MORPHINANDIENONE ALKALOIDS
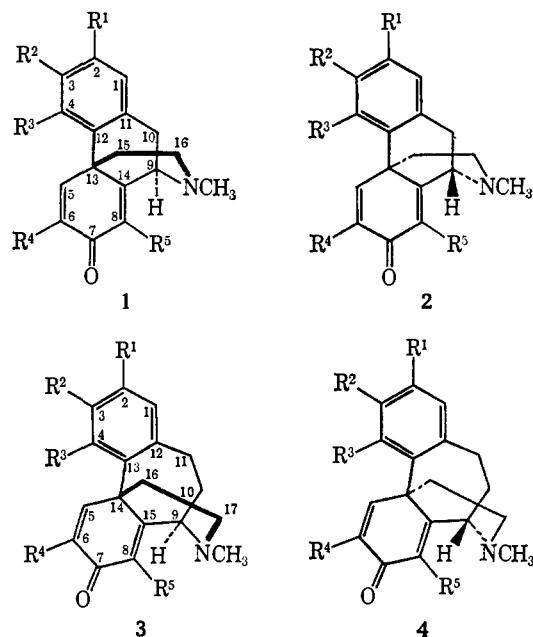
K. L. STUART

Department of Chemistry, University of the West Indies, Kingston 7, Jamaica

Contents

I. Introduction

The term morphinandienone alkaloids was first introduced by Kühn and Pfeifer[1] in 1965 to describe the morphinan-7-one or iminoethanophenanthren-2-one structure and is now in common usage. With the recent isolation and synthesis of several of these alkaloids, it has become clear that this group has certain characteristic properties which set it apart from the majority of other morphinan compounds. It is convenient to relate each member of the group to the morphinandienone skeletons 1 and 2 and the homomorphinandienone skeletons 3 and 4, where 1 and 3 represent the *R* configuration and 2 and 4 the *S* configuration. Reduced morphinandienones isolated from plants are confined to saturation of the 8,14-olefinic bond and reduction of the ketone to form a dienol.

The first indication of the biosynthetic importance of these compounds was the proposal in 1957 by Barton and Cohen[2] that certain members of this group were intermediates in the formation of the alkaloids thebaine (5) and sinomenine (6).
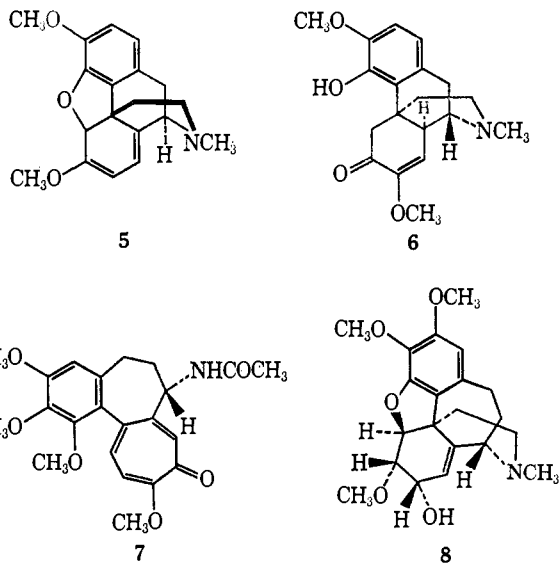

1   2

3   4

The correctness of this proposal is clearly attested to in the discussion set out in section V of this review. Battersby and his research group[3] have also recently shown that the homomorphinandienones are the key to the intriguing problem of the biosynthesis of colchicine (7), and it is now believed that these compounds are precursors to the homomorphine compound kreysiginine (8). To date, morphinandienones and re-

5   6

7   8

duced morphinandienones have been isolated from five genera, namely the *Cassytha, Croton, Corydalis, Papaver,* and

(1) L. Kühn and S. Pfeifer, *Pharmazie,* 20, 659 (1965).
(2) D. H. R. Barton and T. Cohen, "Festschrift Prof. Dr. Arthur Stoll zum Siebzigsten Geburtstag," Birkhauser, Basel, 1957, p 117.
(3) A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Commun.,* 605 (1966).

Sinomenium genera, and they most probably exist in the *Stephania* genus. Homomorphinandienones have so far been isolated from *Androcymbium* and *Colchicium* general but they probably will soon be separated from plants in the *Kreysigia* genus.

All the known morphinandienones are listed in a tabular form in Table I along with their physical properties and those of their derivatives.

II. Important Chemical Reactions

There are some chemical reactions which have proven useful in the elucidation of new morphinandienone structures while others are of biogenetic significance. Since many of these have general applicability to most members of this group, discussion in this section will be confined to these reactions.

A. REDUCTIVE CLEAVAGE

This reduction was carried out with sodium in liquid ammonia. [*1-³H*]Salutaridine (9) was first converted to *O*-methyl-[*1-³H*]salutaridine using methyl *p*-toluenesulfonate and sodium hydride in dimethylformamide. After reductive cleavage, the product was treated with diazomethane to yield radioactive (*R*)-(−)-laudanosine (10).[4] This type of reductive cleavage was first demonstrated in the proaporphine group of alkaloids[5] and is useful in determining the configuration of the single asymmetric center present in these compounds.

9   10
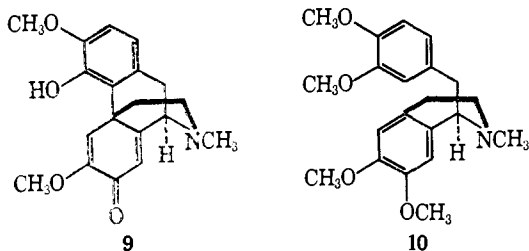
This reaction has also been used in the homomorphinandienone series. *O*-Methylandrocymbine (11) was converted to the 1-phenethylisoquinoline 12. Compound 12 was fully characterized by an unambiguous synthesis, and this reaction in addition to ORD evidence established the *S* configuration of androcymbine.[6]

11   12, R¹ = CH₃
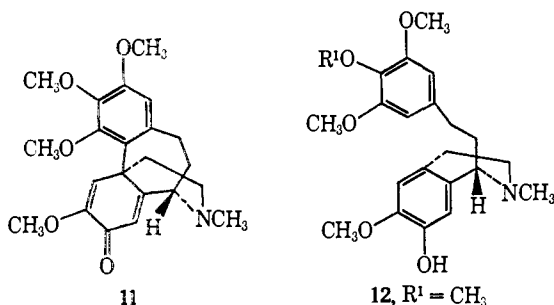
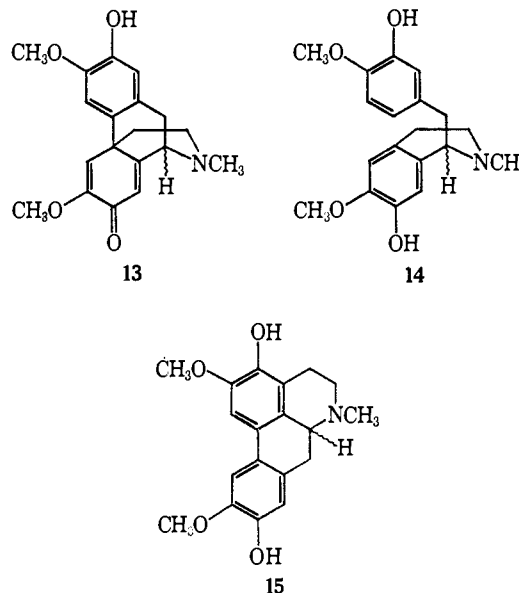(4) D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc. C*, 128 (1967).
(5) M. P. Cava, K. Normura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *Chem. Ind. (London)*, 282 (1964).
(6) A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavy, *Chem. Commun.*, 228 (1965).

B. REARRANGEMENT REACTIONS

1. Aporphines

Isosalutaridine (13), which was synthesized from reticuline (14) by oxidative coupling (see section III), was converted to the aporphine 15 by an acid-catalyzed rearrangement[7] analo-

13   14

15

gous to that shown by morphine.[8]

2. Phenanthrenes

Amurine (16) was converted to 1,2-dihydroxy-4-(β-*N*-methylaminoethyl)-6,7-methylenedioxyphenanthrene (17) when it was heated in 3 *N* hydrochloric acid under nitrogen for 3 hr at 100° in a 92% yield.[9] It has been suggested that the mechanism of this rearrangement is analogous to that proposed by Stork[10] for the transformation of thebaine into thebenine and is as outlined from 16 → 17.

When the dienol nudaurine (18) was heated at 100° for 10 min, a 91% yield of the phenanthrene 19 was obtained.[9]

By using the Hofmann degradation method, amurine methiodide was converted to 2-hydroxy-3-methoxy-6,7-methylenedioxyphenanthrene (20) in 34% yield and with β-dimethylaminoethanol (21) being also formed by a mechanism outlined from 16 → 20 + 21.[9]

In a similar manner, flavinantine (22) was converted to 2-hydroxy-3,6,7-trimethoxyphenanthrene (23) and compound 21. The latter was trapped as the chloroaurate.[11]

3. Morphine-Type Compounds

Salutaridine (9) was first reduced by sodium borohydride to a mixture of corresponding salutaridinols which were then separated chromatographically on aluminia to yield salutaridinol I (24) and salutardinol II (25). Both dienols were then

(7) B. Franck, J. Lubs, and G. Dunkelmann, *Angew. Chem. Int. Ed. Engl.*, 6, 969 (1967).
(8) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, 1954.
(9) W. Döpke, H. Flentje, and P. W. Jeffs, *Tetrahedron*, 24, 4459 (1968).
(10) G. Stork, "The Alkaloids," Vol. II, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1952, p 161.
(11) K. L. Stuart, V. Teetz, and B. Franck, *Chem. Commun.*, 333 (1969).

16

17

18

19

16 1. CH₃I
    2. OH⁻

+ HOCH₂CH₂N(CH₃)₂ CH₃

21

20
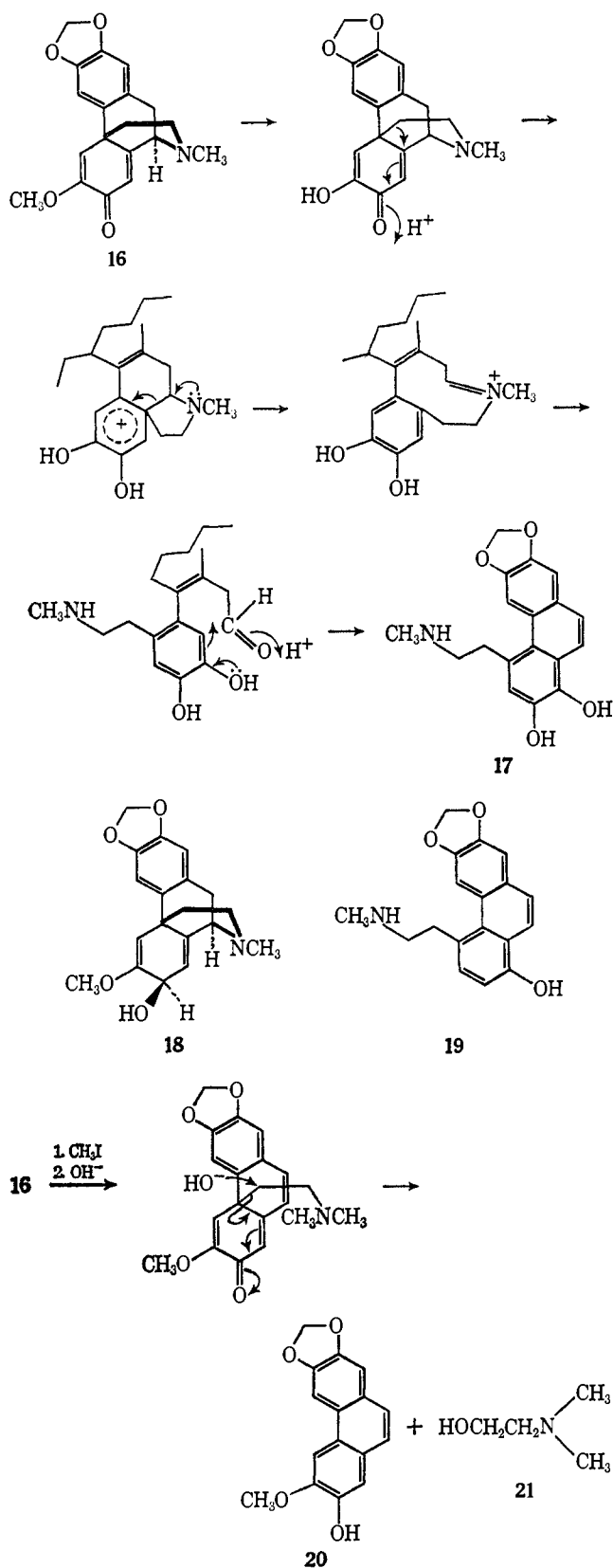
converted to thebaine (5) by allowing solutions of these compounds to stand in 0.2 M phosphate buffer at room temperature for periods varying from 60 to 94 hr (see 24A → 5 for mechanism). This conversion mimicks the now established biosynthetic conversion of salutaridine to thebaine (section V). The in vitro rate of conversion of 24 to thebaine has been

22, R¹ = CH₃

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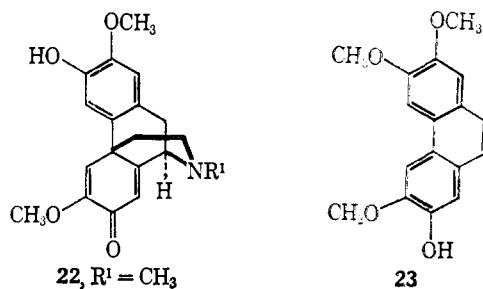
shown to be 1.35 times that of 25.[12] In a similar manner (±)-salutaridine was converted to (±)-thebaine by treating a mixture of (±)-salutaridinols with 1 N hydrochloric acid at room temperature for 1 hr.[13] It has also been demonstrated that sinoacutine (26) can be converted to the enantiomer of thebaine by a similar process.[14]

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24A

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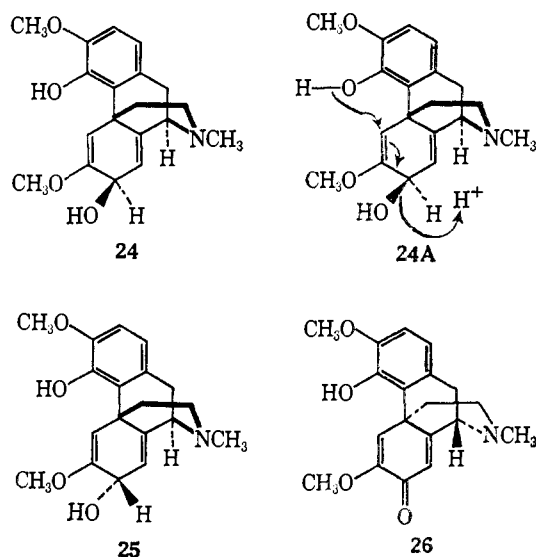
4. New Cross-Conjugated Dienones

There are now two well-documented cases of the acid rearrangement of morphinandienols to new cross-conjugated dienones.[15,16]

Norsinoacutine (27) was first converted to a mixture of N-acetylnorsinoacutinols (28) and allowed to stand overnight at room temperature in 1 N hydrochloric acid; the dienone 29 was isolated.[15] In view of the well-established rearrangement of salutaridinols 24 and 25 to thebaine,[12] these results were surprising. It has been shown recently, however, that thebaine methoperchlorate would be rearranged to 7,8-dehydrometathebaine methoperchlorate (30) by treatment with aqueous perchloric acid,[17] and the intermediacy of the oxonium ion 31 has been established.[18] It was therefore possible, in the case of the N-acetylnorsinoacutinol experiment, that the usual

(12) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, J. Chem. Soc., 2423 (1965).
(13) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, ibid., C, 2030 (1969).
(14) J.-S. Hsu, S.-Y. Lo, and J.-H. Chu, Sci. Sinica, 13, 2016 (1964).
(15) K. L. Stuart, C. Chambers, and D. Byfield, J. Chem. Soc. C, 1681 (1969).
(16) A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber, and J. Staunton, Chem. Commun., 1214 (1968).
(17) W. Fleischhacker, R. Hloch, and F. Viebőck, Monatsh., 99, 1568 (1968).
(18) R. T. Channon, G. W. Kirby, and S. R. Massey, Chem. Commun., 93 (1969).

dehydro furan ring closure was first achieved and it was this product which underwent further rearrangement to yield the dienone 29. A similar dienone, 32, was also obtained from the morphinandienone 33 by way of the mixture of dienols 34 and by acid-catalyzed rearrangement.[16] When the dienone 32 was heated with magnesium iodide and the product reduced with lithium aluminum hydride, the two phenols 35 and 36 were produced.


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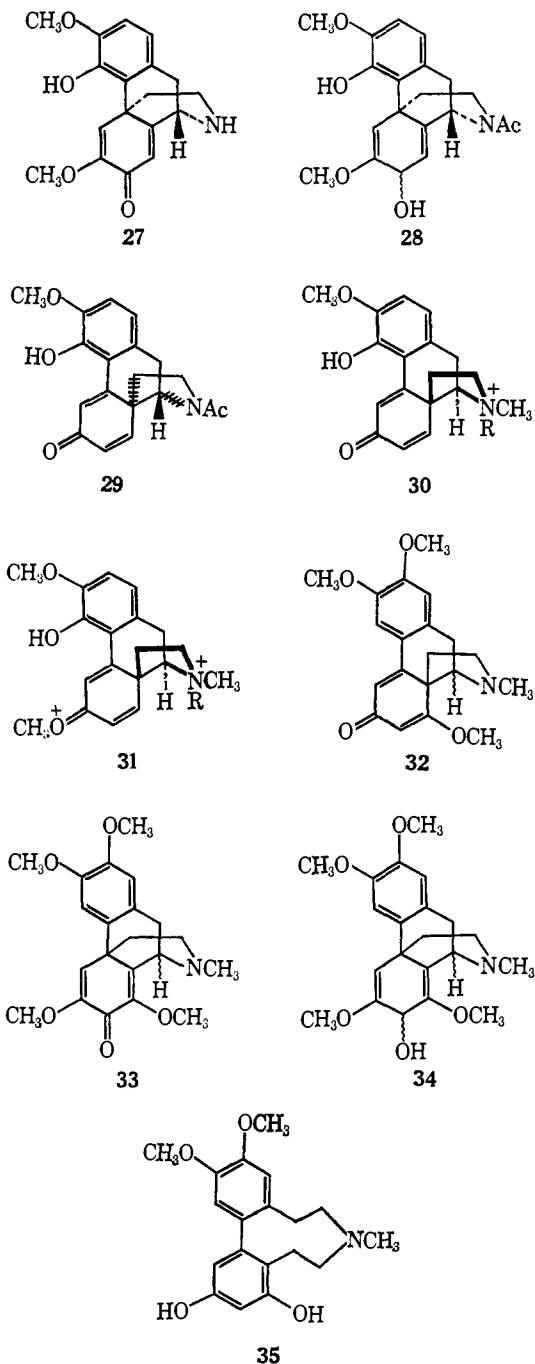
O-Methylation of both 35 and 36 produced protostephanine (37), an alkaloid isolated from *Stephania japonica* Miers (see section V).

C. OZONOLYSIS OF DIENOLS

Sodium borohydride reduction efficiently converts morphin-andienones into the corresponding dienols, and ozonolysis of


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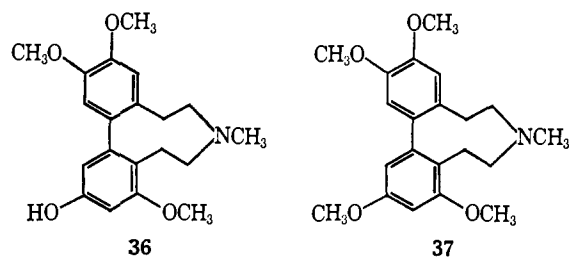
these and the one known naturally occurring morphinandienol, nudaurine (18), have allowed the C-7 configuration to be established. For example, sodium [³H]borohydride reduction of salutaridine (9) yielded [³H]salutaridinol I (38) and [³H]salutaridinol II (39). 38 was ozonized at −70° in ethanol and the reaction mixture hydrogenated directly over Adam's catalyst. After the total product was hydrolyzed with alkali, it was diluted with nonradioactive D-glyceric acid. The *p*-bromophenacyl derivative of this acid was purified by crystallization and chromatography and was shown to be still radioactive. This therefore demonstrated that *p*-bromophenacyl D-[³H]-glycerate was obtained and salutaridinol I must have the configuration at C-7 as shown in 38. In a similar manner salutaridinol II was assigned the configuration at C-7 as shown in 39.[4]

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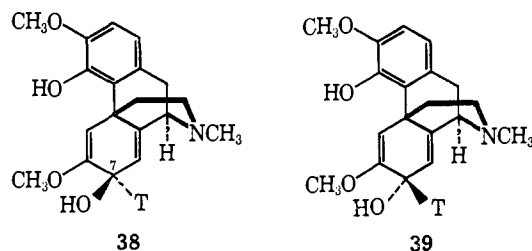
Using a similar series of ozonolysis experiments, it was shown that nudaurine (18) from *Papaver nudicaule* was identical with amurinol I, and so established the C-7 configuration.[19]

D. HYDROGENATION

Hydrogenation experiments have proven very useful in establishing the configuration of reduced morphinandienones. For example, the hydrogenation of salutaridine (9) and 8,14-dihydrosalutaridine (40) with Adam's catalyst in ethanol yielded a common reduction product to which structure 41 could be assigned.[20] This is not an unexpected result if one examines a stereochemical projection of salutaridine (9A).

9A
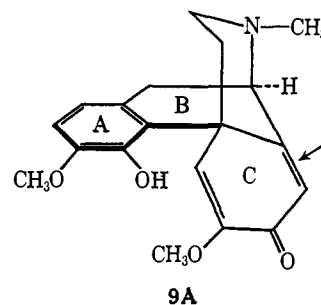
(19) D. H. R. Barton, R. James, G. W. Kirby, W. Döpke, and H. Flentje, *Chem. Ber.*, 100, 2457 (1967).
(20) L. J. Haynes, G. E. M. Husbands, and K. L. Stuart, *J. Chem. Soc. C*, 951 (1968).

The less hindered side of the planar ring C is indicated by the arrow, and so it is reasonable to expect the addition of hydrogen from this side of the molecule. Hydrogenation products from amurine (16) require some comment. When 16 was reduced in the presence of prereduced PdO_2–$BaSO_4$ catalyst in methanol, the two major products obtained were the tetrahydro derivative 42 (65% yield) and hexahydroamurine (43)


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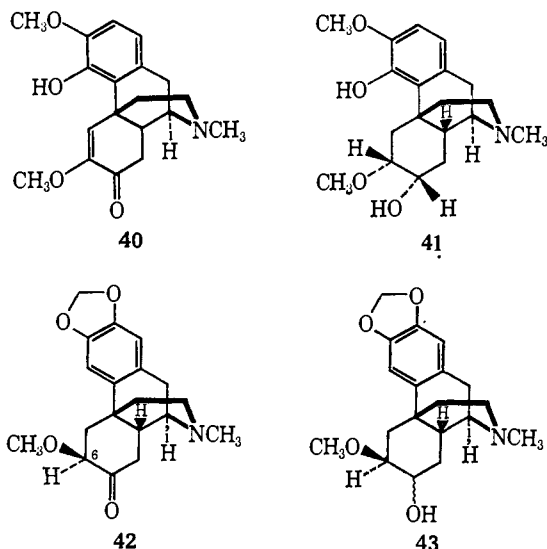
(13% yield). Catalytic reduction over Adam's catalyst only produced 43.[9] The unexpected configuration at C-6 can probably be explained by the fact that this compound was isolated by chromatography over alumina, and it seems very likely that there was equilibration to the more stable form on the column. In the case of compound 43, it is proposed that epimerization at the C-6 center occurred during the Jones oxidation to produce 42, a step necessary for the establishment of structure 43.[9]

E. RADIOISOTOPIC LABELING

Since radioisotopically labeled morphinandienones have played important roles both in biosynthetic studies and in structural elucidation, they will be discussed briefly. Attention will be confined mainly to the introduction of the tritium label. Much of the background to this technique is presented in the paper by Kirby and Ogunkoya.[21] By virtue of the fact that many morphinandienone alkaloids possess an unsubstituted position *para* to a phenolic group, it has been possible to introduce tritium exclusively at this C-1 position. Experimentally the exchange can be accompanied with the minimum of decomposition if it is carried out in dimethylformamide in a sealed tube under nitrogen at 100° for approximately 72 hr.[22,23] The morphinandienones salutaridine, sinoacutine, 8,14-dihydrosalutaridine, and 8,14-dihydronorsalutaridine have been labeled in this manner. It was shown, however, in the case of isosinomenine (44) that when the exchange in tritiated water was carried out in the presence of potassium *t*-butoxide, [8-³H]isosinomenine was the predominant product.[22] It is important in these exchange experiments to establish unequivocally the location of the label. For this reason it

is usual that parallel experiments are carried out using D_2O in conjunction with nmr control. This will indicate the hydrogens replaced under the conditions of the exchange experiment. Wherever possible it is usual to seek further evidence from experiments in which the tritium can be replaced by substitution. In the case of [1-³H]salutaridine, for example, it was determined that 1-bromosalutaridine had less than 1% of the original activity.[12] The use of a parallel deuterium experiment has another advantage. It shows up unexpected results. For example, when sinomenine 6 was heated in deuterium oxide–dimethylformamide containing dimethylamine, the hexadeuterio derivative 6A was obtained.[22] The authors have expressed the view that exchange at C-14 must have involved the formation of the corresponding carbanion which was stabilized by conjugation with the adjacent enone system. Exchange at C-10 probably resulted from an expulsion of the nitrogen by this anion to form the dienone 45. This interme-

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6A

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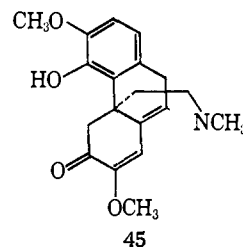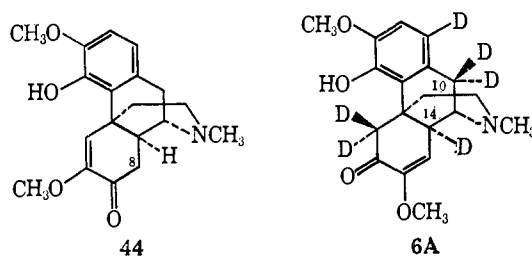
diate allowed exchange at C-10 since it was vinylogously α to the carbonyl group, and as this was conceived as being reversible, sinomenine was re-formed after the exchange.[22]

[6-Methoxy-³H]Isosinomenine was prepared by the equilibration of sinomenine in [methoxy-³H]methanol.[22] If the starting alkaloid is phenolic, a tritiated O-methyl group can be introduced into the molecule by treating the phenol with diazomethane in the presence of tritiated water.[24] An example of this labeling was the preparation of [³H]-O-methylandrocymbine from androcymbine 46.[8]

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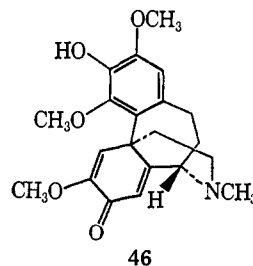
The introduction of tritium at C-7 in morphinandienones, as discussed earlier, can be accomplished quite easily by using sodium [³H]borohydride, so forming the labeled dienol.[12]

(21) G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 6914 (1965).
(22) D. H. R. Barton, A. J. Kirby, and G. W. Kirby, *ibid.*, C, 929 (1968).
(23) K. L. Stuart and L. Graham, unpublished work.
(24) K. J. Van Der Merwe, P. S. Steyn, and S. H. Eggers, *Tetrahedron Lett.*, 3923 (1964).

Although the introduction of tritium into phenolic compounds is now a relatively easy undertaking, it should be remembered that if these are to be used in biosynthetic studies, the effect of the recently discovered "NIH" shift which can occur during enzymatic hydroxylation of aromatic substrates must be borne in mind.[25]

III. Chemical Syntheses

A. OXIDATIVE COUPLING

Several one-electron inorganic oxidizing reagents have been used to perform biosynthetic-type syntheses of some of the phenolic members of this group. Radical producing enzymes like peroxidase, tyrosinase, and laccase have so far not been successfully used in this area.

1. Isosalutaridine and Pallidine (2-Hydroxy-3,6-dimethoxy-morphinandienone)

(±)-Reticuline (14) was oxidized with manganese dioxide in chloroform in the presence of silica gel to yield isosalutaridine (13) in 4% yield.[7] This also achieves the syntheses of (±)-pallidine. (S)-(−)-Pallidine (47) was recently isolated from *Corydalis pallada* var. tenuis Yatabe.[26] Isosalutaridine (0.9%) was also produced when 14 was oxidized using potassium ferricyanide in the two-phase system 5% aqueous sodium hydrogen carbonate–chloroform under nitrogen. Under these conditions (±)-isoboldine (48) was isolated in a 0.4% yield, as well as a compound with an α-methoxylated cross-conjugated cyclohexadienone system (0.05%).[26a] Although no structural assignment was made, this latter compound could be the dimeric alkaloid 49. O-Methylation of isosalutaridine with diazomethane produced (±)-O-methylflavinantine.
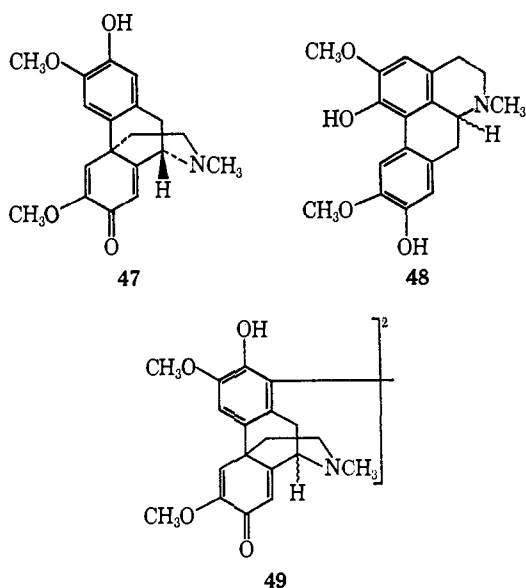
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2. Salutaridine ((R)-4-Hydroxy-3,6-dimethoxymorphinandienone)

Dilution with inactive (+)-salutaridine (9) has been used to prove the formation of this alkaloid when labeled (±)-reticuline (50) was subjected to a variety of oxidizing conditions.[4] When potassium ferricyanide was used, there was a 0.015% yield. Manganese dioxide gave 0.011%, potassium nitrosodisulfonate, 0.0054%, and ferric chloride, ca. ~0.0007% yield of (+)-salutaridine. Potassium ferricyanide oxidation of (−)-reticuline yielded 0.0044% of (+)-salutaridine, while oxidation of labeled (+)-reticuline gave insignificant amounts of labeled (+)-salutaridine. The low yield obtained in these experiments was probably due to the fact that salutaridine itself seemed to be more rapidly oxidized than reticuline.[4] If this is true, an appropriate carbonyl trapping reagent could probably greatly improve these yields. In the potassium ferricyanide experiments there was some evidence that the dimeric compound 1,1'-dehydrodisalutaridine (51) was also formed.

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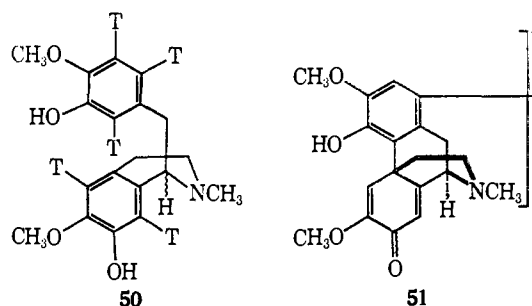
3. 2-Hydroxy-3,6,8-trimethoxy-morphinandienone

Ferricyanide oxidation of the isoquinoline derivative 52 produced the morphinandienone 53 in 1.7% yield as well as (±)-isoboldine (48). O-Methylation of 53 produced protostephanone (33). Formation of (±)-isoboldine required the loss of one methoxy group, probably as formaldehyde.[16]

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4. 2-Hydroxy-3,6-dimethoxy-homomorphinandienone

The $C_{20}H_{23}NO_4$ racemic homomorphinandienone 54 was synthesized from 55 by potassium ferricyanide oxidation of the latter in 5% sodium hydrogen carbonate and chloroform.[27]

5. Unsuccessful Oxidative Attempts

It is instructive to be aware of some of the oxidation experiments which were unsuccessful. For example, oxidation of compound 55 with potassium ferricyanide in 8% ammonium

(25) G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, 157, 1524 (1967).
(26) T. Kametani, M. Ihara, and T. Honda, *Chem. Commun.*, 1301 (1969).
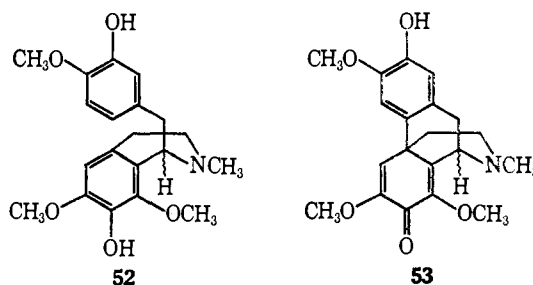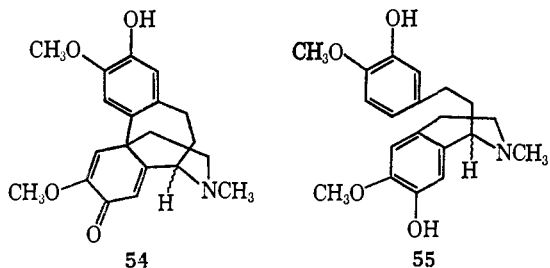(26a) T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, *J. Chem. Soc. C*, 2034 (1969).

(27) T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *Chem. Commun.*, 1605 (1968).

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acetate at room temperature yielded none of the required product, **54,** nor did ferric chloride at room temperature for 7 days. Similarly, compound **56** gave no detectable amounts of homomorphinandienones. In this latter case, steric factors were probably the predominant reason for failure.[28] Several oxidative conditions have been tried in an attempt to produce 2-hydroxy-3,4,6-trimethoxymorphinandienone **(57)** from 1,2,-3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4,5-dimethoxybenzyl)-6-methoxy-2-methylisoquinoline **(58),** but without success. In one case, when **58** was treated with a 35 molar equiv of ferric chloride at room temperature for 20 hr and then at 60–80° for an additional 48 hr, 3-hydroxy-4,5-dimethoxybenzaldehyde **(59)** and cyclopent[ij]isoquinoline **(60)** were the major products. A mechanism for this transformation is also discussed.[29]

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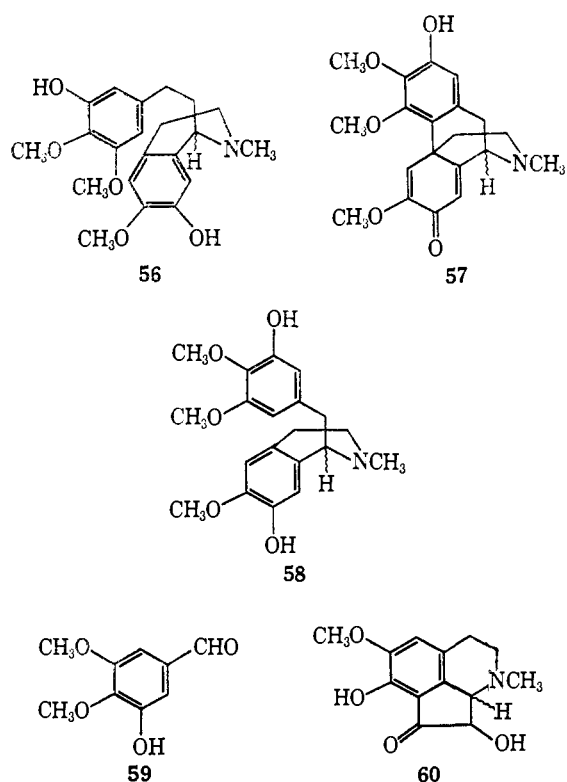
B. PSCHORR-TYPE SYNTHESES

The Pschorr reaction has been used frequently in the past for the syntheses of aporphine alkaloids (example **66**).[30] Hey in a series of papers has shown, however, that the synthesis of dienone-type compounds was possible.[31] For example, the

diazonium salt **61** could be converted to the dienone **62.**

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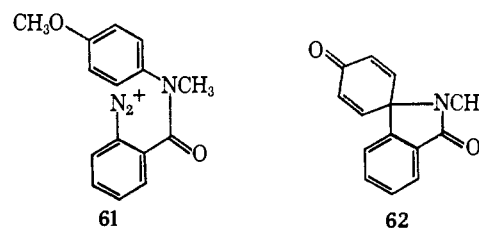
Scheme I indicates the possible reaction pathways, and in the

Scheme I

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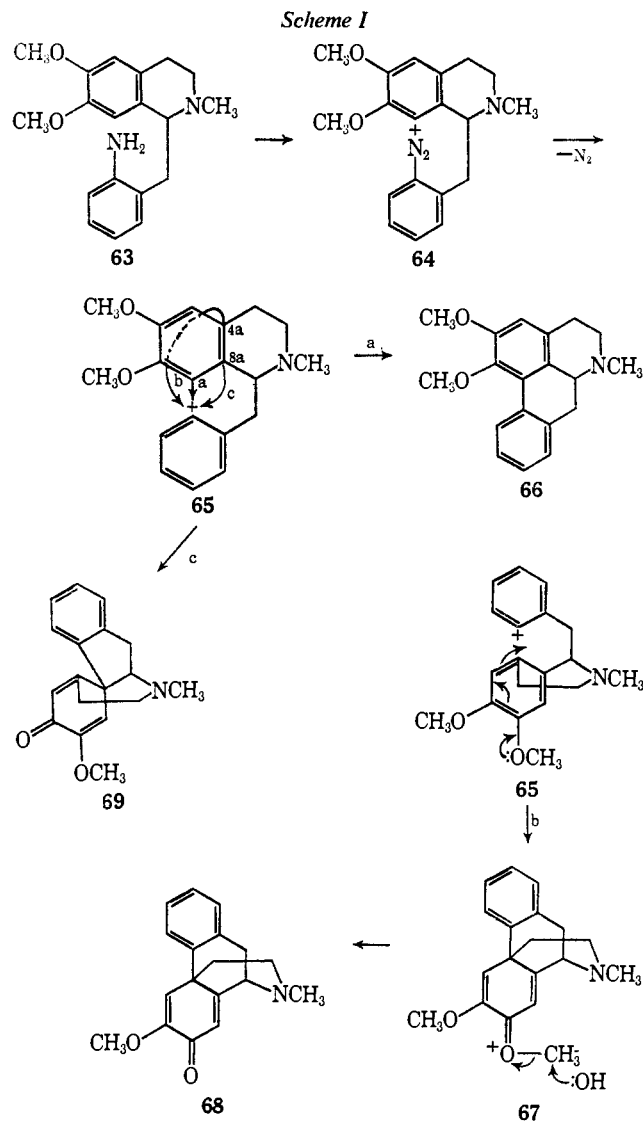
case of the formation of the morphinandienone **68,** the mechanism proposed indicates that the nucleophilic attack on position 4a is facilitated by the E-effect of an alkoxy group.[32]

1. Salutaridine ((R)-4-Hydroxy-3,6-dimethoxymorphinandienone)

(±)-1-(2-Amino-3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetra-hydro-6,7-dimethoxy-2-methylisoquinoline **(70)** was first

(28) T. Kametani, H. Yagi, F. Satoh, and K. Fukumoto, *J. Chem. Soc. C,* 271 (1968).

(29) T. Kametani and I. Noguchi, *ibid., C,* 447 (1968).

(30) M. Shamma and W. A. Slusarchyk, *Chem. Rev.,* 64, 59 (1964).

(31) D. H. Hey, J. A. Leonard, C. W. Rees, and A. R. Todd, *J. Chem. Soc. C,* 1513 (1967), and references cited therein.

(32) T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Pharm. Bull.,* 17, 1809 (1969).

resolved by using (+)-di-p-toluoyltartaric acid. Diazotization was achieved by treatment with sodium nitrite in 1 N sulfuric acid which was followed by thermal decomposition at 70° to yield (+)-salutaridine (9) and (−)-laudanidine (71). Similar treatment of racemic 2-aminobenzylisoquinoline (70) yielded (±)-salutaridine.[18]

70, R¹ = PhCH₂; R² = NH₂
71, R¹ = R² = H
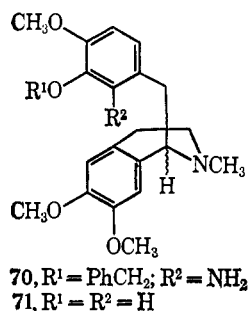
2. Sinoacutine ((S)-4-Hydroxy-3,6-dimethoxymorphinandienone)

Resolution of the 2-aminobenzylisoquinoline (70) with (−)-di-p-toluoyltartaric acid followed by diazotization and thermal decomposition as described above yielded sinoacutine (26) and (+)-laudanidine (71).[18]

3. (±)-Amurine (2,3-Methylenedioxy-6-methoxymorphinandienone)

The structure of amurine (16) isolated from *Papaver amurense*[9] has now been confirmed by the synthesis of (±)-amurine.[33] Diazotization of the aminoisoquinolines 72 and 73 followed

72, R¹ = Et; R² = NH₂
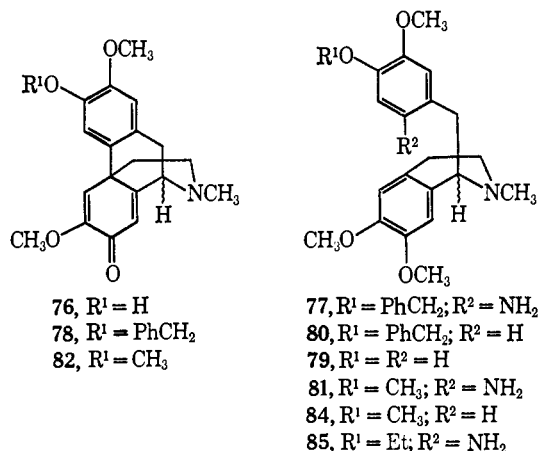73, R¹ = CH₃; R² = NH₂
75, R¹ = CH₃; R² = H

74
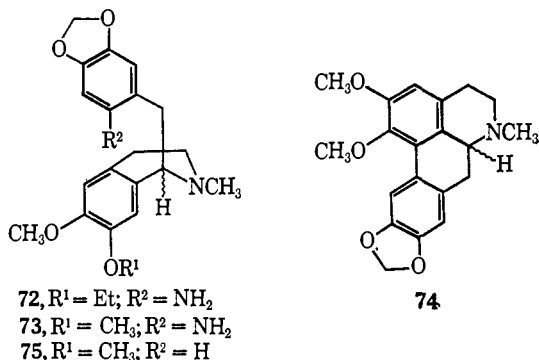
by thermal decomposition both yielded (±)-amurine. In the experiment using 73, the aporphine (±)-epidicentrine (74) and the isoquinoline 75 were also isolated from the reaction product.

## 4. (±)-Flavinantine (3-Hydroxy-2,6-dimethoxymorphinandienone)

Confirmation for the earlier structural proposal for flavinantine[34,35] was obtained by the synthesis of (±)-flavinantine (76). Diazotization of the aminotetraisoquinoline 77 followed by thermal decomposition produced 78 in 8.4% yield. Debenzylation to 76 was achieved by treatment with ethanolic

hydrogen bromide. Deamination products 79 and 80 were also formed.[86]

76, R¹ = H
78, R¹ = PhCH₂
82, R¹ = CH₃

77, R¹ = PhCH₂; R² = NH₂
80, R¹ = PhCH₂; R² = H
79, R¹ = R² = H
81, R¹ = CH₃; R² = NH₂
84, R¹ = CH₃; R² = H
85, R¹ = Et; R² = NH₂

83
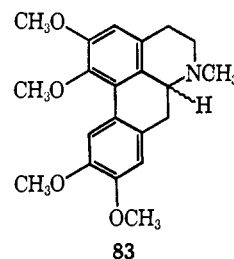
5. (±)-O-Methylflavinantine (2,3,6-Trimethoxymorphinandienone)

In a similar manner to the synthesis of flavinantine, diazotization of 6'-aminolaudanosine (81) at 0–5° followed by an increase of the temperature to 70° for 1 hr produced O-methylflavinantine (82) (1.4% yield) as well as (±)-glaucine (83) and (±)-landanosine (84). Compound 85 was also converted to (±)-O-methylflavinantine using identical conditions. This enabled the authors to rule out structure 86 as that representing

86, R¹ = CH₃ or Et
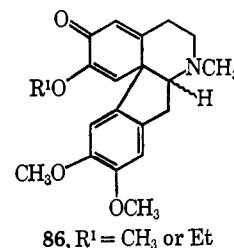
the dienone product.[87] Other workers obtained identical products as shown when the diazonium salt of 6'-aminolandanosine (81) was decomposed at 0° with copper.[88]

6. Protostephanone (2,3,6,8-Tetramethoxymorphinandienone)

Protostephanone (33) was prepared by Pschorr cyclization following the diazotization of the aminoisoquinoline 87 in a 25% yield.[16]

(33) T. Kametani, K. Fukumoto, and T. Sugahara, *J. Chem. Soc. C*, 801 (1969).
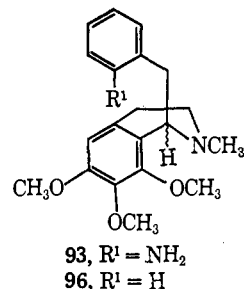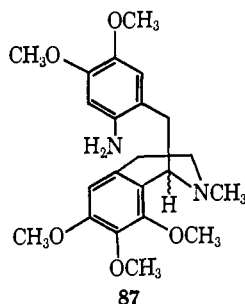(34) C. Chambers and K. L. Stuart, *Chem. Commun.*, 328 (1968).
(35) K. L. Stuart, C. Chambers, and D. Y. Byfield, *J. Chem. Soc. C*, 333 (1969).

(36) T. Kametani, T. Sugahara, H. Yagi and K. Fukumoto, *ibid.*, 1063 (1969).
(37) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1398 (1968); *J. Chem. Soc. C*, 520 (1969).
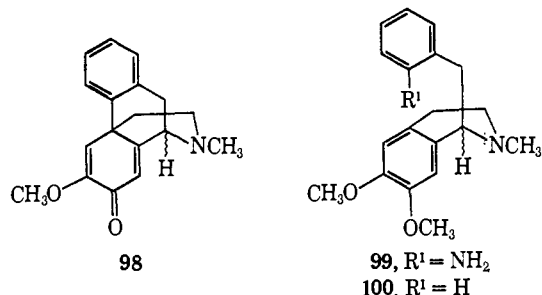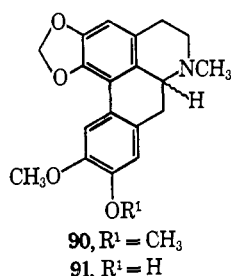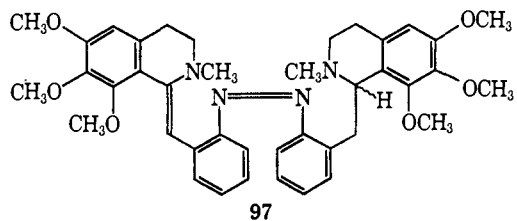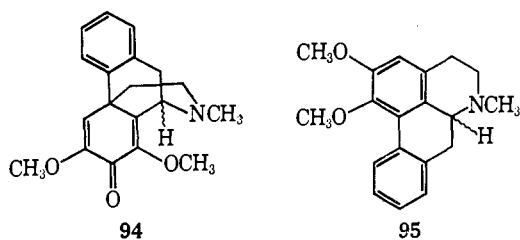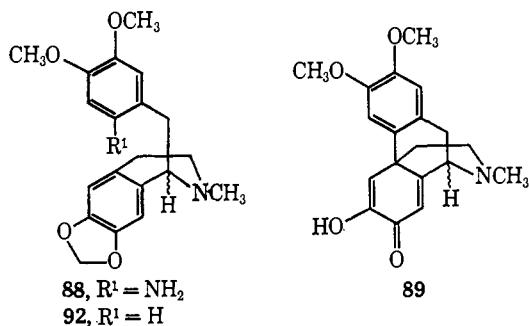(38) B. Gregson-Allcott and J. M. Osbond, *Tetrahedron Lett.*, 1771 (1969).

87

7. 2,3-Dimethoxy-6-hydroxy-morphinandienone

When the aminomethylenedioxyisoquinoline **88** was diazotized and then heated without a metal catalyst, the diosphenol **89**, $C_{19}H_{21}NO_4$, was formed through methylenedioxy cleavage by

88, $R^1 = NH_2$
92, $R^1 = H$

89

90, $R^1 = CH_3$
91, $R^1 = H$

the modified Pschorr cyclization. The aporphine alkaloids (±)-dicentrine (**90**) and (±)-cassythicine (**91**) as well as **92** were produced.[39]

8. 6,8-Dimethoxymorphinandienone

When the aminoisoquinoline **93** was converted to the diazonium salt and this then decomposed with copper at 0°, **94** was obtained in a 7% yield. (±)-Nuciferine (**95**), the isoquinoline **96**, and the orange-yellow base **97** were also produced.[38]

9. 6-Methoxymorphinandienone

6-Methoxymorphinandienone (**98**) was produced from the aminoisoquinoline **99** in a manner similar to the previous synthesis. The main product was **100**; however, (±)-nuciferine (**95**) was produced as well.[38]

(39) T. Kametani, T. Sugahara, and K. Fukumoto, *Chem. Ind.* (*London*), 833 (1969).

93, $R^1 = NH_2$
96, $R^1 = H$

94

95

97

98

99, $R^1 = NH_2$
100, $R^1 = H$

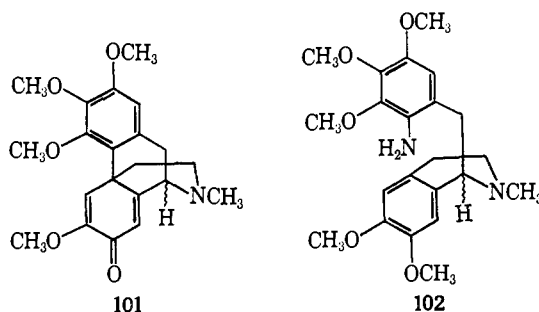### 10. 2,3,4,6-Tetramethoxy-morphinandienone

The morphinandienone **101** was synthesized by the modified Pschorr technique (omission of copper catalyst) from the diazonium salt of the aminoisoquinoline **102**.[32]
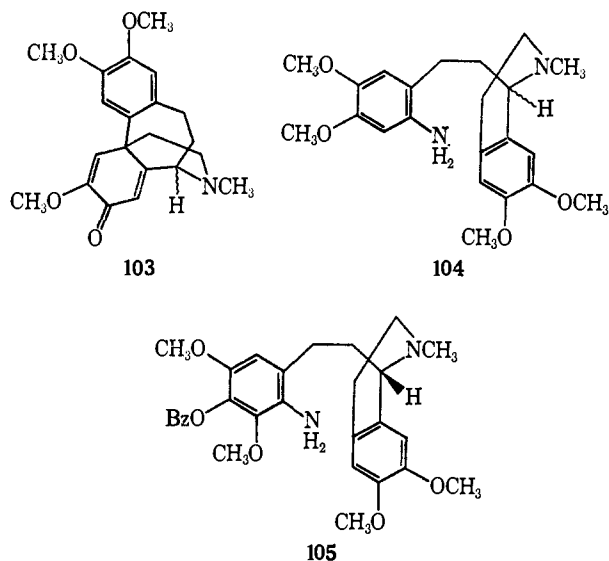
101

102

11. 2,3,6-Trimethoxy-homomorphinandienone

This is the only homomorphinandienone synthesized by the Pschorr method. **103** was formed from the aminoisoquinoline

104 *via* the diazonium salt which was decomposed at 70°.[40]
The utilization of compound **105** by way of the modified

OCH₃

CH₃O

CH₃O

O

H NCH₃

103

CH₃O

CH₃O

N H₂

NCH₃

H

OCH₃

CH₃O

104

CH₃O

BzO

CH₃O

N H₂

NCH₃

H

OCH₃

CH₃O

105

Pschorr technique seems a possible way to achieve the ultimate synthesis of androcymbine (**46**), and this is likely to be achieved by the time this review appears.
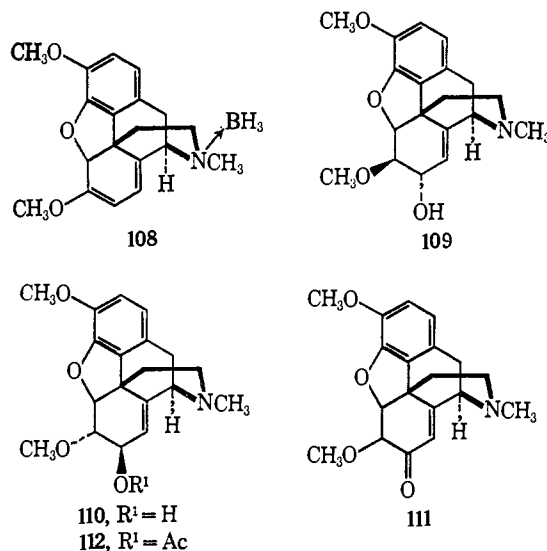
C. MISCELLANEOUS METHODS

1. Salutaridine

a. Method 1

The first synthesis of salutaridine (**9**) was achieved before it was isolated from *Croton salutaris* by Professor R. A. Barnes.[12] Thebaine (**5**) was first reduced with sodium in liquid ammonia to give dihydrothebaine ϕ (**106**). After acetylation, the product

CH₃O

R¹O

NCH₃

H

CH₃O

106, R¹ = H
107, R¹ = Ac
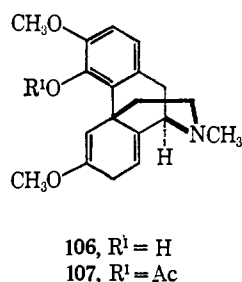
107 was successively oxidized with selenium dioxide and manganese dioxide to produce *O*-acetylsalutaridine. Mild alkali hydrolysis of this produced salutaridine (**9**).

b. Method 2

Hydroboration of thebaine (**5**) produced the thebaine–borane complex **108**, which when allowed to react with 1 equiv of BH₃ formed 7α-isoneopine methyl ether **109** and 7β-neopine methyl ether **110**. MnO₂ oxidation of **109** produced salutaridine and compound **111**, while with **110** no salutaridine (**9**) was obtained. However, oxidation of **110** with acetic anhydride in DMSO produced salutaridine and **112**. These latter reagents reacted on **109** to yield salutaridine acetate.[41]

CH₃O

O

CH₃O

H

BH₃

NCH₃

108

CH₃O

O

CH₃O

H

NCH₃

OH

109

CH₃O

O

CH₃O

H

NCH₃

OR¹

110, R¹ = H
112, R¹ = Ac

CH₃O

O

CH₃O

H

NCH₃

O

111

c. Method 3
(*Via* 4,6-Dihydroxy-3-methoxymorphinandienone)

Thebaine (**5**) was first converted to 14-bromocodeinone (**113**) by treatment with *N*-bromosuccinimide.[42] When 14-bromocodeinone was dissolved in Claisen's alkali (aqueous methanolic KOH) and then neutralized, a compound which was shown to be 6-*O*-demethylsalutaridine (4,6-dihydroxy-3-methoxymorphinandienone) (**114**) was obtained. Diazo-

CH₃O

O

O

H

Br

NCH₃

113

CH₃O

HO

HO

H

NCH₃

O

114
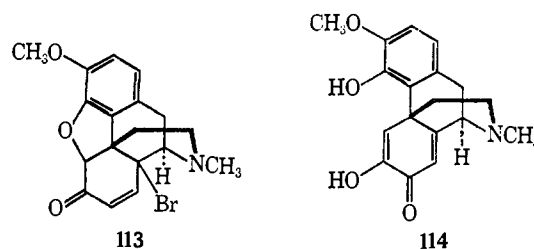
methane was then used to convert this compound to salutaridine (**9**). The mechanism proposed for the ring opening of the oxide ring of **114** is shown below (**113A** → **114A**).[43]

NCH₃

O

Br

O

OH⁻

113A

O

OH

O

OH

OH

114A
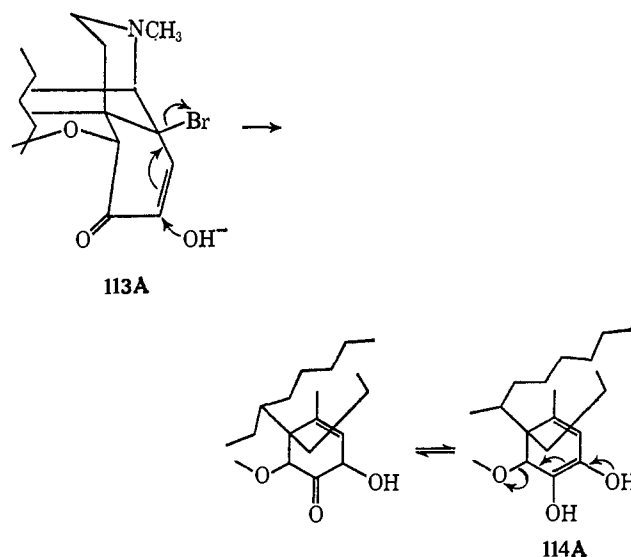
(40) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1001 (1968); *J. Chem. Soc. C*, 3084 (1968).
(41) M. Takeda, H. Inone, and H. Kugita, *Tetrahedron*, **25**, 1839 (1969).
(42) H. Conroy, *J. Amer. Chem. Soc.*, **77**, 5960 (1955).
(43) D. E. Rearick and M. Gates, *Tetrahedron Lett.*, 507 (1970).

2. Isosinomenine

Isosinomenine **44** was produced when sinomenine (**6**) was treated with methanolic hydrogen chloride at room temperature by way of an equilibrium mixture of **44** and **6**.[22]

3. 2,3,6-Trimethoxy-4-hydroxymorphinandienone

When kreysiginine (**8**) was subject to mild Jones oxidation, the enone **115** was produced. Treatment of **115** with base opened the oxide bridge to yield the homomorphinandienone **116**. O-Methylation of this produced a product identical with O-methylandrocymbine.[44]

115   116
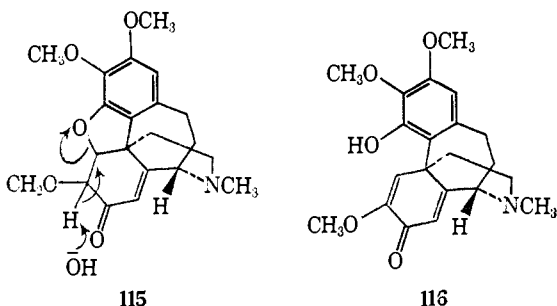
IV. Spectroscopy

A. ULTRAVIOLET AND INFRARED

The morphinandienones show two uv absorption bands, one between 235 and 240 nm and the other between 275 and 290 nm. The molecular extinction coefficient shows a 2:1 ratio for these bands (e.g., O-methylflavinantine, ϵ 13,500:6400). Compounds with C-2 and C-3 substituents usually have the higher wavelength band closer to 290 nm, and in compounds with C-3 and C-4 substituents, this band is near 275 nm.

The ir displays the three bands characteristic of an α-methoxyl cross-conjugated cyclohexadienone system, namely in the region of 1665, 1635, and 1615 cm^{-1}. It was once thought that a strong sharp band at or near 1494 cm^{-1} was evidence of an unsubstituted C-1 position, and the disappearance of this band and the appearance of another at 1475 cm^{-1} indicated the presence of a C-1 substituent. These early observations were made on 1-bromo- (**117**), 1-deuterio- (**117A**), and 1,1'-dimeric salutaridine (**51**).[12] With the isolation of compounds in this series with C-2 and C-3 substituents, for example, flavinantine (**22**), it was shown by appropriate nmr controlled deuterium exchange experiments involving H-4, that these ir changes were also true for the C-4 position as well.[34]


117, R^1 = Br
117A, R^1 = D
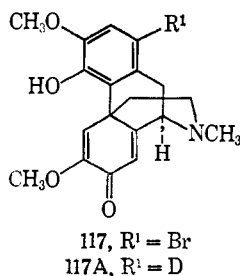
B. CIRCULAR DICHROISM AND OPTICAL ROTATORY DISPERSION

Both CD and ORD have been very useful in the assignment of configuration. The first reported CD study on the morphinandienones was by Snatzke and Wollenberg.[45] Measurements on sinoacutine (**26**), amurine (**16**), and the dienol nudaurine (**18**) were reported and discussed. The band in the region of 291 nm could be clearly ascribed to the substituted aromatic system, but prediction of the sign of the Cotton effect for the dienone system was not as straightforward and more insight into this aspect will probably be forthcoming with the recent development of CD instruments that can make measurements below 200 nm. ORD and CD curves for salutaridine and sinoacutine in the region 400–200 nm have recently been published.[18] ORD data in conjunction with the application of octant rule permitted the assignment of a β configuration to the C-14 center in tetrahydroamurine (**42**).[9]

C. NUCLEAR MAGNETIC RESONANCE

In the nmr spectrum of most morphinandienones and homomorphinandienones, H-5 is the most deshielded proton. Nmr data have been invaluable in establishing the substitution pattern on the aromatic ring in this series of compounds, and in at least one instance, namely nudaurine (**18**), a 100-MHz spectrum was used in carrying out a first-order analysis of the ABX system generated by H-9 and the two C-10 protons.[9] The nmr spectra of N,O-diacetyl-8,14-dihydronorsalutaridine (**118**), N,O-diacetylnorsinoacutine (**119**), and

118   119

120
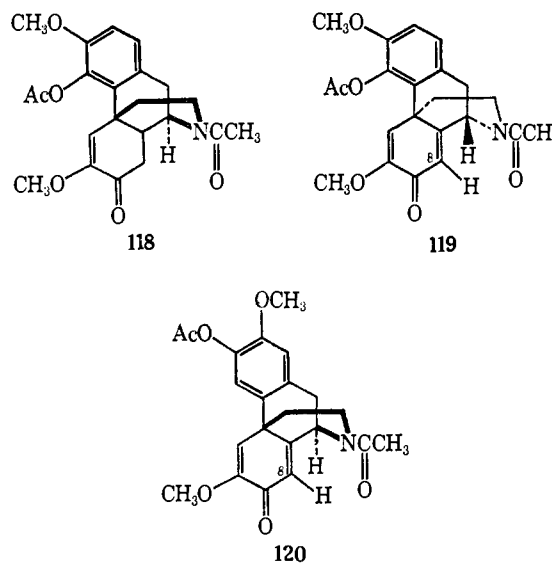
N,O-diacetylflavinine (**120**) are worthy of comment. In all these cases the N-acetyl signals appeared as doublets. In the case of **119** and **120**, H-8 also showed up as doublets.[20] This effect has been ascribed to differential shielding by the anisotropic amide group in the cis and trans configurations.[46]
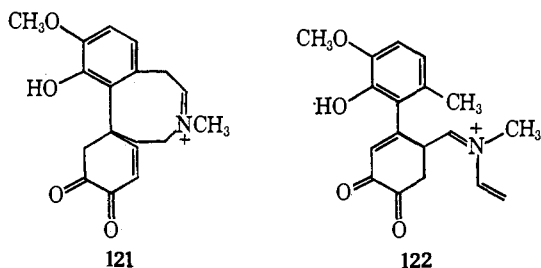
D. MASS SPECTROMETRY

Mass spectral data have been obtained for many morphinandienones and reduced morphinandienones, and in some of these studies fragmentation pathways have been proposed and

(44) A. R. Battersby, M. H. G. Munro, R. B. Bradbury, and F. Šantavý, Chem. Commun., 695 (1968).

(45) G. Snatzke and G. Wollenberg, J. Chem. Soc. C, 1681 (1966).
(46) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, Chem. Commun., 480 (1966).

comparisons made between these compounds and morphinan compounds containing the oxide ring.[47] The loss of a methyl group (M$^+$ − 15) is a common feature of morphinandienones and is probably due to the loss of methyl from C_6-OMe. In the case of salutaridine (9), it has been proposed that an initial cleavage at an allylic or benzylic bond followed by loss of methyl would give the conjugated even-electron ions 121 and 122. M$^+$ − 43 is usually another strong peak observed, and


121   122

this is probably due to the loss of CO and methyl.[33,47]

In the spectrum of amurine, other prominent peaks were due to (M$^+$ − CO − OMe), (M$^+$ − CO − Me − CO), and (M$^+$ − C_3H_7N − CO$^-$). It is now possible to use mass spectrometry in the morphinan series to assign configuration.[48] In the case of tetrahydroamurine 42 the 14-β-hydrogen configuration was obtained from mass spectral data. Only in the case of cis-fused B:C rings does the m/e 59 fragment appear as a high intensity peak, and pathway 42 → 123 → 124 + 125 shows

42   123

124
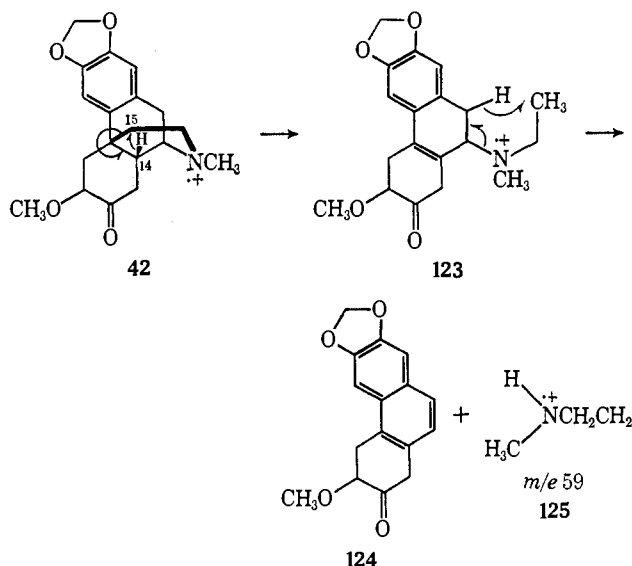
how the close proximity of H-14 to the C-15 carbon is necessary for this to occur. In the case of 8,14-dihydrosalutaridine (40), the fragmentation Scheme II probably best explains some of the main peaks observed. By accurate mass measurements, fragments m/e 178 and 146 have molecular formulas $C_{10}H_{12}NO$ and C_9H_8NO, respectively. The $C_{10}H_{12}NO$ fragment is probably structure 126 and a frequently appearing fragment, C_9H_7
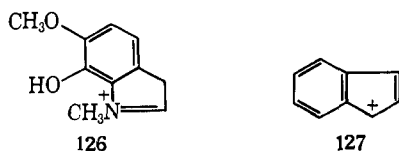
126   127

(m/e 115), was assigned structure 127.[20] Fragmentation pathways have also been proposed for tetrahydrosalutaridinol (41). Several of these spectra have been lodged with the Mass Spectrometry Data Centre, Aldermaston.

V. Biosynthetic Studies

This section on aspects of biosynthesis discusses, in the main, the important role of morphinandienones alkaloids in the formation of other alkaloids. Data are schematically presented and summarize several, and in some cases detailed, radioisotopic studies which have revealed these pathways. The formation of some of these morphinandienones themselves is also reviewed in order to present a unified picture. Reference has been made in some cases to theories which stimulated research in this area, and also to some earlier reviews of some of this work.

A. SALUTARIDINE. FORMATION OF MORPHINE ALKALOIDS

Scheme III outlines our present knowledge of the formation of morphine alkaloids.[2,12,49-71] In the opium poppy, Papaver somniferum, the biosynthetic sequence is as follows: the amino acid tyrosine (128) is converted to (±)-reticuline (14), which by way of the dehydro derivative 129 and then by the ortho-para diradical coupling mode 130, is converted to salutaridine (9). It should be noted that salutaridine was actually isolated from Croton salutaris by Barnes before it was discovered in the opium poppy.[12] Salutaridine is then reduced to salutaridinol I (24), which loses water, probably by an enzymatically controlled process to form thebaine (5). There is still some uncertainty concerning the mechanism by which water is lost, and two possibilities have been proposed.[72] In the termina

(49) R. Robinson and S. Sugasawa, J. Chem. Soc., 3165 (1931); 789 (1932); 280 (1933).

(50) R. Robinson, The Structural Relations of Natural Products, Oxford University Press, London, 1955.

(51) C. Schöpf, Naturwiss., 39, 241 (1952).

(52) A. R. Battersby and B. J. T. Harper, Tetrahedron Lett., 21 (1960).

(53) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, p 288.

(54) H. Rapoport, F. R. Stermitz, and D. R. Baker, J. Amer. Chem. Soc., 82, 2765 (1960).

(55) F. R. Stermitz and H. Rapoport, ibid., 83, 4045 (1961).

(56) A. R. Battersby, Tilden Lecture, Proc. Chem. Soc., 189 (1963).

(57) D. H. R. Barton, Hugo Muller Lecture, ibid., 293 (1963).

(58) A. R. Battersby, R. Binks, and B. J. T. Harper, J. Chem. Soc., 3534 (1962).

(59) E. Leete, J. Amer. Chem. Soc., 81, 3948 (1959).

(60) A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, J. Chem. Soc., 3600 (1964).

(61) A. R. Battersby and R. J. Francis, ibid., 4078 (1964).

(62) E. Leete and S. J. B. Murrill, Tetrahedron Lett., 147 (1964).

(63) D. H. R. Barton, Pure Appl. Chem., 9, 35 (1964).

(64) A. R. Battersby, "Festschrift Kurt Mothes. Geburtstag, 1965," Fischer Verlag, Jena, 1965, p 81.

(65) A. R. Battersby, D. M. Foulkes, and R. Binks, J. Chem. Soc., 3323 (1965).

(66) D. H. R. Barton, Chem. Britain, 330 (1967).

(67) A. R. Battersby, J. A. Martin, and E. Brockmann-Hanssen, J. Chem. Soc. C, 1785 (1967).
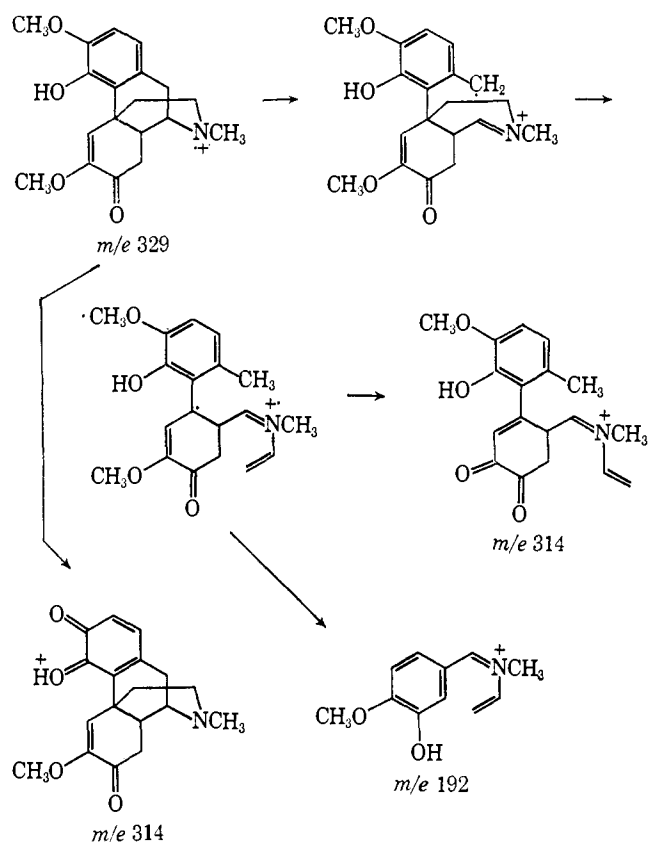
(68) G. W. Kirby, Science, 155, 170 (1967).

(69) G. Blaschke, H. J. Parker, and H. Rapoport, J. Amer. Chem. Soc., 89, 1540 (1967).

(70) I. D. Spenser, "Comprehensive Biochemistry," M. Florkin and E. H. Stotz, Ed., Elsevier, New York, N. Y., 1968, p 231.
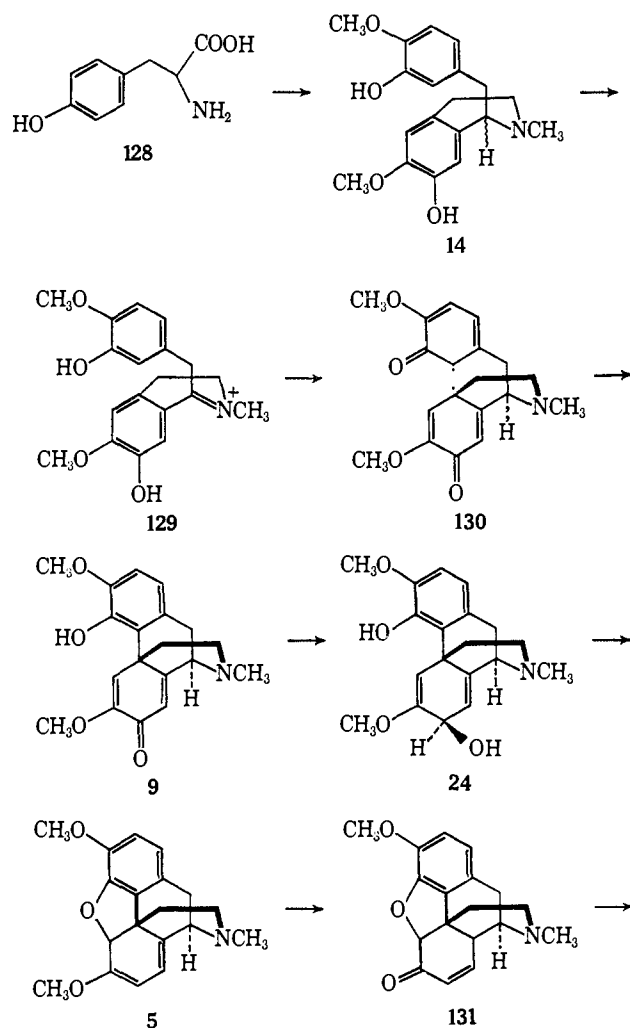
(71) A. R. Battersby, "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Edward Arnold, London, 1967, p 119.

(72) D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, J. Chem. Soc. C, 128 (1967).

(47) D. M. S. Wheeler, T. H. Kinstle, and K. L. Rinehart, J. Amer. Chem. Soc., 89, 4494 (1967).

(48) A. Mandebaum and D. Ginsberg, Tetrahedron Lett., 2479 (1965).

Scheme II

Scheme III

m/e 329

m/e 314

m/e 314

m/e 192

128

14

129

130

9

24

5

131

132, R¹ = CH₃
133, R¹ = H

stages,[67,69] thebaine is converted to codeinone (131) and then to codeine (132), and morphine (133) is formed by demethylation of codeine. The fact that morphine is further metabolized to ill-defined products has been clearly shown by recent studies.[73]

B. SINOACUTINE.
FORMATION OF SINOMENINE

It has been demonstrated that phenylalanine (134) and reticuline (14) can serve as precursors for sinoacutine (26),[11] and that sinoacutine can undergo N-demethylation to form norsinoacutine (27) in *Croton flavens*.[74] In *Sinomenium actum*, it has been clearly demonstrated that sinoacutine (26) is a precursor for sinomenine 6, but neither isosinomenine (44) nor the sinoacutinols (135) seem to be on the main pathway to this alkaloid.[22] It has been postulated, that the terminal stages to the biosynthesis of sinomenine could either involve one of the enones 136 or the α-diketone 137, which could then lead to the α-ketol 138. Since 138 is the βγ isomer of the diosphenol corresponding to sinomenine, methylation subsequent to conjugation would then yield sinomenine.[22] In the *Sinomenium acutum* studies, there was evidence which suggested that the sinoacutinols were oxidized to sinoacutine before incorporation into sinomenine, and recently it has been shown in *Croton flavens* that the norsinoacutinols were reoxidized to norsinoacutine.[74] These two examples suggest that plants which produce morphinandienone alkaloids but do not manufacture
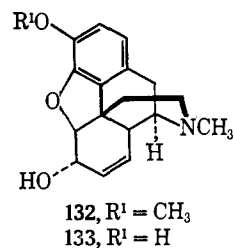
morphine-type alkaloids have, or can be triggered into producing, enzymes systems which oxidize the dienols to dienone and so surpress the required cyclization reaction to morphine alkaloids. From radioisotope feeding experiments in *S. acutum*, it was shown that isosinomenine is not formed from sinoacutine, a transformation merely requiring the reduction of the 8,14 double bond in sinoacutine.[22] In fact, it has been recently reported that isosinomenine is an artifact in *S. acutum*.[75]

C. PROTOSTEPHANONE. FORMATION OF
PROTOSTEPHANINE

Barton proposed that protostephanine (37), isolated from *Stephania japonica* Miers, is biosynthesized from a benzyliso-

(73) J. W. Fairbairn and S. El-Masry, *Phytochemistry*, 7, 181 (1967).
(74) K. L. Stuart and L. Graham, unpublished work.

(75) K. Okabe, K. Hayashi, and Y. K. Sawa, *Chem. Pharm. Bull.*, 16, 1611 (1968).

134

135

136

137

138
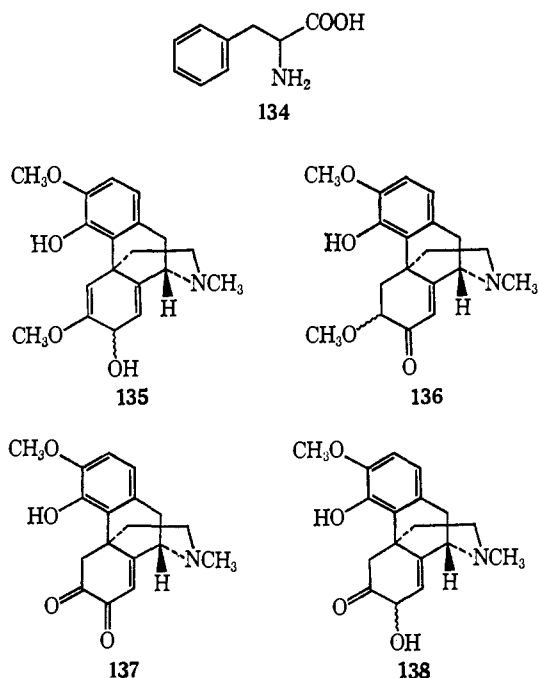
quinoline compound of type **52** *via* a morphinandienone **53**.[68] Hackett has in fact obtained good incorporation (2.9%) of the dienone **53** into protostephanine in this plant,[16] and it seems very likely that **37** is formed by the pathway outlines in Scheme IV (**52 → 37**).

D. FORMATION OF FLAVINANTINE, FLAVININE, AMURINE, NADURINE, AND PALLIDINE

Whereas morphine-type compounds are formed by ortho–para oxidative coupling of reticuline (**14**), it now seems very likely that flavinantine (**22**), flavinine (**141**) (*Croton flavens*), amurine (**16**), nadurine (**18**) (*Papaver nudicale*), and pallidine (**47**) (*Corydalis pallida*) are formed by para–para diradical coupling of reticuline. Biosynthetic studies on the formation of flavinantine[11] have shown that this is the case for this alkaloid. These studies have also indicated that a pathway which utilizes orientaline (**142**) by way of the bis-dienone **143**, the rearrangement of which would give flavinantine directly, does not play a significant role in the biosynthesis of flavinantine. The location of a methoxyl group at C-2 is worthy of comment. It can probably be best explained by assuming the intermediary of isosalutaridine (enantiomer of pallidine **47**) which then undergoes demethylation and remethylation at ring A in a manner analogous to the case involving the formation of crotonosine (**144**) from coclaurine (**145**).[76] Biosynthetic schemes based on the above ideas of para–para coupling of reticuline have been proposed for amurine and nadurine.[9]

E. FORMATION OF 8,14-DIHYDRONORSALUTARIDINE

Experiments with *Croton linearis* showed that tritium-labeled norcoclaurine (**146**), coclaurine (**145**), and isococlaurine (**147**) are incorporated into 8,14-dihydronorsalutaridine (**148**). To accommodate the normal diradical coupling, incorporation of isococlaurine must involve demethylation prior to coupling.[20]

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(76) D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, G. W. Kirby, L. J. Haynes, and K. L. Stuart, *J. Chem. Soc. C,* 1295 (1967).

Scheme IV

52

53

34

139

140

37
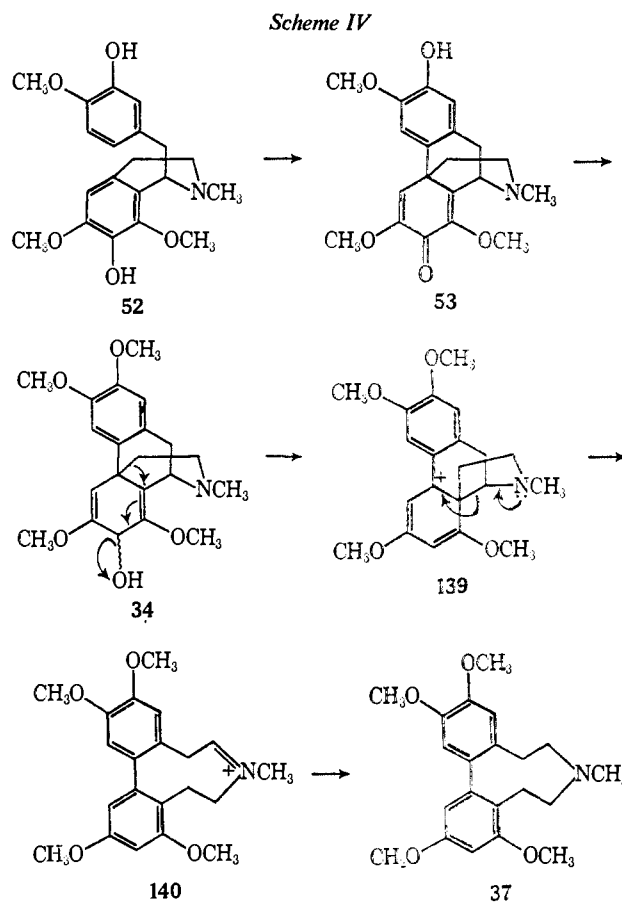
F. ANDROCYMBINE. FORMATION OF COLCHICINE AND HOMOMORPHINE ALKALOIDS

The important role of homomorphinandienones in the biosynthesis of colchicine was not appreciated until very recently. It has been established by feeding experiments in *Colchicum autumnale* and *C. byzantinum* that *O*-methylandrocymbine (**11**) was incorporated into demecolcine (**149**) (49% incorpora-


22, R¹ = CH₃
141, R¹ = H

142

143

144

145, R^1 = CH$_3$; R^2 = H
146, R^1 = R^2 = H
147, R^1 = H; R^2 = CH$_3$

148
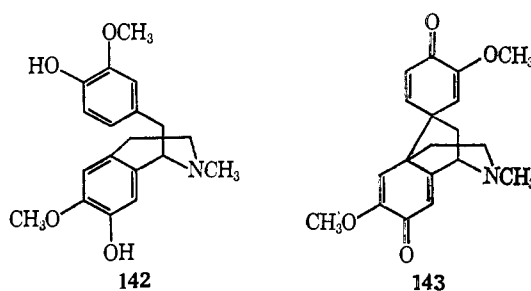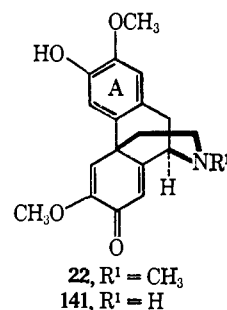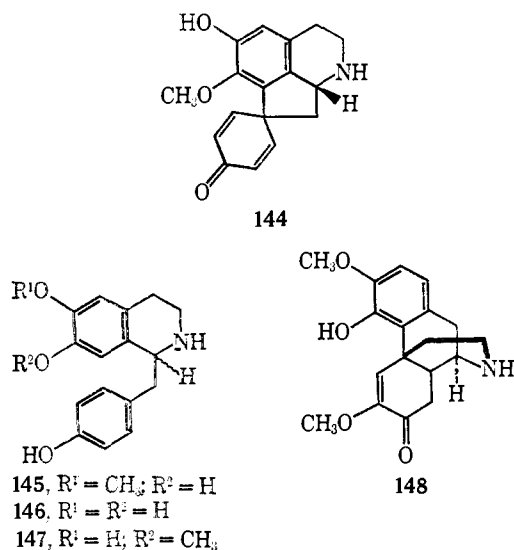
tion) and into colchicine (7) (15%), and there is now good evidence supporting the biosynthetic pathway from the 1-phenethylisoquinoline 150 to 7 (Scheme V). The elucidation

Scheme V

150

11

149

7
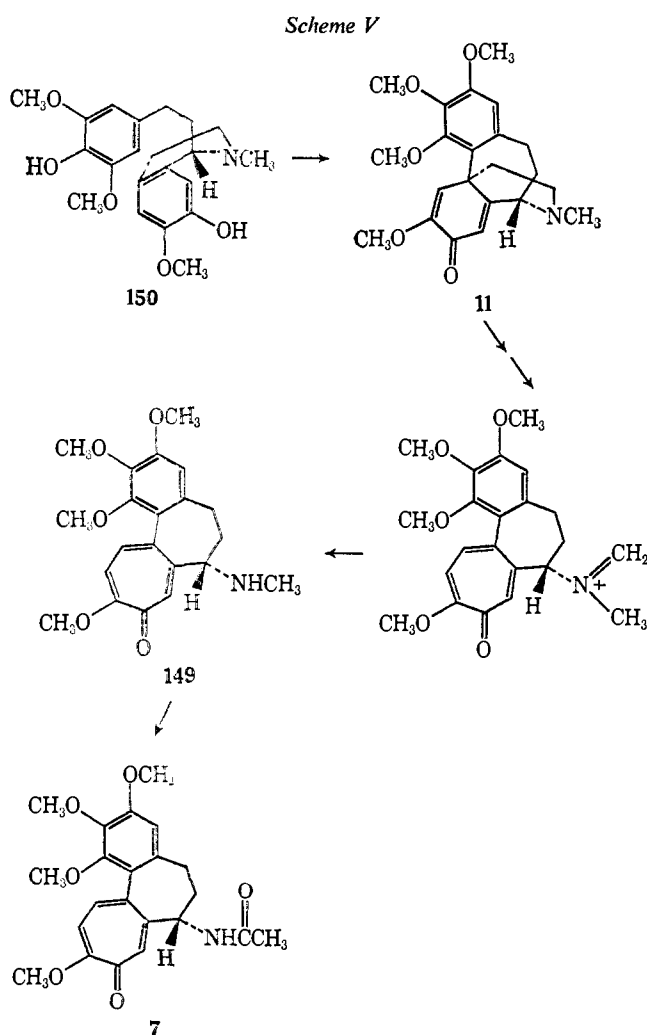
of the structure of kreysiginine (8) from *Kreysigia multi-*

flora[44,77,78] has again focused attention on the very likely role of an androcymbine-type compound as a precursor for its formation. Scheme VI indicates a possible pathway

Scheme VI

151

128

152

153

↓

8
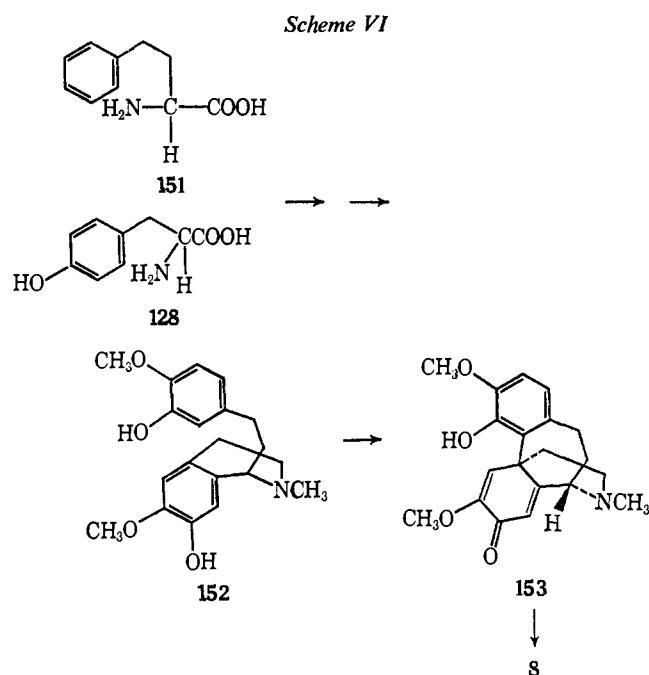
to 8. Tyrosine (128) and γ-phenylbutyrine (151) first form homoreticuline (152) which then couples to yield homosinoacutine (153). 153 would then be transformed into 8.

γ-Phenylbutyrine may be more common than once imagined and has already been isolated from *Nasturtium officinale*.[79] The isolation of *N*-methylhomotyramine (154) from *Croton*

154
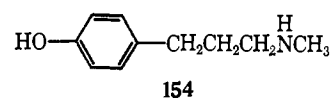
humilis[80] is an indication that this amino acid or homotyrosine may also be present. It should be noted that the location of a secondary hydroxyl group at C-7 in kreysiginine is a significant biogenetic difference from that attested to for morphine, and it is possible that the later stages of homomorphine biosynthesis vary markedly from that of morphine.

The alkaloid CC-21 from *Colchicum cornigerum*[44] has been shown to be enantiomeric with kreysiginine, and a biosynthetic pathway can be outlined similar to Scheme VI, with the only exception being that precursors from 153 on would be of the *R* configuration.

VI. Pharmacology

Some preliminary pharmacological results have been obtained for 8,14-dihydronorsalutaridine (148) and 8,14-dihydrosalutaridine (40). 148 showed evidence of antagonism
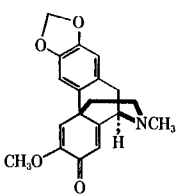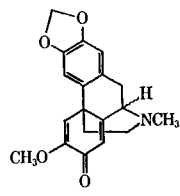
(77) J. Fridrichsons, M. F. Mackay, and A. M. Mathieson, *Tetrahedron Lett.*, 2881 (1968).
(78) N. K. Hart, S. R. Johns, J. A. Lamberton, and J. K. Saunders, *ibid.*, 2891 (1968).
(79) L. Fowden, *Proc. Roy. Aust. Chem. Inst.*, 34, 325 (1967).
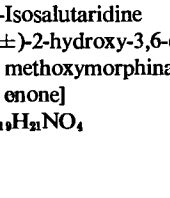(80) K. L. Stuart and D. Y. Byfield, *Phytochemistry*, in press.
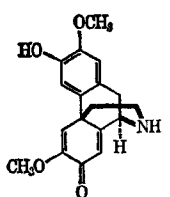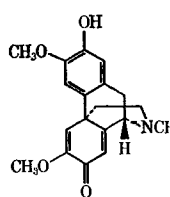
Table I

Physical Properties and Plant Sources

Compound	Derivatives, mp, °C	Optical rotation, deg	Uv, nm (log ε)	Ir, cm⁻¹	Nmr at 60 MHz	Plant source	Ref
Amurine [(R)-2,3-methylenedioxy-6-methoxymorphinandi-enone] $C_{19}H_{19}NO_4$	213–215[a]	$[\alpha]^{26}D$ +10 (CHCl₃)[a]	λ_{max}^{MeOH} 240 (4.239), 290 (3.95)[b]	ν_{max} 1678, 1650, 1627[a]	δ^{CDCl_3} 6.93 (H-4)	Papaver nudicaule var. aurantiacum Loisel[d]	9
	Methiodide, 202–206 dec	$[\alpha]^{23}D$ +13 (H₂O)			6.77 (H-1) 6.40 (H-5)	P. nudicaule var. amurense N. Busche[e]	
	Hydriodide, 216–218				6.35 (H-8) 5.95 (–OCH₂O–)	P. nudicaule var. croceum Lideb[d]	
	Perchlorate, 215–217				3.80 (OCH₃) 3.60–2.72 (12 lines, ABX	P. nudicaule ssp. xantho-petalum (Trautv.) Fedde[e]	
	Picrate, 226–227 dec				pattern; H-9 and 2 H-10) 2.42 (NCH₃)	P. feddei Schwz.	
	Tetrahydroamurine	$[\alpha]^{20}D$ −111 (CHCl₃)		ν_{max} 1725	δ^{CDCl_3} 6.92 (H-1) 6.65 (H-4) 5.94 (–OCH₂O–) 5.94 (4 lines; X part of ABX system, 215.5, 220, 227.5; 233 Hz; H-6) 3.43 (C₆OCH₃) 2.40 (NCH₃)		
	Tetrahydroamurine picrate, 140–145						
	Hexahydroamurine, 136–137	$[\alpha]^{21}D$ −56 (CHCl₃)		ν_{max}^{KBr} 3370			
(±)-Amurine [(±)-2,3-methylenedioxy-6-methoxymorphinandi-enone]			λ_{max}^{MeOH} 240 (4.24)	ν_{max}^{MeOH} 1675, 1645, 1620, 1482	δ^{CDCl_3} 6.82 (H-4) 6.59 (H-1) 6.32 (H-5) 6.28 (H-8) 5.91, t, J = ∼1 cps (–OCH₂O–) 3.79 (OCH₃) 2.44 (NCH₃)		33
	Methiodide, 222–224			ν_{max}^{KBr} 3370, 1670, 1649, 1626			
Flavinantine [(R)-3-hydroxy-2,6-di-methoxymorphinandi-enone] $C_{19}H_{21}NO_4$	130–132	$[\alpha]^{23}D$ −14.5 (EtOH)	λ_{max}^{EtOH} 239 (4.173), 286 (3.849)	$\nu_{max}^{CHCl_3}$ 3448, 1667, 1630, 1626, 1508	$\delta^{(CD_3)_2SO}$ 7.02 (H-8) 6.72 (H-5) 6.22 (H-4, H-1)	Croton flavens	15

				3.79 (OCH$_3$)	
	Acetate, 196–197			3.72 (OCH$_3$)	
				2.32 (NCH$_3$)	
				$\delta^{(CD_3)_2SO}$	
				7.40 (H-5)	
				6.95 (H-4)	
				6.80 (H-1)	
				6.28 (H-8)	
				3.80 (OCH$_3$)	
				3.72 (OCH$_3$)	
				2.33 (NCH$_3$)	
				2.25 (Ar OAc)	

O-Methyl methiodide,
250–252 dec

[4-^2H]Flavinantine $\qquad$ $\nu_{max}^{CHCl_3}$ 1508 band, displaced to 1488

O-Methyl derivative $\qquad$ $\nu_{max}^{CHCl_3}$ 1666, 1642, 1621, 1508

(±)-Flavinantine
[(±)-3-hydroxy-2,6-di-
methoxymorphinandi-
enone]
C$_{19}$H$_{21}$NO$_4$

λ_{max}^{MeOH} 239 (4.17), 286 (3.85) $\qquad$ $\nu_{max}^{CHCl_3}$ 3490, 1665, 1642, 1624 $\qquad$ δ^{CDCl_3} — 36
7.02 (H-5)
6.73 (H-1 or H-4)
6.24 (H-8 + H-1 or H-4)
3.80 (OCH$_3$)
3.73 (OCH$_3$)
2.32 (NCH$_3$)

Methiodide, 235–238 dec

O-Benzyl deriv $\qquad$ λ_{max}^{MeOH} 235 (4.15), 282 (3.83) $\qquad$ $\nu_{max}^{CHCl_3}$ 1663, 1641, 1621 $\qquad$ δ^{CDCl_3} — 36
7.31 (OCH$_2$Ph)
6.76 (H-5)
6.60 (H-1 or H-4)
6.24 (H-8)
6.10 (H-1 or H-4)
5.11 (OCH$_2$Ph)
3.85 (OCH$_3$)
3.60 (OCH$_3$)
2.40 (NCH$_3$)

O-Benzyl methiodide, 208–210 — 36

O-Methyl deriv, 158–160 $\qquad$ λ_{max}^{EtOH} 205 (4.641), 239 (4.25), 285 (3.922) $\qquad$ $\nu_{max}^{CHCl_3}$ 1670, 1640, 1620 $\qquad$ δ^{CDCl_3} — 37, 38
6.60 and 6.47 (aromatic protons)
6.27 (H-5)
3.85 (OCH$_3$)
3.83 (OCH$_3$)
3.77 (OCH$_3$)
2.42 (NCH$_3$)

O-Methyl methiodide, 223–225 dec $\qquad$ λ_{max}^{MeOH} 284, 238 sh $\qquad$ ν_{max}^{KBr} 1669, 1647, 1626, 1518 — 37

Table I (Continued)

Compound	Derivatives, mp, °C	Optical rotation, deg	Uv, nm (log ε)	Ir, cm⁻¹	Nmr at 60 MHz	Plant source	Ref
Flavinine [(R)-N-nor-3-hydroxy-2,6-dimethoxymorphinandienone] $C_{18}H_{19}NO_4$	130–132 (acetone of crystn)	$[\alpha]^{16}D$ −6 (EtOH)	λ_{max}^{EtOH} 238 (4.117), 285 (3.906)	$\nu_{max}^{CHCl_3}$ 3484, 2967, 1667, 1639, 1629, 1503 (acetone)	$\delta^{(CD_3)_2SO}$ 6.97 (H-5) 6.70 (H-1 or H-4) 6.64 (H-4 or H-1) 6.18 (H-8) 3.75 (OCH₃) 3.68 (OCH₃) 2.10 (acetone)	Croton flavens L.	35
	N-Acetate				δ^{CDCl_3} 7.00 (H-5) 6.58 (H-4) 6.40 (H-1 or H-8) 6.35 (H-8 or H-1) 5.68 (H-9) 3.86 (OCH₃) 3.78 (OCH₃) 2.09 (N-Ac)		
	N,O-Diacetate				δ^{CDCl_3} 7.10 (H-5) 6.37 (H-1 or H-8) 6.33 (H-8 or H-1) 5.70 (H-9) 3.80 (OCH₃) 3.81 (OCH₃) 2.30 (O-Ac) 2.10 (N-Ac)		
Pallidine [(S)-2-hydroxy-3,6-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$		$[\alpha]^{18}D$ −32	λ_{max}^{MeOH} 235 (4.08), 283 (3.81)	$\nu_{max}^{CHCl_3}$ 3500, 1666, 1643, 1624	δ^{CDCl_3} 6.77 (H-5) 6.68 (H-1 or H-4) 6.33 (H-4 or H-1) 6.29 (H-8) 3.89 (OCH₃) 3.79 (OCH₃) 2.37 (NCH₃)	Corydalis pallida var. tenuis Yatabe	26
(±)-Isosalutaridine [(±)-2-hydroxy-3,6-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$			λ_{max}^{MeOH} 235 (4.08), 283 (3.81)	$\nu_{max}^{CHCl_3}$ 3500, 1666, 1643, 1624	δ^{CDCl_3} 6.77 (H-5) 6.68 (H-1 or H-4) 6.33 (H-4 or H-1) 6.29 (H-8) 3.89 (OCH₃) 3.79 (OCH₃) 2.37 (NCH₃)		
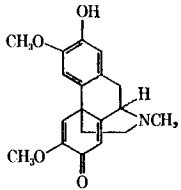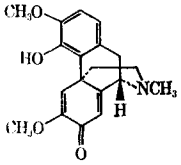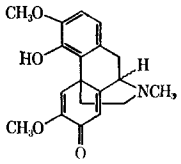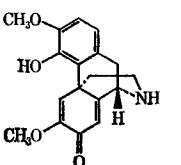
Compound	Derivative, mp	$[\alpha]_D$	UV	IR	NMR	Source	Ref
(structure)	O-Acetate,^{f} 203–204		λ_{max}^{MeOH} 233, 284 λ_{inf} 247	$\nu_{max}^{CHCl_3}$ 1753, 1663, 1642, 1611	δ^{CDCl_3} 6.92 } H-4, H-5 6.83 } 6.36 (H-1) 6.33 (H-8) 3.81 (2 OCH$_3$) 2.47 (NCH$_3$) 2.30 (COCH$_3$)		7
Sinoacutine [(−)-(S)-4-hydroxy-3,6-dimethoxymorphinandienone] C$_{19}$H$_{21}$NO$_4$ (structure)	198 Acetate, 175 Hexahydrosinoacutinol, 216	$[\alpha]_D$ −81.6 (CHCl$_3$) $[\alpha]_D$ −116 (EtOH) $[\alpha]_D$ −125 (EtOH)	λ_{max} 240 (4.25), 277 (3.75)	ν_{max} 3525, 2872, 1672, 1646, 1626, 1296		*Sinomenium acutum* Rehd. et Wils.^{g} *Croton flavens* L. *Cassytha pubescens* R. Br.^{h}	14 12 15
(±)-Sinoacutine [(±)-4-hydroxy-3,6-dimethoxymorphinandienone] (structure)	Picrate, 211–215		λ_{max}^{MeOH} 236 (4.23), 279 (3.76)	$\nu_{max}^{CHCl_3}$ 3560, 1671, 1644, 1642	δ^{CDCl_3} 7.55 (H-5) 6.69 (H-1, d, $J = 7.0$ cps) 6.74 (H-2, d, $J = 7.0$ cps) 6.31 (H-8) 3.88 (OCH$_3$) 3.74 (OCH$_3$) 2.44 (NCH$_3$)		13
Norsinoacutine [(−)-(R)-N-nor-4-hydroxy-3,6-dimethoxymorphinandienone] C$_{18}$H$_{19}$NO$_4$ (structure)	113–115 (acetate of crystn)	$[\alpha]^{16}_D$ −107 (MeOH)	λ_{max}^{EtOH} 241 (4.19), 275 sh (3.83)	ν_{max}^{Nujol} 3400,^{i} 3150, 1672, 1643, 1623	δ^{CDCl_3} 7.62 (H-5)^i 6.70 (H-2) 6.68 (H-1) 6.28 (H-8) 3.88 (OCH$_3$) 3.75 (OCH$_3$) $\delta^{(CD_3)_2SO}$ (+ acetate of crystn) 7.63 (H-5) 6.85 (H-2), d, $J = 8$ cps 6.56 (H-1), d, $J = 8$ cps 6.15 (H-8) 3.75 (OCH$_3$) 3.62 (OCH$_3$)	*Croton flavens* L. *Sinomenium acutum*^{g}	35

Table I (Continued)

Compound	Derivatives, mp, °C	Optical rotation, deg	Uv, nm (log ε)	Ir, cm⁻¹	Nmr at 60 MHz	Plant source	Ref
Norsinoacutine (continued)	N,O-Diacetate				δ^{CDCl_3} 6.93 (H-1, H-2)^j 6.93 (H-5) 6.33 (H-8) 5.53 (H-9, t) 3.82 (OCH₃) 3.75 (OCH₃) 2.42 (OAc) 2.05 (N-Ac)		
	N,O-Diacetate methiodide, 163–166 1-Bromonorsinoacutine, 121–122 Norsinoacutinol, 226–228 [1-³H]Norsinoacutine, 113–115			$\nu^{CHCl_3}_{max}$ 1466 [1486 band missing and new band at 1466]	δ^{CDCl_3} 6.68 band missing		
Salutaridine [(R)-4-hydroxy-3,6-dimethoxymorphinandienone] C₁₉H₂₁NO₄ CH₃O— HO— —NCH₃ H CH₃O— O	197–198	[α]D +111 (EtOH)	λ^{EtOH}_{max} 240 (4.25), 277 (3.755)	$\nu^{CHCl_3}_{max}$ 3560, 1671, 1644, 1624	δ^{CDCl_3} 7.56 (H-5) 6.68, 6.72 (H-1, H-2) 6.32 (H-8), 3.88 (OCH₃) 3.74 (OCH₃), 2.45 (NCH₃) $\delta^{(CD_3)_2NCOH}$ 7.75 (H-5), 6.91, 6.64 (H-2, H-1; J = 8.3 cps) 6.23 (H-8), 3.91 (OCH₃) 3.67 (OCH₃)	Croton salutaris Casar Papaver somniferum var. Noordster^k Croton balsamifera Jacq^i Papaver oriental P. caucasicum Marsch-Bieb Unknown plant source^l P. bracteatum Lindl.^{m} P. floribundum Desf^m Croton plumieri^n	12
	Picrate, 212–216 dec O-Acetate, 171	[α]D +120 (EtOH)			δ^{CDCl_3} 6.96 (H-5) 6.89 (H-1 and H-2) 6.31 (H-8) 3.88 (OCH₃) 3.77 (OCH₃), 2.40 (OAc) 2.46 (NCH₃)		
	O-Methyl deriv, 147–148				δ^{CDCl_3} 6.86 (H-1, H-2) 7.30 (H-5), 6.33 (H-8) 3.94 (OCH₃), 3.80 (OCH₃) 3.86 (OCH₃), 2.49 (NCH₃)		12
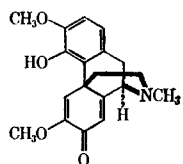
1-Bromo deriv,[a] 196–197

$\nu_{max}^{CHCl_3}$ 3550, 1671, 1646, 1625

$\delta^{(CH_3)_2NCOH}$

7.68 (H-5), 7.22 (H-2)
6.27 (H-8), 3.87
(OCH_3)
3.66 (OCH)_3

1,1'-Dehydrodisalu-taridine, 242–245

$\nu_{max}^{CHCl_3}$ 3560, 1670, 1642, 1624 (1494 band missing)

Salutaridinol I, 227–229 dec   [α]D +42.5 (acetic acid)

$\nu_{max}^{CHCl_3}$ 3620, 3560, 1703, 1661

$\delta^{(CH_3)_2NCOH}$

6.83, 6.56 (H-1, H-2; J = 8.5 cps), 6.42 (H-5)
5.65 (H-8, J = 4.2 cps)
4.48 (H-7, J = 4.2 cps)
3.80 (OCH_3), 3.59 (OCH_3)

72

Salutaridinol II, 132–140   [α]D +24 (acetic acid)
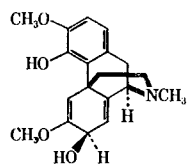
$\delta^{(CH_3)_2NCOH}$

6.83, 6.55 (H-1, H-2; J = 8.3 cps), 6.48 (H-5)
5.45 (H-8, J = 3.3 cps)
4.41 (H-7, J = 3.3 cps)
3.86 (OCH_3), 3.62 (OCH_3)
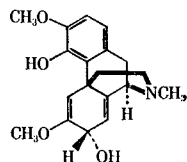
Borane complex, >320
C_19H_26BNO_4

$\nu_{max}^{CHCl_3}$ 3620, 3560, 2300, 2400, 1703, 1661

Tetrahydrosalutaridinol, 214–217

δ^{CDC_3}

6.65 (H-1, H-2)
3.82 (OCH_3), 3.27 (OCH_3)
2.30 (NCH_3)

20
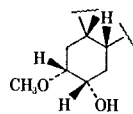
(±)-Salutaridine
[(±)-4-hydroxy-3,6-di-methoxymorphinandi-enone]
C_19H_21NO_4
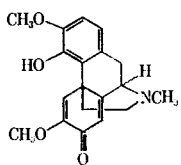
Picrate, 211–215
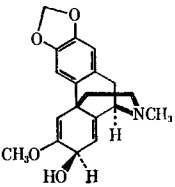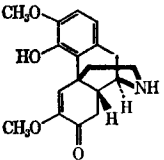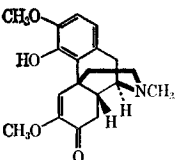
λ_{max}^{MeOH} 236 (4.23), 279 (3.76)

ν_{max}^{CHCl} 3560, 1671, 1644, 1642

δ^{CDCl_3}

7.55 (H-5), 6.74 (H-2, J = 7.0 cps)
6.69 (H-1, J = 7.0 cps)
6.31 (H-8), 3.88 (OCH_3)
3.74 (OCH_3), 2.44 (NCH_3)

13

Table I (Continued)

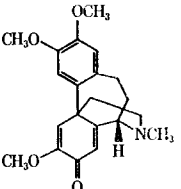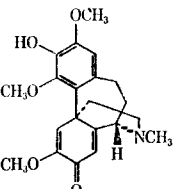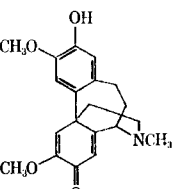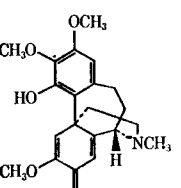| Compound	Derivatives, mp, °C	Optical rotation, deg	Uv, nm (log ε)	Ir, cm⁻¹	Nmr at 60 MHz	Plant source	Ref
Nudaurine (amurinol-1) [(R,R)-2,3-methylenedioxy-6-methoxymorphinan-dienol] $C_{19}H_{21}NO_4$	200–201	$[\alpha]^{19}D$ −48 (CHCl₃)			δ^{CDCl_3} 6.82 (H-4), 6.58 (H-1) 5.92 (OCH₂O), 5.76 (H-8; J = 4.0 Hz), 5.28 (H-5) 4.76 (H-7; J = 4.0 Hz) 3.73 (OCH₃), 2.35 (NCH₃)	Papaver nudicaule var. aurantiacum P. feddei Schwz.[b]	9
	Epinudaurine	$[\alpha]^{11}D$ −23 (CHCl₃)			3.14 (OH) 2.60–3.45 (H-9, H-10A, H-10B, ABX system analyzed at 100 MHz)		
8,14-Dihydronorsalutaridine [(R,R)-N-nor-4-hydroxy-3,6-dimethoxy-8,14-dihydromorphinandienone) $C_{18}H_{21}NO_4$	208–212 (ethyl acetate of cryst)	$[\alpha]^{15}D$ −69.1 (MeOH)	λ_{max}^{EtOH} 206 (4.555), 235 (3.935), 261 (3.95)	ν_{max}^{Nujol} 3250, 1737, 1670, 1625, 1600	δ^{CDCl_3} 6.7 (H-1, H-2) 6.67 (H-5), 3.85 (OCH₃) 3.67 (OCH₃) 3.56 (OH)	Croton linearis Jacq.	20
	N,O-Diacetate			ν_{max}^{Nujo} 1750, 1675, 1600, 1250	δ^{CDCl_3} 6.96 6.93, (H-1, H-2, J = 9 Hz), 6.26 (H-5) 3.67 (OCH₃) 3.80 (OCH₃) 2.35 (OAc), 2.05, and 2.17 (N-Ac) ∼5.0 (H-9)		
	N-Acetate, 250–255				δ^{CDCl_3} 6.71 (H-1, H-2) 6.66 (H-5) 3.87 (OCH₃) 3.68 (OCH₃) 2.05 and 2.15 (NAc with area ratio of ∼2:1)		
8,14-Dihydrosalutaridine [(R,R)-4-hydroxy-3,6-dimethoxy-8,-14-dihydromorphinandienone] $C_{19}H_{23}NO_4$	198–203	$[\alpha]^{15}D$ −76.1 (MeOH)	λ_{max}^{EtOH} 206 (4.514), 238 (3.842), 265 (3.878)	ν_{max}^{Nujol} 1675, 1613, 1575	δ^{CDCl_3} 6.68 (H-1, H-2) 6.76 (H-5) 3.68 (OCH₃), 3.85 (OCH₃), 2.38 (NMe)	Croton linearis Jacq. C. discolor Willd C. plumieri[n]	20
	O-Acetate, 210	$[\alpha]^{15}D$ −22.1 (MeOH)			δ^{CDCl_3} 6.96, 6.88 (H-1, H-2; J = 9 Hz) 6.3 (H-5), 3.70 (OCH₃) 3.80 (OCH₃), 2.32 (NCH₃), 2.45 (OAc)		
	8,14-Dihydrosalutaridinol, 218–220						
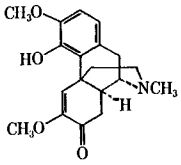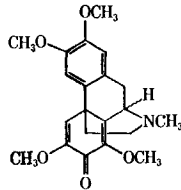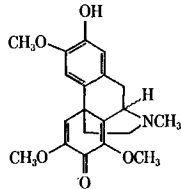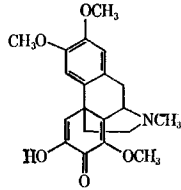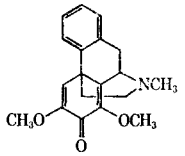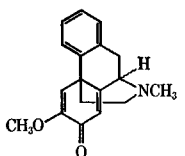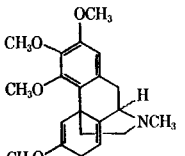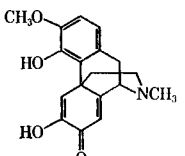
Isosinomenine

[(*S*,*S*)-4-hydroxy-3,6-
dimethoxy-8,14-dihydro-
morphinandienone]

$C_{19}H_{23}NO_4$

198–202 [α]D +73 (EtOH) λ_{max}^{EtOH} 208 (4.499), 238
(3.887), 265 (3.919)

$\nu_{max}^{CHCl_3}$ 1690, 1625

δ^{CDCl_3}
6.79 (H-5)
6.72 (H-1, H-2)
3.86, 3.70
(2 OMe), 2.41 (NCH₃)

Sinomenium acetum[o,p] 22

Picrate, 219–223
1-Bromoisosinomenine,
204–210 dec

$\nu_{max}^{CHCl_3}$ 1690, 1625

Protostephanone

[(±)-2,3,6,8-tetramethoxy-
morphinandienone]

$C_{21}H_{25}NO_5$

ν_{max} 1663, 1628

δ 6.80 (H-4) 71
6.65 (H-1) 16
6.37 (H-5)
4.40 (H-9, dd)
3.88, 3.82 (4 OCH₃)
2.50 (NCH₃)

(±)-2-Hydroxy-3,6,8-tri-
methoxymorphinandi-
enone

$C_{20}H_{23}NO_5$

O-Methyl deriv
(see above)

16

(±)-2,3-Dimethoxy-6-hy-
droxymorphinandienone

$C_{19}H_{21}NO_4$

λ_{max}^{MeOH} 236, 286

$\nu_{max}^{CHCl_3}$ 3400, 1652,
1626

δ^{CDCl_3} 39
6.79, 6.70, 6.37, 5.86
(H-1, H-4, H-5, H-8)
3.87, 3.83, 2.45
(2 OCH₃, NCH₃)

Benzyl deriv

λ_{max}^{MeOH} 236 (4.13),
283 (3.79)

$\nu_{max}^{CHCl_3}$ 1665, 1645,
1620

δ^{CDCl_3} 83
7.32 (OCH₂Ph)
6.59 (H-1), 6.45 (H-5)
6.40 (H-4), 6.30 (H-8)
5.10 (OCH₂Ph)
3.81, 3.65 (2 OMe)
2.34 (NMe)

Methiodide of benzyl
deriv, 225–227°

Table I (Continued)

Compound	Derivatives, mp, °C	Optical rotation, deg	Uv, nm (log ε)	Ir, cm⁻¹	Nmr at 60 MHz	Plant source	Ref
(±)-6,8-Dimethoxymorphin-andienone $C_{19}H_{21}NO_3$	126.5–127.5		λ_{max}^{EtOH} 208 (4.274), 263 (4.049)	ν_{max}^{Nujol} 1670, 1650, 1620	δ^{CDCl_3} 7.35–7.15 (H-1, H-2, H-3, H-4) 6.46 (H-5) 3.80, 3.79 (2 OCH₃) 2.45 (NCH₃) 3.30–1.7 (3 CH₂)		38
(±)-6-Methoxymorphinan-dienone $C_{18}H_{19}NO_2$	183–185		λ_{max} 208 (4.296), 246 (4.138)	$\nu_{max}^{CHCl_3}$ 1665, 1640, 1620	δ^{CCl_4} 7.38, 7.35, 7.25 7.21 (H-1, H-2, H-3, H-4) 6.39, 6.50 (H-5, H-8) 3.84 (OCH₃), 2.49 (N-CH₃)		38
(±)-2,3,4,6-Tetramethoxy-morphinandienone $C_{21}H_{25}NO_5$	Methiodide, 234–235		λ_{max}^{MeOH} 234, 276	$\nu_{max}^{CHCl_3}$ 1665, 1641, 1617	δ^{CDCl_3} 7.22 (H-5) 6.44 (H-1), 6.29 (H-8) 3.98, 3.78 (2 OCH₃) 3.82 (2 OCH₃) 2.44 (NCH₃)		32
4,6-Dihydroxy-3-methoxy-morphinandienone $C_{18}H_{19}NO_4$	220–225 dec Methiodide, 164–166	$[\alpha]^{22}D$ +130 (CHCl₃)	λ_{max}^{EtOH} 240 (4.30) sh, 280 (3.778)	ν_{max}^{Nujol} 1640, sh 1670, 1620, 1600	δ^{CDCl_3} 7.88 (H-5) 6.71, 6.74 (H-1, H-2) 6.43 (H-8) 3.87 (OCH₃) 2.45 (NCH₂)		43
Demethoxy-O-methylandro-cymbine [(±)-2,3,6-trimethoxy-homomorphinandienone] $C_{21}H_{25}NO_4$			λ_{max}^{MeOH} 240 (4.165), 280 (3.765)	$\nu_{max}^{CHCl_3}$ 1667, 1640, 1615	δ^{CDCl_3} 6.90 (H-5) 6.47 (H-1) 6.31 (H-8)		40

Compound / Structure	mp (°C) / Derivative	$[\alpha]_D$	UV	IR	NMR	Source	Ref
	Methiodide 251–252			ν^{KBr}_{max} 3428, 1667, 1646, 1617	6.07 (H-4) 3.88 (OCH₃) 3.81 (OCH₃) 3.62 (OCH₃) 2.35 (NCH₃)		
Androcymbine [(S)-3-hydroxy-2,4,6-tri-methoxyhomomorphinan-dienone] C₂₁H₂₅NO₅	199–201	$[\alpha]^{23}_D$ −260 (CHCl₃)	λ_{max} 216, 240, 278	ν_{max} 1665, 1635, 1615	δ 6.83 (H-5) 6.27 (H-8) 6.27 (H-1) 4.02 (OCH₃) 3.82 (OCH₃) 3.63 (OCH₃) 2.36 (NCH₃)	Androcymbium melanthio-dides[q] var. stricta Baker	6
	O-Methyl deriv 4-Normethyl deriv	$[\alpha]_D$ −295 (CHCl₃)		ν_{max} 1663, 1638, 1613		Colchicum autumnale[r]	44
(±)-2-Hydroxy-3,6-dimethoxy-homomorphinandienone C₂₀H₂₃NO₄	220–221		λ^{MeOH}_{max} 241 (4.22), 282 (3.85)	ν^{CHC}_{max} 3505, 1664, 1642, 1620	δ^{CDCl_3} 6.88, 6.33 (H-5, H-8) 6.56, 6.07 (H-1, H-4) 3.90, 3.64 (2 OCH₃) 2.37 (NCH₃)		27
	Methiodide, 225–226						
2,3,6-Trimethoxy-4-hydroxy-homomorphinandienone C₂₁H₂₅NO₆				ν_{max} 1663, 1638, 1613			44

[a] L. Kühn and S. Pfeifer, Pharmazie, 20, 659 (1965). [b] S. Pfeifer and I. Mann, ibid., 20, 643 (1965). [c] H.-G. Boit and H. Flentje, Naturwiss., 46, 514 (1959). [d] H.-G. Boit and H. Flentje, ibid., 47, 180 (1960). [e] M. Maturová, Planta Med., 10, 345 (1962). [f] T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, J. Chem. Soc. C, 2034 (1969). [g] C. W. Thornber, Phytochemistry, 9, 157 (1970), and references cited. [h] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, Aust. J. Chem., 19, 2331 (1966). [i] C. Chambers, L. J. Haynes, and K. L. Stuart, Chem. Commun., 449 (1966). [j] K. L. Stuart and C. Chambers, Tetrahedron Lett., 2879 (1967). [k] A. R. Battersby and T. H. Brown, Chem. Commun., 170 (1966). [l] A. L. Mndzhoyan, V. A. Mnatsakanyan, and A. P. Mkrtehyan, Arm. Khim. Zh., 20, 376 (1967); Chem. Abstr., 68, 114787 (1968). [m] S. Pfeifer and L. Kühn, Pharmazie, 23, 267 (1968). [n] K. L. Stuart and R. B. Woo-Ming, Phytochemistry, 8, 777 (1969). [o] Reported to be an artifact. [p] Y. Sasaki and S. Ueda, J. Pharm. Soc. Jap., 78, 44 (1958); Y. Sasaki, ibid., 80, 270 (1960). [q] J. Hrbek and F. Šantavý, Collect. Czech. Chem. Commun., 27, 255 (1962). [r] R. Ramage, Ann. Rep. Progr. Chem., B, 64, 515 (1967).

to tetrabenazine (155) which is a reserpine-like compound

155
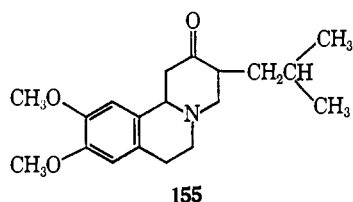
in its action on the central nervous system. 40 produced a moderate reduction of spontaneous motor activity in mice and low body posture at 300 mg/kg.[81]

The recent work by Davis, Walsh, and Yamanaka[82] on the possible link between alcoholism and opiate addiction should stimulate activity in this area. These workers have found that in the presence of ethanol or acetaldehyde, which is derivable from ethanol, the normal metabolic pathway for the degradation of the biologically active amine, dopamine (156), in brain tissue, is inhibited at the stage of the conversion of 3,4-dihydroxyphenylacetaldehyde (157) into 3,4-dihydroxyphenylacetic acid (158). When this block occurs, compound 157 accumulates, and condensation between 156 and 157 is facilitated. This results in the formation of nor-laudanosoline (159). Using ^{14}C-labeled 159 these workers

156   157   158

159   160

161   162
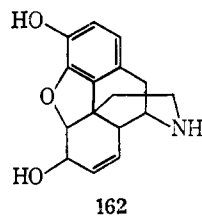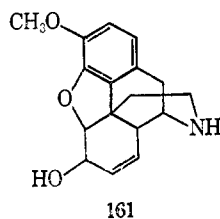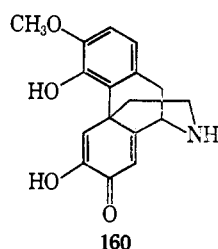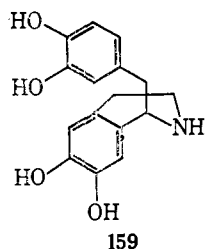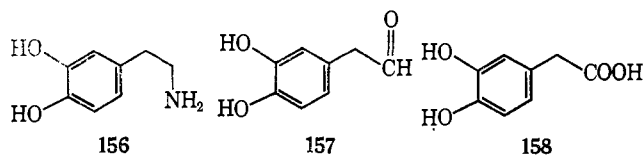
have shown that 50% of the activity was located in the alkaloid fraction. From tlc and glc, this was shown to contain norcodeine (161), codeine (132), and normorphine (162).[82] It seems very likely that a morphinandienone intermediate like compound 160 plays an important role in this biological transformation and an evaluation of the biological activity of such a morphinandienone has some merit. The N-methyl derivative, 114, has in fact been recently prepared.[43]

VII. Addendum

A second synthesis of the diosphenol 89 has appeared recently.[88] A modified Pschorr reaction on the diazonium salt of compound 163 produced 164 as well as the aporphines (+)-benzylpredicentrine (165) and (+)-predicentrine (166).

163   164

165, R¹ = PhCH₂
166, R¹ = H
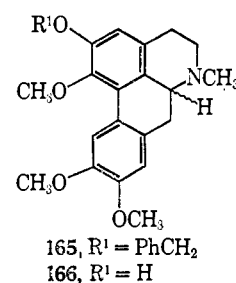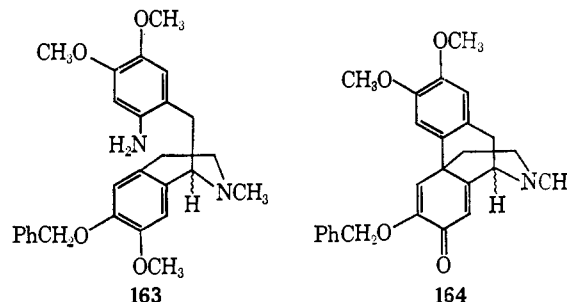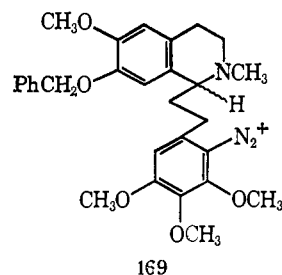
Debenzylation of 164 by hydrobromic acid in methanol produced 89.

The alkaloid delavaine, mp 149–150°, [α]D −240°, has been isolated from Stephania delavayi, and the dihydromorphin-andienone structure 167 or 168 has been proposed.[84]

167, R¹ + R² = CH₂; R³ = CH₃
168, R² + R³ = CH₂; R¹ = CH₃
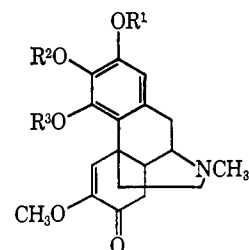
Photolysis of the diazonium salt 169 produced the racemate of O-methylandrocymbine (11).[85]

169

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(81) R. F. Raffauf, unpublished results.

(82) V. E. Davis, M. J. Walsh, and Y. Yamanaka, Chem. Eng. News, 48 (7), 44 (1970).

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(83) T. Kametani, T. Sugahara, H. Yagi, K. Fukumoto, B. R. Pai, and R. Charubala, J. Chem. Soc. C, 624 (1970).

(84) I. I. Fadeeva, T. N. Il'inskaya, M. E. Perel'son, and A. D. Kuzovkov, Khim. Prir. Soedin., 6, 140 (1970); Chem. Abstr., 73, 45639 (1970).

(85) T. Kametani, M. Koizumi, and K. Fukumoto, Chem. Commun., 1157 (1970).