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Transformation Products of Salutarine and Their ^{13}C-Nuclear Magnetic Resonance Spectra

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Salutarine, the principal alkaloid of *Croton salutaris* CASAR has been treated with phenyllithium and methyllithium to yield the corresponding salutarinols. Treatment of 7-phenylsalutarinol (not isolated) with acid produced the racemic form of 7-phenylthebaine. The mixture of epimeric 7-methylsalutarinols yielded mainly the dehydration product, the 7-methylene derivative of salutarine. A comparison of the ^{13}C-nuclear magnetic resonance spectra of these and other derivatives of salutarine permitted a complete assignment of the chemical shifts.

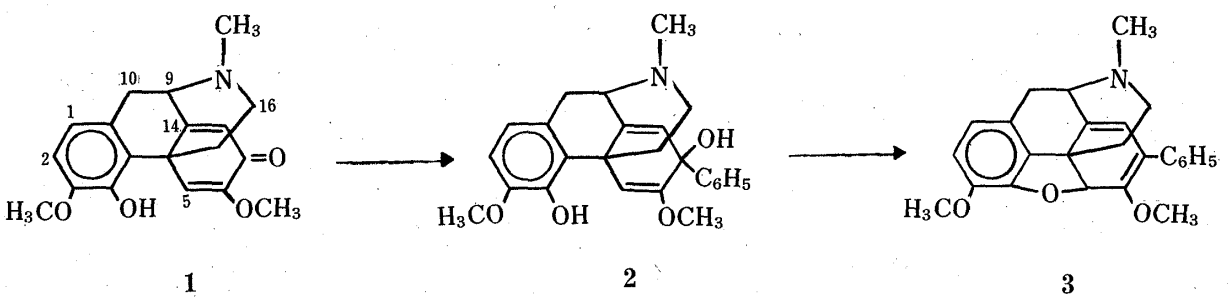
Keywords——*Croton salutaris*; salutarine; addition of organolithiums; acid-catalyzed cyclization; dehydration; ^{13}C-nuclear magnetic resonance of morphinanedienone alkaloids

Croton salutaris CASAR, a tree rather common in the mountains west of Rio de Janeiro, contains the alkaloid salutaridine and its racemic form to which we had given the name salutarine.[1] A recent study[2] in which we observed a seasonal variation in the ratio of salutarine and salutaridine furnished sufficient quantities of the alkaloids to permit the present study.

Barton *et al.*[3] have shown that the biogenetic pathway to the morphine alkaloids involves the reduction of salutaridine to salutaridinol and subsequent cyclization to thebaine. By analogy, it would be expected that the addition of organometallic reagents to salutarine[4] would yield salutarinols which could cyclize to the corresponding (±)-thebaine derivatives.

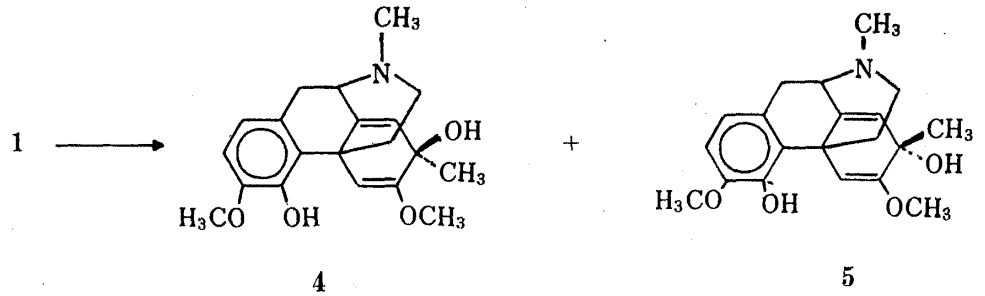
Initially it was thought desirable to protect the phenolic hydroxyl group of salutarine (**1**). However, when an attempt to effect the reaction with trimethylsilyl chloride failed to yield the expected derivative, a reaction was carried out directly using an excess of phenyllithium. Considerable (63%) salutarine was recovered from this reaction. However, the amount of crude 7-phenylsalutarinol (**2**) produced was sufficient to verify that dilute hydrochloric acid converted it to the desired (±)-7-phenylthebaine (**3**). The infrared spectrum of **3** showed that neither carbonyl nor hydroxyl groups were present. The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum showed almost identical chemical shifts for the aromatic protons and methoxyl groups of **3** and unsubstituted thebaine and the expected differences for the hydrogens at carbons 5 and 8.

With methyllithium, an excellent yield of a mixture of the two isomeric methylsalutarinols **4** and **5** was obtained. These two substances were separated by thin layer chromatography



1 2 3

Chart 1

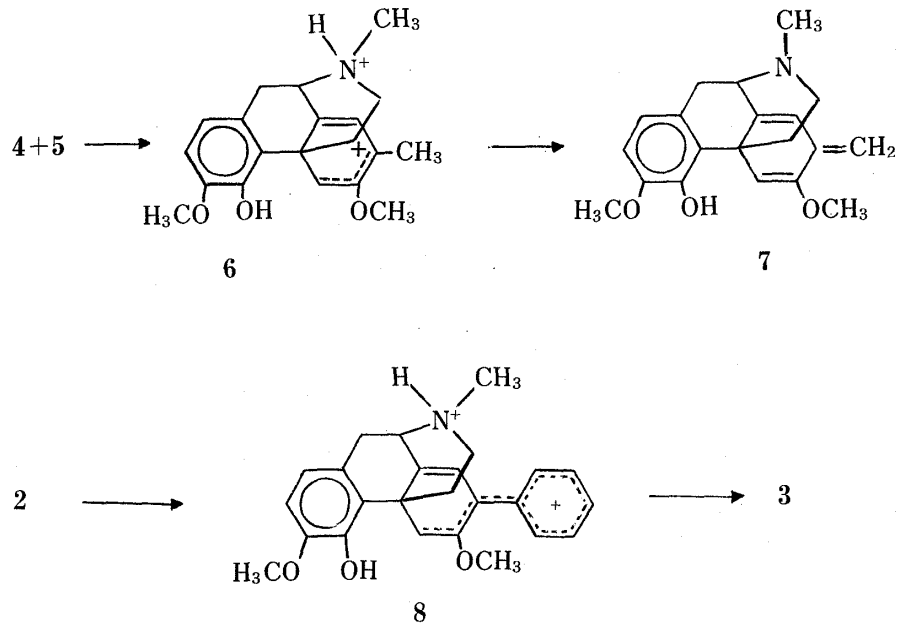


4 5

Chart 2

and found to differ considerably as to stability. The crystalline form was stable, but the liquid isomer decomposed upon standing at room temperature.[5]

The treatment of **4** and **5** with dilute acid using conditions which lead to cyclization of the salutaridinols as well as several variations in solvent and acid concentration did not yield any product which could be identified as the expected 7-methylthebaine. Trifluoroacetic acid at room temperature furnished a mixture from which a major component was isolated by thin layer chromatography (TLC). The spectral data for this product showed that a simple dehydration had taken place to yield 7-methylenesalutarine (**7**). In these reactions the intermediate carbocations are believed to have structures **6** and **8**.



6 7

8

Chart 3

The double bond between carbons 8 and 14 has much reduced participation in distributing the positive charge because this would bring the charge to a position once removed from the positively charged nitrogen atom. Ion **8**, being considerably more stable than **6**, persists in the solution for sufficient time to permit the desired cyclization to occur. Ion **6** has the alternate possibility of losing a proton from the methyl group, and this reaction is believed to be more rapid than the cyclization which depends upon the hydroxyl group being sufficiently near to carbon 5 for bond formation to occur. The observation of Stuart *et al.*[6] that norsinoacutinol (**9**) also did not cyclize may be explained if the less basic nitrogen atom of this molecule permits ion **11** to exist in appreciable concentration in the acid solution. This ion can undergo a 1, 2 shift to the more stable ion **12** which would hydrolyze to the observed final product **13**.

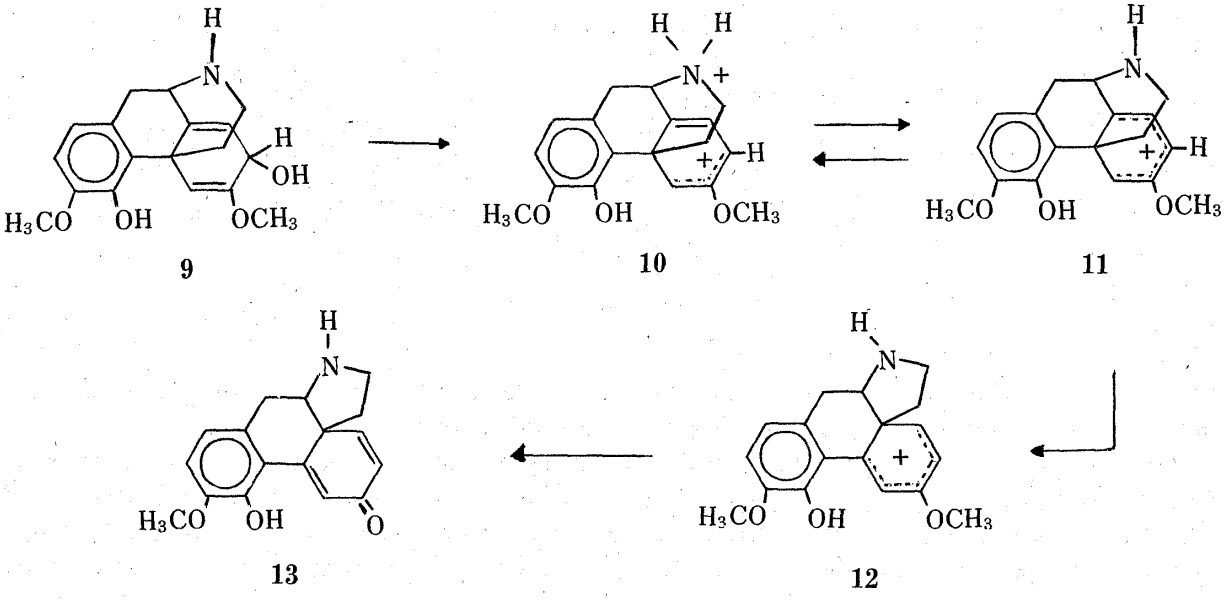


Chart 4

The ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra of the morphinanedione alkaloids has not been recorded although sinomenine has been previously studied.[7] Our observations for salutarine and norsalutaridine[2] as well as the derivatives prepared in the present work permitted the assignments shown in Table I.

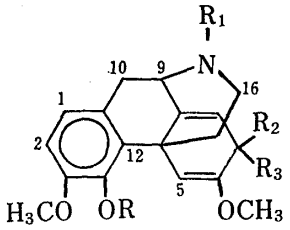
The aliphatic carbons of salutarine were readily assigned since there is only one of each of the following groups: *N*-methyl, *N*-methylene, *N*-methine and quaternary carbon. The two methylene groups at C-10 and C-15 were readily distinguished by the difference in the

Table I. ^{13}C Chemical Shifts of Morphinanedienone Alkaloids[a]

Compd. No.	1	14	15	4	7	16[d]
Carbon atom						
1	118.5	118.7	118.4	118.5	118.6	125.6
2	109.2	109.4	108.7	108.6	108.8	111.2
3	145.3	145.3	144.9	144.8	145.0	149.8
4	143.2	143.3	143.1	143.0	142.9	137.8
5	120.4	120.4[b]	101.9	100.1	104.6	118.5
6	150.7	150.7	153.0	155.5	150.3	150.9
7	181.2	181.4	63.3	66.8	134.4	180.4
8	121.9	120.9[b]	119.1	123.5	121.8	122.0
9	60.9	54.6	60.9	60.8	61.3	60.5
10	32.5	38.8[c]	32.1	31.3	32.2	32.1
11	129.4	129.6	130.0	130.8	129.5	129.0
12	123.8	123.6	127.1	127.0	126.8	131.0
13	43.6	44.1	40.7	40.7	42.3	43.1
14	161.5	163.7	139.9	138.7	137.9	160.7
15	37.6	39.6[c]	37.8	38.5	37.4	38.7
16	46.9	42.9	47.6	47.8	47.6	46.3
N-CH_3	41.5	—	41.7	41.8	41.5	41.3
OCH_3 (3)	56.1	56.2	56.0	56.1	56.1	56.0
OCH_3 (6)	54.7	54.4	54.3	54.3	54.2	54.3
CH_3 (7)	—	—	—	27.6	—	—
CH_2 (7)	—	—	—	—	107.8	—

a) The δ values are in ppm downfield from TMS; the solvent was $CDCl_3$.
b) and *c*) These assignments may be interchanged.
d) The acetate shifts of **16** were δ (C=O), 168.1 and δ (CH_3), 20.9.

residual coupling in the off-resonance spectrum. The aromatic carbons (C-1, C-2, C-3, C-4, C-11 and C-12) were assigned taking into account the strong shielding influence of the methoxyl group on the positions *ortho* to it and the change produced when the phenolic hydroxyl group was acetylated.



14: R=H, R_1=H, R_2-R_3=O
15: R=H, R_1=CH_3, R_2=OH, R_3=H
16: R=$OCOCH_3$, R_1=CH_3, R_2-R_3=O

Chart 5

Examination of the proton coupled spectrum of salutarine and the results of the specific decoupling of protons at carbons 5 and 8 established the assignments of C-5, C-6, C-8 and C-14.

In norsalutaridine (**14**) the replacement by hydrogen of the *N*-methyl group caused the expected upfield shifts at carbons 9 and 16 and the deshielding of carbons 10 and 15 (decrease of the β and γ effects). The remaining carbons of this alkaloid have values very close to those of salutarine.

The changes observed in transforming salutarine to the 7-methylene derivative, upfield shifts at C-5, C-13 and C-14, result from the loss of the carbonyl bond polarization at C-7. In the derivative, the olefinic carbons were distinguished by specific irradiation of the methylene protons according to Bhacca's technique.[8] The remaining carbons had values similar to those of **1** with the exception of C-12 which showed an unexpected downfield shift of about 3 ppm.

The salutarinols (**15**, **4** and **5**) all show changes similar to those of **7** since the carbonyl group has been transformed to hydroxyl. It is interesting that the two methyl carbinols have nearly identical values. Molecular models show that there is no change in steric effects when the methyl and hydroxyl groups are interchanged.

Experimental

The ^{13}C-NMR spectra were observed in 0.6—1 M solutions in $CDCl_3$ using 5 mm tubes and a Varian XL-100-12 spectrometer (23 MHz, spectral width 5 KHz, acquisition time 0.8 s, flip angle 45°, internal ^{2}H pulse lock). The high resolution mass spectra were obtained with a Varian MAT CH-5 spectrometer.

(±)-7-Phenylthebaine (3)——Salutarine (1 g) dissolved in tetrahydrofuran was added to a solution of phenyllithium [prepared from lithium (0.17 g) and bromobenzene (1.3 ml)] in ether. The reaction mixture was stirred at room temperature for 3 h, a saturated solution of ammonium chloride was added and then the mixture was extracted with chloroform. The chloroform solution was distilled and the residue stirred with 1 N hydrochloric acid for 1 h. The solution was made alkaline (pH 10) with 10% sodium hydroxide solution and extracted with chloroform. The residue obtained by concentrating the chloroform solution was chromatographed on a column of florisil. Elution with hexane–chloroform (1: 1) yielded **3** as an oil, 27 mg. IR ν_{max}^{film} cm^{-1}: 1630, 1591, 1496, 1443, 937. UV λ_{max}^{EtOH} nm (log ε) 282 (3.48), 2.35 (4.16). ^{1}H-NMR δ ($CDCl_3$): 2.48 (s, 3H), 3.70 (s, 3H), 3.90 (s, 3H), 5.63 (s, 1H), 5.71 (s, 1H), 6.67 (AB pattern, 2H), 7.50 (m, 5H). High resolution MS calcd for $C_{25}H_{25}NO_3$: 387.1834. Found: 387.1849.

Further elution with hexane–chloroform (3: 7) yielded recovered salutarine (0.63 g).

Methylsalutarinols (4 and 5)——An ether solution of methyllithium (3 ml, 5%, 6.8 mmol) was added slowly to a stirred solution of salutarine (0.5 g, 1.5 mmol) in tetrahydrofuran (50 ml) under nitrogen. After 40 min at room temperature an excess of saturated ammonium chloride solution was added and the product was extracted with chloroform. The partly solid residue (0.55 g) obtained by evaporating the chloroform solution was chromatographed on thin layer plates of alumina using 2% methanol in chloroform. Methylsalutarinol A, *Rf* 0.42, was obtained as a solid, mp 147—148°C, while methyl salutarinol B, *Rf* 0.25, was an oil. The ^{1}H-NMR spectrum of the mixture showed that the ratio of A: B was 7: 3.

Methylsalutarinol A: IR ν_{max}^{KBr} cm^{-1}: 3366, 1635, 1258, 1046, 742. UV λ_{max}^{EtOH} nm (log ε): 284 (3.27), 216

(4.21). ^{1}H-NMR δ ($CDCl_3$): 1.5 (s, 3H), 2.38 (s, 3H), 3.68 (s, 3H), 3.88 (s, 3H), 5.65 (s, 1H), 6.35 (s. 1H), 6.64 (AB pattern, 2H). High resolution MS Calcd for $C_{20}H_{25}NO_4$: 343.1783. Found: 343.1820.

Methylsalutarinol B: IR ν_{max}^{film} cm^{-1}: 3353, 1645, 1272, 1047, 741. UV λ_{max}^{EtOH} nm (log ε): 280 (3.08), 214 (4.13). ^{1}H-NMR δ ($CDCl_3$): 1.35 (s, 3H), 2.43 (s, 3H), 3.70 (s, 3H) 3.88 (s, 3H), 5.68 (s, 1H), 6.10 (s, 1H), 6.66 (AB pattern, 2H). High resolution MS Calcd for $C_{20}H_{25}NO_4$: 343.1783. Found: 343.1811.

3,6-Dimethoxy-4-hydroxy-17-methyl-7-methylene-morphina-5,8(14)-diene (7-Methylene Derivative of Salutarine, 7)——Trifluoroacetic acid (0.5 ml) was added to a stirred solution of a mixture of salutarinols **4** and **5** (0.1 g) in tetrahydrofuran (15 ml). After 20 min at room temperature a solution of ammonium hydroxide (10 ml, 3%) was added and the product was extracted with chloroform. The residue after evaporation of the solvents was chromatographed on thin layer plates of alumina using 3% methanol in chloroform. A major product, **7**, *Rf* 0.65, was obtained as a solid, mp 176—178°C, (0.015 g, 16%). IR ν_{max}^{KBr} cm^{-1}: 3351, 1648, 1575, 1263, 1206, 1039, 876. UV λ_{max}^{EtOH} nm (log ε) 258 (3.97). 246 (4.03), 212 (3.98). ^{1}H-NMR δ ($CDCl_3$): 2.62 (s, 3H), 3.74 (s, 3H), 3.89 (s, 3H), 4.91 (s, 1H), 5.38 (s, 1H), 6.28 (s, 1H), 6.48 (s, 1H), 6.70 (AB pattern, 2H). High resolution MS Calcd for $C_{20}H_{23}NO_3$: 325.1677. Found: 325.1703.

Derivatives of Salutarine——The reduction of **1** was effected by the method which Barton *et al.*[3a] used for salutaridine. The spectroscopic data for salutarinols I (*Rf* 0.25) and II (*Rf* 0.11) TLC using alumina and 2% methanol in chloroform) was identical with those for the corresponding salutaridinols. Salutarinol II (compound **15**) was used for the ^{13}C-NMR spectrum. Salutarinol I was less soluble in $CDCl_3$ and decomposition took place before the spectrum could be completed.

Salutarine (0.1 g) was added to a mixture of pyridine (2 ml) and acetic anhydride (1.5 ml) and the whole was heated at reflux temperature for 1 h. The solvents were removed in a vacuum and the residue was chromatographed on thin layer alumina plates using 3% methanol in chloroform. The fraction containing compound **16** (*Rf* 0.3) had spectroscopic properties identical with those reported for the acetate of salutaridine.[9]

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References and Notes

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