441, sh 400, 539 nm; NMR, see Figure 8; mass spectrum, *m/e* 817-818 (M^+), 683 [$-C(O)C_6H_4SH$]; χ_m (solution, toluene) 4.93 ± 0.06 μ_B. Anal. ($C_{53}H_{33}N_5OSFe$): H; S; Fe; C: calcd 74.72, found 72.62; N: calcd 8.54, found 8.00.

[***meso*-[*o*-[(3-Mercaptophenyl)acetamido]phenyl]triphenylporphyrinato]iron(II), Fe(mPASH)**: UV/vis (toluene) 420 (broad), sh ~400, 440, 526, 548 nm; mass spectrum, *m/e* 831-834 (M^+), 683 [$-C(O)CH_2C_6H_4SH$].

[***meso*-[*o*-(2-Mercapto-3-methylbenzamido)phenyl]triphenylporphyrinato]iron(II), Fe(m3MSH)**: UV/vis (toluene) 418, sh 400, 441, 539 nm; mass spectrum, *m/e* 832-833 (M^+), 681-686 [$-C(O)C_6H_4(CH_3)(SH)$]; χ_m (solution, toluene) 4.94 ± 0.05 μ_B.

Acknowledgment. We are grateful to Professor C. Djerassi and Dr. E. Bunnenberg for use of MCD facilities at Stanford and for consultation on MCD spectroscopy. Mass spectra recorded outside Stanford were obtained through the courtesy of Dr. K. S. Suslick at the University of Illinois, Champaign-Urbana, and Drs. R. Arcus and J. Moncur at Lockheed Missiles and Space Co., Inc., Palo Alto. Thanks are due to Ruth Records for measuring the MCD spectra, to Lois Durham for helpful NMR discussions, and to Luke Erdoes for technical assistance. This work was supported by the National Institutes for Health (Grant GM17880) and the National Science Foundation (Grant CHE78-09443). Spectra were recorded on instruments supported by the following grants: NMR: NIH RR007711 and NSF GP23633 (Bruker HXS-360 MHz, Stanford Magnetic Resonance Laboratory); NSF GP28142 and CHE77-08810 (XL-100, Stanford University); FT IR: NSF CHE78-02070; MCD: NSF CHE80-09240 and NIH GM20276; mass spectra: NIH GM 28352-21. We are also grateful for a NSF Predoctoral Fellowship awarded to S.E.G. (1974-1977).

Registry No. **9**, 75557-89-0; **10**, 75557-90-3; **11a**, 80441-39-0; **11b**, 80441-40-3; **11c**, 80447-62-7; **11d**, 80441-41-4; **11e**, 80441-42-5; **12**, 69082-94-6; **13a**, 80441-43-6; **13b**, 80441-44-7; **13c**, 80441-45-8; **13d**, 80441-46-9; **13e**, 80441-47-0; **13f**, 80441-48-1; **14a**, 80441-49-2; **14b**, 80461-70-7; **15a**, 80441-50-5; **15b**, 80441-51-6; **16a**, 80441-52-7; **16b**, 80441-53-8; **17**, 80441-54-9; mNO_2, 62813-29-0; Fe(tC_5SH), 80441-18-5; Fe(mC_5SH), 80441-19-6; Fe(mC_4SH), 80441-20-9; Fe(mPhSH), 80441-21-0; Fe(mPASH), 80441-22-1; Fe(m3MSH), 80441-23-2; Fe(mC_4SH)(CO), 80441-24-3; Fe(mC_5SH)(CO), 80447-59-2; Fe(tC_5SH)(CO), 80448-78-8; Fe(mPhSH)(CO), 80441-17-4; Fe(m3MSH)(CO), 80461-59-2; Fe(mPASH)(CO), 80447-61-6; ε-caprolactone, 502-44-3; 6-bromohexanoic acid, 4224-70-8; 6-bromchexanoyl chloride, 22809-37-6; trityl mercaptan, 3695-77-0; 6-(tritylthio)hexanoic acid, 80441-55-0; 6-(tritylthio)hexanoyl chloride, 80441-56-1; thioacetic acid, 507-09-5; 6-(acetylthio)hexanoic acid, 80441-57-2; 6-(acetylthio)-hexanoyl chloride, 80441-58-3; 5-bromopentanoic acid, 2067-33-6; 5-bromopentanoyl chloride, 4509-90-4; 2,2'-dithiobis(benzoic acid), 119-80-2; 2,2'-dithiobis(benzoyl chloride), 19602-82-5; 2,2'-dithiobis(3-methylbenzoic acid), 13363-59-2; 2-amino-3-methylbenzoic acid, 4389-45-1; 2-diazonium-3-methylbenzoic acid chloride, 65911-34-4; 2-[(ethoxythioxomethyl)thio]-3-methylbenzoic acid, 80447-63-8; 2-mercapto-3-methylbenzoic acid, 77149-11-2; 2,2'-dithiobis(3-methylbenzoyl chloride), 13363-60-5; (3-aminophenyl)acetic acid, 14338-36-4; (*m*-nitrophenyl)acetic acid, 1877-73-2; 3,3'-dithiobis(phenylacetic acid), 80441-59-4; 3,3'-dithiobis(phenylacetyl chloride), 80441-60-7.

Biosynthesis of the Pyrrolidine Rings of Cocaine and Cuscohygrine from [5-^{14}C]Ornithine via a Symmetrical Intermediate[1]

Edward Leete

Contribution from the Natural Products Laboratory,[2] School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received July 27, 1981*

Abstract: After many unsuccessful attempts, cocaine containing a significant level of radioactivity was obtained by painting the leaves of the *Erythroxylon coca* plant with an aqueous solution of DL-[5-^{14}C]ornithine hydrochloride. A systematic degradation of this cocaine indicated that essentially all the activity was located at the bridgehead carbons (C-1 and C-5) of its tropane moiety and equally divided between these positions. The activities of degradation products of the radioactive cuscohygrine obtained from the same plant were also consistent with symmetrical labeling of the pyrrolidine rings of this alkaloid. These results indicate that the [5-^{14}C]ornithine is incorporated into these alkaloids via a symmetrical intermediate such as putrescine. This biosynthetic pathway to the tropane moiety of cocaine is, thus, different from the one previously established for hyoscyamine and scopolamine in *Datura* species.

Introduction

Cocaine (**12**), the active principle of the coca plant (*Erythroxylon coca*) and other species of the *Erythroxylon* genus,[3] has had a long and interesting history which continues to the present day.[4] The degradative work carried out by Willstätter and others at the end of the 19th century led to the current structure in 1898[5] confirmed by the first total synthesis in 1923.[6] The relative and absolute configuration was not established until the 1950's.[7,8] Stereospecific syntheses of cocaine have recently been described by Tufariello and co-workers.[9]

Cocaine is a tropane alkaloid, characterized by the presence of the 8-azabicyclo[3.2.1]octane ring system. Extensive tracer work dating back to 1954[10] has established that ornithine is incorporated into the pyrrolidine ring of hyoscyamine (**14**) unsymmetrically. Thus, DL-[2-^{14}C]ornithine yielded hyoscyamine which was labeled only at the C-1 bridgehead carbon.[11,12] Scheme I

(1) A preliminary account of part of this work has appeared: Leete, E. *J. Chem. Soc., Chem. Commun.* **1980**, 1170. It was also presented at the 28th Congress of the IUPAC, Vancouver, Canada, Aug 16-22, 1981.

(2) Contribution number 178 from this laboratory. This paper is dedicated to Lorraine Margaret, my fourth daughter, who was born June 23, 1981, the same day that the degradation of the labeled cocaine (from experiment 2) was completed.

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(4) The literature on cocaine, currently indexed in *Chemical Abstracts* as 3-(benzoyloxy)-8-methyl-8-azabicylo[3.2.1]octane-2-carboxylic acid, methyl ester [1*R*-(*exo,exo*)], is vast. Several monographs describing its biological, social, and chemical aspects are available: (a) Mortimer, W. G. "Peru: History of Coca"; Vail and Co.: New York, 1901; reprinted as "History of Coca"; And/Or Press: San Franciso, 1974. (b) Peterson, R. C.; Stillman, R. C., Eds. *NIDA Res. Monogr.* **1977**, *No. 13*. (c) Mulé, S. J., Ed. "Cocaine: Chemical, Biological, Clinical, Social, and Treatment Aspects"; C.R.C. Press: Cleveland, OH, 1976.

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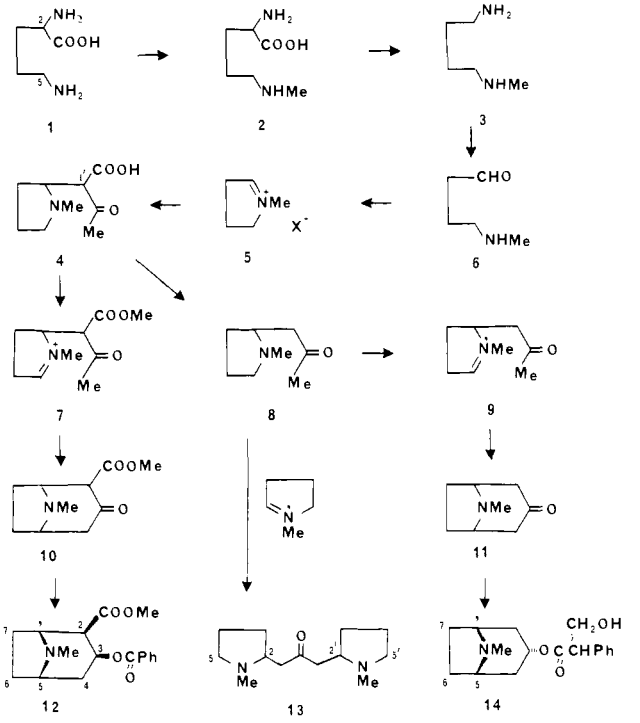
Table I. Feeding to *Erythroxylon coca* Putative Precursors of Cocaine and Activity of the Isolated Alkaloids

expt no.	compd administered (wt, total act.)	method of feeding[a]	date feeding was started (duration, weeks)	fresh wt of plants, g	wt (sp act., dpm/mmol), mg	
					cocaine	cuscohygrine
1	DL-[5-^{14}C]ornithine hydrochloride[b] (2.93 mg, 6.42×10^8 dpm)	LP	July 3, 1980 (4)	190	283 (2.45×10^5)	32 (1.95×10^5)
2	DL-[5-^{14}C]ornithine hydrochloride[b] (47.7 mg, 5.33×10^8 dpm)	LP	Apr 9, 1981 (4)	185	224 (2.06×10^5)	39 (2.62×10^5)
3	DL-[5-^{14}C]ornithine hydrochloride[b] (2.93 mg, 5.15×10^8 dpm)	LP	Nov 20, 1980 (5)	175	212 (1.88×10^4)	26 (3.83×10^4)
4	DL-[2,3-$^{13}C_2$,5-^{14}C]ornithine hydrochloride[c] (25.4 mg, 3.66×10^7 dpm)	ES	Dec 10, 1978 (1)	45	13 ($<1.0 \times 10^3$)	NI[i]
5	DL-[2-^{14}C]ornithine hydrochloride[b] (23.5 mg, 5.2×10^8 dpm)	H	June 6, 1970 (2)	45	200[e] ($<1.0 \times 10^4$)	NI
6	[2-^{13}C,^{14}C]-*N*-methyl-Δ^1-pyrrolinium acetate[f] (96 mg, 0.67 mmol, 8.0×10^7 dpm)	W	Nov 22, 1975 (2)	60	24 (1.5×10^3)	NI
7	[2-^{14}C]-*N*-methyl-Δ^1-pyrrolinium chloride (84 mg, 8.5×10^7 dpm)	W	June 16, 1972 (2)	55	250[e] (1.6×10^4)[g]	NI
8	sodium [1-^{14}C]acetate[h] (16 mg, 2.2×10^9 dpm)	W	June 10, 1971 (2)	65	200[e] ($<1.0 \times 10^4$)	NI
9	[*carboxyl*-^{14}C]nicotinic acid[h] (14.65 mg, 1.15×10^9 dpm)	ES	Nov 8, 1978 (2)	30	200[e] (1.0×10^4)	NI

[a] LP = leaf painting; ES = small branches of the coca plant (~20-cm long) were immersed in an aqueous solution of the tracer; W = cotton wicks were inserted by means of a sewing needle in the many branches (20–30) of a single plant; H = the plants (2–3 years old) were transferred from soil into an aerated hydroponic solution[46] in which the roots were placed. [b] Research Products International Co., an intermediary for labeled compounds synthesized at C.E.A. Gif-sur-Yvette, France. [c] This feeding experiment, and isolation of the cocaine was carried out by Ming-Li Yu, who also synthesized the [$^{13}C_2$]ornithine.[35] [d] Tracer Lab, Waltham, MA. [e] Amount of inactive cocaine added as a carrier during the workup of the plants. [f] This was made as previously described for the ^{14}C-labeled material,[22c] except that the synthesis started with a mixture of potassium [^{13}C]- and [^{14}C]cyanide. [g] Hydrolysis of this cocaine afforded benzoic acid (5.6×10^3 dpm/mmol) and ecgonidine (1.0×10^4 dpm/mmol) indicative of almost uniform labeling of the alkaloid. [h] Amersham Co. [i] NI = not isolated.

illustrates the generally accepted route whereby ornithine is incorporated into the tropane ring system.[13] The first step is considered to be the methylation of ornithine (**1**) to yield N^{δ}-methylornithine (**2**), which has been shown to be a direct precursor of hyoscyamine in *Datura stramonium*[14] and *Atropa belladonna*.[15] This amino acid has been shown to be an authentic natural product, since it was isolated in radioactive form after feeding [5-^{14}C]- or [5-^{3}H]ornithine to *A. belladonna*.[16] Decarboxylation then yields *N*-methylputrescine (**3**), an established precursor of the tropane nucleus of hyoscyamine and scopolamine (the 6,7-epoxide of **14**).[17–19] Oxidation of *N*-methylputrescine affords 4-(methylamino)butanal (**6**), which was detected, labeled with ^{14}C, in the roots of *Datura stramonium* and *A. belladonna* that had been fed [2-^{14}C]ornithine.[20] Condensation of the cyclic form of **6**, namely, the *N*-methyl-Δ^1-pyrrolinium salt **5** with acetoacetate,[21] yields hygrine-1′-carboxylic acid (**4**), hygrine (**8**) being formed on decarboxylation.[22] Hygrine has been shown to be a precursor of the tropane moiety of hyoscyamine, which is plausibly formed via the dehydrohygrine (**9**) and tropinone (**11**).[23–25] A plausible route to cocaine is from the hygrine-1′-carboxylic acid, probably with some kind of protection of the carboxyl group, perhaps as a methyl ester. Compounds **7** and **10** would be reasonable intermediates en route to cocaine. However, no definitive work has been published on the origin of the tropane nucleus of

Scheme I. Generally Accepted Biosynthesis of Cocaine, Cuscohygrine, and Hyoscyamine



cocaine. In 1963 it was found that the administration of [3′-^{14}C]phenylalanine to *Erythroxylon novogranatense* yielded radioactive cocaine in which essentially all the activity resided in the carboxyl group of the benzoic acid moiety of cocaine.[26] At a meeting of the American Society of Pharmacognosy[27] in 1963, it was reported that [3′-^{14}C]phenylalanine, sodium [1-^{14}C]acetate, and [*methyl*-^{14}C]methionine were injected into *E. novogranatense* trees and radioactive alkaloids were obtained. However, no degradations were carried out to determine the location of the

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(22) The biomimetic synthesis of hygrine from **5** and acetone dicarboxylic acid has been achieved in vitro: (a) Galinovsky, F.; Wagner, A.; Weiser, R. *Monatsch. Chem.* **1951**, *82*, 551. (b) El-Olemy, M. M.; Schwarting, A. E.; Kelleher, W. J. *Lloydia* **1966**, *29*, 58. (c) Leete, E. *J. Am. Chem. Soc.* **1967**, *89*, 7081.
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(25) ODonovan, D. G.; Keogh, M. F. *J. Chem. Soc. C* **1969**, 223.
(26) Gross, D.; Schütte, H. R. *Arch. Pharm. (Weinheim, Ger.)* **1963**, *296*, 1.
(27) Tamprateep, P. Taylor, E. H.; Ramstad, E. *Lloydia* **1963**, *26*, 203.

Table II. Activities of Cocaine, Cuscohygrine, and Their Degradation Products

compd	sp act. dpm/mmol × 10^{-5}		RSA[a]	
	from expt 1	from expt 2	from expt 1	from expt 2
cocaine hydrochloride	2.45	2.06	100	100
ecgonidine hydrochloride (15)	2.40	2.02	98	98
benzoic acid[b]	0.03	0.019	1	1
N-methylsuccinimide (17)	2.42		99	
1-methyl-2,5-diphenylpyrrole (16)	2.38		97	
benzoic acid[c] (C-1, C-5)	1.20		49	
N,N-dimethylbenzamide (*N*-Me)		0.006		0.3
cycloheptanecarboxylic acid (21)		2.02		98
barium carbonate[d] (C-9)		0.02		1
(dimethylamino)cycloheptane methiodide (19)		2.01		98
pimelic acid (24)		2.03		99
dianilide of pimelic acid		2.03		99
barium carbonate[e] (C-1, C-2, C-3)		0.24		12
dibenzoylcadaverine		1.54		75
cuscohygrine dipicrate	1.95		100	
cuscohygrine dihydrobromide	1.98		101	
1,11-bis(dimethylamino)-6-undecanol dimethiodide (28)	1.87		96	
3,5-dinitrobenzoate of 6-undecanol	2.03		104	
formaldehyde dimedone (C-5, C-5′)	0.445		23	

[a] Relative specific activity. [b] From the hydrolysis of cocaine. [c] From the oxidation of 16. The $BaCO_3$ was assayed by dissolving in an aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid.[48] [d] From the Schmidt reaction on cycloheptanecarboxylic acid. [e] From the Schmidt reaction on pimelic acid.

^{14}C. In a dissertation,[28] the formation of labeled cocaine from radioactive ornithine and putrescine was claimed; however, since no subsequent publications have resulted, it is assumed that the incorporations were low, rendering it impractical to determine the location of the radioactivity in the cocaine by degradations. Rather strange results were obtained[23] on feeding [1-^{14}C]acetate to *E. coca*. About 60% of the activity of the cocaine was apparently located in the ester methyl group. It seems probable that the cocaine was not radiochemically pure, since the carboxyl group of acetic acid is not usually considered to be a source of one-carbon units. Furthermore, if this had occurred, one would also have expected to find a significant amount of label on the *N*-methyl group of cocaine. The carboxyl group of the benzoic acid moiety contained 30% of the activity, leaving only 8.7% in the ecgonine (3β-hydroxytropane-2β-carboxylic acid) residue. This was distributed as follows: 33% on the carboxyl group, 36% at C-3, and 22% at C-1, C-5, C-6, C-7, and the *N*-methyl group. It was thus claimed, in my opinion, somewhat optimistically, that the acetic acid was incorporated into ecgonine, via acetoacetate, in accord with the previously discussed biosynthetic scheme.

Results and Discussion

I commenced work on the biosynthesis of cocaine over 10 years ago, and the details of the various feeding experiments which have been carried out with *Erythroxylon coca* plants are summarized in Table I. The initial results, in agreement with those discussed in the introduction, were disappointing, very low incorporations of putative precursors (ornithine, acetic acid, and the *N*-methyl-Δ^1-pyrrolinium salt) being obtained. In one case, experiment 7, the cocaine derived from *N*-methyl-Δ^1-[2-^{14}C]-pyrrolinium chloride (**5**) was subjected to a partial degradation (hydrolysis to benzoic acid and ecgonidine). The results indicated considerable scrambling of activity and no support for the direct incorporation of **5** into the tropane moiety of cocaine. These cumulative failures caused me to question the validity of the proposed biosynthetic route to cocaine. An admittedly outlandish idea was that the tropane skeleton was being produced in the *Erythroxylon* genus by a biosynthetic process quite different from that operating in the Solanaceae family, in which all the previous tracer work had been carried out. It was thought that perhaps the piperidine ring present in the tropane moiety was derived from nicotinic acid, the carboxyl group being retained as the carbomethoxy group of the ultimate cocaine.[29] However, the cocaine isolated from plants which were fed by placing excised stems of *E. coca* in a solution of [*carboxyl*-^{14}C]nicotinic acid was almost inactive (experiment 9).

Success was finally achieved (experiment 1) by painting the leaves of the coca plant with an aqueous solution DL-[5-^{14}C]-ornithine which contained a little of the nonionic detergent Tween 80.[30] Nothing is known about the site of cocaine biosynthesis in the plant, and this positive result may indicate that it occurs mainly in the leaves, this method of feeding delivering the precursor efficiently to the synthesis site. There is apparently a seasonal variation in cocaine biosynthesis, since the cocaine isolated from plants which were fed in November (experiment 3) by the same method was much less active (by a factor of 10) than plants fed in July or April (experiments 1 and 2). In recent experiments the leaves were picked off by hand and extracted without drying to afford quite reasonable yields of cocaine (0.15% on the fresh weight). This method has the advantage that the plant is not destroyed. Interestingly, the new leaves which formed on plants which had been fed [5-^{14}C]ornithine and defoliated were found to contain cocaine, but it was almost completely devoid of radioactivity. This result is also consistent with the leaves being the site of cocaine biosynthesis. If the roots had been the site of synthesis, I would have expected some residual radioactive cocaine from the prior feeding to be translocated to the new leaves.

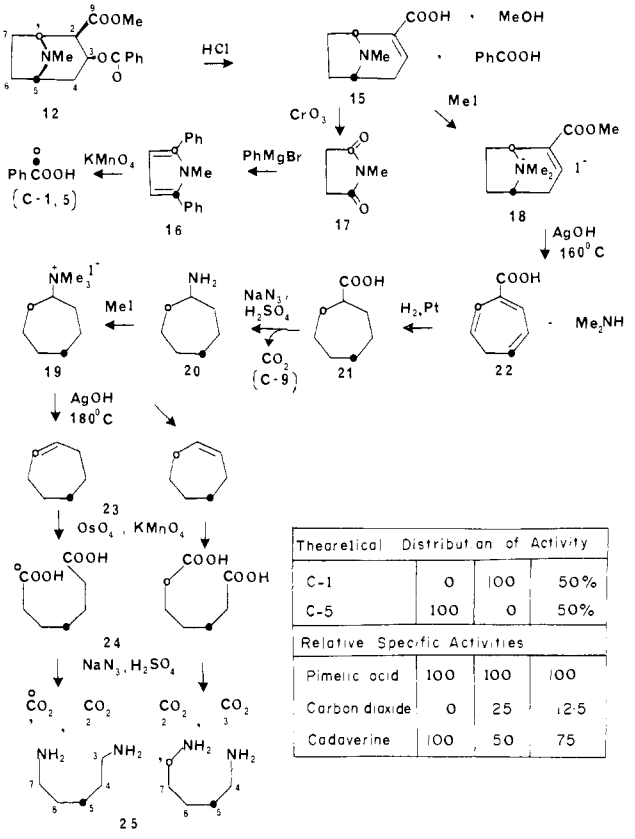
It was hoped that the biosynthesis of cocaine from various precursors could be studied by using ^{13}C-labeled compounds, detecting the position of the isotope by ^{13}C NMR (experiments 4 and 6). So far this has been unsuccessful because of the low incorporations obtained. Thus, in experiment 2, the specific incorporation of the [5-^{14}C]ornithine into cocaine is only 0.009%. Even if the ornithine had been labeled with two contiguous ^{13}C atoms, which give rise to satellites in the ^{13}C NMR, their detection would be beyond the capability of present day NMR spectrometers. I thus had to resort to classical degradative procedures to determine the location of ^{14}C in the labeled cocaine. Fortunately there have been numerous reactions carried out on cocaine which could be utilized to determine the activity at the bridgehead carbons of the tropane ring where activity from [5-^{14}C]ornithine was expected. The method used is illustrated in Scheme II, and

(28) Gross, D. Dissertation, Halle, DDR, 1963; cited in Mothes, K.; Schütte, H. R. "Biosynthese der Alkaloide"; VEB: Berlin, 1969; p 198.

(29) This bizarre idea was rendered a little more acceptable when it was discovered that nicotinic acid is reduced to provide the piperidine ring found in dioscorine: Leete, E. *Phytochemistry* **1977**, *16*, 1705.

(30) This method of feeding also led to the successful incorporation of [1-^{14}C]acetate into dioscorine, other methods of administering tracers to *Dioscorea hispida* having failed: Leete, E.; Pinder, A. R. *Chem. Commun.* **1971**, 1499; *Phytochemistry* **1972**, *11*, 3219.

Scheme II. Degradation of Cocaine to Determine Activity at the Bridgehead Carbons (C-1 and C-5, Which are Indicated with Open and Closed Circles, Respectively)

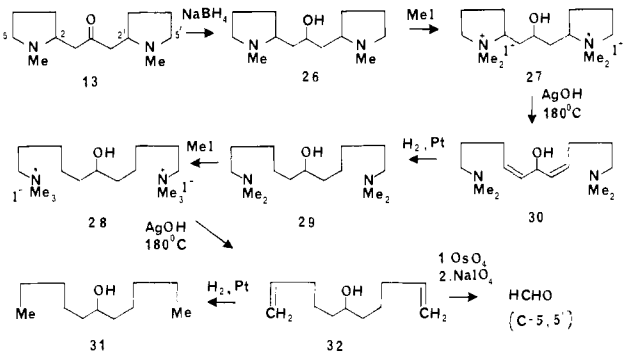


Theoretical Distribution of Activity			
C-1	0	100	50%
C-5	100	0	50%
Relative Specific Activities			
Pimelic acid	100	100	100
Carbon dioxide	0	25	12.5
Cadaverine	100	50	75

the activities of the degradation products of the cocaine derived from [5-^{14}C]ornithine (experiments 1 and 2) are recorded in Table II.

Refluxing cocaine with concentrated HCl results in hydrolysis of the two ester functions, yielding methanol (not isolated) and benzoic acid. The 3-hydroxyl function in the tropane moiety is eliminated, affording ecgonidine (**15**), also known as anhydroecgonine. Oxidation of this compound with a mixture of chromic and sulfuric acids yielded *N*-methylsuccinimide (**17**), which was reacted with phenylmagnesium bromide as previously described[10] to afford 1-methyl-2,5-diphenylpyrrole (**16**). Oxidation of this pyrrole with potassium permanganate yields benzoic acid. The activity of the benzoic acid represents the activity originally present at C-1 and C-5 of cocaine, and the specific activity of the isolated benzoic acid indicated that essentially all the activity was confined to these positions. This degradation does not, of course, distinguish between C-1 and C-5 because of the symmetry of *N*-methylsuccinimide. Accordingly, the ecgonidine was converted to the methiodide of its methyl ester (**18**), which was then subjected to a Hofmann degradation by heating the corresponding methohydroxide at 160 °C[31] in a current of nitrogen. In this reaction, dimethylamine is also eliminated, and this was collected and assayed as its *N*-benzoyl derivative. There has been considerable discussion on the structure of the cycloheptatrienecarboxylic acid which is produced in this reaction.[32,33] Presumably the first compound formed is **22**, but this compound apparently rearranges to a more stable isomer. However, its structure is irrelevant, since it was hydrogenated to afford cycloheptanecarboxylic acid (**21**). A Schmidt reaction on **21** yielded carbon dioxide, representing

Scheme III. Degradation of Cuscohygrine



the activity on the carboxyl group of cocaine and cycloheptylamine (**20**) which was converted to (dimethylamino)cycloheptane methiodide (**19**) by reaction with methyl iodide in the presence of sodium bicarbonate. Another Hofmann reaction yielded cycloheptene (**23**), which was oxidized with osmium tetroxide to cycloheptane-1,2-diol and then to pimelic acid (**24**) with permanganate. The direct oxidation of cycloheptane to pimelic acid gave a poor yield. A Schmidt reaction on the pimelic acid afforded cadaverine (**25**), isolated as its dibenzoyl derivative, and carbon dioxide. The fate of the bridgehead carbons of cocaine in this degradation is indicated with an open circle (C-1) and a black circle (C-5). The carbon dioxide produced in the ultimate Schmidt reaction is thus derived from C-1, C-2, and C-3 of cocaine. The relative specific activities of this carbon dioxide and the cadaverine are indicated in Scheme II for three theoretical distributions of activity between C-1 and C-5.[34] It is apparent from the results recorded in Table II that the activity is equally divided between C-1 and C-5, indicating that the ornithine is not incorporated into the tropane nucleus of cocaine by the same pathway by which the tropine moiety of hyoscyamine is formed. If this had occurred, all the activity from [5-^{14}C]ornithine would have been at C-5. It is thus proposed that ornithine is converted to cocaine via putrescine, *N*-methylputrescine, and the *N*-methyl-Δ^1-pyrrolinium salt. The intermediacy of free putrescine results in equilibration of C-2 and C-5 of the pyrrolinium salt and equal labeling at C-1 and C-5 of the ultimate cocaine. This is the route by which ornithine is incorporated into the pyrrolidine ring of nicotine in *Nicotiana* species.[19,35,36] There is one isolated report[37] that nicotine is present in *Erythroxylon coca*. Nicotine was thus searched for in the crude alkaloids, but none could be detected. The aqueous solution obtained in the initial extraction of the coca plant with chloroform and 10% Na_2CO_3 was examined for the presence of free putrescine derived from the [5-^{14}C]ornithine. This was done by adding unlabeled putrescine to this solution and then reisolating the putrescine as its dibenzoyl derivative. The activity of this derivative was negligible. This result probably indicates that the concentration of free putrescine in the plant is quite low.[38]

The activity detected on the other carbons of cocaine, although quite small,[39] is considered to be real and probably represents general metabolism of the [5-^{14}C]ornithine to yield small molecules such as [1-^{14}C]acetate and $^{14}CO_2$, which are then incorporated into these other positions of cocaine by unexceptional pathways. Radioactive cuscohygrine (**13**), having about the same specific

(31) This is a slight modification of the reaction carried out by Willstätter, R. *Liebigs Ann. Chem.* **1901**, *317*, 204. Starting with 250 g (!) of ecgonidine hydrochloride, he converted this to the ethyl ester and then to the methiodide, which was heated with 30% NaOH to yield 149 g of a cycloheptatrienecarboxylic acid, mp 32 °C.

(32) Büchner, E. *Chem. Ber.* **1898**, *31*, 2241.

(33) DeJong, A. W. K. *Recl. Trav. Chim. Pays-Bas* **1937**, *56*, 198.

(34) Since the Schmidt reaction on pimelic acid yields 2 equiv of CO_2, the specific activity of the CO_2 is half what one might initially predict.

(35) Leete, E.; Yu, M.-L. *Phytochemistry* **1980**, *19*, 1093.

(36) Leete, E. *J. Org. Chem.* **1976**, *41*, 3438.

(37) Fikenscher, L. H. *Pharm. Weekbl.* **1958**, *93*, 932. W. C. Evans, an authority on the *Erythroxylon* genus,[3] has never detected nicotine in any of the Erythroxylon species he has examined (private communication, July 8, 1981).

(38) A similar result was obtained by Schütte, H. R.; Knofel, D. *Z. Pflanzenphysiol.* **1968**, *59*, 80, who failed to detect any activity in cadaverine isolated, by dilution, from *Lupinus luteus* which had been fed [^{14}C]lysine, even though cadaverine is considered to be an intermediate between lysine and the quinolizidine alkaloids produced in this species.

(39) These low levels of activity are considered to be significant, since quite large samples (20–30 mg) were assayed for radioactivity.

activity as cocaine, was isolated from the coca plants which had been fed [5-^{14}C]ornithine by leaf painting (experiments 1–3). It has been established that hygrine is a precursor of this alkaloid,[23,25,40] which is presumably formed by reaction with another molecule of the *N*-methyl-Δ^1-pyrrolinium salt. The cuscohygrine was degraded by the route illustrated in Scheme III, which is based on reactions carried out by Hess and Bappert[41] to determine the structure of the alkaloid. Reduction of cuscohygrine with sodium borohydride yields the alcohol **26**, which was converted into its dimethiodide **27**. A Hofmann degradation affords the open-chain diene **30**, which was hydrogenated to **29** and converted to the dimethiodide **28**. A second Hofmann degradation yielded undeca-1,10-dien-6-ol (**32**), which was cleaved with osmium tetroxide and sodium metaperiodate to yield formaldehyde (isolated as its dimedone derivative), representing the activity at C-5 and C-5′ of the cuscohygrine. The radiochemical purity of the initial cuscohygrine was authenticated by reducing some of **32** to 6-undecanol (**31**) characterized as its 3,5-dinitrobenzoyl derivative.[42] The formaldehyde dimedone was found to have about a quarter of the activity of the cuscohygrine (Table II). This result is, thus, consistent with equal labeling at the C-2, C-2′, C-5, and C-5′ positions of the alkaloid and is in accord with the pattern of labeling found in cocaine.

The insignificant incorporations of other potential precursors of cocaine (sodium acetate and the pyrrolinium salt **5**) which were obtained in the present work and by others is considered to be a function of the method of feeding these compounds to the *Erythroxylon* species. Future efforts will be carried out using the leaf-painting technique for administering potential precursors of cocaine. Hopefully, these experiments will determine whether ornithine is indeed an obligatory biosynthetic precursor of cocaine, since one could always argue that the low but significant incorporation of ornithine into cocaine is the result of a minor or aberrant pathway to the alkaloid.

There are some species in which the presence of nicotine and the tropane alkaloids is well authenticated.[43] I predict that the biosynthesis of the pyrrolidine ring of nicotine and the tropane nucleus in any given species will follow the same biosynthetic route from ornithine. Thus, examples may be discovered in which the pyrrolidine ring of nicotine derived from [2-^{14}C]ornithine is labeled unsymmetrically, if the tropane alkaloids in that species are also labeled unsymmetrically.

Experimental Section[44]

Administration of [5-^{14}C]Ornithine to *Eythroxylon coca* and Isolation of the Alkaloids. The following procedure is the one actually used for the isolation of the alkaloids in experiment 1 (Table I) and is typical for the other experiments. At the time of feeding, the plants were 10–12 years old, about 1 m tall, and growing in a greenhouse (75–85 °F daytime, 60 °F at night). The seeds of the plant were initially obtained from the School of Pharmacy, University of San Marcos, Lima, Peru, through the courtesy of Dr. John Keenan. Over the years, plants have been successfully propagated from the seeds which the plants growing in Minnesota have produced. A voucher specimen of the plant with fruit attached is deposited in the herbarium of the Department of Botany, University of Minnesota, St. Paul campus. License to grow this plant was obtained from the U.S. Department of Justice, Drug Enforcement Administration, registration number AL3947186. The labeled ornithine hydrochloride was dissolved in water (20 mL), which also contained Tween 80 (60 mg). The feeding was spread over 4 days, about 5 mL/day being painted on the top sides of the leaves (about 1000) each morning with an artist's paint brush. No deleterious effect on the leaves was observed. Four weeks after the initial feeding the leaves of the plant were picked (fresh weight 190 g) and extracted immediately without drying. The leaves were chopped up in a Waring Blendor with a mixture of chloroform (2 L) and 10% Na_2CO_3 (100 mL). After standing for 1 day, the mixture was filtered. The brown aqueous layer (260 mL) had an activity of 1.11×10^8 dpm (17.3% of the activity fed). Putrescine dihydrochloride (200 mg) was added to an aliquot (50 mL) of this solution, which was then treated with 10% NaOH (20 mL) and benzoyl chloride (1.0 mL) and shaken for 2 h at 25 °C. The brown residue (224 mg) obtained on filtration was crystallized from ethanol and then sublimed (180 °C, 10^{-4} mm) to yield dibenzoylputrescine, which was crystallized to constant activity from ethanol to afford colorless plates, mp 177–178 °C (1.2 dpm/mg ≡ 0.002% of the activity of the aqueous layer). The chloroform layer was evaporated almost to dryness, diluted with ether, and extracted with 0.5 N HCl (4 × 100 mL). This acidic extract was clarified by extraction with a little ether and then made basic with Na_2CO_3. This solution was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated at 25 °C to afford the crude alkaloids. These were subjected to TLC on several plates of silica gel PF-254 (Merck), developing with a mixture of ethyl acetate–methanol–water–concentrated ammonia (85:13:1:0.5). In this system, cocaine has an R_f of 0.6, readily visible as a dark zone in the UV. This zone was extracted in a Soxhlet with a 1:1 mixture of methanol and ethyl acetate. This extract was evaporated, the residue was dissolved in ethyl acetate the solution was filtered, and the filtrate was treated with a solution of HCl in ethanol. On addition of a little ether, cocaine hydrochloride separated as colorless plates (317 mg). There was essentially no change in the specific activity of this material derived from [5-^{14}C]ornithine on recrystallization from a mixture of ethyl acetate and ether: mp 198–200 °C (lit.[47] mp 200–202 °C); $[\alpha]^{28}_D$ −67° (*c* 10, H_2O) (lit.[47] −71.95°). Its IR spectrum (KBr) was identical with an authentic specimen of cocaine hydrochloride. Radioactive assay of the TLC plates used for the separation of the cocaine indicated that there was considerable activity at lower R_f (0.0–0.15). This zone was extracted with methanol and rechromatographed on silica gel PF-254 (Merck), developing with a mixture of chloroform–ethanol–concentrated ammonia (60:40:5). A prominent zone corresponding to cuscohygrine (R_f 0.3) was evident (detected by spraying an end-strip with I_2 in benzene) and was extracted with methanol. The residue obtained on evaporation of this extract which had been acidified with HCl was made basic with NaOH. This solution was extracted with ether, which was evaporated, and the residue was distilled (140 °C, 10^{-4} mm) into a U-tube cooled in dry ice–acetone. The contents of the U-tube were washed out with ethanol which was treated with an ethanolic solution of picric acid (200 mg) to afford cuscohygrine dipicrate (97 mg), mp 226–227 °C dec, identical (IR, mmp, mass spectrum) with an authentic specimen: mass spectrum, (70 eV, relative percent; no molecular ion), *m/z* 224, 140 (7), 98 (8), 96 (7), 84 (100), 83 (14), 82 (20). On the original TLC plate there was a very faint zone, visible as a darker zone in UV light which had the same R_f (0.35) as nicotine. However, extraction of this zone and purification by distillation yielded no evidence for the presence of nicotine or other pyridines, which are readily detectable by UV spectroscopy. Under the experimental procedure used, 0.01 mg of nicotine would have been observed.

Degradation of the Cocaine from Experiments 1 and 2. Dilutions of the cocaine and its degradation products were carried out when necessary. The specific activities reported in Table II are calculated for undiluted material.

(a) Hydrolysis to Ecgonidine (15). Cocaine hydrochloride (920 mg) was refluxed in concentrated HCl (10 mL) for 18 h and then cooled, diluted with H_2O (20 mL), and extracted with ether. This dried (Na_2SO_4) ether extract was evaporated, and the residue was crystallized from hot water to yield benzoic acid (180 mg, 54%). There was essentially no change in activity after sublimation and recrystallization from aqueous methanol. The aqueous solution from the initial hydrolysis was lyophilized, and the residue was crystallized from a mixture of ethanol and ethyl acetate to yield ecgonidine hydrochloride (521 mg, 87%), mp 253–258 °C (lit.[47] mp 241 °C).

(40) McGaw, B. A.; Woolley, J. G. *Phytochemistry* **1978**, *17*, 257.

(41) Hess, K.; Bappert, R. *Liebigs Ann. Chem.* **1925**, *441*, 137. The sequence of reactions described was carried out by these authors on 161 g of dihydrocuscohygrine (**26**). The ultimate product was a 10:4 mixture of 6-undecanol and undecane, the latter presumably arising by hydrogenolysis of the intermediate allylic alcohol **30** in this sequence.

(42) Ansinger, F.; Fell, B.; Collin, G. *Chem. Ber.* **1963**, *96*, 716.

(43) (a) *Anthoceris frondosa*: Evans, W. C.; Ramsey, K. P. A. *J. Pharm. Pharmacol.* **1979**, *31*(Suppl), 9P. (b) *Anthoceris tasmanica*: *Bick*, I. R. C.; Bremner, J. B.; Gillard, J. W.; Winzenberg, K. N. *Aust. J. Chem.* **1974**, *27*, 2515. (c) *Duboisia myoporoides*: Mortimer, P. I.; Wilkinson, S. *J. Chem. Soc.* **1957**, 3967.

(44) Melting points were determined in glass capillaries and are corrected. IR spectra were determined on a Perkin-Elmer 710 spectrometer. UV spectra were determined on a Cary 17D spectrometer (purchased with NSF Equipment Grant CHE 78-23857). Optical rotations were determined in a Perkin-Elmer 241 polarimeter (donated by E.I. du Pont de Nemours and Co.). Mass spectra were determined by Dr. Roger Upham and his associates on an AEI-30 spectrometer. Radioactive materials were assayed *in* a Nuclear Chicago Mark II liquid scintillation counter using dioxane–ethanol as a solvent with the usual scintillators.[45]

(45) Friedman, A. R.; Leete, E. *J. Am. Chem. Soc.* **1963**, *85*, 2141.

(46) Leete, E. *J. Am. Chem. Soc.* **1956**, *78*, 3520.

(47) Holmes, H. L. In "The Alkaloids"; Manske, R. H. F.; Holmes, H. L., Eds., 1950; Vol. I, p 321.

(48) Leete, E.; Bodem, G. B. *J. Am. Chem. Soc.* **1976**, *98*, 6321.

(b) Oxidation of Ecgonidine to *N*-Methylsuccinimide (17). Ecgonidine hydrochloride (480 mg) in water (10 mL) was treated with a solution of silver sulfate (390 mg) in hot water (30 mL). The AgCl was filtered off, the filtrate was evaporated to 10 mL, which was treated with concentrated H_2SO_4 (3.5 mL) and chromium trioxide (2.0 g), and the mixture was refluxed for 2 h. The reaction mixture was cooled in ice, and sodium sulfite (2 g) was added to reduce the excess chromate. The green solution was extracted with benzene for 18 h. Evaporation of the dried (Na_2SO_4) extract yielded *N*-methylsuccinimide (63 mg, 26%), which was sublimed (90 °C, 10^{-2} mm), mp 66–67 °C.

(c) Conversion of Ecgonidine to Cycloheptanecarboxylic Acid (21). Ecgonidine hydrochloride (450 mg), sodium bicarbonate (1.5 g), methyl iodide (10 mL), and methanol (50 mL) were refluxed together for 24 h. The reaction mixture was filtered hot, and the filtrate was evaporated to dryness. The residue was dissolved in water (10 mL), shaken with moist silver hydroxide (from 2.5 g of $AgNO_3$) for 1 h, filtered, and lyophilized. The gray residue (1.81 g) was heated on a metal bath at 160 °C for 1 h in a N_2 atmosphere, the exit gases from the reaction being passed through aqueous 2 N HCl. This acidic solution was evaporated, and the residue was shaken with 10% NaOH (10 mL) and benzoyl chloride (0.2 mL) for 1 h. This solution was then extracted with ether. The dried ($MgSO_4$) extract was evaporated, and the residue was distilled (120 °C, 10^{-3} mm) to yield *N*,*N*-dimethylbenzamide (220 mg, 73%) as a colorless oil, identical (IR) with an authentic specimen. From hexane at −20 °C were obtained colorless needles, mp 38–40 °C. The main reaction mixture was cooled and dissolved in water (30 mL), and the brown solution was hydrogenated for 5 h at 3 atm in the presence of Adams catalyst (0.1 g). The filtered reaction mixture was acidified with HCl and extracted with ether for 16 h. The dried (Na_2SO_4) extract was evaporated, and the residue was distilled (130 °C, 10^{-3} mm) to afford cycloheptanecarboxylic acid as a colorless oil, with a weak odor (170 mg, 59%) having an IR spectrum identical with an authentic specimen. In a preliminary experiment with nonlabeled ecgonidine, the product was also characterized as its amide, plates from ethanol, mp 199–200 °C (lit.[49] 195 °C).

(d) (Dimethylamino)cycloheptane Methiodide (19). Cycloheptanecarboxylic acid (158 mg) was transferred with ether to a 10-mL pear-shaped flask, the ether then being removed by evaporation in vacuo. Concentrated H_2SO_4 (1.5 mL) was added to the flask, and the solution was cooled to 0 °C. Sodium azide (230 mg) was added, and the flask was connected to a train in which CO_2-free N_2 was bubbled through the reaction mixture, then 5% $KMnO_4$ in 2 N H_2SO_4 (to remove hydrazoic acid), and then into two tubes containing saturated $Ba(OH)_2$ solution. The reaction mixture was slowly warmed to 70 °C during 1 h. After an additional hour the precipitated $BaCO_3$ was filtered off rapidly, washed with H_2O, ethanol, and ether, and dried at 80 °C (199 mg, 91%). The contents of the reaction flask were added to ice, neutralized with NaOH, and extracted with ether (5 × 20 mL). This ether extract (not dried) was evaporated in the presence of methyl iodide (5 mL), and the residue was refluxed with a mixture of methyl iodide (5 mL), sodium bicarbonate (0.5 g), and methanol (20 mL) for 18 h. The residue obtained on evaporation of the reaction mixture was extracted with hot $CHCl_3$. Evaporation and crystallization of the residue from a mixture of ethanol, ethyl acetate, and ether yielded long colorless needles of (dimethylamino)cycloheptane methiodide (249 mg, 82%), mp 274–275 °C dec (lit.[31] mp 259 °C), identical (IR) with material made from authentic cycloheptylamine.

(e) Pimelic Acid (24). (Dimethylamino)cycloheptane methiodide (204 mg) was dissolved in water (5 mL) and shaken with AgOH (from 0.5 g of $AgNO_3$) for 1 h. The filtered reaction mixture was lyophilized at 20 °C, and the residue was heated (180 °C, 10^{-3} mm), the reaction products being condensed in a U-tube cooled in dry ice–acetone. The distillate was dissolved in ether (50 mL) containg a drop of pyridine and osmium tetroxide (270 mg). After standing for 18 h, the black mixture was evaporated, and the residue was refluxed with a mixture of sodium sulfite (1 g), methanol (20 mL), and water (20 mL) for 2 h. The filtered reaction mixture was evaporated to dryness, and the residue was dissolved in water (5 mL) and extracted with ether (5 × 10 mL). The ether was evaporated, and the residue was dissolved in water (20 mL) and heated on a steam bath for 3 h with potassium permanganate (0.4 g). Sulfur dioxide was then passed into the reaction mixture until a clear solution was obtained. After the addition of 2 N H_2SO_4 (1 mL), the solution was extracted with ether for 6 h. Evaporation of the extract yielded pimelic acid (126 mg, 71%), which was sublimed (130 °C, 10^{-3} mm) and crystallized from a mixture of benzene and hexane to afford colorless plates, mp 99–101 °C, identical (mmp, IR) with an authentic specimen. The dianilide was made by stirring together pimelic acid (10 mg), aniline (15 mg), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (50 mg) in water (1 mL). The precipitate which separated almost immediately was crystallized from a mixture of benzene and hexane to afford the dianilide of pimelic acid as silvery plates (11 mg), mp 153 °C. TLC on silica gel PF-254, developing with chloroform–ethyl acetate–ethanol (85:10:5), indicated that the anilide was pure (R_f 0.3), uncontaimated with any dianilide of adipic acid.

(f) Schmidt Reaction on Pimelic Acid. This reaction was carried out as previously described for the conversion of cycloheptanecarboxylic acid to cycloheptylamine. Barium carbonate (104 mg, 95%) was obtained from pimelic acid (45 mg), concentrated H_2SO_4 (0.5 mL), and sodium azide (150 mg). The cooled reaction mixture, which contained crystals of cadaverine sulfate, was added to 10% NaOH (10 mL) and benzoyl chloride (0.2 mL). The precipitate which formed after shaking for 1 h was removed and crystallized from a mixture of benzene and hexane to afford colorless plates of dibenzoylcadaverine (66 mg, 76%), mp 129–130 °C. Further purification was effected by distillation (190 °C, 10^{-4} mm) and crystallization from benzene, mp 132–133 °C (lit.[50] mp 132 °C).

Degradation of the Cuscohygrine (from Experiment 1). Cuscohygrine dipicrate (288 mg) was dissolved in hot water (20 mL) containing 48% HBr (2 mL). The solution was extracted with ether to remove picric acid, and the solution was lyophilized to afford a crystalline residue, which was crystallized from a mixture of 95% ethanol–ethyl acetate to yield cuscohygrine dihydrobromide (115 mg) mp 249 °C (lit.[41] mp 234 °C), as silvery plates. Sodium borohydride (0.25 g) was added to solution of cuscohygrine dihydrobromide (258 mg) in 90% ethanol (10 mL), and the mixture was stirred at 25 °C for 18 h. The solution was acidified with HCl, evaporated to dryness, made basic with NaOH, and extracted with chloroform (3 × 20 mL). Methyl iodide (4 mL) and ethyl acetate (40 mL) were added to this extract, and the mixture was refluxed for 1 h. Evaporation yielded a crystalline residue which was dissolved in water (10 mL) and shaken with AgOH (from 0.5 g of $AgNO_3$) for 1 h. The filtered solution was lyophilized, and the residue was distilled (180 °C, 10^{-4} mm) into a U-tube cooled in dry ice–acetone. The contents of the tube were dissolved in methanol (10 mL) and hydrogenated at 3 atm of pressure in the presence of Adams catalyst (0.1 g) for 1 h. Methyl iodide was added to the filtered solution, and the mixture was refluxed for 2 h. Evaporation afforded the crystalline dimethiodide **28** (152 mg). This was subjected to a second Hofmann degradation using the conditions described for the first one. The contents of the U-tube from the distillation were dissolved in ether (30 mL), containing a drop of pyridine, and osmium tetroxide (300 mg) was added. After standing for 20 h, the mixture was evaporated, and the residue was refluxed with sodium sulfite (1 g), methanol (10 mL), and water (10 mL) for 2 h. The filtered solution was evaporated to dryness, and the residue was extracted with methanol. The residue (102 mg) obtained on evaporation was dissolved in water (10 mL) and $NaIO_4$ (300 mg) was added. After standing for 1 h, the solution was distilled into a solution of dimedone (300 mg) in water. After the solution was left standing for 24 h, the formaldehyde–dimedone was filtered off (73 mg), dried, sublimed (150 °C, 10^{-4} mm), and crystallized from aqueous methanol to afford needles, mp 199–200 °C, identical with an authentic specimen. In a parallel degradation of cuscohygrine, the diene (**32**) from the second Hofmann degradation was dissolved in methanol and hydrogenated (3 atm, 0.1 g of PtO_2). The filtered solution was evaporated, and the residue was distilled (130 °C, 10^{-2} mm) to afford a colorless oil (40 mg). This was dissolved in benzene (5 mL) and refluxed with pyridine (0.5 mL) and 3,5-dinitrobenzoyl chloride (50 mg) for 30 min. Water and ether were added, and the organic layer was washed successively with 1 N HCl, 10% Na_2CO_3, and water and dried over $MgSO_4$. The residue obtained on evaporation was crystallized from methanol to afford colorless needles of the 3,5-dinitrobenzoate of 6-undecanol (27 mg), mp 44–45 °C (lit.[42] 48 °C), identical (IR, MS, mmp) with an authentic specimen.

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Registry No. 13 dipicrate, 80484-34-0; 13 2HBr, 80484-35-1; **15** HCl, 74242-55-0; **18**, 80484-36-2; **19**, 18636-96-9; **24** dianilide, 80484-37-3; **28**, 80484-39-5; 6-undecanol 3,5-dinitrobenzoate, 80484-49-7; cocaine, 50-36-2.

(49) Willstätter, R. *Chem. Ber.* **1898**, *31*, 2498.

(50) von Braun, J.; Pinkernelle, W. *Chem. Ber.* **1934**, *67*, 1056.