tion was quenched with a solution of bromobenzene in toluene, giving a deep-red solution. After addition of saturated aqueous ammonium chloride the ammonia was removed by evaporation. The residue was diluted with water, extracted with ethyl acetate, and the extracts were dried, filtered, and concentrated *in vacuo* to give an oil. This was dissolved in chloroform and filtered through Florisil (2 g). Elution with chloroform removed less polar impurities and elution with 25% ethyl acetate–chloroform yielded 40 mg of a 2:1 mixture of ketones **24** and **35**. Separation by preparative tlc (silica gel PF_{254}) developed twice, 10 cm with 20% ether–methylene chloride) afforded 10 mg (25%) of ketone **35**, whose ir was identical with that of authentic material, and 18 mg (47%) of ketone **24**, mp 156–158°, identical by its ir spectrum with an authentic sample.

Tetracyclic Formamide 39. To an ice-bath-cooled solution of the ketone **35** (30 mg, 0.1 mmol) in methylene chloride (40 ml), boron trifluoride etherate (0.35 ml) was slowly added and the resulting red solution was stirred 11 hr at room temperature. The solution was poured onto cold, saturated ammonium chloride, neutralized with solid potassium carbonate, and extracted with methylene chloride. The extracts were dried, filtered, and concentrated *in vacuo* to give a glass which was dissolved in 50% benzene–chloroform and filtered through Florisil (0.5 g). Elution with additional solvent and concentration of the filtrate yielded a glass which crystallized from ether to give 20 mg (72%) of the amide **39**. An analytical sample was recrystallized from ethyl acetate–cyclohexane: mp 264–266°; ir ($CHCl_3$) 3480, 1660, 1620, 1455, 1435, and 880 cm^{-1}; uv max (95% EtOH) 209 (ϵ 24,800), 240 (sh) (ϵ 13,100), and 308 nm (ϵ 19,200); nmr (100 MHz) ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz), 1.2–1.58 (m, 2), 1.6–2.2 (m, 4), 2.9–3.4 (m, 1.6), 3.9 (m, 0.4), 4.88 and 5.88 (2 d, 1, J = 4 Hz), 5.12 (d, 1, J = 2 Hz), 5.42 (d, 1, J = 2 Hz), 7.1–7.8 (m, 4), 8.02 and 8.40 (2 s, 1), and 8.40 (broad s, 1).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.16; H, 7.13; N, 9.83.

Racemic Uleine. A solution of lithium aluminum hydride in glyme (3.5 ml, ~2% $LiAlH_4$) was added to the amide **39** (35 mg, 0.13 mmol) in glyme (20 ml, freshly distilled from $LiAlH_4$) and the mixture was stirred at room temperature for 2.5 hr. Careful addition of methanol was followed by addition of water (2 ml) to precipitate the inorganic salts. After stirring 10 min the mixture was filtered through a pad of Celite and the precipitate was washed with chloroform. The organic layer was dried, filtered, and concentrated *in vacuo* to give a glass which was chromatographed on alumina (1 g). Elution with 10% chloroform–benzene followed by concentration of the eluent yielded 24 mg (73%) of crystalline racemic uleine (**1**) which was recrystallized from methanol: mp 62–74° (methanol solvate) and 140–148° (lit.[5] mp 61–92°); ir ($CHCl_3$) 3480, 3080, 3005, 1635, 1615, 1460, 1450, 1255, 880, and 845 cm^{-1}; uv max (95% EtOH) 209 (ϵ 24,100), 240 (sh) (ϵ 12,100), 308 (ϵ 18,200), and 315 nm (ϵ 18,000); nmr ($CDCl_3$) δ 0.88 (m, 3,) 1.1–3.0 (m, 8), 2.28 (s, 3), 4.07 (d, 1, J = 2 Hz), 4.95 (s, 1), 5.15 (s, 1), 7.0–7.8 (m, 4), and 8.25 (broad s, 1); mass spectrum (70 eV) *m/e* 266 (M).

Acknowledgments. We are indebted to the National Institutes of Health and to Merck Sharpe and Dohme, Inc., for generous financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann. We wish to thank Professor G. Whitesides for his help with the interpretation of the temperature-dependent nmr spectra.

The Polonovski Transformation of (+)-Nupharidine. A Study of the Stereochemistry and Utility in Synthesis[1,2]

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Abstract: (+)-Nupharidine has been converted by the Polonovski reaction to Δ^6-dehydrodeoxynupharidine. The latter in turn was transformed to (−)-deoxynupharidine, (−)-7-epideoxynupharidine, and (−)-nupharamine. Treatment of nupharidine-6β,7β-d_2 under Polonovski conditions produced Δ^6-dehydrodeoxynupharidine-6-d_1, thus illustrating that the 6α-hydrogen is eliminated. Since an X-ray diffraction study of nupharidine hydrobromide had demonstrated the presence of a cis-fused quinolizidine *N*-oxide, the Polonovski elimination had occurred trans in the labeled nupharidine.

The selective conversion of a quinolizidine type *Nuphar* alkaloid, such as deoxynupharidine, **1a**, or one of its derivatives, to the Δ^6-dehydrodeoxynupharidine, **2a**, was of interest for a number of reasons. Foremost was the potential of using this enamine as an intermediate in the preparation of isotopically labeled deoxynupharidine which would be employed in biogenetic and mass spectral studies. Second, the enamine **2a** offered the potential for converting the quinolizidine type to the less abundant piperidine type *Nuphar* alkaloids,[4] **3**, through cleavage of the enamine double bond.

The abundant, naturally occurring *N*-oxide nupharidine was regarded as a possible starting point to achieve the selective introduction of a double bond into ring B at the C-6 position. Should nupharidine possess a trans-fused, quinolizidine *N*-oxide system as in **4**, a point which was uncertain at the outset, there would be only a single hydrogen cis to the *N*-oxide oxygen atom.

(1) Support of this work by the U. S. Department of Interior, Federal Water Pollution Control Administration, and the McIntire-Stennis Cooperative Forestry Research Program of the U. S. Department of Agriculture is gratefully acknowledged. The support of the National Science Foundation in the purchase of the mass spectrometer used in this work is also acknowledged.

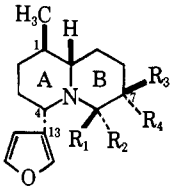
(2) A preliminary account of a portion of this work has been disclosed: E. Auer and R. T. LaLonde, Abstracts of Papers, 157th Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, ORGN 150.

(3) Author to whom inquiries should be addressed.

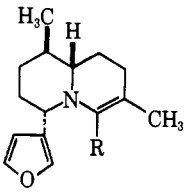
(4) In earlier correlations piperidine alkaloids have been converted to the quinolizidine type, *cf.* nupharamine[5] and nuphamine[6] to deoxynupharidine and 7-epideoxynupharidine.

(5) I. Kawasaki, S. Matsutani, and T. Kaneko, *Bull. Chem. Soc. Jap.*, 36, 1474 (1963).

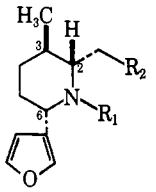
(6) Y. Arata and T. Ohashi, *Chem. Pharm. Bull.*, 13, 1247 (1965).



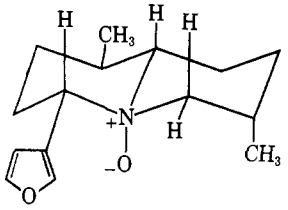
1a, $R_1, R_2, R_3 = H; R_4 = CH_3$
b, $R_1, R_2, R_4 = H; R_3 = CH_3$
c, $R_1, R_3 = D; R_2 = H; R_4 = CH_3$
d, $R_2, R_4 = D; R_1 = H; R_3 = CH_3$



2a, R = H
b, R = D



3a, $R_1 = CHO; R_2 = CH_2COCH_3$
b, $R_1 = H; R_2 = CH_2C(OH)(CH_3)_2$
c, $R_1 = H; R_3 = CH{=}C(CH_3)_2$
d, $R_1 = H; R_2 = CH{=}C(CH_3)CH_2OH$



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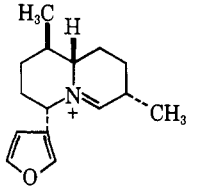

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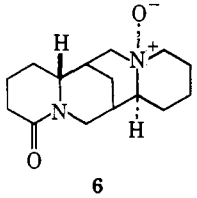
This would be the C-6α hydrogen. Therefore it was reasoned that selective formation of the immonium ion, **5**, would occur if a cis elimination of the *N*-oxide oxygen atom and the adjacent C-6α hydrogen could be effected. The conditions chosen to effect this elimination would be those of the Polonovski reaction,[7] classically a procedure employed to demethylate methylamines but more recently adopted for the preparation of enamines.[8,9] In one such case, lupanine *N*-oxide, **6**, conisdered to possess a cis-fused C–D ring system,[10] produced predominantly the Δ^{11}-immonium ion, **7**, the formation of



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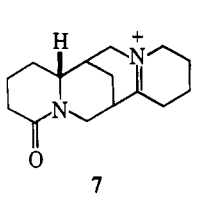


7

which was ascribed to cis elimination.[9a]

Though the stereochemistry of nupharidine ring fusion had not been established nor generally was the preference for cis Polonovski elimination really secure, the expectation for the transformation of nupharidine to the Δ^6-enamine seemed reasonable assuming the quinolizidine *N*-oxide was transfused. In fact the desired transformation was realized in good yield. However, on subsequent investigation it was learned that labeled nupharidine gave the Δ^6-enamine through trans elimination from a cis-fused *N*-oxide. These studies and the transformations of the Δ^6-enamine to deoxynupharidine, 7-epideoxynupharidine, and nupharamine are disclosed here.

Results

(+)-Nupharidine in chloroform solution was treated with a large excess of acetic anhydride initially at 0° for 2 hr and then at 25° for 120 hr. The major product was identified as the desired Δ^6-enamine, **2a**, which was obtained in 82% yield. Careful tlc of the crude product mixture indicated the trace of a second product present in amounts insufficient for identification.

The mass spectrum of the major product showed a parent ion at *m/e* 231 (relative intensity 100%). The most significant features of the nmr were the following. A single vinyl proton at τ 4.34 (ΣJ = 4.5 Hz) was shown by decoupling experiments to be coupled with the vinyl methyl at 8.50 (d, J = 1.5 Hz). A one-proton quartet (J = 8 and 4 Hz) at τ 6.50 was assigned to a hydrogen α to both nitrogen and the furan ring. A methyl doublet (J = 5.5 Hz) at τ 9.06 was assigned to the equatorial methyl at C-1. The infrared spectrum displayed a weak Bohlmann band at 3.95 μ and furan bands at 6.26, 6.65, and 11.46 μ. The presence of signals at τ 2.59 (2 H) and τ 3.56 (1 H) in the nmr confirmed the presence of the 3-furanyl group. Absorption at 243 nm (ϵ 4500) in the ultraviolet spectrum appeared as a shoulder of the end absorption. The ORD displayed a negative Cotton effect. In comparison, deoxynupharidine shows only a negative plain curve.

The infrared also showed a very strong olefinic band at 5.96 μ, a position somewhat below the normal range of enamine absorption.[11] On converting the Δ^6-enamine to its crystalline perchlorate, the olefin band did not shift but was greatly reduced in intensity. This behavior indicated the enamine had undergone nitrogen rather than carbon protonation. It was not surprising then to find that the Δ^6-enamine did not undergo hydrolysis at pH 2; neither did the Δ^6-enamine undergo hydrolysis in neutral or alkaline solution. Similarily, alkylation with methyl iodide produced the crystalline *N*-methyl iodide whose nmr revealed the presence of a three-proton singlet ammonium methyl signal at 6.4, one-vinyl hydrogen at 4.10, a broad singlet vinyl methyl at 8.13, and the C-1 methyl doublet (J = 5.5 Hz) at 8.84. The infrared displayed a weak olefinic band at 5.94 μ and furan bands at 6.23, 6.69, and 11.49 μ.

Hydrogenation of the Δ^6-enamine over palladium on charcoal gave a mixture of two products present in the ratio of 7:1. The major hydrogenation product was identified as deoxynupharidine, **1a**, by comparison spectra and the mixture melting point of the hydrochloride salt. The minor product was identified as 7-epideoxynupharidine, **1b**, on the basis of the reported[5] properties of a synthesized sample and comparison spectra of a sample subsequently isolated from a natural source.[12]

(7) See G. A. Russell and G. J. Mikol, "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1968, p 176.
(8) A. Ahond, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan, and P. Potier, *J. Amer. Chem. Soc.*, **90**, 5622 (1968).
(9) (a) P. Baranowski, M. Wiewiorowski, and L. Lompa-Krzymien, *Ann. Soc. Chim. Polonorum*, **40**, 73 (1966); (b) M. Wiewiorowski and P. Baranowski, *Bull. Acad. Polon. Sci., Sir. Sci. Chim.*, **10**, 549 (1962).
(10) (a) M. Wiewiorowski and P. Baranowski, *ibid.*, **10**, 537 (1962); (b) *ibid.*, 11, 761 (1963); (c) P. Baranowski, J. Skolik, and M. Wiewiorowski, *Tetrahedron*, **20**, 2383 (1964).
(11) J. Szmuszkovicz, *Advan. Org. Chem.*, 4, 96 (1963).
(12) C. F. Wong and R. T. LaLonde, *Phytochemistry.*, **9**, 659 (1970).

In other preparations of the Δ^6-enamine the reaction conditions were varied somewhat. Optimum conditions for effecting the transformation of nupharidine to the Δ^6-enamine have not been systematically investigated as yet. However, the best yields of the Δ^6-enamine were observed when the reaction was carried out under nitrogen for periods of 75–120 hr at 25° using a six- to eightfold excess of acetic anhydride in chloroform solution. A reaction carried out on a steam bath brought about the formation of a dark product mixture which was difficult to purify. Replacing acetic anhydride with trifluoroacetic anhydride resulted in a slower rate of conversion. Thus under conditions which otherwise were very much the same, acetic anhydride gave a 55% yield of the Δ^6-enamine in a quarter of the time that trifluoroacetic anhydride gave a 42% yield.

Osmium tetroxide–paraperiodic acid oxidation of the Δ^6-enamine in pyridine–water–dioxane solution gave a product in 95% yield whose elemental analysis and spectral properties were consistent with the structure of the formamido ketone **3a**. Interestingly the nmr of β-furanyl, formyl, C-6, and C-2 protons each appeared as pairs of signals. The four pairs are believed to arise as a result of restricted rotation of the formyl group and the consequent differences in magnetic environments of the various protons. The restricted rotation of amides is a well-known observation in nmr spectroscopy and has been encountered previously for acylated piperidines.[13]

Treatment of the formamido ketone **3a** with a large excess of methylmagnesium iodide in refluxing ether furnished (−)-nupharamine, **3b**, in 62% yield. The nupharamine obtained in this manner exhibited physical properties identical with those of an authentic sample of the alkaloid.

Contrasting with the ease of enamine formation by the Polonovski reaction, the mercuric acetate oxidation of deoxynupharidine, carried out in 5% aqueous acetic acid at 100° for 1 hr or 25° for 20 hr, afforded mixtures containing unconsumed deoxynupharidine and inseparable, more polar substances of molecular weight in excess of 400 as determined by mass spectrometry. None of the Δ^6-enamine **2a** nor any other isomeric enamine could be detected in these mixtures.

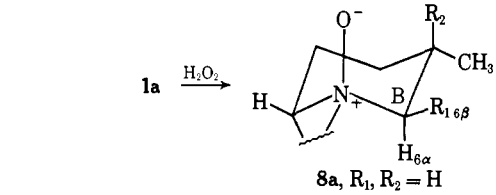
In view of the ease, high yield and selectivity of the Polonovski transformation of nupharidine, an attempt was made to learn which of the two hydrogens at C-6 were eliminated. The Δ^6-enamine was converted to deoxynupharidine-$6\beta,7\beta$-d_2, **1c**, through catalytic addition of deuterium. The stereochemistry of the deuterium atoms of the labeled deoxynupharidine was based in part on preferred cis catalytic hydrogenation from the β-side of the enamine as evidenced by the preponderance of deoxynupharidine formation. Additional evidence for the C-6 deuterium stereochemistry came from comparing the nmr of the labeled and unlabeled deoxynupharidine. The τ 7.30 quartet (J = 12.5, 2.5 Hz) assigned[14] to the equatorial C-6α hydrogen of deoxynupharidine had been reduced to a broad singlet in the spectrum of the labeled deoxynupharidine. At the same time, the τ 8.12 quartet (J = 12.5, 2.5 Hz) assigned to the axial C-6β hydrogen had disappeared.

(13) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).
(14) C. F. Wong, E. Auer, and R. T. LaLonde, *ibid.*, **35**, 517 (1970).

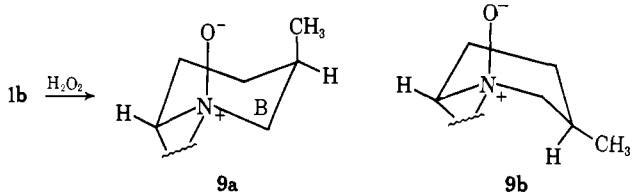
Deoxynupharidine-$6\beta,7\beta$-d_2 was converted to nupharidine-$6\beta,7\beta$-d_2 with hydrogen peroxide in ethanol. Treatment of the labeled nupharidine under the Polonovski conditions already described, gave the Δ^6-enamine, **2b**. Among the more important pieces of spectral evidence for the presence of deuterium at C-6 were the parent ion at m/e 232 (d_0 4%, d_1 96%) in the mass spectrum and the very small fraction (<10%) of a vinyl proton at τ 4.34 in the nmr. Therefore, it was the 6α-hydrogen which had been eliminated in the Polonovski elimination. This result seemed to be consistent with the expected cis elimination from the assumed trans-fused nupharidine. However, in the course of our studies, we observed that the oxidation of deoxynupharidine to nupharidine was nearly three times faster than the oxidation of 7-epideoxynupharidine to 7-epinupharidine. Thus under precisely the same reaction conditions that a nearly quantitative conversion of deoxynupharidine to nupharidine was realized, only 36% of 7-epideoxynupharidine was converted to 7-epinupharidine. However when the oxidation of 7-epideoxynupharidine was carried out for extended periods, a greater conversion to *N*-oxide resulted.

The greater rate of deoxynupharidine oxidation was difficult to understand in terms of the formation of a trans-fused quinolizidine *N*-oxide. If both deoxynupharidine and 7-epideoxynupharidine were to undergo oxidation with retention to give trans-fused quinolizidine *N*-oxides, the oxidations would have to occur from the crowded bottom side, the side shielded by α- or β-furanyl hydrogens.[15] In the case of deoxynupharidine, this mode of oxidation would be even more unfavorable because of the developing 1,3-diaxial interaction of the C-7 methyl and the *N*-oxide oxygen. Accordingly, oxidation of deoxynupharidine would be expected to proceed slower, not faster, than the oxidation of 7-epideoxynupharidine.

The best way to explain the rate result seemed to be in terms of oxidation of deoxynupharidine with inversion of nitrogen to give a cis-fused quinolizidine *N*-oxide, **8a**. Oxidation with inversion of 7-epideoxynupharidine, if



8a, $R_1, R_2 = H$
b, $R_1, R_2 = D$



9a **9b**

(15) α- or β-furanyl hydrogen shielding of the underside of the nitrogen atom is a consequence of the nearly perpendicular orientation of the furan ring with respect to the quinolizidine carbon–nitrogen framework. This orientation of the furan ring has been observed,[16] by X-ray diffraction studies, in the case of neothiobinupharidine, and models of deoxynupharidine show that this same conformation would be the preferred one. The greater shielding of the underside of Δ^6-dehydrodeoxynupharidine, 2, is manifest in the preferential catalytic hydrogenation from the top side in giving predominantly deoxynupharidine.
(16) G. I. Birnbaum, *Tetrahedron Lett.*, 4149 (1965).

actually preferred over oxidation with retention, would result in the development of a 1,3-diaxial interaction of methyl and *N*-oxygen should ring B assume a chair from (**9a**). Should ring B assume a boat form (**9b**), the *C*-methyl would be equatorial but the underside of the molecule would be severely crowded. Irregardless of whether 7-epideoxynupharidine were to undergo N oxidation with inversion or retention the steric repulsions appeared to be greater in either event than those developing in the oxidation with inversion of deoxynupharidine.

An X-ray diffraction study of nupharidine hydrobromide has been carried out in order to obtain an unequivocal solution to the question of the *N*-oxide configuration.[17] The important structural and stereochemical results of this study are: (1) the quinolizidine *N*-oxide system is built of two cis-fused six-membered rings in chair conformations; (2) viewing down the C-4, C-13 bond, the plane of the furan ring is nearly normal to the C-4, N-5 bond; (3) the absolute configuration is in agreement with results from an earlier determination by chemical methods.[14]

Discussion

The results disclosed in the preceding section and the X-ray study show that nupharidine is a *cis*-quinolizidine *N*-oxide which readily undergoes a Polonovski transformation giving Δ^6-dehydrodeoxynupharidine. Since the 6α-hydrogen atom is removed from nupharidine-6β,7β-d_2 **8b**, the transformation represents a trans elimination process. Clearly the high preference for Δ^6-enamine formation results because the only hydrogen atom trans to the *N*-oxide function is located at C-6.

Our finding of trans Polonovski elimination appears to be in conflict with results of another work pertaining to the stereochemical mode of Polonovski elimination. As noted elsewhere, the transformation of lupanine *N*-oxide, **6**, to the immonium ion, **7**, was believed to represent cis elimination from a cis-fused quinolizidine *N*-oxide system. After completion of our work with nupharidine, a search was made for the basis of the lupanine *N*-oxide stereochemical assignment. The configuration of the *N*-oxide center seems to have been based on the appearance in the infrared of a hydrogen bonded amide band in the protonated *N*-oxide.[10a] The interaction, which also involved a molecule of water of hydration, was viewed as intramolecular in nature. Later, however, hydrogen bonding was ascribed to symmetrical dimeric association.[10c] It is not clear why the reported infrared properties necessarily eliminate a polymeric hydrogen bonded structure from consideration but in either case the assignment of *N*-oxide configuration based on these infrared properties is equivocal.

A suggested mechanism[18] for the conversion of nupharidine to Δ^6-dehydrodeoxynupharidine involves first the formation of an *N*-acyloxyammonium acetate which then undergoes trans-β elimination giving the immonium ion **5** which in turn rapidly loses a proton from C-7 to give the Δ^6-enamine. The immonium salt has never been isolated nor was its presence detected when the reaction was carried out in an nmr tube. Possibly the immonium ion undergoes the loss of the C-7 proton much too rapidly to be present in concentrations detectable by nmr.

The precise timing for the loss of the *N*-acyloxy group and the C-6 proton is not known. But judging from the lower yield of the Δ^6-enamine when trifluoroacetic anhydride is used instead of acetic anhydride, it would appear that the basic strength of the anion is important here as in other cases[19] and hints further that the mechanism involves the loss of the C-6 proton in the slow step which follows *N*-acyloxyammonium ion formation.

Elimination through Polonovski-like reactions has been regarded as playing an important biogenetic role in the evolvement of different alkaloids from a common alkaloid precursor.[20] It would seem on the basis of work reported here that the direction of alkaloid evolution would be strongly biased by the stereochemical preference of Polonovski elimination. Curiously, the *Nuphar* alkaloids discovered to date, with but one exception,[21] would all appear to be derivable through oxidative elaboration of ring B of deoxynupharidine. These alkaloids include neothiobinupharidine and piperidine types. Interestingly, enamine formation is selectively directed into ring B when nupharidine undergoes Polonovski elimination.

Experimental Section

Spectra were obtained as follows: nmr in solution as indicated, 2% TMS (τ 10, 0.00 Hz), Varian A-60A and determined by Mrs. H. Jennison and Mrs. M. Green; ir in solution or KBr as indicated, Perkin-Elmer 137; ORD Durrum-Jasco spectropolarimeter-5 and determined in 95% EtOH solution of the concentration indicated; mass, Hitachi-Perkin-Elmer RMU6E using an all-glass heated inlet system, 70 eV, chamber temperature 160–165° and were determined by Mrs. H. Jennison. Melting points were determined on a Köfler micro hot stage and are uncorrected; optical rotations on a Perkin-Elmer 141 polarimeter. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(+)-Nupharidine. A 23.3-g sample of twice-recrystallized acetic acid salt[12] of nupharidine was dissolved in concentrated aqueous sodium hydroxide. The solution was extracted repeatedly with methylene chloride. The extracts were dried. Removal of solvent at the rotary evaporator gave 20.2 g of nupharidine: $[\alpha]^{25}D$ +14.8 (lit.[22] +13.0°); mp 218–224° (lit.[22] mp 212°); mp hydrochloride salt 228° (lit.[22] mp 196°).

(−)-Δ^6-Dehydrodeoxynupharidine. A solution of 1 g of nupharidine (4.0 mmol) in 20 ml of anhydrous alcohol-free chloroform was cooled to 0° under nitrogen. When 3 g of freshly distilled acetic anhydride (29.5 mmol) was added, the solution warmed slightly. The resulting solution was kept at 0° for 2 hr and 25° for 120 hr. A gentle stream of dry nitrogen was bubbled into the reaction mixture throughout. Chloroform was removed at the rotary evaporator. Methanolic KOH (10%) was added to the residue until pH 10. The mixture was taken up in ether and the resulting solution was washed three times with small portions of water. Evaporation of the water gave 120 mg of unconverted nupharidine.

The ether solution was dried (anhydrous Na_2SO_4). Evaporation of the ether at the rotary evaporator gave 800 mg of brown oil which was chromatographed on 48 g of neutral alumina (act. II). The Δ^6-enamine (700 mg, 74% conversion, 82% yield) came off as a sharp band after eluting with about 40 ml of hexane–ether (95:5). On storing at −10° for several days the liquid became solid Δ^6-enamine, **2a**: mp ~30°; $[\alpha]^{25}D$ −137.4° (40 mg, 2 ml of EtOH);

(17) This study was carried out in collaboration with Dr. R. Parthasarathy and Miss Jean M. Ohrt, The Center for Crystallographic Research, Roswell Park Division of Health Research Inc., Buffalo, N. Y. Complete details of the X-ray structure determination will appear as a separate article published elsewhere.

(18) A recent treatment of general mechanistic considerations can be found in the work cited as ref 7.

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(22) M. Kotake, I. Kawasaki, S. Matsutani, S. Kusumoto, and T. Kaneko, *Bull. Chem. Soc. Jap.*, 35, 698 (1962).

ir (CH_2Cl_2) 3.95 (sh) Bohlmann, 5.96 (s) (C_2C=CHC), 6.26 (m), 6.65 (m), 11.46 (s) (furan), 6.88 (m), 6.96 (m), 7.28μ (m) (CH_2 and CH_3); mass spectrum 231 (% relative intensity, 100) M^+, 216 (46), 176 (31), 174 (19), 95 (64); uv (MeOH) λ_{sh} 243 nm (ϵ 4500); nmr ($CDCl_3$) 9.06 (d, 5.5 Hz, 3 H, $CHCH_3$), 8.50 (d, 1.5 Hz, 3 H, CH_3-C=C) (a singlet when decoupled from τ 4.3 proton), 6.50 (q, 8 and 4 Hz, 1 H, C-4 H) 4.34 (s, ΣJ = 4.5 Hz, 1 H, C=CH) (ΣJ = 2.5 Hz, when decoupled from 8.50 CH_3), 3.56 (m, 1 H, furanyl H β to 0), 2.59 (m, 2 H, furanyl H α to 0); nmr (C_6H_6) 9.18 (d, 6.0 Hz, 3 H, $CHCH_3$), 8.43 (d, 1-2 Hz, 3 H, CH_3C=C), 6.55 (q, 8 and 4 Hz, 1 H, C-4 H), 4.13 τ (m, 1 H, C=CH); ord (C 18 mg, 100 ml of EtOH) $[\Phi]_{360}$ −200°, $[\Phi]_{300}$ +2200°, $[\Phi]_{267}$ −6900°, $[\Phi]_{260}$ −6300°, $[\Phi]_{246}$ 0°; $[\Phi]_{240}$ +5700°, $[\Phi]_{235}$ +12,700°. Deoxynupharidine: ord (C, 100 mg, 100 ml of EtOH) $[\Phi]_{400}$ −1000°, $[\Phi]_{340}$ −1700°, $[\Phi]_{300}$ −2700°, $[\Phi]_{250}$ −6700°, $[\Phi]_{232}$ −11,100°.

To 85 mg of the Δ^6-enamine in 0.5 ml of absolute ethanol was added 3 drops of 70% perchloric acid. The resulting solution was diluted with ether and cooled several hours at −10°. The crystalline solid was recrystallized twice from ethanol–ether to give 45 mg of crystalline $HClO_4$ salt: mp 140–146°; ir (KBr) 5.94 (w) (C=C).

To 120 mg of the Δ^6-enamine in 2 ml of absolute ethanol was added 0.3 ml of methyl iodide. A few drops of petroleum ether was added and the resulting mixture was stored at −10° for 24 hr. Recrystallization of the solid from ethanol–ether gave 35 mg of light brown crystals: mp 178–176°; ir (CH_2Cl_2) 5.94 (w) (C_2C=CHC), 6.24 (w), 6.69 (m), 11.49μ (s) (furan); nmr ($CDCl_3$) 8.84 (d, 5.5 Hz, 3 H, $CHCH_3$), 8.13 (br s, 3 H, CH_3C=C), 6.47 (s, 3 H, $CH_3N^+<$), 4.10 (d, 2.5 Hz, 1 H, C=CH), 3.51 (m, 1 H, β-furanyl H), 2.66 (m, 2 H, α-furanyl H).

Anal. Calcd for $C_{16}H_{24}NOI$: C, 51.49; H, 6.45; N, 3.75. Found: C, 51.28; H, 6.61; N, 3.60.

(−)-Δ^6-Dehydrodeoxynupharidine Using $(CF_3CO_2)_2O$. A solution of 1 g of nupharidine (4 mmol) in 15 ml of dry methylene chloride was cooled to 0° and treated with 890 mg of trifluoroacetic anhydride (4.2 mmol) at 0° for 2 hr and at 25° for 80 hr under nitrogen. The methylene chloride was evaporated and the residue was basified with 10% methanolic potassium hydroxide. The methanol was evaporated and the residue triturated with ether. The ether solution was washed with water then dried (Na_2SO_4). Evaporation of the combined water wash solution afforded 396 mg of unconverted nupharidine.

Evaporation of the ether gave 390 mg of crude Δ^6-enamine identified by ir and nmr.

Hydrogenation of Δ^6-Enamine. A 600-mg sample of the Δ^6-enamine in 10 ml of 95% ethanol was shaken with 0.3 g of 10% palladized charcoal under 1 atm of hydrogen at 25°. Hydrogen consumption was complete after 0.5 hr. Removal of the catalyst by filtration and the solvent by evaporation produced a light yellow oil: tlc (alumina) two spots; the more mobile (Dragendorff, orange) had an R_f value identical with deoxynupharidine ($[\alpha]^{25}D$ −105° (48.6 mg, 2 ml of EtOH) (lit.[23] −112.5°); mp HCl salt 268° (lit.[23] 262°), mmp 267–268°), a 178-mg sample of which was obtained by the hydrogenation of 200 mg of nupharidine in ethanol over 100 mg of 10% palladized charcoal; the less mobile spot (Dragendorff, yellow) proved later to have an R_f value identical with 7-epideoxynupharidine. Elution on neutral alumina (act. III) with 35 ml of hexane–ether (95:5) gave 469 mg of deoxynupharidine: $[\alpha]^{25}D$ −114.6° (ethanol); ir 3.59 (m), 3.62 (m), 3.65 (sh), 6.69 (s), 8.49 (w), 8.68 (m), 8.95 (m), 9.36 (s), and 11.49μ (s); mass spectrum 233 (relative intensity %, 40) (M^+), 136 (39), 107 (22), 98 (100), 97 (27), 94 (68); nmr ($CDCl_3$) 6 H, 9.09 (d, ~5 Hz) and 9.01 (d, 7 Hz), 8.12 (0.5H d, 3 Hz), 7.30 (1 H, q, 12 and 2 Hz), 7.12 (1 H, q, 8.0 and 6.2 Hz), 3.57 (1 H, m), τ 2.62 (2 H, m), mp HCl salt 263–266° (lit.[23] 262°).

Continued elution of the column with 45 ml of hexane–ether (95:5) produced 70 mg of 7-epideoxynupharidine: $[\alpha]^{25}D$ −95° (ethanol) (lit.[5,12] −110°, −89°); mp HCl salt 252–256° (lit.[5] 256–258°); spectral properties as reported earlier.[12]

Anal. Calcd for $C_{15}H_{24}ONCl$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.56; H, 9.01; N, 5.03.

Deoxynupharidine-6β,7β-d_2. A 440-mg of the Δ^6-enamine in 10 ml of dry tetrahydrofuran was shaken with 0.2 g of 10% predeuterated palladized charcoal under 1 atm of deuterium at 25°. Processing the mixture in the same manner as described for the hydrogenation afforded 394 mg of deoxynupharidine-6β,7β-d_2: mass spectrum 235 (M^+) (3% d_0, 14% d_1, 78% d_2, 5.0% d_3); ir (CH_2Cl_2) 4.68 (w), 4.72 (w), 4.93μ (w); nmr ($CDCl_3$) 9.12 (d, 5 Hz, 3 H, C-1 CH_3), 9.03 (s, 3 H, C-7 CH_3), 7.35 (br s, ΣJ = 5 Hz, 1 H, C-6 H); 7.02 (q, 1 H, C-4 H).

Nupharidine-6β,7β-d_2. A solution of 180 mg of deoxynupharidine-6β,7β-d_2 in 1 ml of ethanol was treated with 1 ml of 30% hydrogen peroxide for 60 hr at 25°. Water (15 ml) was added and the mixture extracted three times with chloroform. The extract was dried (Na_2SO_4). Evaporation of the solvent gave 136 mg of residue which after recrystallization from acetone–methylene chloride melted at 214–218° dec, nmr 9.17 (s, 3 H, C-7 CH_3), 9.0 (d, 3 H, C-1 CH_3).

Δ^6-Dehydrodeoxynupharidine-6-d_1. To a cooled solution of 130 mg (0.52 mmol) of nupharidine-6β,7β-d_2 in 6 ml of alcohol-free chloroform was added 430 mg (4.2 mmol) of acetic anhydride. The resulting mixture was kept at 0° for 2 hr and at 25° for 75 hr under nitrogen. The mixture was processed in the same manner as described for nupharidine. In this manner was obtained 110 mg (90%) of Δ^6-dehydrodeoxynupharidine-6-d_1: mp 51–53°; mass spectrum 232 (M^+) (4% d_0, 96% d_1); ir (CH_2Cl_2) 5.98 (m), 6.24 (w), 6.66 (m), 7.28 (m) 11.48; (s); nmr τ 8.51 (s, 3 H), 4.34 (<0.10).

Formamido Ketone 3a. Osmium tetroxide (13 mg, 0.02 mmol) and 10 drops of pyridine were added to a solution of 46 mg of Δ^6-dehydrodeoxynupharidine (0.2 mmol) in 25 ml of dioxane. The solution was stirred for 10 min and 460 mg of paraperiodic acid (2.4 mmol) in 25 ml of water was added. The mixture was stirred at 25° for 15 hr during which time the color of the solution slowly turned red. A concentrated aqueous sodium sulfite solution was added until the reaction mixture again was colorless. The resulting solution was extracted three times with chloroform and the combined extract was washed several times with 0.1 *N* hydrochloric acid and dried (Na_2SO_4). Evaporation of the chloroform gave 52 mg of light yellow liquid which was eluted from alumina (act. II) using hexane–ether (95:5). In this manner was obtained 50 mg (95%) of the formamido ketone **3a** as a pale yellow oil: $[\alpha]^{25}D$ −154.6° (*c* 40.9 mg, 2 ml of EtOH); ir (CH_2Cl_2) 3.42 (s), 5.84 (s), 6.03 (s), 6.68 (w), 6.89 (w), 7.13 (m), 7.39 (m), 8.61 (m), 9.39 (w), 9.74 (m), 10.14 (w), 11.45 (s) and 12.43μ (m); mass spectrum 263 (% relative intensity 47), 234 (92), 192 (50), 107 (100), 94 (76); nmr 8.94 (d, 7 Hz, 3 H, C-3 CH_3), 8.0 (s, 3 H, CH_3COC), 6.82 (br t, 7.5 Hz, 0.65 H, C-2 H), 5.86 (br t, 7.5 Hz, 0.35 H, C-2 H), 5.86 (m, ΣJ = 8 Hz, 0.35 H, C-6H) 4.43 (m, ΣJ = 8 Hz, 0.65 H, C-6H), 3.69 (br s, 0.35 H, β-furanyl H), 3.58 (br s, 0.65 H, β-furanyl H), 265 (m, 2 H, α-furanyl H), 1.99 (s, 0.65 H, HCON), 1.64 (s, 0.35 H, HCON).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.39; H, 7.98; N, 5.33. Found: C, 68.20; H, 8.06; H, 5.15.

Nupharamine. A solution of methylmagnesium iodide in 15 ml of anhydrous ether was prepared from 400 mg of methyl iodide and 70 mg of magnesium. To this solution was added dropwise 120 mg of the formamido ketone **3a** (0.45 mmol) in 4 ml of anhydrous ether. After heating the resulting stirred mixture to reflux for 3 hr, ice and a few milliliters of 25% aqueous NH_4Cl solution were added. The ether layer was separated and the aqueous layer was extracted several times with small portions of ether. The combined ether extract was washed with water and dried (Na_2SO_4). Evaporation of the ether left 105 mg of yellow oil which was eluted from alumina (act. III) with hexane–ether (1:1). This gave fractions 1–6 (fraction number, volume of eluent, and weight of the fraction in milligrams are as follows: 1, 10, 16; 2, 6, 0; 3, 8, 23; 4, 6, 33; 5, 9, 6; 6, 10, 2) and elution with 10 ml of ether gave fraction 7 (20 mg). Fractions 5 and 6 (8 mg) contained a mixture of nearly equal amounts of unconverted formamido ketone and nupharamine. Fraction 7 contained unconverted formamido ketone. Fractions 3 and 4 contained pure nupharamine: $[\alpha]^{25}D$ −39.5° (*c* 25 mg, 1.5 ml of EtOH) (lit.[24] −35.4°); mp $HClO_4$ salt 163–166°; ir (CH_2Cl_2) 3.19 (m), 3.44 (s), 3.52 (s), 6.30 (w), 6.69 (m), 6.90 (m), 7.00 (m), 7.28 (m), 7.39 (m), 8.64 (s), 9.82 (m), 11.48 (s), 12.60μ (s); nmr 9.10 (d, 5 Hz, 3 H, C-3 CH_3), 8.78 (s, 6 H, $(CH_3)_2(HO)C$), 7.62 (m, 1 H, C-2 H), 6.43 (m), 3.53 (m, 1 H, β-furanyl H), 2.63 (m, 2 H, α-furanyl H). These properties were identical with those of a sample of natural nupharamine prepared from the perchlorate salt.[25]

7-Epinupharidine. A 170-mg sample of 7-epoxynupharidine in the minimum quantity of ethanol sufficient for homogeneity was

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(24) Y. Arata and T. Ohashi, *ibid.*, **77**, 792 (1957).

(25) We wish to express our gratitude to Professor I. Kawasaki, Osaka University, Osaka, Japan, for a sample of nupharamine perchlorate.

treated with 1 ml of 30% H_2O_2 at 25° for 30 hr. The reaction flask was evacuated at 35° for 30 min. The residual solution was basified with aqueous NaOH to pH 10 and extracted with ether. The ether extract was dried (Na_2SO_4). Evaporation of the ether left 32 mg of unconverted 7-epideoxynupharidine. The aqueous layer was saturated with NaCl and extracted repeatedly with small amounts of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4). Evaporation of the CH_2Cl_2 left 108 mg of solid which from a column of alumina (5g of act. II) was eluted with two 20-ml portions of hexane–ether (95:5) to give fractions 1 (0.6 mg) and 2 (0.2 mg), 40 ml of benzene to give fraction 3 (1 mg), and 20 ml of benzene–$CHCl_3$ (1:1) to give fraction 4. Fraction 4 amounted to 66.2 mg of 7-epinupharidine: mp 199–202°; nmr ($CDCl_3$) 9.20 (d, 6.0 Hz, C-1 CH_3), 9.06 (d, 6.5 Hz, 1 H, C-7 CH_3), 7.23 (d of t, 12.5, 2.5, 2.5 Hz, 1 H, C-6 H), 6.85 (d of d, 7 and 2 Hz, 1 H, C-4 H), 6.09 (d of d, 12.5 and 2.5 Hz, 1 H, C-6 H), 3.25 (m, 1 H, β-furanyl H), 2.60 (m, 1 H, α-furanyl H), 2.33 (m, 1 H, α-furanyl H); ir (KBr) 6.28, 6.67, 11.5 μ.

In another preparation, 179 mg of 7-epideoxynupharidine in 2 ml of acetone was treated with 0.5 ml of 30% H_2O_2 at 25 for 1 week. After removal of the solvent by evaporation, the residue was chromatographed on 5 g of alumina (act. II) to obtain fractions 1 (50 ml of benzene, 25.7 mg), 2 (50 ml of CH_2Cl_2, 14.5 mg), and 3 (30 ml of methanol, 129 mg). Fractions 2 and 3 contained pure 7-epinupharidine (75% yield) according to tlc data (Al_2O_3, $CHCl_3$–Et_2NH (9:1), R_f 0.6).

Anal. Calcd for $C_{15}H_{23}NO_2$; C, 72.26; H, 9.29; N, 5.62. Found: C, 72.27; H, 9.40; N, 5.54.

Biogenetic-Type Synthesis of β-Resorcylic Acids. Isolation and Characterization of the Aldol Intermediate[1a]

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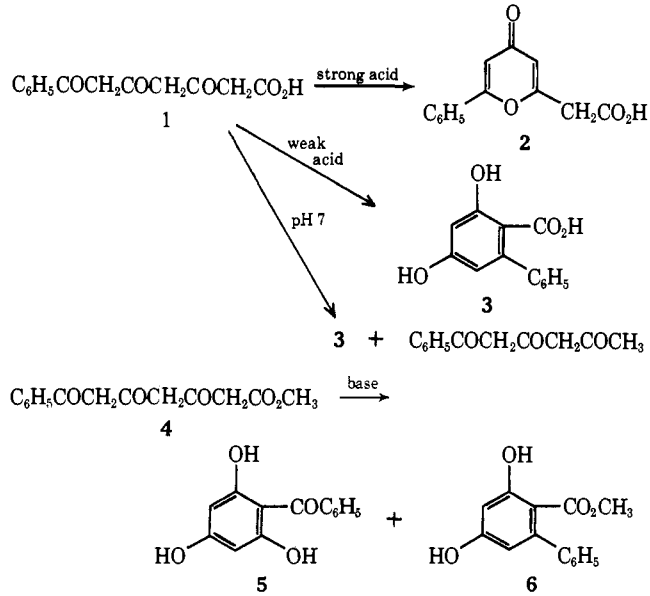
Abstract: The base-promoted cyclization of 3,5,7-trioxo-7-phenylheptanoic acid (**1**) afforded dianion **10** of hitherto unknown 6-hydroxy-2,4-dioxo-6-phenylcyclohexanecarboxylic acid; dehydration to form β-resorcylic acid **3** occurred when isolation of the free acid was attempted. The methyl ester of **1** cyclized similarly to give epimeric monoanions **12a** and **b**. Careful acidification afforded the major epimer **14a**, the relative configuration of which has been established. Epimerization of **12a** occurred in base primarily by ionization of the 1-proton rather than by reversal of the cyclization process. Facile aromatization of **14a** and **b** in acid gave β-resorcylic ester **6**. The stability of the cyclization products is discussed with reference to the role of similar compounds in the biosynthesis of naturally occurring, acetate-derived β-resorcylic acids and related compounds.

Recent reports from this laboratory have described the synthesis of a number of 3,5,7-triketo acids.[2] These compounds, although stable enough to be isolated and characterized, are highly reactive under some conditions. For example, in strongly acidic solutions **1** forms 4-pyronecarboxylic acid **2** and in weakly acidic solutions it is converted into 6-phenyl-β-resorcylic acid (**3**) by an intramolecular aldol condensation (Scheme I). At pH 7 decarboxylation of **1** becomes competitive with aldol cyclization. However, the corresponding triketo ester (**4**), which cannot decarboxylate, affords acylphloroglucinol **5** by an intramolecular Claisen condensation as well as resorcylic ester **6** when treated with basic reagents. All of these reactions occur at ambient temperature. The reactions are of interest because of their formal relationship to the postulated pathways by which acetate-derived phenolic natural products[3] are biosynthesized.[4,5]

Scheme I



In vivo studies have demonstrated the incorporation of acetate and/or malonate into phenolic metabolites in a number of instances.[5] However, more detailed study of the biosynthetic pathways has had to await the preparation and purification of cell-free extracts retaining aromatic synthetase activity. This problem has been under investigation in a number of laboratories.[6,7]

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(3) The metabolites are often called polyketides or acetogenins.

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