MORPHINANDIENONE ALKALOIDS

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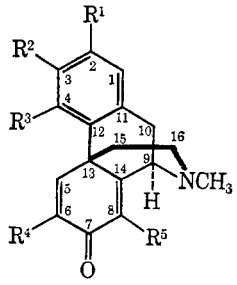
Contents

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**).



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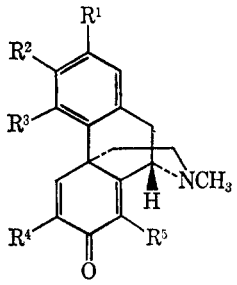

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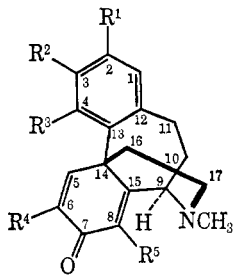

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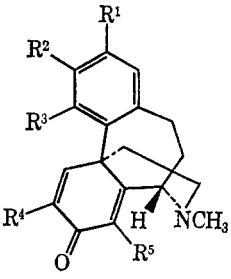

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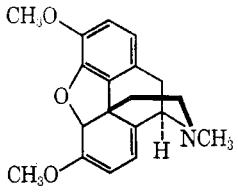
The correctness of this proposal is clearly attested to in the discussion set out in section V of this review. Battersby and his research group[3] have also recently shown that the homomorphinandienones are the key to the intriguing problem of the biosynthesis of colchicine (**7**), and it is now believed that these compounds are precursors to the homomorphine compound kreysiginine (**8**). To date, morphinandienones and reduced morphinandienones have been isolated from five genera, namely the *Cassytha*, *Croton*, *Corydalis*, *Papaver*, and



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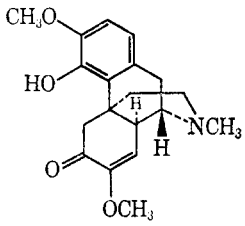

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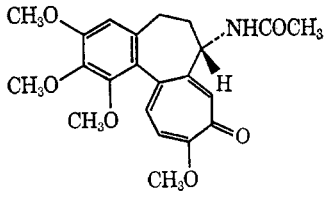

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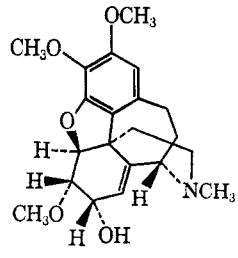

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(1) L. Kühn and S. Pfeifer, *Pharmazie*, **20**, 659 (1965).

(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.

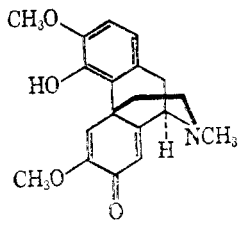
All the known morphinandienones are listed in a tabular form in Table I along with their physical properties and those of their derivatives.

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.



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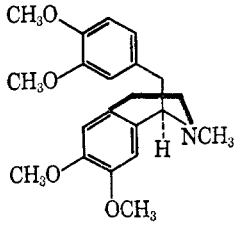

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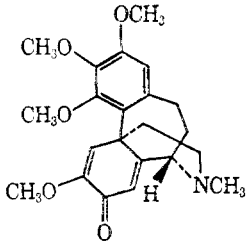
This reaction has also been used in the homomorphinandienone series. *O*-Methylandrocymbine (**11**) was converted to the 1-phenethylisoquinoline **12**. Compound **12** was fully characterized by an unambiguous synthesis, and this reaction in addition to ORD evidence established the *S* configuration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



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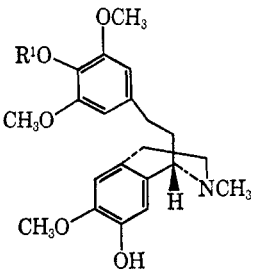


12, $R^1 = CH_3$

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

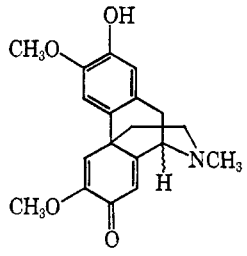
(5) M. P. Cava, K. Normura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *Chem. Ind. (London)*, 282 (1964).

(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-



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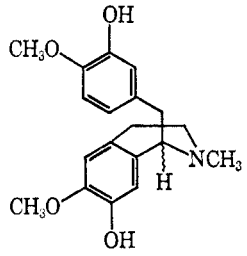

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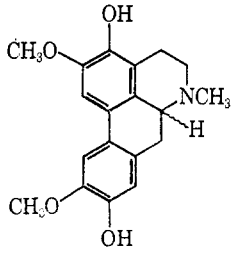

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gous to that shown by morphine.[8]

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

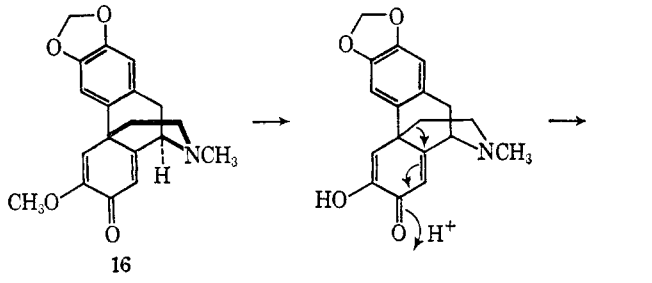
(7) B. Franck, J. Lubs, and G. Dunkelmann, *Angew. Chem. Int. Ed. Engl.*, **6**, 969 (1967).

(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).



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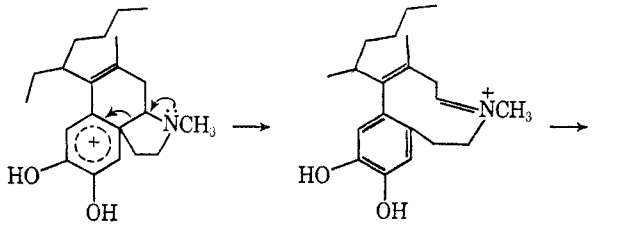

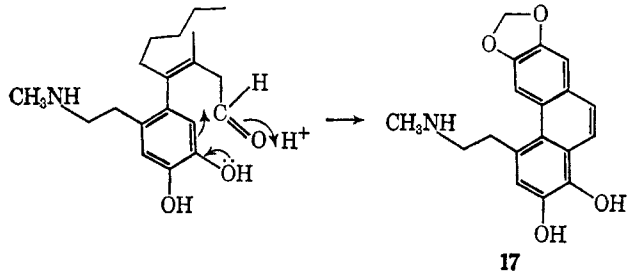

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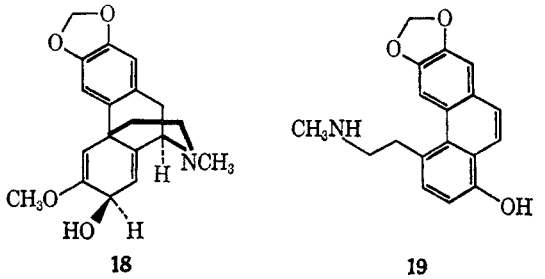

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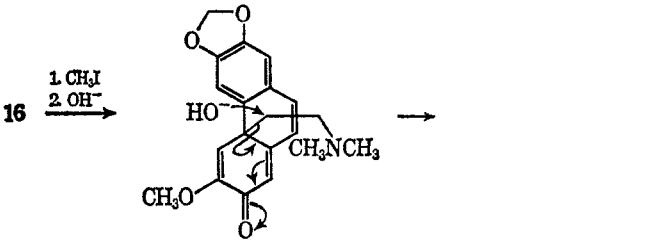

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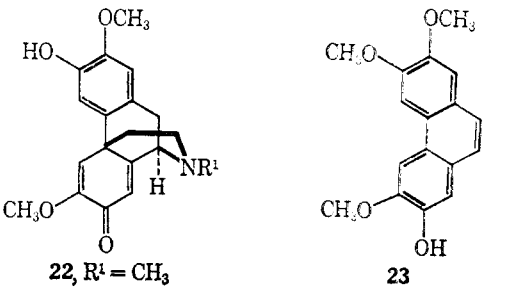
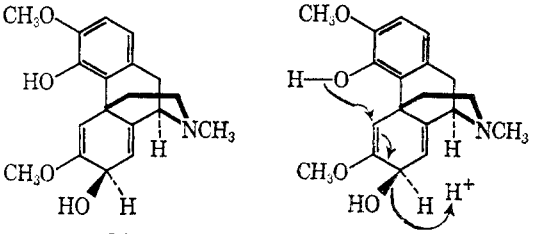
converted to thebaine (**5**) by allowing solutions of these compounds to stand in 0.2 *M* phosphate buffer at room temperature for periods varying from 60 to 94 hr (see **24A** → **5** for mechanism). This conversion mimicks the now established biosynthetic conversion of salutaridine to thebaine (section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



22, $R^1 = CH_3$ 23

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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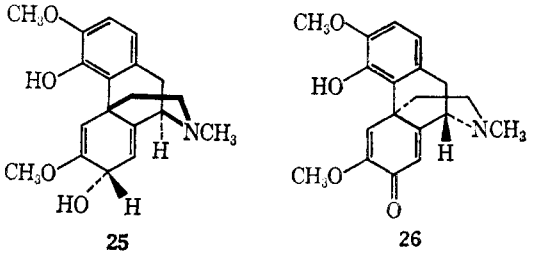

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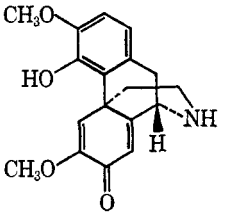
4. New Cross-Conjugated Dienones

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. Viebock, *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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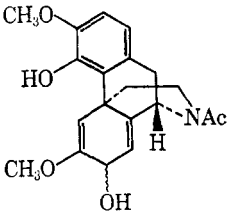

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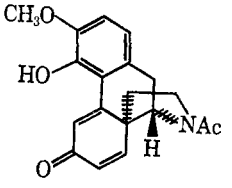

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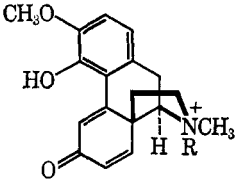

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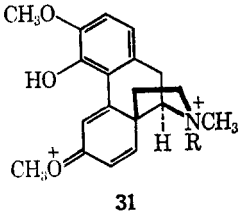

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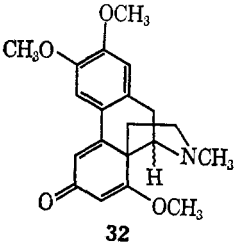

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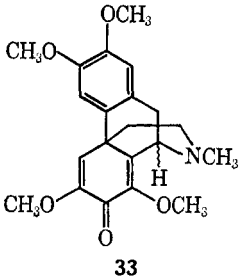

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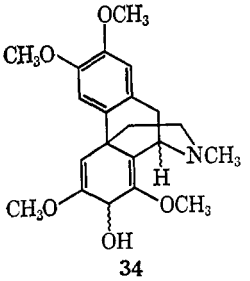

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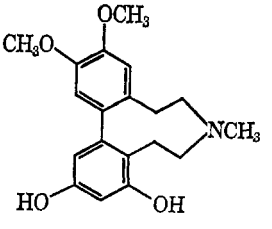

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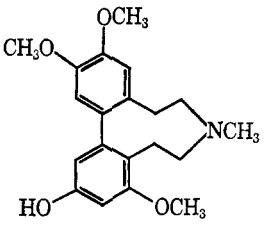
O-Methylation of both **35** and **36** produced protostephanine (**37**), an alkaloid isolated from *Stephania japonica* Miers (see section V).

C. OZONOLYSIS OF DIENOLS

Sodium borohydride reduction efficiently converts morphinandienones into the corresponding dienols, and ozonolysis of



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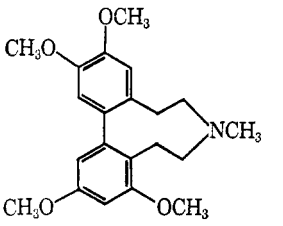

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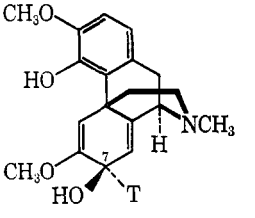
these and the one known naturally occurring morphinandienol, nudaurine (**18**), have allowed the C-7 configuration to be established. For example, sodium [^3H]borohydride reduction of salutaridine (**9**) yielded [^3H]salutaridinol I (**38**) and [^3H]salutaridinol II (**39**). **38** was ozonized at −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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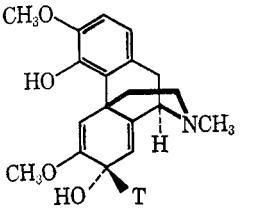

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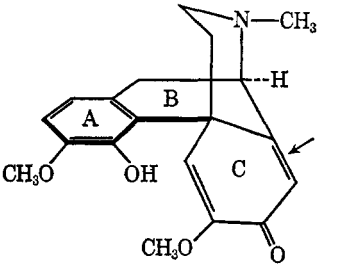
Using a similar series of ozonolysis experiments, it was shown that nudaurine (**18**) from *Papaver nudicaule* was identical with amurinol I, and so established the C-7 configuration.[19]

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**).

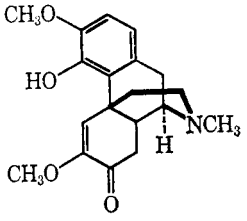


9A

(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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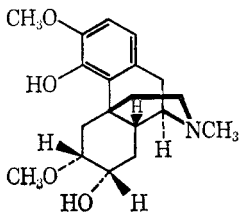

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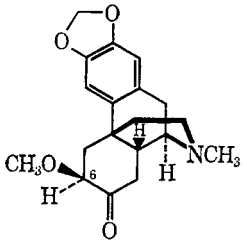

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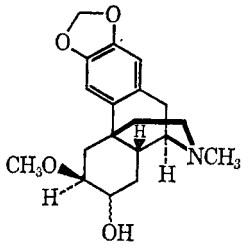
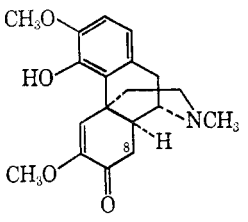


43

(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 intermediate 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]



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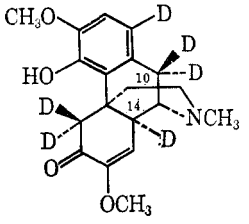
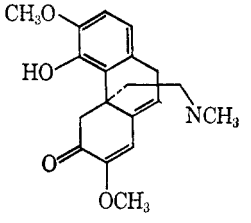


6A



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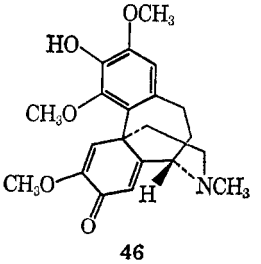
[*6-Methoxy*-^3H]Isosinomenine was prepared by the equilibration of sinomenine in [*methoxy*-^3H]methanol.[22] If the starting alkaloid is phenolic, a tritiated *O*-methyl group can be introduced into the molecule by treating the phenol with diazomethane in the presence of tritiated water.[24] An example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



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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]

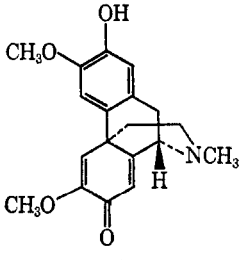
III. Chemical Syntheses

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-dimethoxymorphinandienone)*

(±)-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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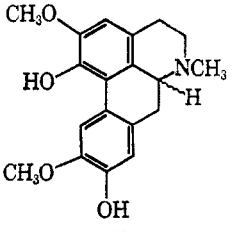

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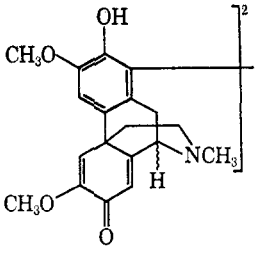


49

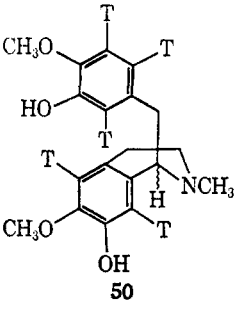
(25) G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, **157**, 1524 (1967).

(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).

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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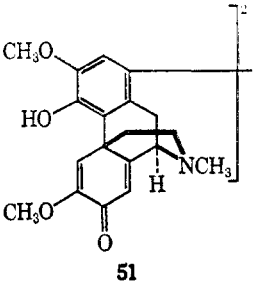

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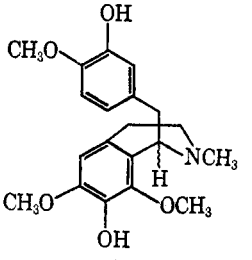
3. *2-Hydroxy-3,6,8-trimethoxymorphinandienone*

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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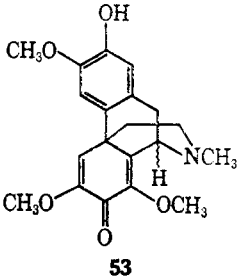


53

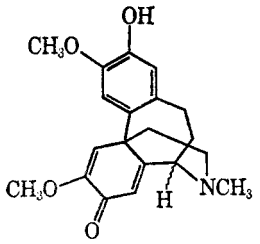
4. *2-Hydroxy-3,6-dimethoxyhomomorphinandienone*

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

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



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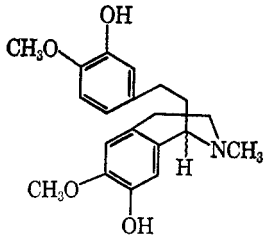

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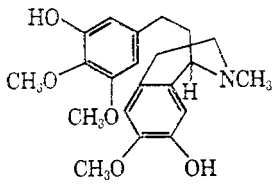
acetate at room temperature yielded none of the required product, **54**, nor did ferric chloride at room temperature for 7 days. Similarly, compound **56** gave no detectable amounts of homomorphinandienones. In this latter case, steric factors were probably the predominant reason for failure.[28] Several 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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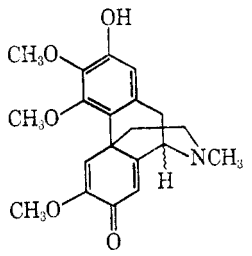

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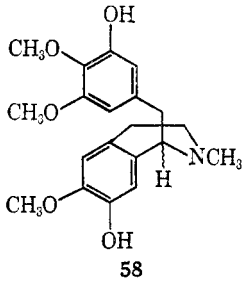

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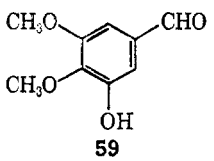

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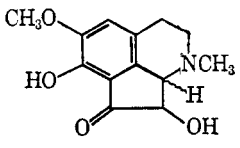

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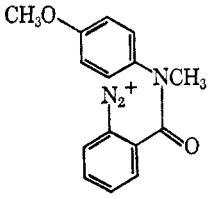
B. PSCHORR-TYPE SYNTHESES

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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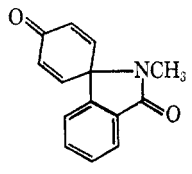

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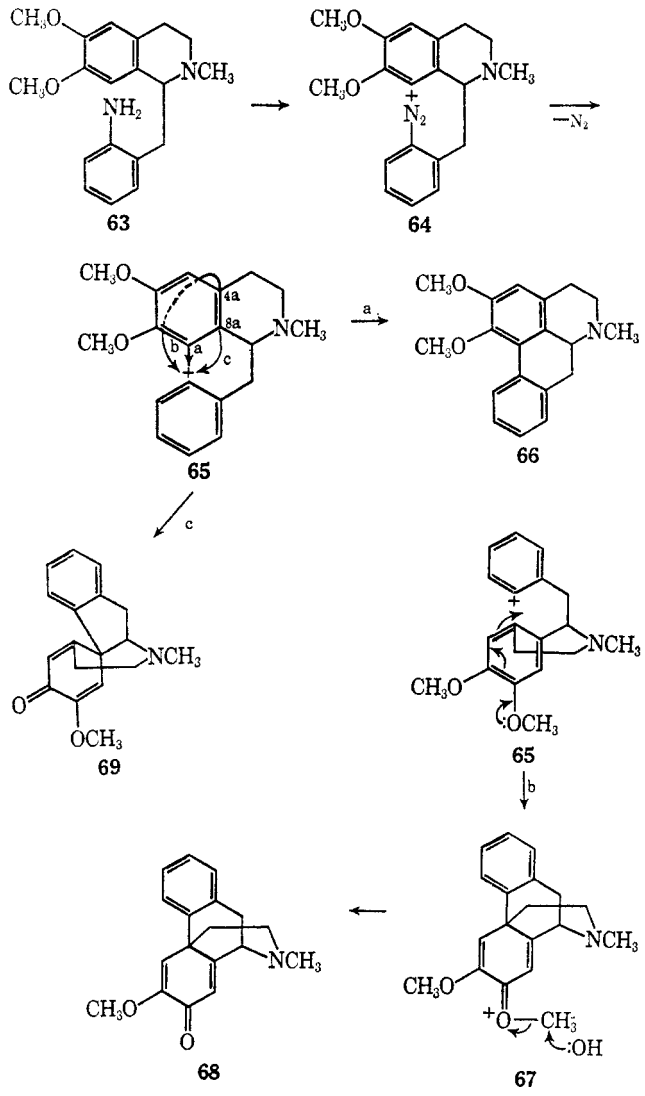
Scheme I indicates the possible reaction pathways, and in the

Scheme I



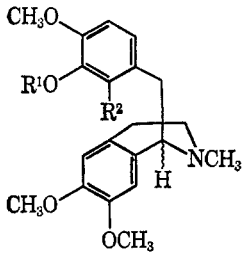
case of the formation of the morphinandienone **68**, the mechanism proposed indicates that the nucleophilic attack on position 4a is facilitated by the E-effect of an alkoxy group.[32]

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

(±)-1-(2-Amino-3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-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]



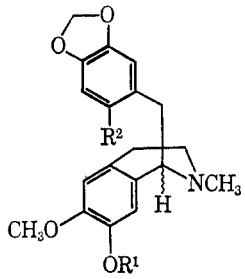
70, $R^1 = PhCH_2$; $R^2 = NH_2$
71, $R^1 = R^2 = H$

2. *Sinoacutine* (*(S)-4-Hydroxy-3,6-dimethoxymorphinandienone*)

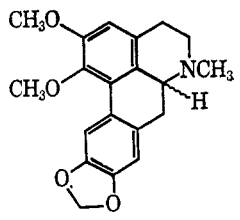
Resolution of the 2-aminobenzylisoquinoline (**70**) with (−)-di-*p*-toluoyltartaric acid followed by diazotization and thermal decomposition as described above yielded sinoacutine (**26**) and (+)-laudanidine (**71**).[18]

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, $R^1 = Et$; $R^2 = NH_2$
73, $R^1 = CH_3$; $R^2 = NH_2$
75, $R^1 = CH_3$; $R^2 = H$

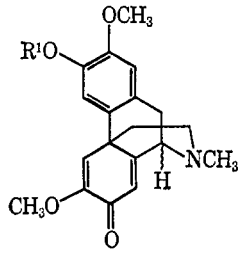


74

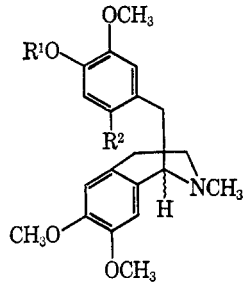
by thermal decomposition both yielded (±)-amurine. In the experiment using **73**, the aporphine (±)-epidicentrine (**74**) and the isoquinoline **75** were also isolated from the reaction product.

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

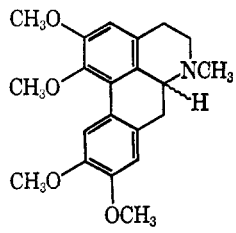
Confirmation for the earlier structural proposal for flavinantine[34,35] was obtained by the synthesis of (±)-flavinantine (**76**). Diazotization of the aminotetraisoquinoline **77** followed by thermal decomposition produced **78** in 8.4% yield. Debenzylation to **76** was achieved by treatment with ethanolic hydrogen bromide. Deamination products **79** and **80** were also formed.[36]



76, $R^1 = H$
78, $R^1 = PhCH_2$
82, $R^1 = CH_3$



77, $R^1 = PhCH_2$; $R^2 = NH_2$
80, $R^1 = PhCH_2$; $R^2 = H$
79, $R^1 = R^2 = H$
81, $R^1 = CH_3$; $R^2 = NH_2$
84, $R^1 = CH_3$; $R^2 = H$
85, $R^1 = Et$; $R^2 = NH_2$



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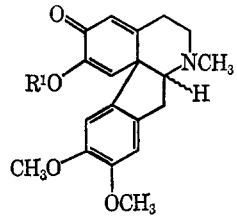
5. (±)-*O-Methylflavinantine* (*2,3,6-Trimethoxymorphinandienone*)

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



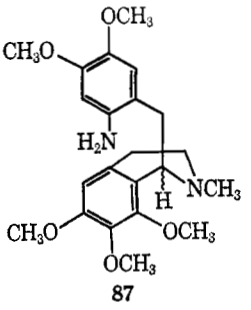
86, $R^1 = CH_3$ or Et

the dienone product.[37] Other workers obtained identical products as shown when the diazonium salt of 6′-aminolandanosine (**81**) was decomposed at 0° with copper.[38]

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]

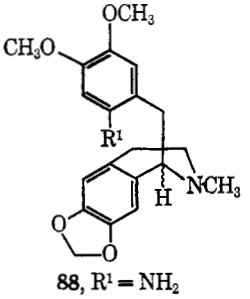
(33) T. Kametani, K. Fukumoto, and T. Sugahara, *J. Chem. Soc. C*, 801 (1969).
(34) C. Chambers and K. L. Stuart, *Chem. Commun.*, 328 (1968).
(35) K. L. Stuart, C. Chambers, and D. Y. Byfield, *J. Chem. Soc. C*, 333 (1969).
(36) T. Kametani, T. Sugahara, H. Yagi and K. Fukumoto, *ibid.*, 1063 (1969).
(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).



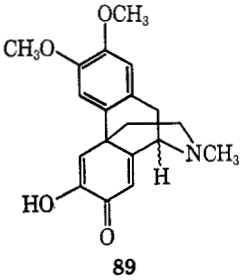
87

7. *2,3-Dimethoxy-6-hydroxymorphinandienone*

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, $R^1 = H$



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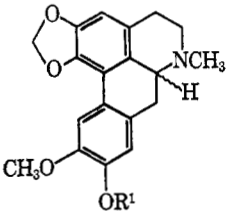


90, $R^1 = CH_3$
91, $R^1 = H$

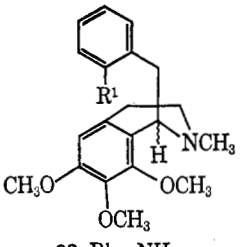
the modified Pschorr cyclization. The aporphine alkaloids (±)-dicentrine (**90**) and (±)-cassythicine (**91**) as well as **92** were produced.[89]

8. *6,8-Dimethoxymorphinandienone*

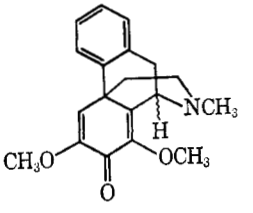
When the aminoisoquinoline **93** was converted to the diazonium salt and this then decomposed with copper at 0°, **94** was obtained in a 7% yield. (±)-Nuciferine (**95**), the isoquinoline **96**, and the orange-yellow base **97** were also produced.[88]

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.[88]



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



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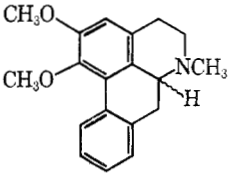

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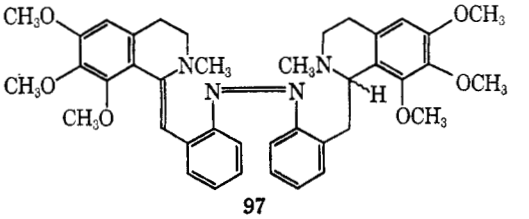

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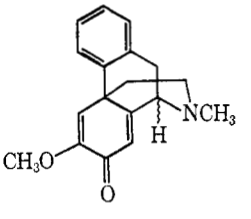

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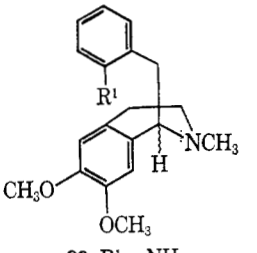
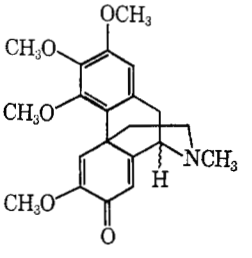


99, $R^1 = NH_2$
100, $R^1 = H$

10. *2,3,4,6-Tetramethoxymorphinandienone*

The morphinandienone **101** was synthesized by the modified Pschorr technique (omission of copper catalyst) from the diazonium salt of the aminoisoquinoline **102**.[82]



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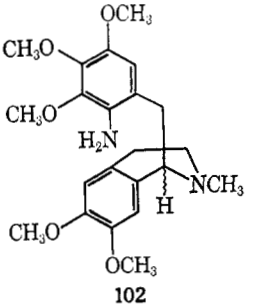


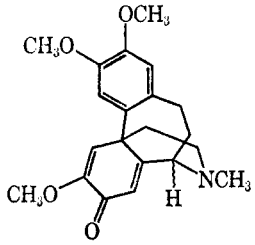
102

11. *2,3,6-Trimethoxyhomomorphinandienone*

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

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

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



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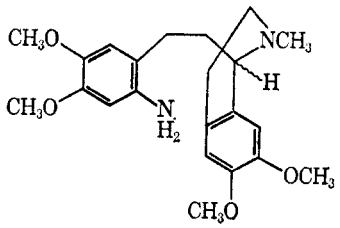

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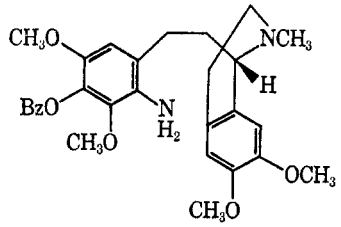


105

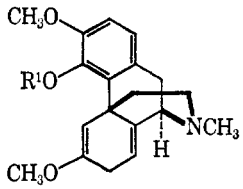
Pschorr technique seems a possible way to achieve the ultimate synthesis of androcymbine (**46**), and this is likely to be achieved by the time this review appears.

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

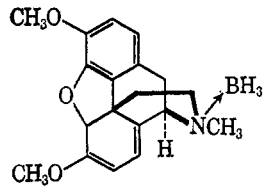


106, $R^1 = H$
107, $R^1 = Ac$

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 BH_3 formed 7α-isoneopine methyl ether **109** and 7β-neopine methyl ether **110**. MnO_2 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]



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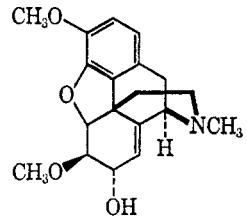

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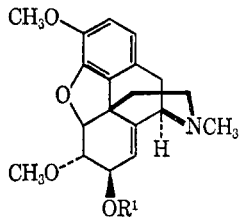
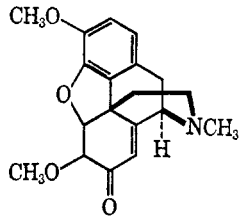


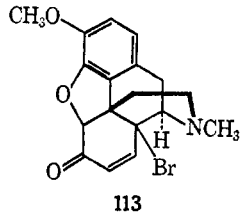
110, $R^1 = H$
112, $R^1 = Ac$



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. Diazomethane 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]



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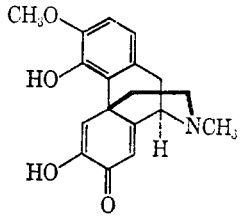

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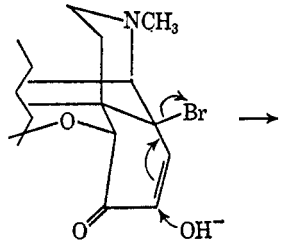
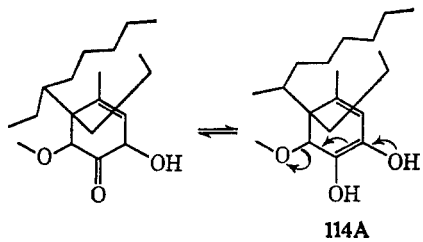


113A



114A

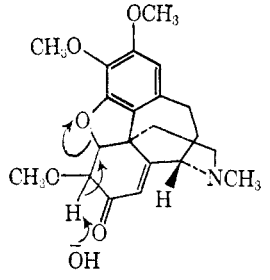
(40) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1001 (1968); *J. Chem. Soc. C*, 3084 (1968).
(41) M. Takeda, H. Inone, and H. Kugita, *Tetrahedron*, **25**, 1839 (1969).
(42) H. Conroy, *J. Amer. Chem. Soc.*, **77**, 5960 (1955).
(43) D. E. Rearick and M. Gates, *Tetrahedron Lett.*,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

2. *Isosinomenine*

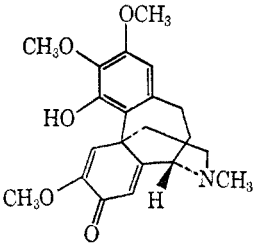
Isosinomenine **44** was produced when sinomenine (**6**) was treated with methanolic hydrogen chloride at room temperature by way of an equilibrium mixture of **44** and **6**.[22]

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



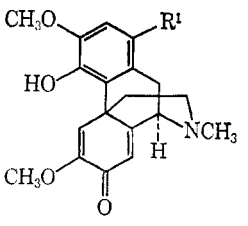
116

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]



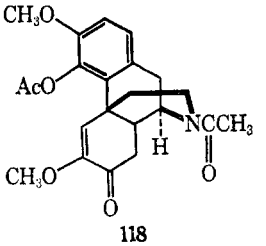
117, R^1 = Br
117A, R^1 = D

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



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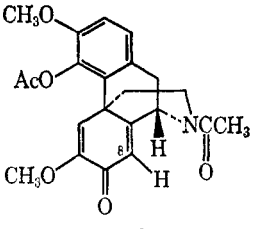

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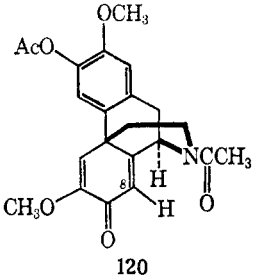


120

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

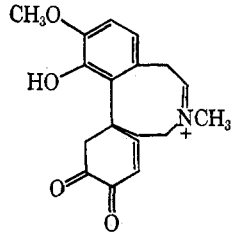
Mass spectral data have been obtained for many morphinandienones and reduced morphinandienones, and in some of these studies fragmentation pathways have been proposed and

(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



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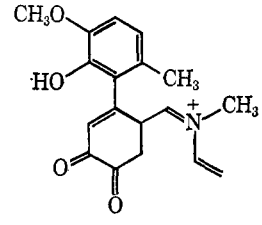
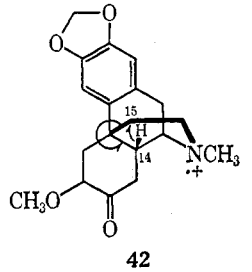


122

this is probably due to the loss of CO and methyl.[38,47]

In the spectrum of amurine, other prominent peaks were due to ($M^+ - CO - OMe$), ($M^+ - CO - Me - CO$), and ($M^+ - C_8H_7N - CO^-$). 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



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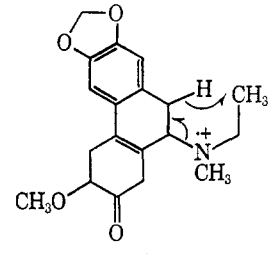
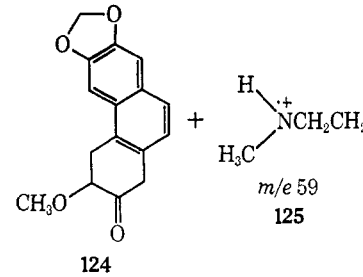


123

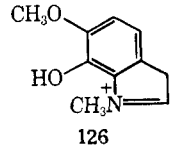


124

m/e 59

125

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



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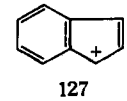


127

(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).

(*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).

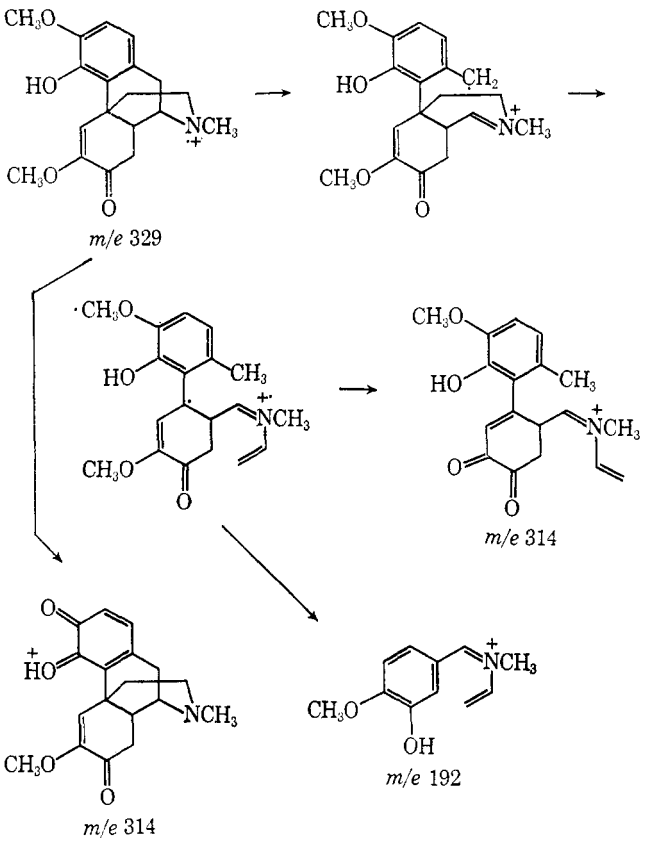
(69) G. Blaschke, H. J. Parker, and H. Rapoport, *J. Amer. Chem. Soc.*, **89**, 1540 (1967).

(70) I. D. Spenser, "Comprehensive Biochemistry," M. Florkin and E. H. Stotz, Ed., Elsevier, New York, N. Y., 1968, p 231.

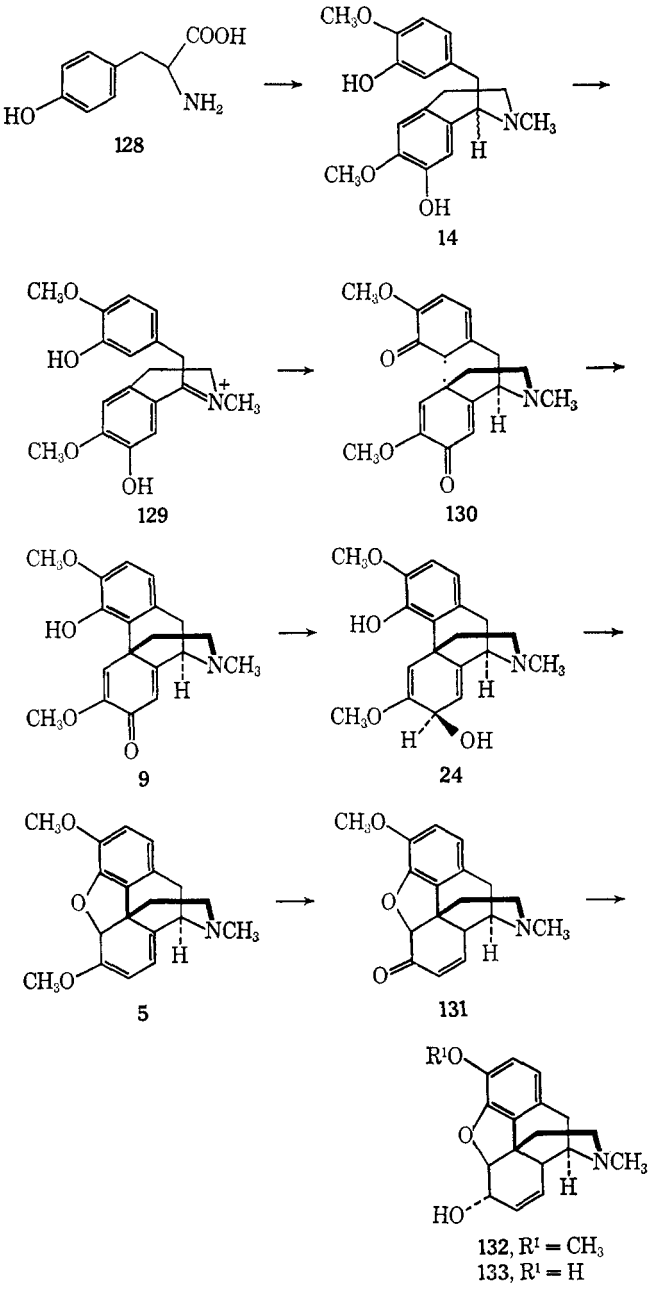
(71) A. R. Battersby, "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Edward Arnold, London, 1967, p 119.

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

Scheme II



Scheme III



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]

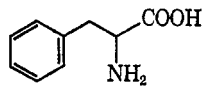
B. SINOACUTINE. FORMATION OF SINOMENINE

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 $\beta\gamma$ 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]

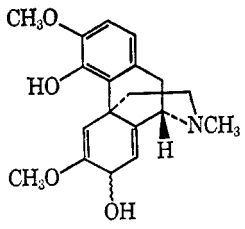
C. PROTOSTEPHANONE. FORMATION OF PROTOSTEPHANINE

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

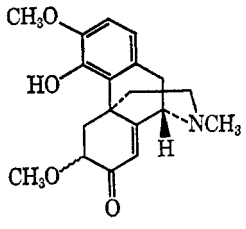
(73) J. W. Fairbairn and S. El-Masry, *Phytochemistry*, 7, 181 (1967).
(74) K. L. Stuart and L. Graham, unpublished work.
(75) K. Okabe, K. Hayashi, and Y. K. Sawa, *Chem. Pharm. Bull.*, 16, 1611 (1968).



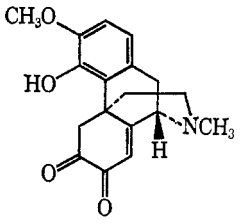
134



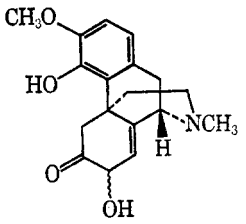
135



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

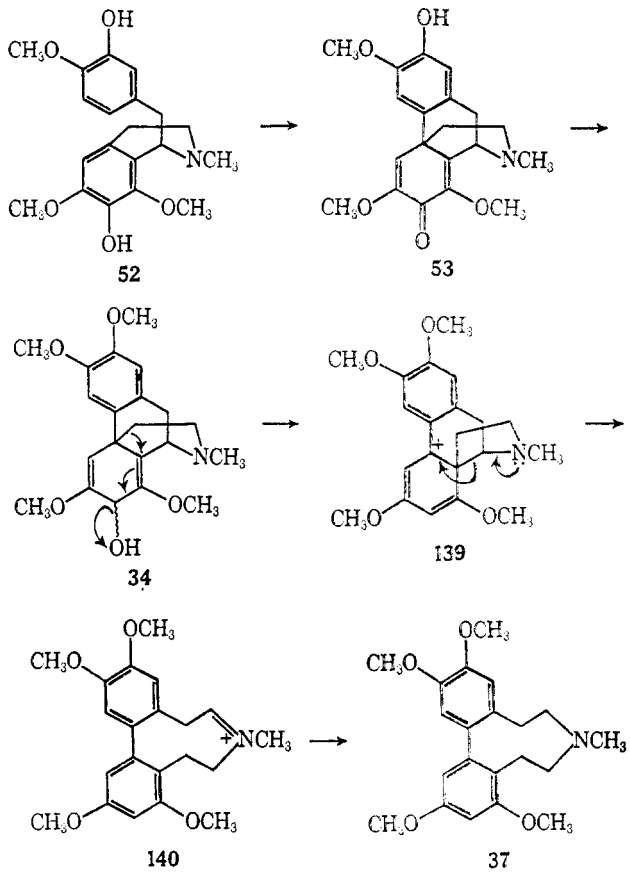
Whereas morphine-type compounds are formed by ortho–para oxidative coupling of reticuline (**14**), it now seems very likely that flavinantine (**22**), flavinine (**141**) (*Croton flavens*), amurine (**16**), nadurine (**18**) (*Papaver nudicale*), and pallidine (**47**) (*Corydalis pallida*) are formed 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]

(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).

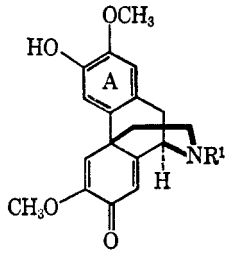
Scheme IV



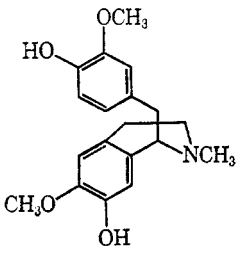
52 53 34 139 140 37

F. ANDROCYMBINE. FORMATION OF COLCHICINE AND HOMOMORPHINE ALKALOIDS

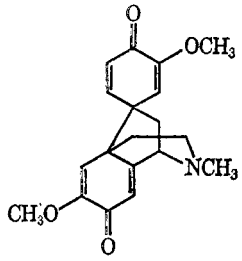
The important role of homomorphinandienones in the biosynthesis of colchicine was not appreciated until very recently. It has been established by feeding experiments in *Colchicum autumnale* and *C. byzantinum* that *O*-methylandrocymbine (**11**) was incorporated into demecolcine (**149**) (49% incorpora-



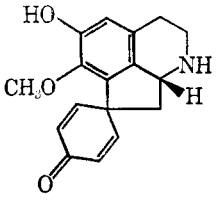
22, $R^1 = CH_3$
141, $R^1 = H$



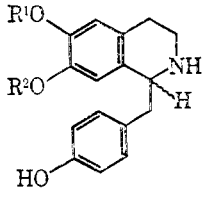
142



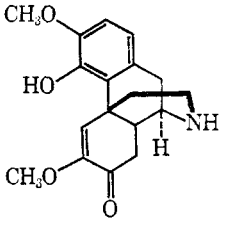
143



144



145, $R^1 = CH_3$; $R^2 = H$
146, $R^1 = R^2 = H$
147, $R^1 = H$; $R^2 = CH_3$



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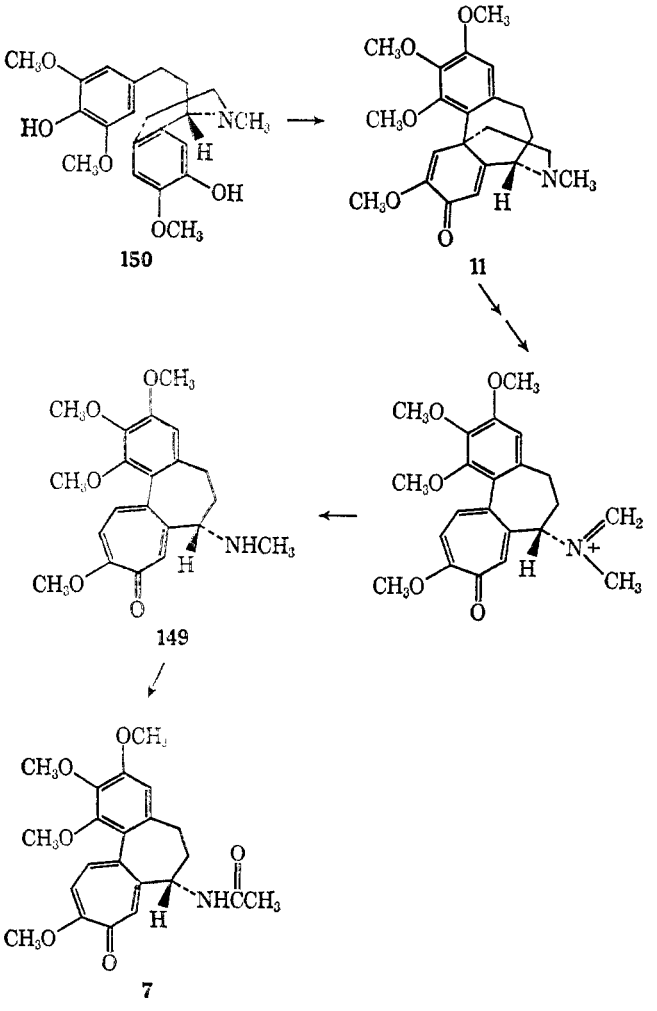
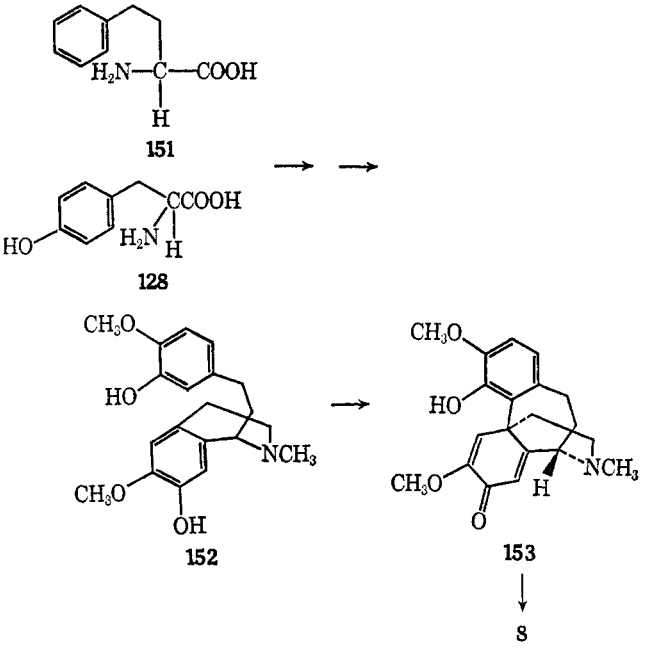
tion) and into colchicine (7) (15%), and there is now good evidence supporting the biosynthetic pathway from the 1-phenethylisoquinoline **150** to **7** (Scheme V). The elucidation

Scheme V



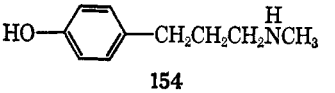
of the structure of kreysiginine (**8**) from *Kreysigia multiflora*[44,77,78] has again focused attention on the very likely role of an androcymbine-type compound as a precursor for its formation. Scheme VI indicates a possible pathway

Scheme VI



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*



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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.

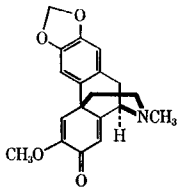
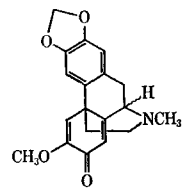
VI. Pharmacology

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-methoxymorphinandienone] $C_{19}H_{19}NO_4$ 	213–215[a]	$[\alpha]^{26}D$ +10 ($CHCl_3$)[a]	λ_{max}^{MeOH} 240 (4.239), 290 (3.95)[b]	ν_{max} 1678, 1650, 1627[a]	δ^{CDCl_3} 6.93 (H-4) 6.77 (H-1) 6.40 (H-5) 6.35 (H-8) 5.95 (–OCH_2O–) 3.80 (OCH_3) 3.60–2.72 (12 lines, ABX pattern; H-9 and 2 H-10) 2.42 (NCH_3)	*Papaver nudicaule* var. aurantiacum Loisel[d] *P. nudicaule* var. amurense N. Busche[c] *P. nudicaule* var. croceum Lideb[d] *P. nudicaule* ssp. xanthopetalum (Trautv.) Fedde[e] *P. feddei* Schwz.	9
	Methiodide, 202–206 dec	$[\alpha]^{23}D$ +13 (H_2O)					
	Hydriodide, 216–218						
	Perchlorate, 215–217						
	Picrate, 226–227 dec						
	Tetrahydroamurine	$[\alpha]^{20}D$ −111 ($CHCl_3$)		ν_{max} 1725	δ^{CDCl_3} 6.92 (H-1) 6.65 (H-4) 5.94 (–OCH_2O–) 5.94 (4 lines; X part of ABX system, 215.5, 220, 227.5; 233 Hz; H-6) 3.43 (C_6OCH_3) 2.40 (NCH_3)		
	Tetrahydroamurine picrate, 140–145						
	Hexahydroamurine, 136–137	$[\alpha]^{21}D$ −56 ($CHCl_3$)		ν_{max}^{KBr} 3370			
(±)-Amurine [(±)-2,3-methylenedioxy-6-methoxymorphinandienone] 			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 (–OCH_2O–) 3.79 (OCH_3) 2.44 (NCH_3)		33
	Methiodide, 222–224			ν_{max}^{KBr} 3370, 1670, 1649, 1626			
Flavinantine [(*R*)-3-hydroxy-2,6-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$	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

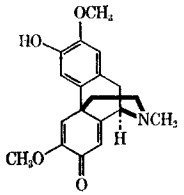
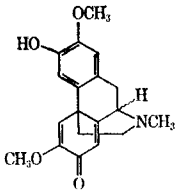
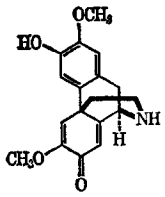
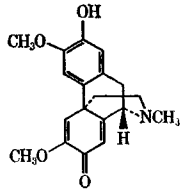
	Acetate, 196–197			3.79 (OCH_3) 3.72 (OCH_3) 2.32 (NCH_3) $\delta^{(CD_3)_2SO}$ 7.40 (H-5) 6.95 (H-4) 6.80 (H-1) 6.28 (H-8) 3.80 (OCH_3) 3.72 (OCH_3) 2.33 (NCH_3) 2.25 (Ar OAc)	
	O-Methyl methiodide, 250–252 dec				
	[4-^2H]Flavinantine		$\nu_{max}^{CHCl_3}$ 1508 band, displaced to 1488		
	O-Methyl derivative		$\nu_{max}^{CHCl_3}$ 1666, 1642, 1621, 1508		
(±)-Flavinantine [(±)-3-hydroxy-2,6-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$		λ_{max}^{MeOH} 239 (4.17), 286 (3.85)	$\nu_{max}^{CHCl_3}$ 3490, 1665, 1642, 1624	δ^{CDCl_3} 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)	36
	Methiodide, 235–238 dec				
	O-Benzyl deriv	λ_{max}^{MeOH} 235 (4.15), 282 (3.83)	$\nu_{max}^{CHCl_3}$ 1663, 1641, 1621	δ^{CDCl_3} 7.31 (OCH_2Ph) 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_2Ph) 3.85 (OCH_3) 3.60 (OCH_3) 2.40 (NCH_3)	36
	O-Benzyl methiodide, 208–210				36
	O-Methyl deriv, 158–160	λ_{max}^{EtOH} 205 (4.641), 239 (4.25), 285 (3.922)	$\nu_{max}^{CHCl_3}$ 1670, 1640, 1620	δ^{CDCl_3} 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)	37, 38
	O-Methyl methiodide, 223–225 dec	λ_{max}^{MeOH} 284, 238 sh	ν_{max}^{KBr} 1669, 1647, 1626, 1518		37

Table II (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 (OCH_3) 3.68 (OCH_3) 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 (OCH_3) 3.78 (OCH_3) 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 (OCH_3) 3.81 (OCH_3) 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 (OCH_3) 3.79 (OCH_3) 2.37 (NCH_3)	*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 (OCH_3) 3.79 (OCH_3) 2.37 (NCH_3)		

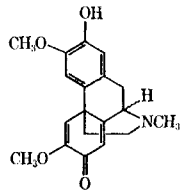
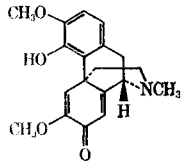
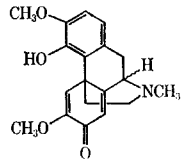
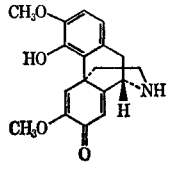
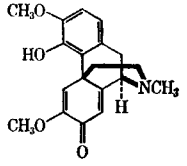
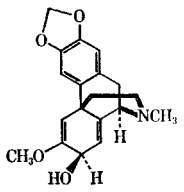
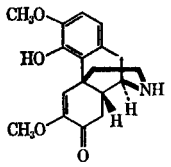
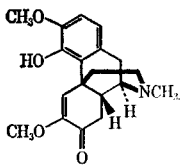
	*O*-Acetate,[f] 203–204		λ_{max}^{MeOH} 233, 284 λ_{inf} 247	$\nu_{max}^{CHCl_3}$ 1753, 1663, 1642, 1611	δ^{CDCl_3} 6.92 } H-4, H-5 6.83 } 6.36 (H-1) 6.33 (H-8) 3.81 (2 OCH_3) 2.47 (NCH_3) 2.30 ($COCH_3$)		7
Sinoacutine [(−)-(*S*)-4-hydroxy-3,6-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$	198	$[\alpha]_D$ −81.6 ($CHCl_3$) $[\alpha]_D$ −116 (EtOH)	λ_{max} 240 (4.25), 277 (3.75)	ν_{max} 3525, 2872, 1672, 1646, 1626, 1296		*Sinomenium acutum* Rehd. et Wils.[g]	14 12
	Acetate, 175 Hexahydrosinoacutinol, 216	$[\alpha]_D$ −125 (EtOH)				*Croton flavens* L. *Cassytha pubescens* R. Br.[h]	15
(±)-Sinoacutine [(±)-4-hydroxy-3,6-dimethoxymorphinandienone]			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
	Picrate, 211–215						
Norsinoacutine [(−)-(*R*)-*N*-nor-4-hydroxy-3,6-dimethoxymorphinandienone] $C_{18}H_{19}NO_4$	113–115 (acetate of crystn)	$[\alpha]^{16}_D$ −107 (MeOH)	λ_{max}^{EtOH} 241 (4.19), 275 sh (3.83)	ν_{max}^{Nujo} 3400,[i] 3150, 1672, 1643, 1623	δ^{CDCl_3} 7.62 (H-5)[j] 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)	*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)[i] 6.93 (H-5) 6.33 (H-8) 5.53 (H-9, t) 3.82 (OCH_3) 3.75 (OCH_3) 2.42 (OAc) 2.05 (N-Ac)		
	N,O-Diacetate methiodide, 163–166 1-Bromonorsinoacutine, 121–122 Norsinoacutinol, 226–228 [*1-²H*]Norsinoacutine, 113–115			$\nu_{max}^{CHCl_3}$ 1466 [1486 band missing and new band at 1466]	δ^{CDCl_3} 6.68 band missing		
Salutaridine [(*R*)-4-hydroxy-3,6-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$ 	197–198	$[\alpha]_D$ +111 (EtOH)	λ_{max}^{EtOH} 240 (4.25), 277 (3.755)	$\nu_{max}^{CHCl_3}$ 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 (OCH_3) 3.74 (OCH_3), 2.45 (NCH_3) $\delta^{(CD_3)_2NCOH}$ 7.75 (H-5), 6.91, 6.64 (H-2, H-1; J = 8.3 cps) 6.23 (H-8), 3.91 (OCH_3) 3.67 (OCH_3)	*Croton salutaris* Casar *Papaver somniferum* var. Noordster[k] *Croton balsamifera* Jacq[g] *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	$[\alpha]_D$ +120 (EtOH)			δ^{CDCl_3} 6.96 (H-5) 6.89 (H-1 and H-2) 6.31 (H-8) 3.88 (OCH_3) 3.77 (OCH_3), 2.40 (OAc) 2.46 (NCH_3)		
	O-Methyl deriv, 147–148				δ^{CDCl_3} 6.86 (H-1, H-2) 7.30 (H-5), 6.33 (H-8) 3.94 (OCH_3), 3.80 (OCH_3) 3.86 (OCH_3), 2.49 (NCH_3)		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′-Dehydrodisalutaridine, 242–245			$\nu_{max}^{CHCl_3}$ 3560, 1670, 1642, 1624 (1494 band missing)		
Salutaridinol I, 227–229 dec	$[\alpha]_D$ +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	$[\alpha]_D$ +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 $C_{19}H_{26}BNO_4$			$\nu_{max}^{CHCl_3}$ 3620, 3560, 2300, 2400, 1703, 1661		
Tetrahydrosalutaridinol, 214–217				δ^{CDCl_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-dimethoxymorphinandienone] $C_{19}H_{21}NO_4$		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
Picrate, 211–215					

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-methoxymorphinandienol] $C_{19}H_{21}NO_4$ 	200–201	$[\alpha]^{19}D$ −48 ($CHCl_3$)			δ^{CDCl_3} 6.82 (H-4), 6.58 (H-1) 5.92 (OCH_2O), 5.76 (H-8; J = 4.0 Hz), 5.28 (H-5) 4.76 (H-7; J = 4.0 Hz) 3.73 (OCH_3), 2.35 (NCH_3) 3.14 (OH) 2.60–3.45 (H-9, H-10A, H-10B, ABX system analyzed at 100 MHz)	*Papaver nudicaule* var. aurantiacum *P. feddei* Schwz.[b]	9
	Epinudaurine	$[\alpha]^{11}D$ −23 ($CHCl_3$)					
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)	$[\alpha]^{16}D$ −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 (OCH_3) 3.67 (OCH_3) 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 (OCH_3) 3.80 (OCH_3) 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 (OCH_3) 3.68 (OCH_3) 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	$[\alpha]^{16}D$ −76.1 (MeOH)	λ_{max}^{EtOH} 206 (4.514), 238 (3.842), 265 (3.878)	ν_{max}^{Nujal} 1675, 1613, 1575	δ^{CDCl_3} 6.68 (H-1, H-2) 6.76 (H-5) 3.68 (OCH_3), 3.85 (OCH_3), 2.38 (NMe)	*Croton linearis* Jacq. *C. discolor* Willd *C. plumieri*[n]	20
	O-Acetate, 210	$[\alpha]^{16}D$ −22.1 (MeOH)			δ^{CDCl_3} 6.96, 6.88 (H-1, H-2; J = 9 Hz) 6.3 (H-5), 3.70 (OCH_3) 3.80 (OCH_3), 2.32 (NCH_3), 2.45 (OAc)		
	8,14-Dihydrosalutaridinol, 218–220						

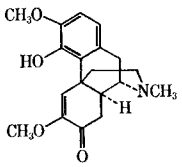
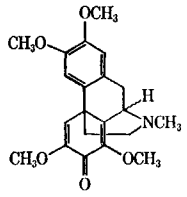
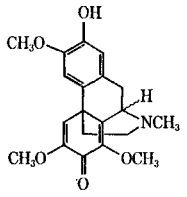
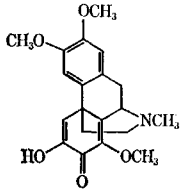
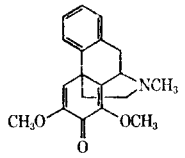
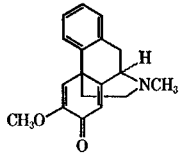
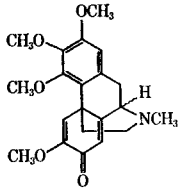
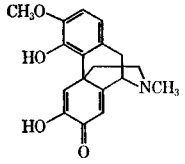
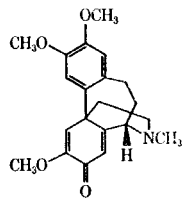
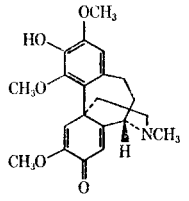
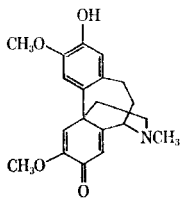
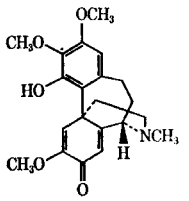
Isosinomenine [(*S*,*S*)-4-hydroxy-3,6-dimethoxy-8,14-dihydromorphinandienone] $C_{19}H_{23}NO_4$ 	198–202	$[\alpha]_D$ +73 (EtOH)	λ_{max}^{EtOH} 208 (4.499), 238 (3.887), 265 (3.919)	$\nu_{max}^{CHCl_3}$ 1690, 1625	δ^{CDCl_3} 6.79 (H-5) 6.72 (H-1, H-2) 3.86, 3.70 (2 OMe), 2.41 (NCH_3)	*Sinomenium acetum*[o,p]	22
	Picrate, 219–223 1-Bromoisosinomenine, 204–210 dec			$\nu_{max}^{CHCl_3}$ 1690, 1625			
Protostephanone [(±)-2,3,6,8-tetramethoxymorphinandienone] $C_{21}H_{25}NO_5$ 				ν_{max} 1663, 1628	δ 6.80 (H-4) 6.65 (H-1) 6.37 (H-5) 4.40 (H-9, dd) 3.88, 3.82 (4 OCH_3) 2.50 (NCH_3)		71 16
(±)-2-Hydroxy-3,6,8-trimethoxymorphinandienone $C_{20}H_{23}NO_5$ 	*O*-Methyl deriv (see above)						16
(±)-2,3-Dimethoxy-6-hydroxymorphinandienone $C_{19}H_{21}NO_4$ 			λ_{max}^{MeOH} 236, 286	$\nu_{max}^{CHCl_3}$ 3400, 1652, 1626	δ^{CDCl_3} 6.79, 6.70, 6.37, 5.86 (H-1, H-4, H-5, H-8) 3.87, 3.83, 2.45 (2 OCH_3, NCH_3)		39
	Benzyl deriv		λ_{max}^{MeOH} 236 (4.13), 283 (3.79)	$\nu_{max}^{CHCl_3}$ 1665, 1645, 1620	δ^{CDCl_3} 7.32 (OCH_2Ph) 6.59 (H-1), 6.45 (H-5) 6.40 (H-4), 6.30 (H-8) 5.10 (OCH_2Ph) 3.81, 3.65 (2 OMe) 2.34 (NMe)		83
	Methiodide of benzyl deriv, 225–227°						

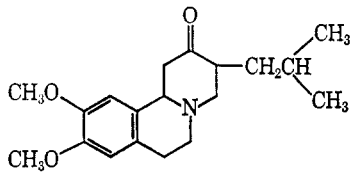
Table I (Continued)

Compound	*Derivatives, mp, °C*	*Optical rotation, deg*	*Uv, nm (log ε)*	*Ir, cm⁻¹*	*Nmr at 60 MHz*	*Plant source*	*Ref*
(±)-6,8-Dimethoxymorphinandienone $C_{19}H_{21}NO_3$ 	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 OCH_3) 2.45 (NCH_3) 3.30–1.7 (3 CH_2)		38
(±)-6-Methoxymorphinandienone $C_{18}H_{19}NO_2$ 	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 (OCH_3), 2.49 ($N\text{-}CH_3$)		38
(±)-2,3,4,6-Tetramethoxymorphinandienone $C_{21}H_{25}NO_5$ 	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 OCH_3) 3.82 (2 OCH_3) 2.44 (NCH_3)		32
4,6-Dihydroxy-3-methoxymorphinandienone $C_{18}H_{19}NO_4$ 	220–225 dec Methiodide, 164–166	$[\alpha]^{22}D$ +130 ($CHCl_3$)	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 (OCH_3) 2.45 (NCH_3)		43
Demethoxy-*O*-methylandrocymbine [(±)-2,3,6-trimethoxyhomomorphinandienone] $C_{21}H_{25}NO_4$			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

	Methiodide 251–252			ν_{max}^{KBr} 3428, 1667, 1646, 1617	6.07 (H-4) 3.88 (OCH_3) 3.81 (OCH_3) 3.62 (OCH_3) 2.35 (NCH_3)		
Androcymbine [(*S*)-3-hydroxy-2,4,6-trimethoxyhomomorphinandienone] $C_{21}H_{25}NO_5$	199–201	$[\alpha]^{22}D$ −260 ($CHCl_3$)	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 (OCH_3) 3.82 (OCH_3) 3.63 (OCH_3) 2.36 (NCH_3)	*Androcymbium melanthioides*[q] var. stricta Baker	6
	*O*-Methyl deriv 4-Normethyl deriv	$[\alpha]D$ −295 ($CHCl_3$)		ν_{max} 1663, 1638, 1613		*Colchicum autumnale*[r]	44
(±)-2-Hydroxy-3,6-dimethoxyhomomorphinandienone $C_{20}H_{23}NO_4$	220–221		λ_{max}^{MeOH} 241 (4.22), 282 (3.85)	ν_{max}^{CHC} 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 OCH_3) 2.37 (NCH_3)		27
	Methiodide, 225–226						
2,3,6-Trimethoxy-4-hydroxyhomomorphinandienone $C_{21}H_{25}NO_5$				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. Mkrtchyan, *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).

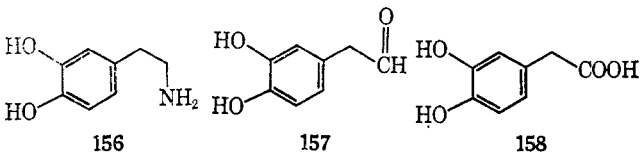
to tetrabenazine (**155**) which is a reserpine-like compound



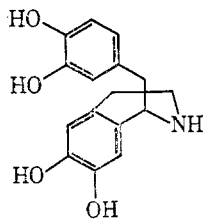
155

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 norlaudanosoline (**159**). Using ^{14}C-labeled **159** these workers



156 157 158



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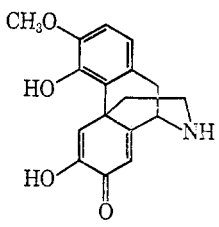

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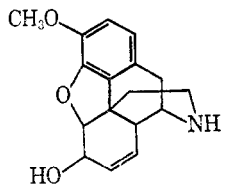
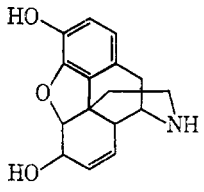


161



162

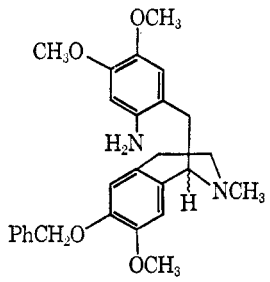
have shown that 50% of the activity was located in the alkaloid fraction. From tlc and glc, this was shown to contain norcodeine (**161**), codeine (**132**), and normorphine (**162**).[82] It seems very likely that a morphinandienone intermediate like compound **160** plays an important role in this 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]

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

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

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**).



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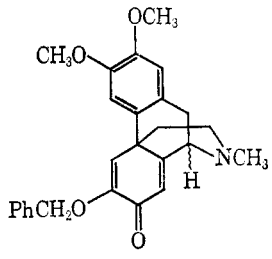
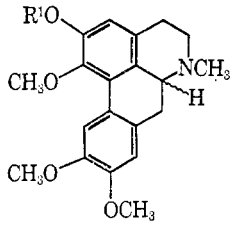


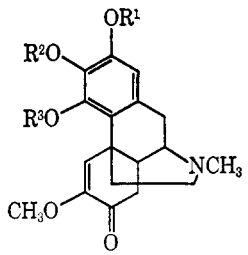
164



165, $R^1 = PhCH_2$
166, $R^1 = H$

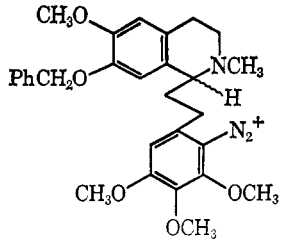
Debenzylation of **164** by hydrobromic acid in methanol produced **89**.

The alkaloid delavaine, mp 149–150°, $[\alpha]D$ −240°, has been isolated from *Stephania delavayi*, and the dihydromorphinandienone structure **167** or **168** has been proposed.[84]



167, $R^1 + R^2 = CH_2$; $R^3 = CH_3$
168, $R^2 + R^3 = CH_2$; $R^1 = CH_3$

Photolysis of the diazonium salt **169** produced the racemate of *O*-methylandrocymbine (**11**).[85]



169

(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).