constant (k_2) for this reaction, catalyzed by riboflavin, is the highest among all these systems. The efficient electron transfer reported[3] for **5** is a property of the reactive substrate used in the reaction rather than the advantage gained by binding of the substrate to the artificial enzyme. The highest accelerator factor (6.5×10^2) exhibited by **1** over riboflavin[15] can be attributed to an effective flavin–substrate geometry within the enzyme–substrate complex, and these important geometric considerations are discussed elsewhere.[8b]

The artificial redox enzyme investigated herein exemplifies two of the advantages that artificial enzymes can offer to a reaction. (1) It converts a sluggish reaction, which cannot be completely catalyzed by flavin, into an efficient reaction. (2) It can benefit from reaction conditions (photochemical in this case) that are not commonly used by real enzymes.

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Supplementary Material Available: Experimental details for the oxidation of *p-tert*-butylbenzyl alcohol (8 pages). Ordering information is given on any current masthead page.

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Biosynthesis of 6β-Hydroxytropine in *Datura stramonium*: Nonregiospecific Incorporation of [1,2-$^{13}C_2$]Acetate†

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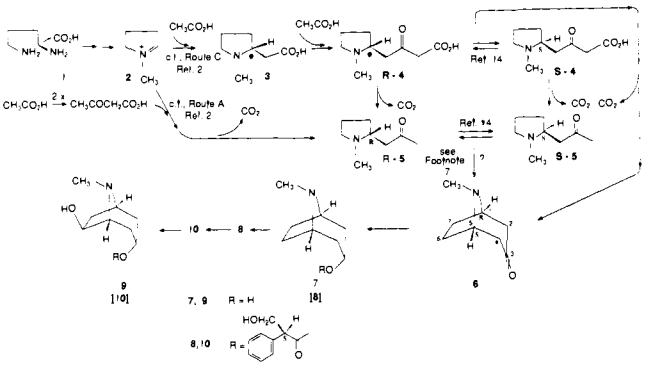
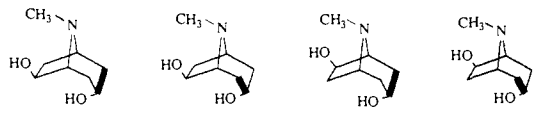
Recent investigations of the formation of the acetate-derived segment of cocaine[1] and of *N*-methylpelletierine[2] provide evidence for unexpected biochemical diversity in biosynthetic processes leading from one and the same substrate to analogous fragments in structurally related natural products.

In further exploration of this theme we have investigated the entry of [1,2-$^{13}C_2$]acetate into the C_3 bridge of 6β-hydroxytropine (= 3α,6β-dihydroxytropane = 3-*endo*, 6-*exo*-3,6-dihydroxytropane) (**9**) in *Datura stramonium*. It has been inferred from tracer experiments that the ring skeleton arises from ornithine[3] (**1**) and two acetate units,[4] that *N*-methyl-Δ^1-pyrrolinium ion[5] (**2**) and hygrine[6,7] (**5**) are intermediates, and that the entry of the hydroxy group into the ornithine-derived ring of tropine (**7**) takes

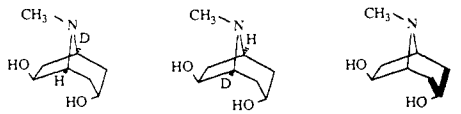
Scheme I



place late in the biosynthetic process[8,9] (Scheme I).[10] By analogy with the findings in *N*-methylpelletierine and cocaine, incorporation of sodium [1,2-$^{13}C_2$]acetate (49% $^{13}C_2$, 1 g, in 40 mL of water)[2] into 6β-hydroxytropine (**9**) was anticipated to lead to a product showing either one or the other of the two labeling patterns, **9A** or **9B**. Unexpectedly, a different result was obtained: the ^{13}C NMR spectrum (125 MHz, 104 000 scans) of the 6β-hydroxytropine that was isolated[11] (5 mg in 0.6 mL of $CHCl_3$; % enrichment: C-2, 0.38%; C-3, 0.76%; C-4, 0.42%) showed that the product consisted of a mixture of **9A** and **9B**,[12] equimolar within the limits of determination (δ 27.8 C-2 (d), 30.5 C-4 (d), 74.5 C-3 (d) ppm, $J_{2,3} = J_{3,4} = 35$ Hz). Such an outcome can arise from one of several variations in the entry of the side chain into the *N*-methyl-Δ^1-pyrrolinium ion (**2**) and the further elaboration of the intermediates, so generated, into tropine (**7**) and 6β-hydroxytropine (**9**). The experiment with [1,2-$^{13}C_2$]acetate cannot distinguish among these alternatives.



9 A **9 B** **9 C** **9 D**



9 E **9 F** **9 G**

Firstly, introduction of the side chain into **2** might take place stereospecifically and concurrently by both the "pelletierine mechanism"[2] (analogous to route A in ref 2) (**2** → → **5**, Scheme I) and the "cocaine mechanism"[1] (analogous to route C in ref 2) (**2** → **3** → **4**, Scheme I), and the intermediates between **2** and **6** maintain their chirality.

The result of a second experiment, with sodium [1,2,3,4-$^{13}C_4$]acetoacetate (49% $^{13}C_4$, 1 g, in 40 mL of water)[2] as the substrate, disposes of any scheme that implicates the "pelletierine" mechanism: the ^{13}C NMR spectrum of the sample of 6β-hydroxytropine from this experiment (7 mg in 0.6 mL of $CHCl_3$; % enrichment: C-2/C-4, 0.7%; C-3, 1.4%) showed the presence of a doublet (J = 34 Hz) in each of the signals due to C-2 and

† This paper is dedicated to the memory of Professor Edward Leete, who died in February 1992 after a long and courageous battle with cancer.

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(7) A few months before his death E. Leete informed us of recent results in his laboratory that threw doubt on the intermediacy of hygrine (**5**) in the biosynthesis of tropine. In the light of this finding, Scheme I shows the intermediacy of (*R*)-**5** ⇌ (*S*)-**5** as doubtful (?) and indicates the formation of tropinone (**6**) directly from *N*-methylpyrrolidineacetoacetate ((*R*)-**4** ⇌ (*S*)-**4** (by dehydrogenation and ring closure accompanied by decarboxylation).
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(11) The crude alkaloid mixture obtained by conventional methods was hydrolyzed with methanolic ammonia (10% v/v) for 2 days at room temperature, and 6β-hydroxytropine was separated from other alkaloids by chromatography on silica gel and elution with chloroform/methanol/0.880 ammonia (85:14:1 followed by 65:34:1).
(12) A recently reported independent investigation of the incorporation of [1,2-$^{13}C_2$]acetate into the 6β-hydroxytropine moiety of 6β-hydroxyhyoscyamine in *Hyoscyamus albus* gave an analogous result.[13]
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C-4 and also in that due to C-3, indicating formation of 6β-hydroxytropine with the labeling pattern **9A** plus **9B**, identical with that found in the experiment with [1,2-$^{13}C_2$]acetate. Incorporation of an intact C_3 unit (**9G**), as observed in the case of *N*-methylpelletierine,[2] would have resulted in a doublet of doublets in the signal due to the CHOH group, C-3. Since the pattern of incorporation of ^{13}C from [1,2,3,4-$^{13}C_4$]acetoacetate was identical with that from [1,2-$^{13}C_2$]acetate, the acetoacetate had cleaved to acetate before incorporation of the label. Thus, the C_3 unit, C-2-4, was generated from two discrete acetate units, as demanded by the "cocaine mechanism"[1] (**2** → **3** → **4**, Scheme I), and not from an intact acetoacetate-derived C_3 unit, as demanded by the "pelletierine mechanism"[2] (**2** → → **5**, Scheme I).

Secondly, entry of the side chain into **2** may take place stereospecifically, eventually leading to a uniquely labeled tropine (**7**), but the hydroxylation whereby the 6β-OH group is introduced into the ornithine-derived moiety of the tropine unit of hyoscyamine (**8**), while diastereospecific, is not enantiospecific with respect to the tropine unit, forming a pair of diastereomers, (3*S*,6*S*)-6β-hydroxyhyoscyamine (**10**) and (3*R*,6*R*)-6β-hydroxyhyoscyamine (also known as 7β-hydroxyhyoscyamine), from which a pair of enantiomeric molecules, **9A** plus **9C** or **9B** plus **9D**, is generated on hydrolysis.

This explanation of the labeling pattern requires that the biosynthetic sample of 6β-hydroxytropine be a racemate, consisting of the (3*S*,6*S*) isomer (**9**) (see also **9A** and **9B**) and the (3*R*,6*R*) isomer (occasionally referred to erroneously as 3α,7β-dihydroxytropane,[15] i.e., 7β-hydroxytropine) (**9C** and **9D**). Esters of both enantiomers of 6β-hydroxytropine occur in plants of the genus Solanaceae, including several species of *Datura*, but no racemates have been reported, and the enzymic hydroxylation process whereby the 6β-hydroxy group is introduced into one of the alkaloids, (−)-hyoscyamine (**8**), is stereospecific[8] as well as substrate specific.[9] Furthermore, in the instances when diastereomeric alkaloids, namely, the *O*-3 (−)-(*S*)-tropic acid esters of (3*S*,6*S*)-dihydroxytropane ((−)-6β-hydroxyhyoscyamine) (**10**) and of (3*R*,6*R*)-dihydroxytropane ((−)-7β-hydroxyhyoscyamine), were isolated from the same plant, the latter compound was much less abundant than the former.[15,16] It is unlikely that hydrolysis of a mixture of ester alkaloids should fortuitously yield an equimolar mixture of the two enantiomeric dihydroxytropanes. This explanation of the incorporation pattern is thus unlikely.[17]

Thirdly, addition of the acetate-derived side chain to the *N*-methyl-Δ^1-pyrrolinium ion[5] (**2**) may take place by the "cocaine mechanism"[1] (analogous to route C in ref 2), yielding an equimolar mixture of (*R*)- and (*S*)-*N*-methylpyrrolidineacetoacetate (**4**), both of which are then further elaborated into tropine (**7**) either via (*R*)- and (*S*)-hygrine[7] (**5**) or directly. The mixture of (*R*)- and (*S*)-**4** can originate either by racemization[14] of a chiral species, namely (*R*)-**4** which is originally generated,[6] or less probably can be formed directly by nonstereospecific entry of the side chain into **2**.

A third experiment, with *N*-methyl-Δ^1-[2-^{2}H]pyrrolinium chloride (500 mg, 98% ^2H; prepared from DL-[2-^{2}H]proline by Eschweiler-Clarke methylation,[18] followed by heating with $POCl_3$[19]) as the substrate, provides evidence for the implication of racemic intermediates between **2** and **6**. This experiment gave a sample of 6β-hydroxytropine (ca. 3 mg, % enrichment 0.3%) whose ^2H NMR spectrum (76 MHz, 16 000 scans) indicated the presence of deuterium, equimolar within the limits of detection, at each of the two bridgehead sites (δ = 3.0, 3.6 ppm)[15] of the molecule, which thus consisted of an equimolar mixture of **9E** and **9F**. This result disposes of any scheme that does not accommodate the involvement of both enantiomers of *N*-methylpyrrolidineacetoacetate (**4**) (or of hygrine[7] (**5**)). Any mechanism that involves chiral intermediates (e.g., (*R*)-**4** and (*R*)-**5**) would have produced **9E** as the sole product rather than an equimolar mixture of **9E** and **9F**.

The evidence here presented leads to the inference that, contrary to conventional wisdom, the non-ornithine-derived moiety of the tropane ring system of 6β-hydroxytropine in *D. stramonium* does not originate from acetoacetate but by stepwise incorporation of acetate, whose nonregiospecific distribution within the C_3 unit implies the involvement of a racemic intermediate on the pathway.

Registry No. 9, 41164-06-1; acetate, 64-19-7.

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Solid-State Structures of "Rosette" and "Crinkled Tape" Motifs Derived from the Cyanuric Acid-Melamine Lattice[1]

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We are using the pattern of hydrogen bonds present in the 1:1 complex formed from cyanuric acid and melamine (CA·M) as the basis for the design of self-assembling structures.[2-5] We have described a solid-state structure based on a "linear" tape motif taken from this lattice (**3**, Figure 1),[3] and we have inferred the existence of cyclic aggregates containing three melamine and three isocyanurate moieties in solution.[4,5] Here we report solid-state structures of a new type of tape format (a "crinkled tape", **4**) and a cyclic structure (a "rosette", **5**), both obtained by combination of *N*,*N*′-bis(*p*-substituted phenyl)melamine (**1**) and 5,5-diethylbarbituric acid (**2**). We believe that the three solid-state structures **3**–**5** are the most plausible structural motifs that can be derived from the CA·M lattice: other, more collapsed tape or cyclic structures (e.g., **6** and **7**, and larger cyclic structures containing these units) are destabilized by nonbonded steric interactions (indicated by arrows in Figure 1). These two new structures, together with the structure of a linear tape (X = H) already described,[3] serve as paradigms for use in the design of self-assembling structures based on the CA·M lattice and provide structural parameters applicable to evaluation of the energetics of these structures using molecular mechanics.[6]

Figure 2 (middle) shows the structure of the 1:1 complex of **1a** (X = CO_2CH_3) and **2**.[7] This crinkled format occurs commonly: of 15 structures we have determined in the series of cocrystals incorporating substituted diphenylmelamines and **2**, three are crinkled tapes. The complex **1a·2** crystallizes from

(1) Supported by the National Science Foundation, Grant CHE-88-12709 to G.M.W., Grant DMR-89-20490 to the Harvard University Materials Research Laboratory, and Grant CHE 80-00670 for the purchase of the Siemens X-Ray diffractometer.
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