producing a white crystal, which was found to be $C_{15}H_{25}ON \cdot HI$ by analysis. After removing the crystal, we obtained an oily material by evaporation of the solvent. This oil was dissolved in water, made alkaline by dil. Na_2CO_3 and divided into two parts by extracting first with ether, then with $CHCl_3$. The former showed b. p. 156–7°(5mm.) and $[\alpha]_D^8$ –49.75° after rectificatien and was found to correspond to $C_{15}H_{25}ON \cdot CH_3$ (VII) by analvsis.

Anal. Calcd. for $C_{16}H_{29}ON$: C, 76.49; H, 11.59; N, 5.58.
Found: C, 76.11; H, 11.67; N, 5.78.

The latter melted at 144–5° and was identified with methyliodide of (VII). $[\alpha]_D^{5.5}$: –5.13°.

Anal. Calcd. for $C_{17}H_{32}ONI$: C, 51.90; H, 8.20.
Found: C, 51.82; H, 8.35.

$C_{15}H_{25}ON(CH_3)_2$ (IX). ……18.5g. of (VIII) was dissolved in 50% methanol and treated with Ag_2O. We obtained a liquid of b. p. 163–163.5° (7mm.). Yield, 12g.

Anal. Calcd. for $C_{17}H_{31}ON$: C, 76.91; H, 11.78; N, 5.28.
Found: C, 76.62; H, 12.10; N, 5.38.

$C_{15}H_{27}ON(CH_3)_2$ (X). …… (X) was obtained by catalytic reduction with Pd–C at room temperature. b. p. 162–3° (6mm.).

Anal. Calcd. for $C_{17}H_{33}ON$: C, 76.32; H, 12.44; N, 5.24.
Found: C, 75.74; H, 12.63; N, 5.40.

$C_{15}H_{26}O$ (XI). ……The methyliodide of (X) was produced by refluxing the solution of methyliodide and (X) in methanol. This methyliodide was dissolved in 50% methanol and treated with Ag_2O. After filtration the solvent was distilled, giving trimethylamine as its byproduct. The residue was washed with dil. HCl and distilled in vacuum, b.p. 155–6° (18mm.), $[\alpha]_D^{23}$ ($CHCl_3$): –3·986°.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.08; H, 11.80.
Found: C, 80.57; H, 12.20.

$C_{15}H_{25}ON \cdot CH_3I$ (IV). ……Prism, b. p. 236°.

Anal. Calcd. for $C_{15}H_{25}ON \cdot CH_3I$: C, 50.91; H, 7.84; N, 3.72.
Found : C, 50.93; H, 7.64; N, 4.44.

$C_{15}H_{24}ON \cdot CH_3$ (V) ..... Colorless lipuid, b. p. 162–3° (8mm.).

Anal. Calcd. for $C_{15}H_{24}ON \cdot CH_3$: C, 77.04; H, 10.92.
Found : C, 76.52; H, 11.07.

$C_{15}H_{24}O$ (XXV). .....The mixture of (XXIII), acetone and methyliodide was left for 2 days. After evaporation of the solvent, the residue was dissolved in H_2O and treated with Ag_2O. After filtration the residue was distilled in vacuum. The distillate was dissolved in ether, washed by 5% HCl and then redistilled after evaporation of ether, b. p. 140–3° (9mm.).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.74; H, 10.98.
Found : C, 81.35; H, 11.30.

Oxidation of (XI) by O_3. ..... 4.5g. of (X) was ozonized in $CHCl_3$ solution. After distillation of the solvent in vacuum, the residue was warmed with water on a water bath for 3.5 hours, then made alkaline with sodium bicarbonate and extracted with ether. We obtained (A) 3g. of neutral substance from ether extract and (B) 1.5g. of acidic substance which smelled like valeric acid from the alkaline solution.

The former smelled like aldehyde but could not be isolated as a solid by treating with thiosemicarbazide or semicarnazide.

The latter gave an anilide when heated with aniline at 150° for 3 hours. This anilide was distilled in vacuum of 0.4mm. The fraction which distilled between 130–160° of oil bath solidified. It melted at 102–5° after recrystallization from peteroleum ether. This substance produced no m.p. depression with isovaleric anilide.

Anal. Calcd. for $C_{11}H_{15}ON$: C, 74.53; H, 8.54; N, 7.91.
Found : C, 74.60; H, 8.28; N, 8.14.

Oxidation of (XXV) by O_3. .....4g. of (XXV) was ozonized in $CHCl_3$. After hydrolysis we obtained 2.9g. of neutral substance and 2.2g. of acidic substance. The acidic one gave an anilide which melted at 44–6° and produced no m.p, depression with formic anilide.

$C_{15}H_{28}O$ (XII). .....(XI) was reduced catalytically with Pd-C in alcoholic solution. B.p. 134–5° (6mm.).

Anal. Calcd. for $C_{15}H_{28}O$: C, 80.28; H, 12.57.
Found : C, 80.06; H, 12.88.

Oxidation of $C_{15}H_{28}O$ (XII) by $KMnO_4$. ..... To a suspension of 5.2g. of (XII) in 100cc. water was gradually added 600cc. of 3% $KMnO_4$ with warming on a water bath and stirring. The filtrate was concentrated in vacuum, made acidic with H_2SO_4 and extracted with ether. The ether solution was shaken with dil. ammonia. Calcium oxalate was precipitated when $CaCl_2$ was given into the water layer. After filtration the alkaline solution was again made acidic with dil. HCl and shaken with ether. After evaporation of ether, we obtained 1.2g. of brown stimulant liquid which was fractionated.

Fraction I ..... 140° (temperature of bath) a little.
〃 II 140 ..... 165° (〃) 0.15g. Colorless stimulant liquid.
〃 III 165 ..... 200° (〃) 0.15g. Colorless liquid.
〃 IV 200 ..... 210° at 8mm. (〃) 0.15g. Colorless viscous liquid.

Anilide of Fract. II and III produced no m.p. depression with acetanilid. A part of Fract. IV crystallized out, m.p. 181°. This crystal produced no m.p. depression with succinic acid.

Dehydrogenation of the mixture of (III) and (VI) by Pd. .....6g. of the raw product of desoxynupharidin which was reduced by Pd with warming, was heated with 2g. of 50% Pd-asbestos at 280–300° for 2.5. hours. Evanescence of 1340cc. of H_2 was then observed. The reaction product was extracted with ether and the ether solution was shaken with 10% KH_2PO_4. Evaporation of ether gave 4g. of brown liquid. This liquid was fractionated into 2 parts of b.p. 130–5° (22mm.) and b.p. 145–6° (6mm.).

$C_{15}H_{23\text{-}25}N$ (XXVII). .....The above mentioned distillate of b.p. 130–5° (22mm.).

Anal. Calcd. for $C_{15}H_{25}N$: C, 82.12; H, 11.49; N, 6.39.
$C_{15}H_{23}N$: C, 82.87; H, 10.67; N, 6.45.
Found : C, 82.23; H, 11.30; N, 6.63.
82.50; 11.50.

Picrlolnate, crystallized from 60% alcohol : Needle, m.p. 116–117.5°.

Anal. Calcd. for $C_{15}H_{25}N \cdot C_{10}H_8O_5N_4$: C, 62.07; H, 6.88; N, 14.49.
$C_{15}H_{23}N \cdot C_{10}H_8O_5N_4$: C, 62.33; H, 6.49; N, 14.56.
Found : C, 62.19; H, 6.78; N, 14.29.

$C_{15}H_{21\text{-}23}$ ON (XXVIII). ..... The distillate of b.p. 145-6° (6mm.). It reacted positively against Ehrlich's reagent.

Anal. Calcd. for $C_{15}H_{23}ON$: C, 77.19; H, 9.94; N, 6.01.
$C_{15}H_{21}ON$: C, 77.87; H, 9.16; Nm 6.06.
Found : C, 77.53; H, 9.60; N, 5.93.

Picrolonate. recrystallized from 60% alcohol : Needle, m.p. 114–6°.

Anal. Calcd. for $C_{15}H_{23}ON \cdot C_{10}H_8O_5N_4$: C, 60.33; H, 6.28; N, 14.08.
$C_{15}H_{23}ON \cdot C_{10}H_3O_5N_4$: C, 60.57; H, 5.90; N, 14.14.
Found : C, 60.06; H, 5.94; N, 14.34.

Dehydrogenation of the mixture of (III) and (VI) by Se. .....29g. of the material and 35g. of Se were heated at 260–300° in nitrogen stream for 28 hours.

After cooling the mixture was shaken with ether. The ether solution was shaken with dil. HCl. We obtained neutral liquids of b.p. 109–112. (14mm.) and b.p. 145–150° (20mm.) from the ether layer and weak alkaline liquids of b.p. 130–4° (22mm.) and b.p. 159–160° (8mm.) from the water layer.

$C_{12}H_{24}$ (XXIX). .....The above mentioned neutral liquid of b.p. 112° (109mm.).

Anal. Calcd. for $C_{14}H_{24}$: C, 85.62; H, 14.38.
Found : C, 85.45; H, 14.05.
85.33; 14.43.

$C_{12}H_{24}O$ ..... The above mentioned neutral liquid of b.p. 145–150° (20mm.).

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.18; H, 13,13.
Found : C, 78.64; H, 12.88.
78.37; 12.90.

$C_{15}H_{23\text{-}25}N$ ..... The above mentioned alkaline liquid of b.p. 130–4° (22mm.).

Anal. Calcd. for $C_{15}H_{25}N$: C, 82.12; H, 11.49; N, 6.39.
$C_{15}H_{23}N$: C, 82.87; H, 10.67; N, 6.45.
Found : C, 82.16; H, 11.10; N, 6.66.

Picrolonate. .....m.p. 116-117.5°. This picrolonate produced no m.p. depression with that of (XXVII).

$C_{15}H_{21\text{-}23}ON$. .....The above mentioned alkaline liquid of b.p. 159–160° (7mm.). It reacted positivly against Ehrlich's reagent.

Anal. Calcd. for $C_{15}H_{23}ON$: N, 6.01.
$C_{15}H_{21}ON$: N, 6.06.
Found : N, 5.85.

Picrolonate, recrystallized from 60% alcohol: Needle, m.p. 110–2°.

This picrolonate produced no m.p. depression with that of (XXVIII).

Oxidation of (XXVII) by $MMnO_4$. .....1470cc. of 4% $KMnO_4$ was added drop by drop to 3.3g. of (XXVII), with stirring and warming on a water bath. After filtration the mixture was made acidic with H_2SO_4 and subjected to continuous ether extraction. Ca. 0.4g. of crystal remained undissolved

in the extraction apparatus, m.p. 254° after recrystallizations from alcohol–acetic ester, then from H_2O. This substance produced no m.p. depression with synthetic pyridin-2,5-dicarbonic acid.

Anal. Calcd. for $C_7H_5O_4N$: C, 50.28; H, 3.02; N, 8.39.
Found: C, 49.93; H, 2.75; N, 8.23.

$C_{15}H_{22}ON\cdot CH_3$ (XIV). ..... B.p. 155–9° (7.5mm.).

Anal. Calcd. for $C_{15}H_{22}ON\cdot CH_3$: C, 77.67; H, 10.19; N, 5.67.
Found: C, 77.62; H, 9.88; N, 5.78.
77.72; 10.08.

$C_{15}H_{22}ON\ (CH_3)_2I$ (XV). ..... M.p. 149–151°.

$C_{15}H_{21}ON\ (CH_3)_2$ (XVI). ..... B.p. 160–4° (4mm.).

Anal. Calcd. for $C_{15}H_{21}ON(CH_3)_2$: C, 78.10; H, 10.42; N, 5.36.
Found: C, 77.89; H, 10.39; N, 5.04.

$C_{15}H_{21}ON\ (CH_3)_3I$ ((XVII). ..... M.p. 179–182°.

Anal. Calcd. for $C_{15}H_{21}ON(CH_3)_3I$: N, 3.47.
Found: N, 3.38.

$C_{15}H_{20}O$ (XVIII). .....This was gained from (XVII) by the action of Ag_2O in 50% methanol.

Oxidation of $C_{15}H_{20}O$ (XVIII) by $KMnO_4$. .....To 2.5g. of (XVIII) in 50cc. acetone was added 2% $KMnO_4$ solution in acetone and water (1:1) and the mixture was warmed on a water bath. 38g. of $KMnO_4$ was used. After filtration the solution was condensed in vacuum to 20cc., made acidic with H_2SO_4 and shaken with ether. The ether layer was shaken with dil. ammonia. When $CaCl_2$ was added to the alkaline solution, calcium oxalate precipitated out. After filtration the mother liquor was made again acidic and shaken with ether. From the ether solution we obtained two substances, one of which is easily soluble in ether, the other being less soluble. The less soluble material melted at 182°, produced no m.p. depression with succinic acid, and its p-bromophenacylester also produced no m.p. depression with that of succinic acid. The easily soluble material gave p-bromophecacylester of m.p. 136–7° which produced no m.p. depression with that of d-methylsuccinic acid.

Anal. Calcd. for $C_5H_6O_4\cdot C_{16}H_{12}O_2Br_2$: C, 47.91; H, 3.54; Br, 30.38.
Found: C, 47.50; H, 3.53; Br, 29.98.

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1) Journal of the Pharmaceutical Society of Japan Vol. 68, 74.
2) 〃 Vol. 68, 77.
3) 〃 Vol. 66, 55.
4) Journal of the Chemical Society of Japan Vol. 52, 815.
5) Proceedings of the Imperial Academy Vol. 19, 490.