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LABORATORY REALIZATION OF THE SCHÖPF-OECHLER SCHEME OF VASICINE SYNTHESIS[1,2]

Nelson J. Leonard and Michael J. Martell, Jr.

The Noyes Chemical Laboratory, University of Illinois,

Urbana, Illinois

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ALTHOUGH syntheses of the alkaloid vasicine (peganine) (IV) have been reported,[3,4,5] the original facile scheme (I + II ⟶ III ⟶ IV) proposed by Schöpf and Oechler,[6] based on implied biogenesis, has remained untested due to the unavailability of the requisite precursor, γ-amino-α-hydroxybutyraldehyde (II). We now wish to report the synthesis of the long-sought II (as its diethyl acetal), which we required also in model syntheses of hydroxylated pyrrolizidines,[7] and its ready conversion to dl-vasicine (IV) under mild conditions.

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[2] Presented in part at the International Symposium on the Chemistry of Natural Products, International Union of Pure and Applied Chemistry, Australia, August, 1960.

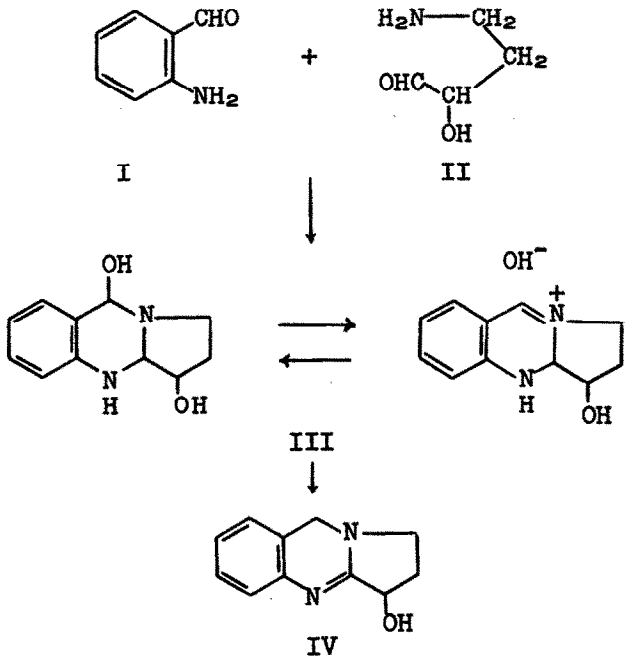
[3] E. Späth, F. Kuffner and N. Platzer, Ber. 68, 699 (1935).

[4] E. Späth and N. Platzer, ibid. 69, 255 (1936).

[5] P. L. Southwick and J. Casanova, Jr., J. Am. Chem. Soc. 80, 1168 (1958).

[6] C. Schöpf and E. Oechler, Ann. 523, 1 (1936).

[7] N. J. Leonard and S. W. Blum, J. Am. Chem. Soc. 82, 503 (1960).



β-Cyanolactaldehyde diethyl acetal, b.p. 87-88° /0.5 mm., n_D^{25} 1.4344 (Found: C, 55.39; H, 8.85; N, 8.02. $C_8H_{15}NO_3$ requires: C, 55.47; H, 8.73; N, 8.09%), was formed from acrolein diethyl acetal chlorohydrin,[8,9] or more conveniently from glycidaldehyde diethyl acetal[10] (70%) with potassium cyanide in aqueous ethanol. That epoxide ring opening had occurred in the desired manner[11]

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[8] A. Wohl, Ber. 31, 1796 (1898).

[9] D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. I. Fairburn and S. T. Rolfson, J. Am. Chem. Soc. 75, 5893 (1953).

[10] We are grateful to the Shell Development Company, Emeryville, California, for a generous sample of glycidaldehyde and directions for its conversion to the diethyl acetal.

[11] R. E. Parker and N. S. Isaacs, Chem. Revs. 59, 737 (1959).

was established by forming the tosylate of the cyanohydroxy-acetal with p-toluenesulfonyl chloride in pyridine and then reducing the crude tosylate with lithium aluminum hydride in tetrahydrofuran. Distillation of the residue afforded pure γ-aminobutyraldehyde diethyl acetal,[12] b.p. 84-85° /ca. 12 mm., n_D^{25} 1.4260 (34% over-all) (Found: C, 59.33; H, 11.87; N, 8.51. $C_8H_{19}NO_2$ requires: C, 59.59; H, 11.88; N, 8.69%), which was converted (85%) to γ-2,4-dinitrophenylaminobutyraldehyde diethyl acetal, m.p. 53.5-54.5° (Found: C, 51.65; H, 6.59; N, 12.66. $C_{14}H_{21}N_3O_8$ requires: C, 51.37; H, 6.47; N, 12.84%), identical with the derivative obtained by reaction of 2,4-dinitrofluorobenzene (DNFB) with authentic γ-aminobutyraldehyde in water at 40°. Reduction of the β-cyanolactaldehyde diethyl acetal in ether with lithium aluminum hydride proceeded smoothly to give the diethyl acetal of γ-amino-α-hydroxybutyraldehyde (II) (63%), b.p. 77-78° /0.4 mm., n_D^{25} 1.4479 (Found: C, 54.22; H, 10.68; N, 7.74. $C_8H_{19}NO_3$ requires: C, 54.21; H, 10.81; N, 7.90%); N-2,4-dinitrophenyl derivative, m.p. 76-77° (Found: C, 48.95; H, 6.18; N, 11.94. $C_{14}H_{21}N_3O_7$ requires: C, 48.97; H, 6.17; N, 12.24%).

With γ-amino-α-hydroxybutyraldehyde diethyl acetal in hand, the synthesis of vasicine was readily accomplished, parallel to the path leading to desoxyvasicine.[6,13,14] Liberation of II from the diethyl acetal in dilute aqueous solution at pH

[12] R. H. F. Manske, Can. J. Research 5, 592 (1931).

[13] L. Macholán, Collection Czech. Chem. Communs. 24, 550 (1959).

[14] L. Skursky, Z. Naturforsch. 14B, 474 (1959).

2.5 at 85° during 35 minutes followed by reaction with o-aminobenzaldehyde at pH 5.5 (aqueous phosphate buffer) for 3 days at room temperature gave an orange solution, which was then stirred vigorously with palladium-on-barium-sulfate catalyst under a stream of hydrogen at 60° for 1.5 hours. Basification and continuous ether extraction yielded (39% overall) dl-vasicine, m.p. 211-211.5° (slight dec., evac. cap.) after recrystallization and sublimation at 160° /0.05 mm. (Found: C, 70.33; H, 6.32; N, 14.80. $C_{11}H_{12}N_2O$ requires: C, 70.18; H, 6.43; N, 14.88%). This product was in every way identical with a sample of racemized[15] l-vasicine.[16] Since dl-vasicine has been resolved,[15] the synthesis will also provide the active forms. It may also be pointed out that the simple combination of γ-amino-α-hydroxybutyraldehyde with substituted o-aminobenzaldehydes could lead to a variety of substituted vasicines.

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[15] E. Späth, F. Kuffner and N. Platzer, Ber. 68, 1384 (1935).

[16] We are grateful to Prof. Roger Adams for a sample of l-vasicine.