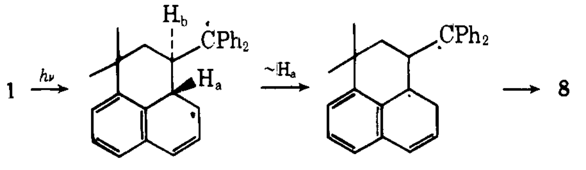


11 (2)

6.80–7.43 (m, 13, arom) ppm. Particularly noteworthy points about this spectrum are (a) H$_{a-c}$ are coupled to each other but show no observable coupling to any other hydrogens, and (b) the large coupling constant (17.3 Hz) between H$_d$ and H$_e$ indicates that they are geminal.[10]

Chemical evidence that the product isolated does have structure **8** was provided by its ozonolysis to a dialdehyde (**10**), the NMR spectrum of which showed two distinctive aldehyde signals: a singlet at δ 10.67 and a doublet of doublets (J = 2.2, 2.5 Hz) at 9.15. (We did not isolate **10** in pure form; the NMR spectrum was taken of the crude ozonolysis reaction product.) The dialdehyde that would be obtained from **9** would not show this splitting pattern for the aldehyde hydrogens. Structure **8** is the one compatible with all our evidence.

The most likely pathway for the formation of **8** from **1** involves initial bonding between C-8 of the naphthalene ring and C-2 of the double bond to form 1,4 diradical **11** followed by hydrogen migration and ring closure (eq 2).[11] We note, though, that such a mechanism ascribes exceedingly novel behavior to **11**, for the normal modes of reaction of 1,4 diradicals are either fragmentation to olefins or cyclization to cyclobutanes.[12,13] However, inspection of molecular models helps to elucidate why such an unusual reaction course is followed in the present case. Thus, the sterically most favorable mode of initial vinyl–naphthyl bonding is that which results in diradical **11** having H$_a$ and H$_b$ trans to each other. Closure of **11** to a cyclobutane would involve considerable strain; the p orbitals which must join to form the four-membered ring cannot become optimally aligned for bonding. Likewise, fragmentation of **11** to **1** is hindered by poor overlap between the newly formed bond and the p orbital on C-7 of the naphthalene ring; cleavage to starting olefin therefore does not totally dominate the chemistry of **11**.[14] On the other hand, in **11** the bond to H$_a$ on the naphthalene C-8 is nearly parallel to the adjacent p orbital on C-7, an arrangement optimal for migration of this hydrogen. Thus with the normal fragmentation and cyclization processes hindered, an unusual hydrogen migration prevails.

The migration of hydrogen to an adjacent radical center such as that postulated in eq 2 has not been observed to occur in monoradicals.[15,16] In the present case, however, we are dealing with a diradical, and the following points should be noted. (1) The conversion of **11** to **8** may be a concerted process—the homologue of the commonly observed conversion of a 1,3 diradical to an olefin.[17] Simultaneous carbon–carbon bond formation would lower the normally high barrier to migration. (2) The ^{1}S state of a diradical species such as **11** has considerable zwitterionic character.[18] It is possible that a polarization[19] of **11** in its ^{1}S state considerably enhances hydrogen migration relative to a similar migration in a monoradical.

The high yield, facile conversion of cyclopropane **8** to **2** is not unusual. Analogous reactions have been found by Griffin and others to occur with good efficiency upon irradiation of numerous 2-alkylarylcyclopropanes.[2b,20]

Acknowledgement. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. This investigation was also supported in part by National Institutes of Health Research Grant No. 1-P07-PR00798 from the Division of Research Resources.

Supplementary Material Available. The experimental details of this work (13 pages). Ordering information is given on any current masthead.

References and Notes

(1) (a) S. S. Hixson, *J. Am. Chem. Soc.*, **94**, 2507 (1972); (b) S. S. Hixson and T. P. Cutler, *ibid.*, **95**, 3032 (1973); (c) S. S. Hixson, *J. Chem. Soc., Chem. Commun.*, 515 (1975); (d) S. S. Hixson, *J. Am. Chem. Soc.*, **98**, 127 (1976).

(2) The first examples of the 1,2 shifts that we have studied were provided by Griffin; see, e.g., (a) G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson, and G. Close, *J. Am. Chem. Soc.*, **87**, 1410 (1965); (b) H. Kristinsson and G. W. Griffin, *ibid.*, **88**, 378 (1966); (c) G. W. Griffin, A. F. Marcantonio, H. Kristinsson, R. C. Petterson, and C. S. Irving, *tetrahedron Lett.*, 2951 (1965).

(3) (a) S. S. Hixson, *J. Am. Chem. Soc.*, **97**, 1981 (1975); (b) S. S. Hixson, J. C. Tausta, and J. Borovsky, *ibid.*, **97**, 3230 (1975).

(4) A Hanovia 450-W medium-pressure mercury arc, equipped with a Corex filter, was used.

(5) J. J. Eisch, *J. Org. Chem.*, **28**, 707 (1963).

(6) Ketones **6** and **7** (Scheme I) were readily differentiated on the basis of their UV and IR spectra; see D. G. Hawthorne and Q. N. Porter, *Aust. J. Chem.*, **19**, 1909 (1966), and N. H. Cromwell and G. V. Hudson, *J. Am. Chem. Soc.*, **75**, 872 (1953).

(7) See, e.g., (a) J. J. McCullough and C. W. Huang, *Can. J. Chem.*, **47**, 757 (1969); (b) F. Quina, Ph.D. Thesis, California Institute of Technology, 1973.

(8) E.G., (a) J. J. McCullough, R. C. Miller, D. Fung, and W.-S. Wu, *J. Am. Chem. Soc.*, **97**, 5942 (1975); (b) R. M. Bomman, T. R. Chamberlain, C. W. Huang, and J. J. McCullough, *ibid.*, **96**, 692 (1974); (c) T. R. Chamberlain and J. J. McCullough, *Can. J. Chem.*, **51**, 2578 (1973); (d) T. Teitei, D. Wells, and W. H. F. Sasse, *Aust. J. Chem.*, **26**, 2129 (1973); (e) C. Pac, K. Mizuno, T. Sugioka, and H. Sakurai, *Chem. Lett.*, 187 (1973); (f) C. Pac, T. Sugioka, K. Mizuno, and H. Sakurai, *Bull. Chem. Soc., Jpn.*, **46**, 288 (1973).

(9) We have not assigned signals to the individual hydrogens H$_a$, H$_b$, and H$_c$ or to H$_d$ and H$_e$.

(10) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", Wiley, New York, N.Y., 1967, pp 131 ff; L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, New York, N.Y., 1969.

(11) The reaction could well involve prior formation of an intramolecular exciplex; however, we have no evidence for such exciplex formation. The fluorescence spectrum (room temperature, cyclohexane) of **1** is identical with that of 2-methyl-2-(1-naphthyl)-propan-1-ol (**13**), though the emission quantum yield of **1** is only 30% of that of **13** (nondegassed samples).

(12) See, e.g., (a) P. J. Wagner, *Acc. Chem. Res.*, **4**, 168 (1971); (b) P. J. Wagner, P. A. Kelso, A. E. Kemppainen, J. M. McGrath, H. N. Schott, and R. G. Zepp, *J. Am. Chem. Soc.*, **94**, 7506 (1972).

(13) Disproportionation via 1,5-hydrogen transfer is a major process of 1-hydroxy 1,4 diradicals.[12b]

(14) Diradical **11** may well undergo reversion to **1**; such a process would not be detected. However, the transformation of **1** to **8** is qualitatively an efficient one. This efficiency is indicative of some difficulty in the cleavage process.

(15) One may regard the process shown in eq 2 as a [1,6] as well as a [1,2] shift of hydrogen to a radical center.

(16) J. W. Wilt, in "Free Radicals", Vol. 1, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 378.

(17) R. G. Bergman, in ref 16, p 191.

(18) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972).

(19) See, e.g., V. Bonacic-Koutecky, P. Bruckmann, P. Hiberty, J. Koutecky, C. Leforestier, and L. Salem, *Angew. Chem., Int. Ed. Engl.*, **14**, 575 (1975).

(20) (a) H. Kristinsson and G. W. Griffin, *Tetrahedron Lett.*, 3259 (1966); (b) P. H. Mazzochi and R. L. Lustig, *J. Am. Chem. Soc.*, **97**, 3707 (1975), and references therein.

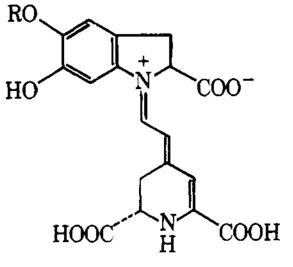
Stephen S. Hixson,* Joseph C. Tausta
Department of Chemistry, University of Massachusetts
Amherst, Massachusetts 01002

Received April 7, 1976

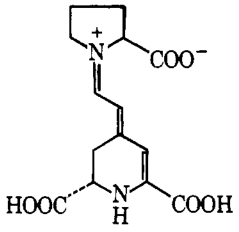
A Synthesis of Betalamic Acid

Summary: N-Benzylnorteloidinone (**6**) available by Robinson–Schöpf synthesis was converted to the ortho ester **7** with methyl orthoformate; catalytic debenzylation followed by addition of allylmagnesium bromide gave **9** which was transformed to the O-benzoylhydroxylamine **10** with benzoyl peroxide; acetylation and deprotection gave diol **12**, which on two consecutive oxidations furnished the aldehyde **14**; betalamic acid dimethyl ester was obtained from **14** by oxidation with lead tetracetate in methanol; and the latter was converted to betanidin trimethyl ester following a known procedure.

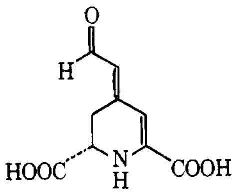
Sir: Betalains are water-soluble red-violet and yellow pigments, occurring naturally in plants belonging to the order *Centrospermae.*[1] Extensive work on their structures culminated in 1965 when Dreiding and coworkers[2] proposed expression 1 for betanin, the red pigment of the beet (*Beta vulgaris*). Shortly thereafter indicaxanthin was isolated from the cactus *Opuntia ficus indica Mill.* and shown to have structure 3.[3] The long suspected relationship between the red betacyanins and the yellow betaxanthins was confirmed by chemical interconversion of betanidin (2) and indicaxanthin (3).[4] Betalamic acid (4), the precursor of the 1,7-diazaheptamethinium unit in these coloring matters was subsequently detected as such in nature[5] while muscaflavin (5) and muscaaurin were isolated from the fungus *Amanita muscaria.*[6] The former is an isomer of betalamic acid (4) and the latter a new betaxanthin containing ibotenic acid.[6]



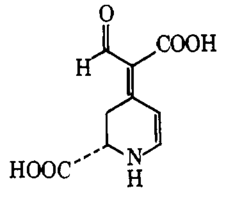
1, R = β-D-glucose
2, R = H



3



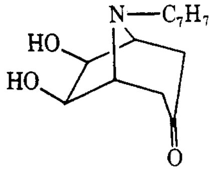
4



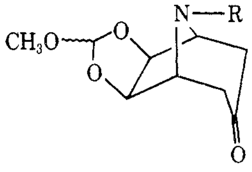
5

Betalamic acid (4) and betanidin (2) were found to be sensitive to oxidation and easily afford pyridines. Consequently it was decided to synthesize betalamic acid (4) on a structural framework that did not allow such unwanted aromatizations until the final product had been reached.[7]

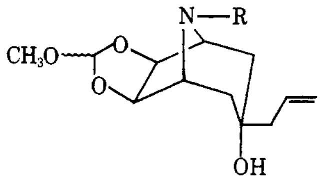
N-Benzylnorteloidinone (6), mp 84–85 °C,[8] obtained in 40–50% yield by Robinson–Schöpf synthesis[9] was converted to a 10:1 mixture (major epimer mp 101 °C) of ortho esters 7 by heating the diol with excess methyl orthoformate in methylene chloride–trifluoroacetic acid for 2 h at reflux (98% yield). The secondary amine 8, mp 106–108 °C, available by hydrogenolysis of 7 in methanol–trifluoroacetic acid over a palladium-on-carbon catalyst (97%) was combined with allylmagnesium bromide in ether–tetrahydrofuran at 0 °C to yield 72% carbinol 9, mp 137 °C.[10] Condensation with dibenzoyl peroxide[11] in DMF containing suspended potassium carbonate (10–30 h, 25 °C) afforded the *O*-benzoylhydroxylamine 10, mp 109 °C (80–100%). The carbinol 10 was acetylated with acetic anhydride in the presence of 4-dimethylaminopyridine[12] (8 days' reflux in ether) and the product was submitted to aqueous oxalic acid (30 min, 25 °C). Monoformate 11, mp 159–160 °C, obtained in 93% yield was saponified to the diol 12, mp 171–175 °C[13] (86%), by exposure to aqueous sodium bicarbonate (25 °C, 7 days). Oxidation to the orange diketone 13 [mp 146 °C; visible max ($CHCl_3$) 496 nm (ε 45); IR ($CHCl_3$) 1790, 1777, 1745 cm^{-1}] was accomplished in 76% yield with *N*-chlorosuccinimide–dimethyl sulfide[14] at −30 °C in toluene followed by treatment with triethylamine. Ozonolysis of 13 in ethyl acetate–methanol at −78 °C and reduction with dimethyl sulfide[15] gave the orange aldehyde 14 [mp 134 °C dec; visible max ($CHCl_3$) 497 nm (ε 25); IR 1785, 1775, 1750 cm^{-1} (80%)]. In a further oxidation this nonenolizable diketone 14 was cleaved with lead tetraacetate[16] in benzene–methanol 1:1 (0 °C, 45 min) and the product purified by column chromatography over silica gel. The resulting racemic betalamic acid dimethyl ester was characterized as the stable semicarbazone[20] (34%) [mp 183–188 °C (lit.[17] mp 204–205 °C for optically active material prepared from natural betalamic acid); UV max (95% C_2H_5OH) 375, 265 nm (ε 33 700, 10 500)] whose NMR spectrum in $(CD_3)_2SO$ was identical with that published in ref 17. Condensation of betalamic acid dimethyl ester semicarbazone with L-cyclodopa methyl ester in methanolic hydrochloric acid is known to afford betanidin (2) trimethyl ester hydrochloride.[7] We have verified this observation by condensing the synthetic semicarbazone in water at pH 4.5 with racemic *O*,*O*-diacetylcyclodopa methyl ester hydrochloride.[18] The resulting violet-red solution exhibited visible max 550 nm typical for betanidin.



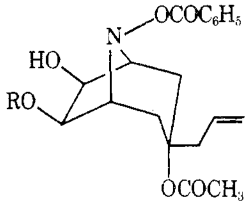
6



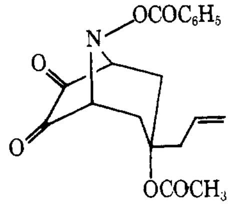
7, R = C_7H_7
8, R = H



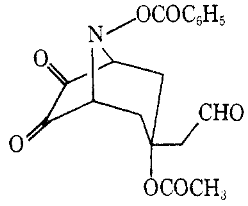
9, R = H
10, R = $OCOC_6H_5$



11, R = HCO
12, R = H



13

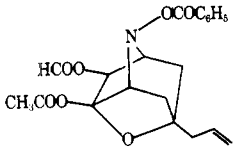


14

Acknowledgment. We thank the National Institutes of Health (GM 09686) for financial support.

References and Notes

(1) Reviews: T. J. Mabry in "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand Reinhold, New York, N.Y., 1970, Chapter 13; M. Piatelli in "Chemistry and Biochemistry of Plant Pigments", T. W. Goodwin, Ed., Academic Press, London, 1976, 2nd ed, Vol. I, Chapter 11.
(2) M. E. Wilcox, H. Wyler, T. J. Mabry, and A. S. Dreiding, *Helv. Chim. Acta*, **48**, 252 (1965).
(3) M. Piatelli, L. Minale, and G. Prota, *Tetrahedron*, **20**, 2325 (1964).
(4) H. Wyler, M. E. Wilcox, and A. S. Dreiding, *Helv. Chim. Acta*, **48**, 361 (1965); M. Piatelli, L. Minale, and R. H. Nicolaus, *Phytochemistry*, **4**, 817 (1965).
(5) L. Kimler, R. A. Larson, L. Messenger, J. B. Moore, and T. J. Mabry, *Chem. Commun.*, 1329 (1971).
(6) H. Döpp and H. Musso, *Chem. Ber.*, **106**, 3473 (1973).
(7) In the first synthesis of betalamic acid, 4-hydroxy-2,6-piperidinedicarboxylic acid was chosen as starting material. The second carbon–carbon double bond was introduced in the last step by a Pfitzner–Moffatt oxidation: K. Hermann and A. S. Dreiding, *Helv. Chim. Acta*, **58**, 1805 (1975).
(8) All new compounds gave NMR, IR, and mass spectra in agreement with their structures as well as satisfactory combustion analyses.
(9) Procedure of J. C. Sheehan and B. M. Bloom, *J. Am. Chem. Soc.*, **74**, 3825 (1952).
(10) The configuration of the carbinol was verified by preparing the hemiketal acetate i.



i

(11) Procedure of R. Huisgen and F. Bayerlein, *Justus Liebigs Ann. Chem.*, **630**, 138 (1960).

(12) W. Steglich and G. Höfle, *Angew. Chem. Int. Ed. Engl.*, **8**, 981 (1969).

(13) NMR spectra of compounds **12** and **10** revealed the presence of two N invertomers.

(14) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).

(15) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

(16) L. Canonica, B. Danielli, P. Manitto, and G. Russo, *Gazz. Chim. Ital.*, 1026 (1970).

(17) M. E. Wilcox, H. Wyler, and A. S. Dreiding, *Helv. Chim. Acta*, **48**, 1922 (1965).

(18) G. Büchi and T. Kamikawa, *J. Org. Chem.*, in press; H. Wyler and J. Chiovini, *Helv. Chim. Acta*, **51**, 1476 (1968); U. Wölcke, A. Kaiser, W. Koch, and M. Scheer, *Helv. Chim. Acta*, **53**, 1704 (1970).

(19) NIH Predoctoral Trainee, 1975–present (Grant 1 T32 CA 09112).

(20) **Note Added in Proof.** The identity of betalamic acid dimethyl ester semicarbazone has been confirmed by comparison with a sample kindly provided by Professor A. S. Dreiding.

George Büchi,* Hans Fliri, Rafael Shapiro[19]
Department of Chemistry,
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received April 7, 1977