BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 2629—2635 (1967)

The Synthesis of *N*-Methylnupharamine

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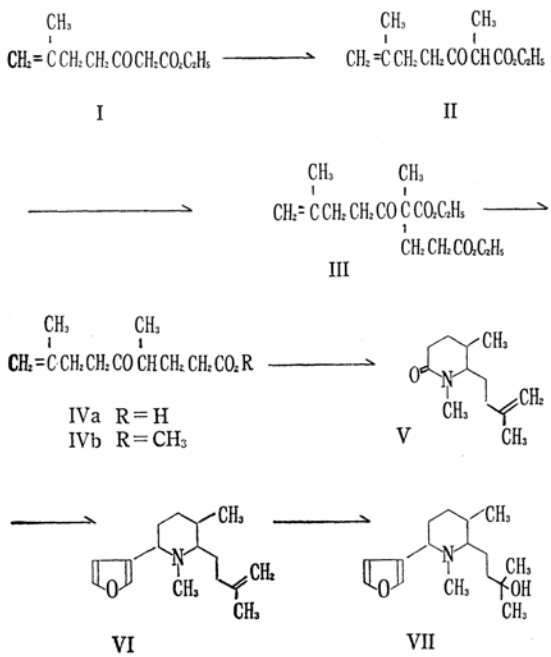
(Received May 19, 1967)

Studying the synthesis of nupharamine, a minor alkaloid isolated from *Nuphar japonicum* DC., *N*-methylnupharamine was synthesized and its stereoisomers were characterized.

Nupharamine is a minor alkaloid isolated from *Nuphar japonicum* DC. and the chemical structure was determined by Arata and Ohashi.[1-3] The absolute configuration of this alkaloid was elucidated by us by the chemical correlation with deoxynupharidine (main alkaloid) and its diastereoisomer.[4] In the course of the attempted synthesis of nupharamine, *N*-methylnupharamine was synthesized as following scheme;



Alkylation of keto ester I, which was prepared from methallyl chloride according to the method of Crombie,[5] with methyl iodide in the presence of sodium ethylate in ether solution gave α-methyl keto ester II. The compound II was neither condensed with β-bromopropiophenone ethylene ketal nor α-acetoxy-γ-bromopropylbenzene, but condensed with ethyl β-bromopropionate to give III using sodium hydride in ether in good yield. The acid hydrolysis of the keto diester III was found unfavorable. In this condition, the compound III was hydrolyzed, decarboxylated and cyclized to 1, 3-cyclohexadione derivative[6] and the enolized hydroxy group of this diketone attacks to the double bond in the side chain and forms a enol ether ring. The product VIII showed NMR signals at 1.18 and 1.07 ppm (two doublet due to C-methyl groups), from which it was considered that the product contained two isomers having a methyl group on six membered ring at different position. The compound VIII was boiled with sodium hydroxide to give a hydroxy diketone IX which showed in NMR signal one C-methyl

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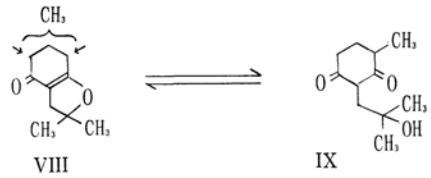
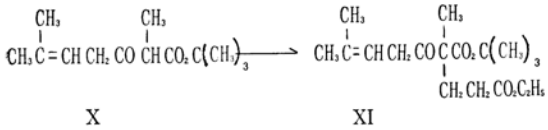
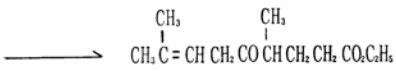
1) Y. Arata and T. Ohashi, *Yakugaku Zasshi (J. Pharm. Soc. Japan)*, **77**, 792 (1957).
2) T. Ohashi, *ibid.*, **79**, 729, 734 (1959).
3) Y. Arata, T. Ohashi, J. Okumura, Y. Wada and M. Ishikawa, *ibid.*, **83**, 79 (1963).
4) I. Kawasaki, S. Matsutani and T. Kaneko, This Bulletin, **36**, 1474 (1963).
5) L. Crombie, A. J. B. Edgar, S. H. Harper, M. W. Lowe and D. Thompson, *J. Chem. Soc.*, **1950**, 3552.
6) T. Hanshall, W. E. Silberman and F. G. Webster, *J. Am. Chem. Soc.*, **77**, 6656 (1955).



VIII IX



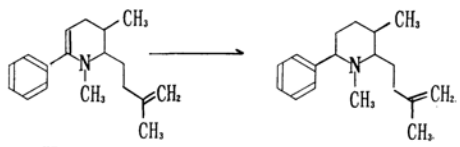
X XI



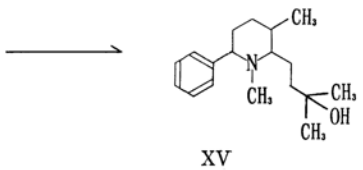
XII

doublet at 1.20 ppm. When the hydroxy diketone IX was boiled with hydrochloric acid, the enol ether VIII reproduced. The keto diester III was stirred in alcoholic sodium hydroxide solution at room temperature and neutralized with 50% sulfuric acid, then decarboxylation was occurred and IVa was obtained in good yield. γ-Methyl keto acid IVa and its methyl ester IVb and XII, as mentioned below, afforded the oximes in usual way, but the reduction of these oximes by the use of zinc and acid or Bouveault-Blanc method were not favorable.

Another synthetic route, the Blaise reaction of γ, γ-dimethyl allylcyanide with *t*-butyl α-bromopropionate gave *t*-butyl 2, 6-dimethyl-3-oxo-5-heptenoate (X). Condensation of X with ethyl β-bromopropionate and subsequent thermal decarboxylation of the product XI afforded ethyl 4, 8-dimethyl-5-oxo-7-nonenoate (XII) in 40% yield. Preparative method of IV was practically more convenient than that of XII for our purpose of the synthesis of unsaturated keto ester.



XIII XIV



XV

The methyl ester IVb was treated with methanolic methylamine in a sealed tube at 100°C for 24 hr to give *N*-methyl lactam V in good yield. Treatment of lactam V with phenyllithium at −20°C gave an enamine XIII which on hydrogenation in the presence of platinum oxide afforded 1, 3-dimethyl-2-isoamyl-6-phenylpiperidine, but reduction of the immonium salt of the enamine XIII with sodium borohydride produced a mixture of stereoisomers of 1, 3-dimethyl-6-phenyl-2-(3-methyl-3-butenyl)-piperidine (XIV). The NMR signal due to olefinic proton of this compound appeared at 4.66 ppm. Hydration of XIV with 50% sulfuric acid led to a mixture of stereoisomers of the phenyl analogue XV of *N*-methylnupharamine with an almost quantitative yield.

In the same manner, the condensation of lactam V with 3-furyllithium at −40°C gave an enamine and reduction of the immonium salt of the enamine with sodium borohydride in methanol produced a mixture of conformational isomers of 1, 3-dimethyl-6-(furyl-3)-2-(3-methyl-3-butenyl)-piperidine (VI), which was separated into three fractions by the aid of column chromatography on alumina. The first fraction eluted initially with petroleum ether - 5% ether was hydrated with 50% sulfuric acid and the products obtained as a viscous oil which showed two spots on TLC over silicagel GF plate were then successfully separated by preparative TLC method to give VII A (bp 120°C/0.01 mmHg) and VII B (mp 68—69.5°C). Both NMR and IR spectra of VII A were identical with those of (−)*N*-methylnupharamine, which derived from natural nupharamine.

The following fraction eluted with petroleum ether - ether was hydrated to give isomer VIIC and the hydration of the last fraction eluted with ether only gave isomerVIID.

The data of four isomers were summarized in table and IR spectra were shown in the figure.

The lactam V exists as a mixture of cis and trans isomers with respect to the C_3-methyl and C_2-alkyl groups. The immonium salt of the reaction product of V with furyllithium seems to exist as two thermodynamically stable conformers presented as *i* and *ii*.[7] The preferred conformer (*i*), if boronate ion attacks the double bond from the upper side of the molecule (*i*) will afford the most stable conformer (*iv*) of VI, which has C_2-alkyl (eq), C_3-methyl (eq) and C_6-furyl (eq) group. The isomer VIIA derived from this conformer was identical with natural *N*-methylnupharamine.

On the other hand, the approach of boronate ion from the under side of the molecule (*i*) will cause to dispose the C_6-furyl group axial. In this case, ring inversion will occur and the resulting conformation of the molecule will be expressed

7) F. Bohlmann, E. Winterfeldt, G. Boroschewski, R. Mayer-Mader and B. Gatscheff, *Chem. Ber.*, **96**, 1792 (1963).

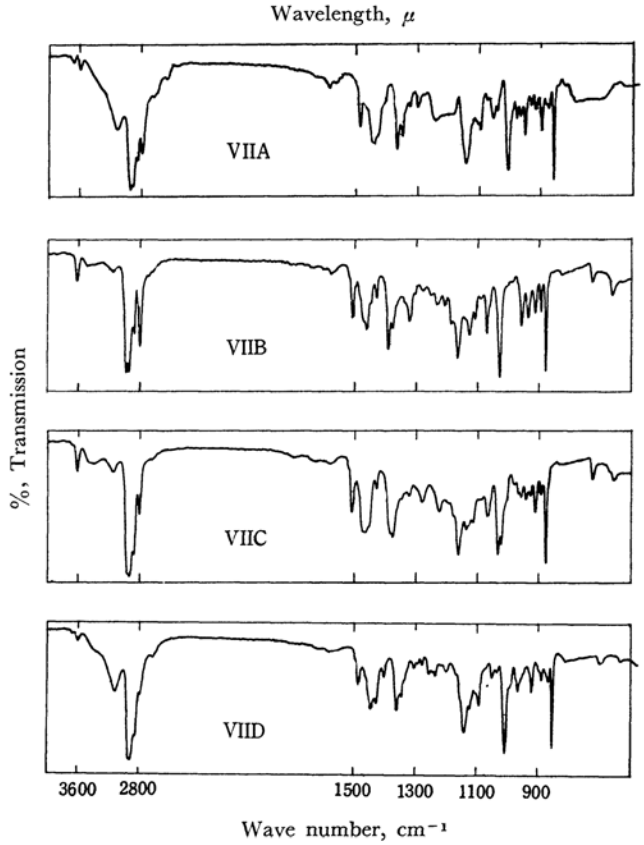


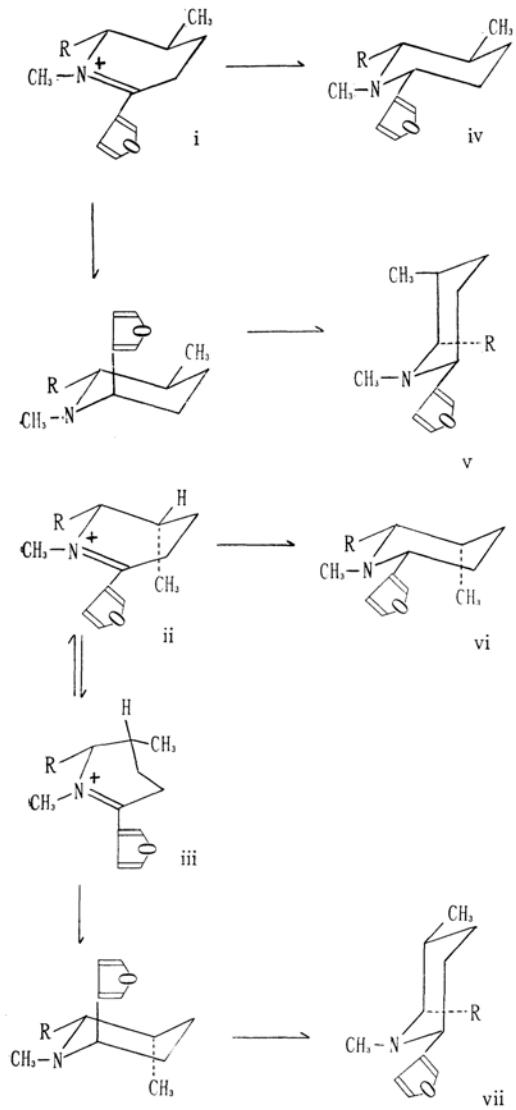
Fig. 1. IR spectra of 1,3-dimethyl-6-(furyl-3)-2-(3-methyl-3-hydroxy-butyl)-piperidine (VII) in CCl_4.

TABLE 1

		VII A	VII B	VII C	VII D
Bp, °C/mmHg		120/0.05	120/0.01	120/0.01	120/0.05
Mp, °C			68—69.5		
Methiodide (mp, °C)		168—169		191—192	147—149
NMR	C_2-H	>2.1	>2.1	2.45 *Wh*=10	2.36 *Wh*=12
(δ; ppm)	C_3-CH_3	0.88 *J*=6	1.00 *J*=7	0.98 *J*=6	0.88 *J*=7
	C_6-H	3.16 *Wh*=15	2.85 *Wh*=20	3.62 *Wh*=10	3.82 *Wh*=17
	N-CH_3	2.07	2.0	2.21	2.13
	Fu(β)	6.41	6.31	6.36	6.45
	Fu(α)	7.29	7.23	7.28	7.19, 7.29
IR (cm^{-1})	OH	3134	3620	3620	3134
	N-CH_3	2800 s	2800 s	2800 w	2800 w

as formula *v*. The isomer VIID isolated in a reasonable yields from reaction products corresponds with the isomer which will be obtained from *v* on hydration. It is suggested that another conformer (*ii*), having C_3-axial methyl and C_6-equatorial side chain, may be equilibrium with *iii* which have C_3-quasi equatorial and C_2-quasi axial groups together with ring distortion. The attack of boronate ion to the conformer (*ii*) from the upper side will lead to the conformer (*vi*) having C_2-alkyl (eq), C_3-methyl (ax) and C_6 furyl (eq) from which the isomer VII B must be obtained on hydration.

As a result of under side attack of boronate ion to *iii* will yield the conformer (*vii*) having C_2-alkyl (ax), C_3-methyl (eq) and C_6-furyl (eq) from which the isomer VIIC must be obtained on hydration. It is considered that these isomers VIIC and VIID would suffer from some distortion on the piperidine ring by the influence of the bulkier



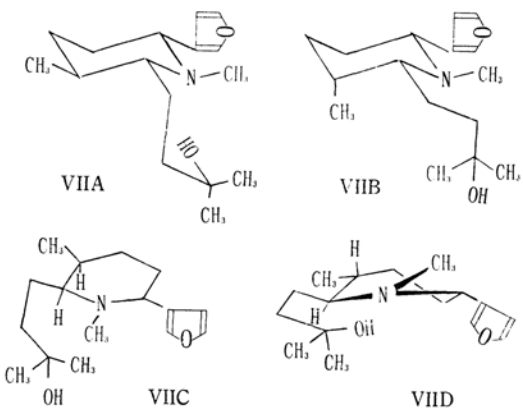
axial substituents.

The IR spectra of four isomers show difference in the finger print region and VIIA and VIIB have stronger band of *N*-methyl group at 2800 cm^{-1} and also show NMR signal of *N*-methyl group at higher field than that of VIIC and VIID. Thus the conformation of *N*-methyl group of VIIC and VIID is supposed to take quasi axial orientation.

The signal of C_2-proton of VIIC and VIID appears in lower field at 2.3—2.5 ppm and that of VIIA and VIIB shifts to higher fields more than 2.1 ppm and takes refuse in the CH-proton signals.

It has been suggested that the great difference in chemical shift between axial and equatorial protons at 2 position of *N*-alkyl piperidine[8] and that of 4 position of quinolizidine[9] are due to stereospecific shielding of the axial proton by the lone pair being situated trans-coplanary on the adjacent nitrogen atom. According to this criterion, VIIA and VIIB must have a trans coplanar relationship between C_2-proton, C_6-proton and the lone pair of nitrogen, and C_2-proton and C_6-proton must be axial disposition.

We have observed previously that the signals due to axial C-methyl group occurs at lower field than that of their equatorial analogue in methylquinolizidine.[10] Hence it is suggested that VII A has the equatorial C_3-methyl group and VIIB has the axial one. Moreover, the evidence that the IR spectrum of VIIA reveals the absorption due to a strong N···H–O hydrogen bonding in carbon tetrachloride solution supports the fact that VIIA has a C_2-equatorial side chain. The absence of the absorption due to the hydrogen bonding in VIIB might be well rationalized from the following consideration that the formation of N···H–O hydrogen bonding is interrupted by the 1, 3-diaxial interaction between the C_3-axial methyl and the $\alpha\beta$-carbon-carbon bond of C_2-alkyl side chain. VIID has a strong hydrogen bonding, but VIIC has not. As two axial substituents at C_2 and C_3 will increase the distortion of the piperidine ring, VIID is able to form the hydrogen bonding, but the hydrogen bonding in VIIC is disturbed by the deficiency of ring distortion caused by the orientation of substituents. The NMR signal of the C_3-methyl group of VIID appeared at higher field than that of the C_3-methyl in VIIC, but the coupling constant of the methyl doublet of VIID was splitting larger than that of VIIC and the signal of the C_2-proton of VIID showed also higher field than that of the other. The NMR spectra mentioned above also support these conformations presented as follows;



8) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).

9) T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

10) M. Kotake, I. Kawasaki, T. Okamoto, S. Matsutani, S. Kusumoto and T. Kaneko, This Bulletin, **35**, 1335 (1962).

Experimental

All melting points are uncorrected. NMR spectra were obtained with a Varian A-60 spectrometer in carbon tetrachloride solution and chemical shifts are given from TMS as an internal reference.

Ethyl 6-Methyl-3-oxo-6-heptenoate (I). Ethyl 6-methyl-3-oxo-6-heptenoate was prepared from methallyl chloride according to the method of Crombie.[5] Bp 120—128°C/18 mmHg.

Ethyl 2, 6-Dimethyl-3-oxo-6-heptenoate (II). A solution of keto ester I (92 g) in anhydrous ether (100 m*l*) was added to a suspension of sodium ethylate (34 g) in ether (300 m*l*). After the mixture had been stirred for 1 hr, methyl iodide (72 g) was added dropwise and heated under reflux for 3 hr, then water was added. The separated aqueous layer was extracted with ether and the combined ethereal extracts were washed and dried. On distillation, was obtained II (78 g, 83%), bp 125—128°C/18 mmHg.

IR: 1748, 1710, 1670, 885 cm^{-1}. NMR: 4.70 (2H singlet due to olefinic proton), 1.74 (3H singlet), 1.3 (3H doublet $J=8$), 4.2 (2H quartet $J=7$), 1.28 ppm (3H triplet $J=7$).

Ethyl 4, 8-Dimethyl-4-carbethoxy-5-oxo-8-nonenoate (III). A solution of the keto ester II (40 g) in anhydrous ether (100 m*l*) was added to a suspension of sodium hydride dispersion (in mineral oil; hydride content: 50%, 9.6 g) in ether (200 m*l*) under cooling in an ice bath. After being stirred for 1 hr, to this mixture ethyl β-bromopropionate (37 g) in anhydrous ether (100 m*l*) was added slowly over a period of half an hour, and then stirred for 3 hr at room temperature and for an additional 2 hr under reflux. Water (300 m*l*) was added to the reaction mixture and the organic layer was separated, washed successively with dilute hydrochloric acid, sodium bicarbonate solution and finally with saturated sodium chloride solution. On distillation, was obtained III (49 g, 75%) bp 130—135°C/0.3 mmHg.

Found: C, 64.33; H, 8.68%. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78%.

Acid Hydrolysis of Keto Ester III. The mixture of III (5 g), acetic acid (40 m*l*) and concentrated hydrochloric acid (10 m*l*) was heated at 130—140°C for 24 hr, then the solution was evaporated *in vacuo*. The residue was dissolved in ether and extracted with sodium bicarbonate solution. The acidic (*ca.* 0.1 g) and neutral products were obtained by the usual way. The latter was distilled at 75—80°C/0.05 mmHg (VIII, 2.9 g, 94%).

Found: C, 73.10; H, 8.86%. Calcd for $C_{11}H_{16}O_2$: C, 73.30, H, 8.95%. IR: 1658, 1635, 810 cm^{-1}. NMR: 1.41 (6H singlet), 2.53 (1H singlet), 2.54 (1H singlet), 1.18 (1.5H doublet), 1.07 ppm (1.5H doublet).

The mixture of VIII (2.9 g), sodium hydroxide (3 g) and water (30 m*l*) was boiled for 30 min. The cooled solution was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried and the ether was removed by evaporation. The residue was recrystallized from ether yielding *ca.* 2 g of IX, mp 103—104°C.

Found: C, 66.66; H, 9.05%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%. IR: 3280, 1605 cm^{-1}. NMR: 1.67 (6H singlet), 1.20 ppm (3H doublet).

IX (0.7 g) was heated with a mixture of acetic acid and hydrochloric acid to afford an oil (0.5 g), which was identical with the compound VIII in IR spectra.

Methyl 4, 8 - Dimethyl-5-oxo-nonanoate. IVb (0.5 g) was hydrogenated in the presence of platinum oxide in ethanol. After 1 mol of hydrogen had been absorbed, the catalyst was removed by filtration and the solvent was evaporated. On distillation of the residual oil, there was obtained methyl 4, 8-dimethyl-5-oxo-nonanoate (0.45 g), bp 90°C/0.4 mmHg (bath temperature). IR spectrum of this compound was identical with that of the methyl ester obtained from XII as described below. XII (1.2 g) was hydrogenated in the same manner as above yielding 1.1 g of an oil, bp 90—95°C/0.45 mmHg (bath temperature). Alkaline hydrolysis of this ethyl ester and following esterification with diazomethane afforded the methyl ester (0.5 g), bp 89—91°C/0.4 mmHg (bath temperature.)

γ, γ - Dimethylallylbromide. γ, γ - Dimethylallylbromide was prepared from isoprene according to the method of Bass.[11] Bp 40—43°C/30 mmHg.

γ, γ - Dimethylallylcyanide. γ, γ - Dimethylallylcyanide was prepared according to the method of Supniewsky[12] from γ, γ-dimethylallylbromide. Bp 60—64°C/19 mmHg. This cyanide was also prepared according to the method of Letch[13] from cyanoacetic acid and isobutylaldehyde.

***t*-Butyl 2, 6-Dimethyl-5-heptenoate (X).** Cupric chloride (0.5 g), zinc dust (47 g) and dry benzene (90 m*l*) were placed in a flask and then 80 m*l* of benzene was slowly distilled off. To the residue, was added rapidly the mixture of γ, γ-dimethylallylcyanide (45 g) and *t*-butyl α-bromopropionate (95 g). The reaction mixture was heated under reflux for 50 min and then cooled in an ice bath. To the cooled solution was added (below 10°C) 7 N sulfuric acid (300 m*l*) and the solution was stirred for 45 min at room temperature. The organic layer was separated and the aqueous layer was extracted with benzene. The combined benzene extracts were washed with sodium bicarbonate solution followed by water. Distillation under reduced pressure gave *t*-butyl 2, 6-dimethyl-5-heptenoate, bp 91—103°C/1 mmHg (33 g, 31%).

Found: C, 69.06; H, 9.81%. Calcd for $C_{13}H_{22}O_2$: C, 68.99; H, 9.80%. IR: 1740, 1720, 1640, 840 cm^{-1} NMR: 4.7 (1H broad, $Wh=6$ cps due to olefinic proton).

Ethyl 4, 8-Dimethyl-5-oxo-7-nonenoate (XII). A solution of X (20.6 g) in anhydrous ether (50 m*l*) was added dropwise with stirring to a suspension of sodium hydride dispersion (in mineral oil; hydride content: 50%, 4.8 g) in anhydrous ether (300 m*l*). After the mixture had been stirred at room temperature for 30 min, a solution of ethyl β-bromopropionate (18.5 g) in anhydrous ether (50 m*l*) was added. The reaction mixture was stirred for 5 hr and warmed under reflux for an additional 3 hr, then water (100 m*l*) was added. The separated aqueous layer was extracted with ether and the ethereal extract was washed with sodium bicarbonate solution followed by water and dried.

11) J. L. Baas, A. Davies-Fidder and H. O. Huisman, *Tetrahedron*, **22**, 259 (1966).
12) J. V. Supniewski and P. L. Salzberg, "Organic Syntheses," Coll. Vol. I, p. 46 (1952).
13) R. A. Letch and R. P. Linstead, *J. Chem. Soc.*, **1932**, 443.

The solvent was evaporated and the residual oil was distilled under reduced pressure to give keto diester (XI) (11.8 g, 40%). Bp 130—136.5°C/0.5 mmHg. The distillate obtained above was heated under reflux for 15 min in stream of nitrogen to accomplish the decarboxylation and the resulting XII was distilled (5.1 g, 52%), bp 86—87°C/0.2 mmHg.

IR: 1730, 1720, 850 cm^{-1}. NMR: 4.65 ppm (1H broad singlet due to olefinic proton).

The oxime of XII obtained by the usual manner had bp 119—120°C/0.3 mmHg.

Found: C, 64.83; H, 9.76; N, 5.68%. Calcd for $C_{13}H_{23}O_3N$: C, 64.70; H, 9.61; N, 5.80%.

4, 8-Dimethyl-5-oxo-8-nonenoic Acid (IVa). To a solution of the keto ester III (30 g) in ethanol (30 m*l*) was added a solution of sodium hydroxide (8.5 g) in water (170 m*l*). The reaction mixture was stirred for 5 hr and allowed to stand at room temperature overnight. The resulting clear solution was treated with 50% sulfuric acid (17 m*l*) stirred at room temperature for 1 hr and then extracted with ether. The ethereal solution was extracted with sodium bicarbonate solution and the aqueous layer was acidified with dilute sulfuric acid and reextracted with ether. The ether extract was dried, evaporated and distilled. Bp 130—135°C/0.3 mmHg (IVa, 16.8 g, 84%).

Found: C, 66.11; H, 9.04%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%. IR: 1710, 1705 due to carbonyl, 1660, 885 cm^{-1} due to double bonds. NMR: 4.72 (2H singlet), 1.77 (3H singlet), 1.11 ppm (3H doublet $J=7$).

Methyl 4, 8-Dimethyl-5-oxo-8-nonenoate (IVb). Above acid IVa (37.9 g) in ether (100 m*l*) was esterified with diazomethane in ether, bp 83—84°C/0.2 mmHg (39.6 g, 98.5%).

IR: 1740, 1720, 885 cm^{-1}.

Oxime of IVa, bp 146—152°C/0.001 mmHg. Found: C, 61.94; H, 8.98%. Calcd for $C_{11}H_{19}O_3N$: C, 62.36; H, 9.02%.

Oxime of IVb, bp 137—139°C/0.1 mmHg. Found: C, 63.38; H, 9.24%. Calcd for $C_{12}H_{21}O_3N$: C, 63.41; H, 9.31%.

1, 3-Dimethyl-2-(3-methyl-3-butenyl)-piperidone-6 (V). A mixture of methyl 5-oxo-4, 8-dimethyl-8-nonenoate IVb (13 g) and 90 m*l* of methanol containing 30% of methylamine was allowed to stand in a sealed tube at room temperature for 24 hr and then heated at 90—100°C for an additional 24 hr. The resulting solution was evaporated and the residue was dissolved in 100 m*l* of methanol, which was then reduced with sodium borohydride (2.4 g) in methanol. The reaction mixture was stirred for 3 hr and decomposed with acetic acid and evaporated to dryness. The residue was extracted several times with boiling chloroform and the solvent was removed by evaporation. To the residue (12.4 g) was added barium hydroxide (17.3 g) and water (330 m*l*) and the mixture was refluxed for 15 hr. The resulting clear solution was saturated with carbon dioxide and the precipitate was filtered off. The filtrate was evaporated to dryness. The crude lactam (7.6 g, bp 98—101°C/0.22 mmHg) obtained on distillation was chromatographed on silica gel. The fractions eluted with ether gave pure lactam (4.8 g, 46%).

Found: N, 7.42%. Calcd for $C_{12}H_{21}ON$: N, 7.17%. IR: 3080, 1645, 885 cm^{-1}. NMR: 4.74 (2H singlet), 1.73 ppm (3H singlet).

1, 3-Dimethyl-2-(3-methyl-3-butenyl)-piperidine. A solution of V (1.4 g) in anhydrous tetrahydrofuran (15 m*l*) was added dropwise to a solution of lithium aluminum hydride (0.5 g) in anhydrous tetrahydrofuran (60 m*l*). After refluxed for 24 hr, the reaction mixture was decomposed with the required amount of water and the precipitate was extracted with boiling ether. The ethereal extract was evaporated and the residue distilled, bp 104—107°C/21 mmHg (1.1 g, 85%).

The picrate, recrystallized from methanol-ether, melted at 104—106°C.

Found: C, 52.33; H, 6.47; N, 13.70%. Calcd for $C_{18}H_{26}O_7N_4$: C, 52.67; H, 6.39; N, 13.65%.

1, 3-Dimethyl-6-phenyl-2-(3-methyl-3-butenyl)-piperidine (XIV). Phenyllithium was prepared from lithium metal (0.3 g in 8 m*l* of anhydrous ether) and bromobenzene (3.7 g in 10 m*l* of anhydrous ether) as usual manner. To the resulting solution was added with stirring under cooling at −20°C over a period of 40 min a solution of lactam V (2.3 g) in anhydrous ether (15 m*l*). The reaction mixture was stirred for an additional 4 hr at −20°C and poured into a mixture of ice (90 g) and concentrated sulfuric acid (10 g). The aqueous layer was separated, and after washing with ether to remove a little neutral material was made basic with addition of potassium carbonate and extracted with ether. The combined ether extracts were dried and evaporation of the solvent gave the unstable enamine base XIII (1.53 g), which was dissolved in ethanol (20 m*l*) and hydrogenated in the presence of platinum oxide. After absorption of 2 mol of hydrogen, the catalyst was filtered off and the solvent evaporated. Distillation of the residue gave 1, 3-dimethyl-2-isoamyl-6-phenylpiperidine (1.36 g), bp 130°C/0.52 mmHg.

Found: C, 83.35; H, 11.26; N, 5.62%. Calcd for $C_{18}H_{29}N$: C, 83.33; H, 11.27; N, 5.40%.

The enamine base XIII (1.65 g) was dissolved in methanol (20 m*l*) and was treated with a calculated amount of concentrated hydrochloric acid to make it an immonium salt. The resulting solution was reduced under ice cooling with sodium borohydride (0.9 g) in methanol (25 m*l*), which was then acidified with acetic acid and evaporated. The residue was made basic with addition of 20% potassium hydroxide solution and extracted with ether. The ether extract was dried and evaporated to give an oil. On distillation, was obtained XIV (1.57 g), bp 130—135°C/0.7 mmHg.

Found: C, 84.20; H, 10.55; N, 5.71%. Calcd for $C_{18}H_{27}N$: C, 83.99; H, 10.59; N, 5.66%. IR: 885 cm^{-1}.

1, 3-Dimethyl-6-phenyl-2-(3-methyl-3-hydroxybutyl)-piperidine (XV). To unsaturated base XIV (132 mg) was dissolved in 50% sulfuric acid (6 m*l*) and allowed to stand at room temperature for 60 hr. The resulting clear solution was diluted with a small amount of water and made basic with addition of potassium carbonate and extracted with ether. The ether extract was dried, evaporated and on distillation of the residual oil was obtained XV (137 mg), bp 150°C/0.09 mmHg (bath temperature) as a viscous oil. The hydrochloride, recrystallized from ethanol-ether, had mp 194—195.5°C.

Found: C, 69.21; H, 9.77; N, 4.51%. Calcd for $C_{18}H_{30}ONCl$: C, 69.31; H, 9.69; N, 4.49%.

1, 3-Dimethyl-6-(furyl-3)-2-(3-methyl-3-butenyl)-piperidine (VI). Butyllithium in ether was prepared from lithium metal (230 mg) in anhydrous ether (8 m*l*) and *n*-butylbromide (2.23 g) in anhydrous ether (8 m*l*) at −10°C as usual manner. The reaction mixture was then cooled to −40—45°C. A solution of 3-iodofuran (3.0 g) in anhydrous ether (8 m*l*) was added gradually with stirring and the stirring was continued for 20 min. To this solution, was added dropwise a solution of lactam V (2.3 g) in anhydrous ether (10 m*l*) and the mixture was stirred for an additional 4 hr at −40—45°C. The reaction mixture was allowed to stand overnight and then was poured into a mixture of ice (90 g) and concentrated sulfuric acid (10 g). The aqueous layer was separated and the isolation of enamine was worked up as described for XIV. Crude enamine (635 mg) was obtained as a brownish oil, which was then dissolved in methanol (10 m*l*) and reduced with sodium borohydride to give VI. Distillation gave VI as an oil (508 mg), bp 110—115°C/0.25 mmHg (bath temperature).

Found: C, 77.65; H, 10.18; N, 5.83%. Calcd for $C_{16}H_{25}ON$: C, 77.67; H, 10.18; N, 5.66%. IR: 1503, 873 cm^{-1} due to β-furan, 885 cm^{-1} due to endo methylene.

***dl*-*N*-Methylnupharamine and Its Stereoisomers (VII).** The unsaturated base VI (500 mg) obtained above was separated into three fractions by the aid of chromatography on alumina (20 g) as follows:

The first fraction initially eluted with petroleum ether - 5% ether gave 101 mg of isomers as an oil. The second fraction obtained by the successive elution with petroleum ether - 5% ether and ether gave 288 mg of isomers. This fraction was further separated into two fractions by the rechromatography on alumina. The third isomer was obtained on the elution with petroleum ether - 5% ether and the last isomer with ether only. The oil obtained from the first fraction was hydrated as in the case of XIV to give a mixture of stereoisomer VIIA and VIIB, which were separated with the aid of preparative TLC method into two isomers using silica gel GF plates and a solvent system of $CHCl_3$: MeOH : H_2O, 5 : 1 : 0.12.

VIIA: having slightly higher R_f value than VII B in the above solvent system, bp 120°C/0.05 mmHg (bath temperature). The IR and NMR spectra were both identical with those of natural (−) *N*-methylnupharamine in CCl_4 solution.

Found: 72.18; H, 10.28%. Calcd for $C_{16}H_{27}O_2N$: C, 72.41; H, 10.26%.

Methiodide, mp 168—169°C (from ethanol-ether).

Found: C, 50.21; H, 7.54%. Calcd for $C_{17}H_{30}O_2NI$: C, 50.12; H, 7.42%.

VIIB: bp 120°C/0.01 mmHg (bath temperature), crystallized on cooling, mp 69—69.5°C (from *n*-pentane).

Found: C, 72.46; H, 10.46; N, 7.64%.

The other two isomers obtained from the second fraction were hydrated respectively in the same manner. The resulting hydroxy bases were purified by preparative TLC method using silica gel GF plates and the same solvent system. Two isomeric base VIIC and VIID were obtained.

VIIC: bp 120°C/0.01 mmHg (bath temperature).

Methiodide, mp 191—192°C (from acetone-ethylacetate).

Found: C, 50.31; H, 7.40; N, 3.26%.

VIID: having slightly heigher R_f value than VIIC, bp 120°C/0.05 mmHg (bath temperature).

Methiodide, mp 147—149°C (from acetone-ether).

Found: C, 50.41; H, 7.42; N, 3.14%.

(−)*N*-Methylnupharamine. A mixture of natural (−)nupharamine (3.42 g), formalin (37% aqueous solution, 25 m*l*) and 85% formic acid (25 m*l*) were heated on a boiling water bath for 3 hr. The reaction mixture was cooled and made basic with addition of potassium carbonate. The resulting solution was extracted several times with ether and the ether solution was extracted with 2 N hydrochloric acid. The acidic aqueous layer was basified with potassium carbonate and reextracted with ether. The product (4.0 g) was chromatographed on alumina and the fractions eluted with ether gave pure *N*-methylnupharamine (893 mg), bp 118—120°C/0.001 mmHg, $[\alpha]_D^{24}$ −27.5±0.5° (*c* 0.974, ethanol).

Found: C, 72.26; H, 10.12; N, 5.34%. Calcd for $C_{16}H_{27}O_2N$: C, 72.41; H, 10.26; N, 5.28%.

Methiodide, mp 202—203°C (from ethanol).

Found: C, 50.38; H, 7.48; I, 31.42%. Calcd for $C_{17}H_{30}O_2NI$: C, 50.12; H, 7.42; I, 31.16%.

A part of this work was performed at Shionogi Research Laboratory. We are most grateful to Dr. Kenichi Takeda and Dr. Tokuo Kubota of Shionogi & Co., Ltd. for their helpful facilities given to this work.