(7) N. D. Zelinsky and N. V. Elagina, *C. R. Acad. Sci. URSS*, **49**, 568 (1945); see also D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **76**, 2753 (1954).
(8) Satisfactory infrared (ir), proton magnetic resonance (pmr), and high resolution mass spectral data were obtained on chromatographically homogeneous samples of each new compound reported herein.
(9) In each cycle after the addition of 1 equiv of *n*-butyllithium and heating at reflux for 5 min, exactly 1 equiv of methanol was added. In this way a good yield of **5** could be obtained directly despite the occurrence of proton transfer from **4** to the lithium reagent in competition with carbonyl addition; see E. J. Corey and R. D. Balanson, *J. Amer. Chem. Soc.*, **96**, 6512 (1974).
(10) Because of the acid sensitivity of the product, 4 equiv of pyrrolidine was added prior to work-up. The olefin **6** was purified by chromatography on silica gel impregnated with silver nitrate which removed minor amounts of isomeric hydrocarbons.
(11) For a review of such functionalization processes, see K. Heusler and J. Kalvoda in "Organic Reactions in Steroid Chemistry," Vol. II, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, New York, N. Y., 1972, Chapter 12.
(12) Hydrolysis of the oxime **8** afforded the corresponding ketone which showed ir(max) at 1735 cm^{-1} (in CCl_4) indicating a cyclopentanone structure. The oxime **8** was readily purified by chromatography on alumina.
(13) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972).
(14) Generously supplied by Dr. B. Witkop.
(15) Kindly carried out by Professor E. X. Albuquerque.
(16) The R_f values found for **3** and the epimer at the amyl-bearing carbon on silica gel plates using 20% THF in hexane saturated with ammonia were 0.50 and 0.45, respectively.
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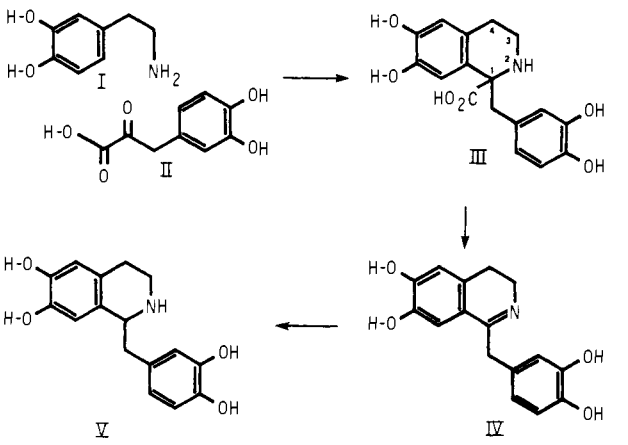
E. J. Corey,* John F. Arnett, Gary N. Widiger
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received September 20, 1974

Studies on the Early Stages of *Papaver* Alkaloid Biogenesis[1]

Sir:

The Pictet-Spengler condensation of a β-arylethylamine with a carbonyl derivative has long been cited as the probable mechanism for the biogenesis of tetrahydroisoquinoline and β-carboline skeletons of diverse alkaloids.[2] In the synthesis of indole alkaloids of *Vinca rosea*,[3] the participating carbonyl group has been shown by tracer studies to be the aldehyde of secologanin, whereas for certain methyl tetrahydroisoquinolines the ketone of pyruvic acid has been implicated.[4] For *Papaver* alkaloids the carbonyl donor has not been identified. Labeled dopamine (*I*) has been incorporated solely into the upper half of the benzyltetrahydroisoquinoline structure whereas tyrosine labels both C_6–C_2 moieties.[2]

Scheme I



To examine its possible role in the latter pathway, 3,4-dihydroxyphenylpyruvate (II)[5] has been prepared and subjected to Pictet-Spengler condensation[6] with dopamine (I) (Scheme *I*). The product, norlaudanosolinecarboxylic acid (III) was purified as its hydrochloride: mp 287–295° dec; uv λ_{max} (0.1 *N* HCl) 284 nm (log ϵ 3.79); ir λ_{max} (KBr) 1730 cm^{-1}; nmr (CD_3OD) δ 6.7–7.6 (m, aromatic H's), 3–4.1 (m αH, H-1, H-3, H-4); mass spec *m/e* 331 (M^+ 0.7%), 284 (23%), 208 (18%), 164 (100%), 124 (77%), 123 (33%). Another potential intermediate, 1,2-dehydronorlaudanosoline (IV), was synthesized by a modification of the method for the synthesis of norlaudanosoline (V).[7] It was characterized as its HCl salt: 287–290° dec; uv λ_{max} (0.1 *N* HCl) 244, 302, 352 nm (log ϵ 4.14, 3.92, 3.88, respectively); ir λ_{max} (KBr) 3550 (sh), 3250 (br), 1650 cm^{-1}; nmr (CD_3OD) δ 7.4 (s, H-7), 6.7 (m aromatic H's), 4.12 (s, αH), 3.82 (t, H-3) 3.0 (t, H-4); mass spec m/e 285 (M^+ 64%), 284 (100%), 268 (22%), 267 (11%), 162 (20%), 124 (20%), 123 (20%). Norlaudanosoline (V) obtained by published procedures[7,8] gave spectral data consistent with reported values and its hydrochloride melted without depression, mp 278–280°, when measured with an admixture of an authentic sample kindly provided by Dr. A. S. Teitel of Hoffman La Roche.

With *Papaver* alkaloids III–V in hand *in vivo* tracer experiments were undertaken using 15-day old *Papaver orientale* seedlings as well as with latex expressed from capsules of this plant harvested immediately after petal fall. After incubation with 1 μCi of ^{14}C-labeled precursor (4 hr for latex, 8–24 hr for seedlings), the plant material was homogenized with 1 *N* HCl containing 20 mg of carrier alka-

Table I

Expt	Precursor	System	Alkaloid isolated	% incorp
1	[1-^{14}C-2-^{3}H]I	Seedling	III	0.07
	$^{3}H/^{14}C$ = 2.0		$^{3}H/^{14}C$ = 2.0	
2	[1-^{14}C-2-^{3}H]I	Latex	III	4.1
	$^{3}H/^{14}C$ = 3.56		$^{3}H/^{14}C$ = 3.42	
			V	5.0
			$^{3}H/^{14}C$ = 3.46	
3	[Carboxy-^{14}C]dopa	Seedling	III	0.73[a]
4	[Carboxy-^{14}C]dopa		III	0.45
			V	<0.001
5	[Carboxy-^{14}C]dopa	Latex	III	6.0
6	[2-^{14}C]Dopa	Seedling	III	0.08
			IV	0.02
7	[1,2-^{14}C]Dopa	Seedling	III	0.86[a]
8			III	0.57[a]
9	[3-^{14}C-4-^{3}H]III	Latex	V	2.2
	$^{3}H/^{14}C$ = 4.1		$^{3}H/^{14}C$ = 4.25	

[a] Decarboxylation of the isolated amino acid (III) afforded CO_2 with at least 80% of the total activity in experiment 3 and 9 and 13% of the total activity of III in experiments 7 and 8, respectively.

loid(s) and subjected to cation exchange chromatography (Carboxymethyl cellulose eluted with H_2O, 0.5 and 1% acetic acid). the labeled alkaloids were then recrystallized to constant specific activity.[9] As seen in experiments 1 and 2 (Table I) doubly labeled dopamine (I) was incorporated into norlaudanosoline (V) and norlaudanosolinecarboxylic acid (III) with no change in $^3H/^{14}C$ ratios. [Carboxy-^{14}C]D,L-dopa was efficiently utilized by *P. orientale* for the synthesis of amino acid III, but expectedly no label was found in norlaudanosoline (V) (experiments 3-5). [2-^{14}C]D,L-Dopa was incorporated into both 1,2-dehydronorlaudanosoline (IV) and amino acid (III). Experiments 1-6 establish direct conversion of dopamine and dopa into the tetrahydroisoquinoline alkaloids, *i.e.*, with minimal reutilization of their degradation products by CO_2 fixation.

These results suggest that dopa may be metabolized by *P. orientale* in at least two ways, decarboxylation and transamination. In experiments 7 and 8, [1,2-^{14}C]D,L-dopa was fed to *Papaver* seedlings and the norlaudanosolinecarboxylic acid (III) was isolated, purified, and subjected to decarboxylation. The CO_2 trapped possessed an average of 11% of the total specific activity in III. Since equal amounts of label were introduced into the 1 and 2 carbons of precursor dopa, the ratio of 78/11 represents the extent of decarboxylation over transamination.[10] This conclusion is valid if metabolism of dopa occurs solely within a putative vacuolar site of alkaloid synthesis as has been proposed for at least the latex system of *Papaver somniferum* by Fairbairn[12] and Roberts.[13,14]

Finally to establish the intermediacy of norlaudanosolinecarboxylic acid (III), we have synthesized a doubly labeled form and incubated it with latex of poppy capsules. As seen in Table I (experiment 9) III is readily converted to norlaudanosoline (V) with no change in the $^3H/^{14}C$ ratio. These results suggest that norlaudanosolinecarboxylic acid (III), as the first tetrahydroisoquinoline alkaloid of the series, is converted to norlaudanosoline which in turn has been shown to be a precursor of thebaine and isothebaine in this plant and related alkaloids in the Papaveraceae and other plant families.[2]

Biogenetic-type chemical synthesis of amino acid (III) from dopamine (I) and 3,4-dihydroxyphenylpyruvic acid (II) were affected under physiological conditions[6] in yields up to 80%. Chemical decarboxylation of III to afford at least 20% of 1,2-dehydronorlaudanosoline (IV) under physiological conditions[16] was also observed. In fact facile chemical Pictet-Spengler condensation has thwarted attempts to identify an enzymatic process using cell-free extracts from seedlings.

The above experiments support the putative intermediacy of imine (IV) in this pathway. Since dopa incorporation into IV was observed to occur at a relatively low rate, in experiment 6 the possibility of chemical decarboxylation of amino acid to afford IV during the isolation procedure cannot be excluded. However, a mechanism for decarboxylation of amino acid (III) to afford norlaudanosoline (V) directly has to our knowledge no precedent in nature.

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References and Notes

(1) Presented at the 9th International Symposium on the Chemistry of Natural Products, IUPAC, Ottawa, Canada, June 24–28, 1974.
(2) For an excellent review of alkaloid biosynthesis in general see I. D. Spenser in "Comprehensive Biochemistry," Vol. 20, M. Florkin and E. H. Stotz, Ed., Elsevier, Amsterdam, 1968.
(3) A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc. C*, 1187, 1193 (1969).
(4) G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayez, Y. S. Vaishnar, and H. M. Fales, *J. Amer. Chem. Soc.*, **92**, 6943 (1970); I. J. McFarlane and M. J. Slaytor, *Phytochemistry*, **11**, 229, 235 (1972).
(5) G. Billek and E. F. Herrmann, *Monatsh. Chem.*, **90**, 89 (1959); F. Weygand, W. Steglich, and H. Tanner, *Justus Liebigs Ann. Chem.*, **650**, 128 (1962).
(6) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6** (1951).
(7) S. Teitel, J. O'Brien, and A. Brossi, *J. Med. Chem.*, **15**, 845 (1972).
(8) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).
(9) All final specific radioactivities were higher than 300 cpm/mg, and recrystallization was continued until three successive values varied by less than 5%.
(10) This is identical with the ratio of decarboxylation to transamination of dopa observed in rat liver *in vitro*.[11]
(11) G. H. Wada and J. H. Fellman, *Biochemistry*, **12**, 5212 (1973).
(12) J. W. Fairbairn, F. Hakim, and Y. E. Kheir, *Phytochemistry*, **13**, 1133 (1974).
(13) M. F. Roberts, *Phytochemistry*, **13**, 119 (1974).
(14) Although we used seedlings instead of latex in this experiment, the compartmentalization of alkaloid synthesis may occur in both. We have recently gained evidence[15] that an enzyme involved in the biosynthesis of indole alkaloids is located in vacuoles of 5-day old seedlings of *Vinca rosea*.
(15) K. M. Madyastha, J. Dwyer, T. Meehan, and C. J. Coscia, unpublished observations.
(16) M. L. Wilson and C. J. Coscia, manuscript in preparation.

M. L. Wilson, C. J. Coscia*
Department of Biochemistry
St. Louis University School of Medicine
St. Louis, Missouri 63104
Received September 24, 1974

Chemistry of Electrogenerated Diarylnitrenium Ions. Absorption Spectra of Stable Protonated Nitrenium Ions

Sir:

Anodic oxidation of di-*p*-anisylamine in nitromethane or acetonitrile solutions has been used as a route to the cation radical.[1] We have studied the hydrolysis of the dication by residual water in the CH_3CN medium and we have observed this species in organic solutions of Lewis acids.[2] Recently, a note has been published about the isolation of a salt of the di-*p*-anisylamine dication generated by $SbCl_5$ oxidation of a CH_2Cl_2 solution of this amine.[3] We wish to report the strong effect of the number of methoxyl groups upon the stability of the dioxidized species formed from diphenylamines **1**. The hexasubstituted compound **1a** allows the generation of both the dication and its stable deprotonated form, the diarylnitrenium ion, in CH_3CN.

This study was performed with 10^{-3} *M* solutions of amines **1** in anhydrous CH_3CN and 10^{-1} *M* Et_4NClO_4 (water level near 3.10^{-3} *M*). At a platinum disk electrode, compounds **1a** and **1b** give a cyclic voltammogram with two reversible one-electron redox couples for a voltage sweep rate equal to 33 mV sec^{-1}. The mean of the oxidation and reduction peak potentials matches the half-wave potentials, $E_{1/2}$, recorded at a rotating disk electrode (Table I). The first one-electron transfer produces the cation radical **2** and further oxidation gives the dication **3**. The lifetime of this last species from **1a** and **1b** is larger than 1 sec in contrast with the low stability of the dication **3c**. Exhaustive oxidation at the level of the first wave requires 1.0 faraday/mol and gives the stable cation radicals **2** characterized by their uv-visible absorption spectra (Table I). Macroscale electrolysis for a fluoroborate solution allows the isolation[4] of the salts of **2a** and **2b**. During the one-electron oxidation of **2a** the green color of the radical changes into a deep blue (λ_{max} 590 nm) of the dication **3a**. However, this species disappears more or less quickly by reaction with residual water which leads to the monoprotonated quinone imine **4a**. The addition of a base such as acetate produces the neutral form