Thermal Decomposition of (IVa) in Solution——A suspension of 0.30 g. of (IVa) in 20 cc. of toluene was refluxed in an oil bath for 5 hr. Toluene was evaporated to dryness in a reduced pressure and the resinous residue was digested with H_2O. The aqueous solution was evaporated to dryness in a reduced pressure and the residue was allowed to stand in a desiccator but it did not crystallize. Picrate : m.p. 198°, undepressed on admixture with 1-methoxy-4-aminoquinolinium picrate. Yield, 0.18 g. (69%).

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Summary

Quaternary salts of 4-azidoquinoline and 4-azidoquinoline 1-oxide were synthesized and their reaction was examined. Their decomposition with alkali afforded 1-methyl-(or methoxy)-4(1*H*)-quinolone. Treatment of 1-methoxy-4-azidoquinolinium methosulfate with sodium alkoxides resulted in a reaction at room temperature to form 4-alkoxyquinolines. These compounds reacted with compounds possessing an active methylene to form 1-methyl (or methoxy)-4-aminoquinolinium methosulfate, instead of undergoing triazole cyclization. Thermal decomposition in toluene or catalytic hydrogenation also furnished the same amino compound.

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108. **Yoshio Arata, Toshiko Nakanishi, and Yoko Asaoka** : Constituents of Rhizoma Nupharis. XVIII.[*1] Synthesis of Alkaloids from *Nuphar japonicum* DC. I. Synthesis of *rac*-Deoxynupharidine.

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The formula (XVII)[1~3] was proposed for deoxynupharidine isolated from the rhizome of *Nuphar japonicum* DC. (Japanese name "Kôhone") and this structure was proved to be correct by synthesis, as was briefly reported.[4] The route of this synthesis will be described in detail in the present paper.

In order to examine the reaction conditions necessary for the synthesis of deoxynupharidine, 4-(3-furyl)octahydroquinolizine (V) was synthesized by the route shown in Chart 2.

Reaction of octahydro-4-quinolizinone (I) and ethyl 3-furoate, in the presence of sodium hydride, afforded a condensate (II) of m.p. 86~88°, which colored reddish purple

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[*1] Part XVII : Yakugaku Zasshi, **82**, 326 (1962).
[*2] Tsuchitoriba-naga-machi, Kanazawa (荒田義雄, 中西外志子, 浅岡陽子).
1) Y. Arata : Yakugaku Zasshi, **76**, 1447 (1956).
2) Y. Arata, *et al.* : *Ibid.*, **77**, 236 (1957).
3) M. Kotake, *et al.* : Ann., **606**, 148 (1957).
4) Y. Arata, *et al.* : Yakugaku Zasshi, **80**, 856 (1960).

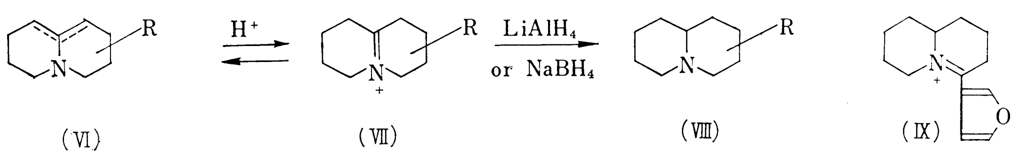

Chart 1.

to ferric chloride. Heating of (II) with hydrochloric acid gave (IV) of m.p. 57°, with infrared absorption band at 1640 cm^{-1} ($>$C=C-N-R). In this reaction, (II) is considered to undergo hydrolysis accompanied with decarboxylation to form (III), which further underwent dehydrative cyclization to (IV). Leonard[5,6] had shown that the compounds of hexahydroquinolizine series (VI) form iminium salt ($>C=\overset{+}{N}<$) by the action of an acid, as shown in Chart 1. (IV) would naturally form (IX) in an acid solution but (IV) was so labile in solution that no detailed examination could be made. (IV) was easily reduced by sodium borohydride in ethanol to form (V). According to Leonard,[5] lithium aluminium hydride does not react with $>$C=C$<$ group in hexahydroquinolizine (VI) but reduces the double bond in its salt (VII) to form (VIII). There are numerous examples of the reduction of (VII) with sodium borohydride but not that of (VI). It is therefore interesting that (IV) was reduced by sodium borohydride.

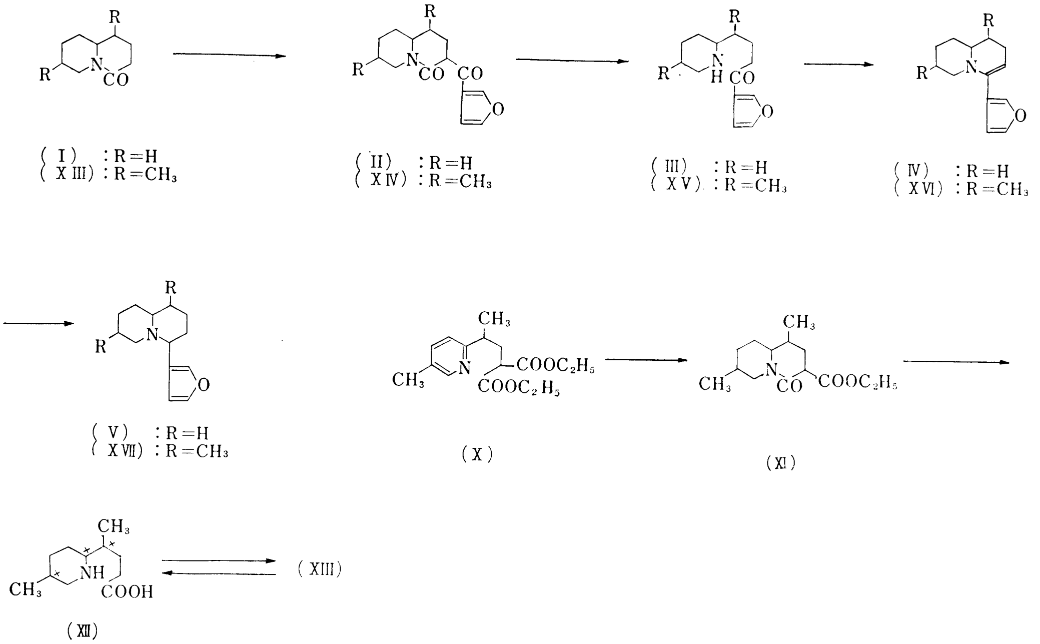

Chart 2.

From the reduction product (V) thereby obtained, two isomers were isolated in 15:1 ratio of (Va) to (Vb). (Va) formed a perchlorate of m.p. 138~139° and a picrate of m.p. 168~169°, while (Vb) formed a picrate of m.p. 142~143°. Both isomers exhibited absorption bands at 2740 and 2790 cm^{-1} due to the *trans*-quinolizidine, as pointed out by Bohlmann.[7] On the other hand, catalytic reduction of (IV) over palladium-carbon only gave (Va).

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[5] N. J. Leonard, *et al.* : J. Am. Chem. Soc., **77**, 439 (1955).

[6] *Idem* : *Ibid.*, **78**, 3457 (1956).

[7] F. Bohlmann : Angew. chem., **69**, 641 (1957).

By the route analogous to the synthesis of (V), synthesis of *rac*-deoxynupharidine (XVII) was carried out. Catalytic reduction of (X)[8,9] in glacial acetic acid solution derived it to (XI) which underwent decarboxylative hydrolysis when heated with hydrochloric acid and formed the amino acid (XII). (XII) has three asymmetric carbons and should form four kinds of racemate but the product (XII) was not separated into each racemate. Heating of (XII) resulted in dehydration to (XIII) and heating of (XIII) with hydrochloric acid reverted it to (XII). Condensation of (XIII) and ethyl 3-furoate, in the presence of sodium hydride, afforded (XIV), which colored indigo with ferric chloride. Heating of (XIV) with 10% hydrochloric acid formed (XVI)[9] which exhibited infrared absorption at 1640 cm^{-1} (>C=C-N-R), but boiling of (XIV) with 18% hydrochloric acid gave a substance, assumed to be (XV), which showed infrared absorptions at 1690 ($\nu_{C=0}$) and 3440 cm^{-1} (ν_{NH}). Reduction of (XVI) with sodium borohydride gave the amine (XVII) which was separated into three kinds of reacemate by derivation to a perchlorate or picrate and repeated recrystallization. (XVIIa) formed a perchlorate of m.p. 205~207° and a picrate of m.p. 165~166°, (XVIIb)[*3] (m.p. 720) formed a perchlorate of m.p. 193~194° and a picrate of m.p. 196°, and (XVIIc)[*3] formed a perchlorate of m.p. 223° (decomp.) and a picrate of m.p. 181~182°. The infrared spectrum (in carbon tetrachloride solution) of (XVIIa) showed absorptions[4] identical with that of (−)-deoxynupharidine isolated from *Nuphar japonicum* DC. It follows, therefore, that (XVIIa) is *rac*-deoxynupharidine. Kawasaki[9] had obtained the same substance (XVII), which formed a perchlorate of m.p. 193~194°, by a different route from the present one and concluded that this substance might be *rac*-deoxynupharidine.

Both (XVIIa) and (XVIIc) show infrared absorption bands due to *trans*-quinolizidine[7] but this absorption is not present in the spectrum of (XVIIb). Therefore, the former two are assumed to take the *trans*-quinolizidine type and the latter, the *cis*-quinolizidine type. The presence of a *cis*-type compound has already been revealed in the compounds of polycyclic quinolizidine series but it is interesting that a labile *cis* compound had been obtained from the compound (XVII) of single quinolizidine series.

Experimental

3-(3-Furoyl)-octahydro-4-quinolizinone (II)——To 4.8 g. of 54.5% NaH in oil suspended in 30 cc. of benzene, 14.5 g. of octahydro-4-quinolizinone (I) was added dropwise and the mixture was stirred for 2 hr. To this mixture, 13 g. of ethyl 3-furoate was added in drops, the mixture was stirred for 2 hr., and heated at 60~70° for 7 hr. The reaction mixture was acidified with HCl and shaken with Et_2O. The Et_2O layer was washed with H_2O, dried, and evaporated. The residue was distilled and 12 g. of turbid, viscous liquid was obtained as a fraction of $b.p_2$ 120~200°. Treatment of this liquid effected solidification and recrystallization of this solid from EtOH gave colorless needles, m.p. 86~88°. EtOH solution of this substance colors reddish purple to $FeCl_3$ solution. *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93. Found : C, 68.44; H, 6.90.

4-(3-Furyl)-1,6,7,8,9,9a-hexahydro-2*H*-quinolizine (IV)——A mixture of 9 g. of the above condensate (II) and 100 cc. of 10% HCl was heated for 5 hr. The solvent was evaporated to dryness in a reduced pressure, the residue was dissolved in water, and shaken with Et_2O to remove Et_2O-soluble substance. The aqueous layer was basified with K_2CO_3, the precipitate was extracted with Et_2O, and the extract solution was washed with H_2O. After dehydration, Et_2O was evaporated and 4.2 g. of a colorless liquid, b.p 2.5 110°, was collected from the residue. The liquid soon solidified and was recrystallized from EtOH to colorless needles, m.p. 57°, which colored gradually. *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N. 6.89. Found : C, 76.81, H, 8.61; N, 6.59. IR ν_{max}^{Nujol} cm^{-1} : 872, 1018, 1505, 1588, 3100 (furan), 1640 (C=C-N-R).

4-(3-Furyl)-octahydroquinolizine (V)——i) Reduction with $NaBH_4$: A mixture of 2.5 g. of (IV) dissolved in 25 cc. of EtOH and added with 0.5 g. of $NaBH_4$ was stirred for 5 hr. EtOH was eva-

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[*3] *rac*-Deoxynupharidine had been synthesized earlier[4] and it was designated as base-B but this notation will henceforth be abolished and the notations given in this paper will be adopted.

8) Y. Arata, *et al.* : Yakugaku Zasshi, **79**, 1442 (1959).

9) I. Kawasaki : Nippon Kagaku Zasshi, **81**, 156 (1960).

porated from the reaction mixture in a reduced pressure, H_2O was added to the residue, and the precipitate thereby appeared was taken up in Et_2O. The Et_2O layer washed with H_2O, dried, and Et_2O was evaporated, leaving 1.5 g. of a colorless liquid (V), b.p$_3$ 95°.

(Va): The total amount of (V) obtained as above was derived to the perchlorate and recrystallized from 70% EtOH to colorless plates, m.p. 138~139°. *Anal.* Calcd. for $C_{13}H_{19}O_5NCl$: C, 51.21; H, 6.30; N, 4.60. Found: C, 51.22; H, 6.65; N, 4.68.

Picrate: Derived from the purified perchlorate and recrystallized from AcOEt to yellow plates, m.p. 168~169°. *Anal.* Calcd. for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.78; H, 5.37; N, 13.06.

The free base (Va) was obtained as a colorless liquid, b.p$_3$ 95°. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 2740, 2790 (*trans*-quinolizidine), 872, 1020, 1500, 1565, 3080 (furan).

(Vb): The recrystallization mother liquor of the above perchlorate was evaporated to dryness and the residue was recrystallized again from 70% EtOH to separate the perchlorate of (Va). The picrate derived from this mother liquor was recrystallized from AcOEt to remove the precipitated picrate of (Va). This mother liquor was evaporated to dryness and the residue was recrystallized from 70% EtOH to yellow prisms, m.p. 142~143°. *Anal.* Calcd. for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.83; H, 5.23; N, 12.85.

The free base (Vb) was obtained as a colorless liquid which distilled out at 115~120° (bath temp.)/3 mm.Hg. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 2740, 2790 (*trans*-quinolizidine), 872, 1027, 1500, 1565, 3080 (furan).

The formation ratio of (Va) to (Vb) was approximately 15:1.

ii) Catalytic Reduction: A solution of 0.34 g. of (IV) dissolved in 15 cc. of EtOH and added with Pd-C (prepared from 0.2 cc. of 2% $PdCl_2$ and 0.1 g. of C) was shaken in H_2 stream and 1.2 moles of H_2 was absorbed during ca. 20 min. The reaction mixture was filtered, the solvent was evaporated from the filtrate in a reduced pressure, K_2CO_3 solution was added to the residue, and extracted with Et_2O. The extract solution washed with H_2O, dried, and Et_2O was evaporated. The residue afforded 0.25 g. of a colorless liquid, b.p$_3$ 100~120° (bath temp.).

This residue was derived to a perchlorate and recrystallized from EtOH to colorless plates, m.p. 138~139°. The picrate derived from this purified perchlorate formed yellow plates (from AcOEt), m.p. 169~171°. These salts showed no depression of m.p. on admixture with the perchlorate and picrate of (Va).

Ethyl 4-oxo-1,7-dimethyl-octahydro-4*H*-quinolizine-3-carboxylate (XI)——A solution of 16 g. of (X)[8] dissolved in 30 cc. of AcOH and added with 1.2 g. of PtO_2 was shaken in H_2 stream and 4200 cc. of H_2 was absorbed. The mixture was filtered, the solvent was evaporated from the filtrate in a reduced pressure, and the residue was basified with K_2CO_3 solution. The precipitate was taken up in Et_2O, Et_2O layer was washed with H_2O, dried, and evaporated. The residue furnished 8 g. of yellowish liquid, b.p$_3$ 158~162°. *Anal.* Calcd. for $C_{14}H_{23}O_3N$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.07; H, 9.51; N, 5.41.

1,7-Dimethyl-octahydro-4-quinolizinone (XIII)——A mixture of 7 g. of (XI) and 18% HCl was heated for 7 hr. and the reaction mixture was evaporated to dryness in a reduced pressure. The residue was dissolved in 50 cc. of H_2O, an excess of Ag_2CO_3 was added, and the mixture was stirred and filtered. H_2S was passed through this filtrate, precipitated Ag_2S was filtered off, and the filtrate was evaporated to dryness in a reduced pressure at below 50°, leaving a very viscous liquid (XII). Distillation of (XII) afforded a colorless liquid (XIII), b.p$_{2.5}$ 107~109°. *Anal.* Calcd. for $C_{11}H_{19}ON$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.70; H, 10.92; N, 7.78.

On heating (XIII) with 10% HCl for 8 hr. and evaporation of the reaction mixture to dryness in a reduced pressure at below 50° reverted it to the hydrochloride of (XII).

3-(3-Furoyl)-1,7-dimethyl-octahydro-4-quinolizinone (XIV)——A mixture of 17.2 g. of (XIII) added into a suspension of 4.7 g. of 54.5% NaH in oil in 20 cc. of benzene was stirred for 2 hr. Into this mixture, 14.5 g. of ethyl 3-furoate was added dropwise with stirring and the stirring was continued for 2 hr. The mixture was then warmed at 60~75° for 7 hr., acidified with HCl, and the precipitate was taken up in Et_2O. The Et_2O layer was washed with H_2O, dehydrated, and the residue obtained on evaporation of Et_2O was distilled to collect 21 g. of a milky white, very viscous fraction of b.p$_3$ 163~215° (bath temp.). This fraction contained the oil used with NaH. Yield, 72.4%. The EtOH solution of this product colors indigo blue to $FeCl_3$ solution.

4-(3-Furyl)-1,7-dimethyl-1,6,7,8,9,9a-hexahydro-2*H*-quinolizine (XVI)——A mixture of 20 g. of (XIV) in 150 cc. of 10% HCl and 50 cc. of AcOH was heated for 10 hr. and the mixture was evaporated to dryness in a reduced pressure. The residue was shaken with Et_2O and H_2O, the aqueous layer was basified with K_2CO_3, and shaken with Et_2O. The upper Et_2O layer was washed with H_2O, dehydrated, and the residue obtained on evaporation of Et_2O was distilled to collect 7.8 g. of a pale yellow liquid of b.p$_3$ 110~113°. This liquid turned brown on being left in the air. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15. Found: C, 78.34; H, 9.62. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 879, 1060, 1500, 1582, 3100 (furan), 1640 (>C=C-N-R).

The liquid, b.p$_2$ 115~120 (bath temp.), obtained by heating (XIV) with 20% HCl for 8 hr. was assumed to be (XV) containing a trace of (XVI), from its analytical data (C, 70.19; H, 10.32) and infrared measurement (liquid) of 1790 (C=O), 3440 (NH), and 1640 (>C=C-N-R) cm^{-1}.

Reduction of (XVI) with $NaBH_4$: Formation of *rac*-Deoxynupharidine (XVIIa), (XVIIb), and (XVIIc)——To a solution of 7 g. of the above amine compound (XVI) dissolved in 13 cc. of EtOH, 3 g. of EtOH, 3 g. of $NaBH_4$ was added and the mixture was stirred for 5 hr. H_2O was added to this mixture and the precipitate was taken up in Et_2O. The Et_2O layer was washed with H_2O, dehydrated, and the residue (7 g.) obtained on evaporation of Et_2O was heated with 15 cc. of Ac_2O and 0.7 g. of AcONa for 1.5 hr. Ac_2O was distilled off in a reduced pressure and the residue was shaken with HCl and Et_2O. The Et_2O layer was washed with H_2O, dehydrated, and the residue obtained on evaporation of Et_2O was was distilled to collect 5 g. of a colorless liquid (XVII) of b.p$_3$ 105~108°.

rac-Deoxynupharidine (XVIIa)[*3] : Five grams of (XVII) was derived to its perchlorate ndd recrystallized 5 times from 60% EtOH, 10 times from 50% EtOH, and once from EtOH to colorless needles (1.4 g.), m.p. 205~207°. *Anal.* Calcd. for $C_{15}H_{24}O_5NCl$: C, 53.96; H, 7.25; N, 4.20. Found : C, 53.86; 7.27; N, 4.46.

The infrared spectra (in CCl_4 solution) of the base (colorless liquid, b.p$_3$ 105~108°), liberated from the purified perchlorate and of (−)-deoxynupharidine isolated from the rhizome of *Nuphar japonicum* DC. were entirely identical.[*4,4)] IR $\nu_{\max}^{CCl_4}$ cm^{-1} : 872, 1028, 1500, 1570, 3100 (furan), 2770, 2795 (*trans*-quinolizidine).

Picrate : Recrystallized from EtOH to yellow needles, m.p. 165~166°. *Anal.* Calcd. for $C_{21}H_{26}O_8N_4$: C, 54.52; H, 5.67; N, 12.12. Found : C, 54.49; H, 5.88; N, 12.03.

(XVIIb) : The recrystallization mother liquor of the perchlorate of (XVII) from 60% EtOH was basified with Na_2CO_3 and the precipitate was taken up in Et_2O. The Et_2O layer was washed with H_2O, dehydrated, and the residue obtained on evaporation of Et_2O afforded 3.5 g. of a colorless liquid, b.p$_3$ 109~110°. This product was derived to the picrate and recrystallized from EtOH to long yellow needles, m.p. 196°. *Anal.* Calcd. for $C_{15}H_{26}O_8N_4$: C, 54.52; H, 5.67; N, 12.12. Found : C, 54.50; H, 5.72; N, 12.00.

The perchlorate derived from the purified picrate was recrystallized from 60% EtOH to colorless plates, m.p. 193~194°. *Anal.* Calcd. for $C_{15}H_{24}O_5NCl$: C, 53.96; H, 7.25; N, 4.20. Found : C, 53.74; H, 7.50; N, 4.23.

The free base (XVIIb) liberated from the purified picrate was distilled to collect a fraction of b.p$_{3.5}$ 120°(bath temp.), which soon solidified, m.p. 73°. IR $\nu_{\max}^{CCl_4}$ cm^{-1} : 871, 1025, 1500, 1570, 3110 (furan).

(XVIIc) : The recrystallization mother liquor of (XVIIb) picrate was evaporated to dryness in a reduced pressure and the residue was recrystallized from EtOH to yellow sandy crystals, m.p. 181~182°b. *Anal.* Calcd. for $C_{21}H_{26}O_8N_4$: C, 54.52; H, 5.67; N, 12.12. Found : C, 54.90; H, 5.88; N, 11.79.

The perchlorate derived from the purified picrate was recrystallized from 60% EtOH to colorless needles, m.p. 223°(decomp.). *Anal.* Calcd. for $C_{15}H_{24}O_5NCl$: C, 53.96; H, 7.25; N, 4.20. Found : C, 54.42; H, 6.97; N, 4.45.

The free base (XVIIc) formed a colorless liquid, b.p$_3$ 120°(bath temp.). IR $\nu_{\max}^{CCl_4}$ cm^{-1} : 871, 1028, 1500, 1570 (furan), 2750 (sh.), 2780 (*trans*-quinolizidine).

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Summary

Condensation of octahydro-4-quinolizinone (I) and ethyl 3-furoate affords (II) which, on being heated with dilute hydrochloric acid, forms a compound (IV) of hexahydroquinolizine series. Reduction of (IV) with sodium borohydride gives (V) which is separated into two kinds of racemate showing infrared absorption band due to *trans*-quinolizidine.

By the route shown above, (XVII) was obtained from 1,7-dimethyloctahydro-4-quinolizinone (XIII) and (XVII) was separated into three kinds of bases. From the result of infrared spectral measurement, (XVIIa) and (XVIIc) were assumed to be *trans*-quinolizidine compound and (XVIIb) was assumed to be *cis*-quinolizidine compound. The infrared spctra (in carbon tetrachloride solution) of (XVIIa) and (−)-deoxynupharidine isolated from *Nuphar japonicum* DC. were found to be entirely identical and (XVIIa) was concluded to be *rac*-deoxynupharidine.

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[*4] (XVIIa) shows entirely identical absorption as *rac*-deoxynupharidine derived from one of the isomers isolated from (XVI). The admixture of the perchlorates of these two substances showed no depression of the melting point.