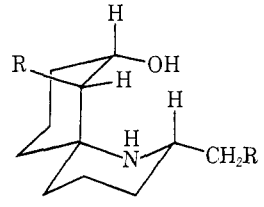
A Simple Total Synthesis of (±)-Perhydrohistrionicotoxin

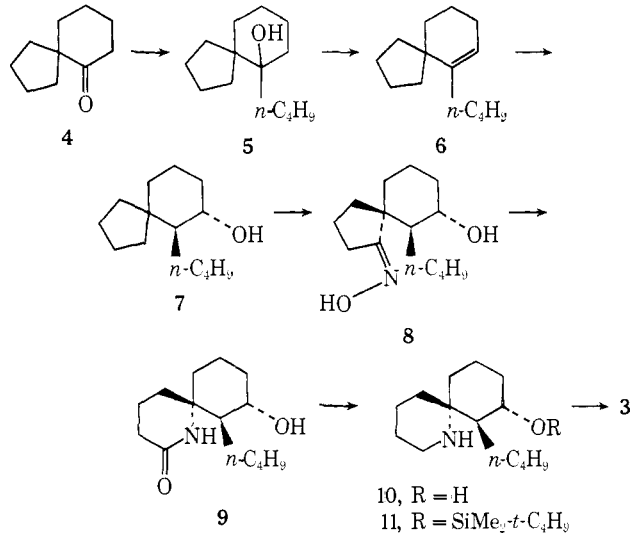
Sir:

The pioneering studies of Dr. Bernhard Witkop and collaborators on the isolation and characterization of toxins from the venom of the Colombian frog *Dendrobates histrionicus* has led to the recognition of three substances of high biological activity, histrionicotoxin (**1**)[1,2] and its octahydro (**2**)[3] and perhydro (**3**)[4] derivatives. These compounds have been found to be of extraordinary promise as probes of the phenomena involved in neuromuscular transmission.[3,4] This fact coupled with the extreme scarcity of natural material lends an unusual urgency to the development of chemical syntheses of these substances. We are most grateful to Dr. Witkop for suggesting to us the investigation of such synthesis and for arousing our interest in this area. A simple total synthesis of (±)-perhydrohistrionicotoxin (**3**) has been devised and is described herein.[5]

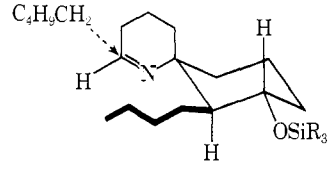


1, R = -HC$\overset{cis}{=}$CHC≡CH
2, R = -CH_2CH_2CH=CH_2
3, R = -$CH_2CH_2CH_2CH_3$

Cyclopentanone pinacol, prepared in 65% yield by a modification of the Mukaiyama method,[6] was converted to the spiro ketone **4** by acid-catalyzed rearrangement as previously described.[7] Conversion of **4** to the tertiary alcohol **5**, bp 95° (0.7 mm),[8] was effected in 95% yield by three cycles of reaction with *n*-butyllithium in hexane—ether[9] at reflux. The olefin **6** was obtained from **5** in 86% yield by reaction with 1 equiv of thionyl chloride and 2.05 equiv of pyridine in pentane at −78° for *ca.* 6 hr[10] and further converted by hydroboration-oxidation (alkaline hydrogen peroxide) to the alcohol **7** (78% yield), mp 64-64.5°.



Irradiation of the nitrite ester of **7** (prepared by reaction of **7** with 1.2 equiv of nitrosyl chloride in 1.4 equiv of pyridine in methylene chloride at <0°) in pyridine as solvent under argon using a Pyrex container and an external sun lamp (100-W Westinghouse H38-4G5) afforded the desired oxime **8**, mp 124-125°, (*ca.* 20%) together with an isomeric oxime produced by functionalization of the *n*-butyl group.[11,12] Beckmann rearrangement of the oxime was effected by reaction with 1 equiv of tosyl chloride and 2.4 equiv of pyridine in benzene at 25° for 12 hr to give as sole product the lactam **9**, mp 132-133°, which clearly possessed the structure shown rather than that with NH and CO groups transposed as indicated by the pmr spectrum. Reduction of **9** with excess lithium aluminum hydride in THF at reflux for 36 hr produced cleanly the corresponding amino alcohol **10** which was converted to the *tert*-butyldimethylsilyl derivative **11**[13] by reaction with 1 equiv of *tert*-butyldimethylchlorosilane in THF for 2 hr at 25° in the presence of 1.3 equiv of sodium hydride. The synthesis of (±)-perhydrohistrionicotoxin was completed without isolation of intermediates by the sequence: (1) conversion of **11** to the corresponding *N*-bromoamine with a slight excess of *N*-bromosuccinimide in THF at 0° for 1 hr, (2) dehydrobromination to the imine with excess potassium *tert*-amyloxide in THF at −40° for 2 hr, (3) removal of THF and reaction with excess *n*-amyllithium in hexane at 25° for 12 hr, and (4) desilylation with tetra-*n*-butylammonium fluoride[13] in THF at 25° (*ca.* 50% overall). The product obtained in this way was purified by chromatography on silica gel using 20% THF in hexane saturated with ammonia for elution and shown to be identical with naturally derived perhydrohistrionicotoxin[14] by ir, pmr, and mass spectral comparison of chromatographically homogeneous material. Further confirmation of the synthetic material as (±)-perhydrohistrionicotoxin was obtained by the identity of the R_f values in several different solvent systems on silica gel and alumina plates and also by measurements of biological activity.[15] In addition to **3**, a small amount of the isomer epimeric at the amyl-bearing carbon was produced in the above described process for introduction of the *n*-amyl appendage. In contrast, when the free alcohol **10** was used directly in the sequence *N*-bromoamine → imine → *n*-amyl-substituted amine, the major product was the epimer of **3**.[16] The stereoselective addition of *n*-amyllithium to the silylated imine to form **3** (in contrast to results with the unsilylated imine) may be a consequence of a transition state (**12**) in which each ring possesses the alternative chair form from that expressed in **3** and the shielding by the *n*-butyl group of one face of the imine π-system.[17]



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References and Notes

(1) For a fascinating early account see B. Witkop, *Experientia*, **27**, 1121 (1971).
(2) J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1870 (1971).
(3) Personal communication from Dr. Witkop.
(4) E. X. Albuquerque, E. A. Barnard, T. H. Chiu, A. J. Lapa, J. O. Dolly, S. Jansson, J. Daly, and B. Witkop, *Proc. Nat. Acad. Sci. U. S.*, **70**, 949 (1973).
(5) For an earlier study in which a method was devised for the introduction of cis enyne units as in **1**, see E. J. Corey and R. A. Ruden, *Tetrahedron Lett.*, 1495 (1973).
(6) T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, 1041 (1973). To 2 atom equiv of amalgamated magnesium in dry tetrahydrofuran (THF) under nitrogen at −10° was added rapidly 0.45 molar equiv of titanium tetrachloride. One equivalent of cyclopentanone in THF solution was added at ≤0°, and after further reaction for 15 min the mixture was quenched with 10% aqueous potassium carbonate, and the product was isolated. Yields of only *ca.* 30% were obtained by previously described procedures; see P. A. Naro and J. A. Dixon, *J. Amer. Chem. Soc.*, **81**, 1681 (1959).

(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.
(17) This work was assisted financially by a grant from the National Science Foundation.

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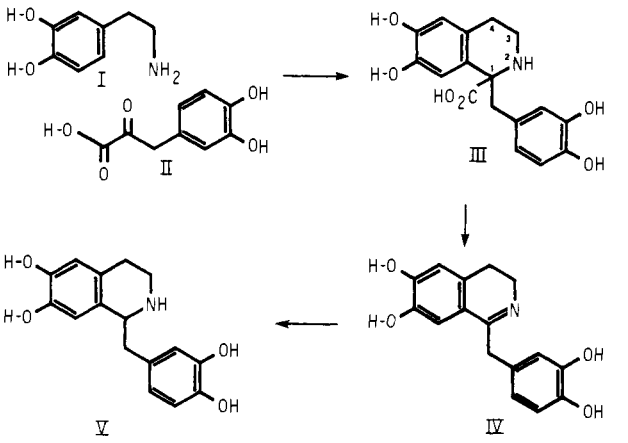
Studies on the Early Stages of *Papaver* Alkaloid Biogenesis[1]

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.