Anal. Calcd for $C_{20}H_{20}N_2O_7$; C, 59.98; H, 5.04; N, 6.99. Found: C, 59.72; H, 4.99; N, 6.72.

**1-(3',4'-Methylenedioxy-6'-nitrobenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (9).** Dihydroisoquinoline (8, 1.11 g) was suspended in 150 ml of methanol and with stirring 800 mg of sodium borohydride was added in portions over 30 min. After an additional 1 hr the pH was adjusted to near pH 5 with acetic acid. After removal of all solvent under reduced pressure the residue was dissolved in $CHCl_3$, washed with dilute base and water, dried, and evaporated to dryness to give the tetrahydroisoquinoline as a white solid. This was immediately dissolved in 30 ml of pyridine and treated with 8 ml of acetyl chloride. After 3 hr at room temperature, the solution was treated with dilute base and extracted with $CHCl_3$. The combined organic layers were washed with 2% HCl and then water, dried over $Na_2SO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel using benzene–acetone (8:1) as the eluent and afforded a yellow oil which crystallized from methanol to give 840 mg of **9**: mp 159–160°; ir ($CHCl_3$) 1630 $cm^{-1}$ (C=O); NMR ($CDCl_3$) $\delta$ 7.66 and 7.53 (1 H total, s, PhH), 6.87 and 6.75 (1 H total, s, PhH), 6.63 and 6.57 (1 H total, s, PhH), 6.18 and 6.12 (2 H total, s, $OCH_2O$), 4.00–3.83 (9 H, $OCH_3$), 2.02 and 1.62 (3 H total, s, $NCOCH_3$).

Anal. Calcd for $C_{22}H_{24}N_2O_8$; C, 59.44; H, 5.45; N, 6.30. Found: C, 59.13; H, 5.49; N, 6.25.

**1-(3',4'-Methylenedioxy-6'-aminobenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (10).** A 94-mg sample of **9** was suspended in 50 ml of methanol and with stirring 0.5 g of zinc dust was added slowly followed by 2 ml of 1 *N* $H_2SO_4$ added dropwise. The suspension was stirred for 30 min at room temperature, filtered, adjusted to pH 8 with $NH_3$, and then evaporated to dryness. The residue was taken up in $CHCl_3$, washed with water, dried, and evaporated to dryness, leaving a residue which was further purified by chromatography over silica gel. Elution with benzene–acetone (8:1) and crystallization from alcohol gave 55 mg of **10**: mp 189–190°; ir (KBr) 3440, 3350, 3240 ($NH_2$), and 1630 $cm^{-1}$ (C=O).

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.33; N, 6.76. Found: C, 63.38; H, 6.31; N, 6.77.

**(±)-3-Methoxy-*N*-acetylnornantenine (4).** A 56-mg sample of **10** was added to a solution of 0.58 ml of glacial acetic acid and 0.04 ml of concentrated sulfuric acid at 10° and allowed to warm to 20°. A solution of sodium nitrite (11.6 mg in 0.1 ml of $H_2O$) was added and the solution was stirred at 20° for 50 min. The solution was allowed to warm to room temperature and then 1 mg of sulfamic acid, 0.5 mg of cuprous chloride, and 1.2 ml of acetone were added and the solution refluxed for 30 min. After cooling, the solution was concentrated to about 3 ml, adjusted to pH 8.5 with $NH_4OH$, and extracted with ether (5 × 10 ml). The combined extracts were dried and evaporated to give a yellow gum which was chromatographed over silica gel. Elution with benzene–acetone (8:1) and crystallization from alcohol gave 7 mg of racemic **4**, mp 174–175°. The synthetic product had the same $R_f$ values in four TLC systems, the same NMR, uv, and mass spectra, and superimposable ir ($CHCl_3$) spectra as that of natural **4**.

**Acknowledgment.** This work was supported in part by a Faculty Research Grant, University of Mississippi, and the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. The authors are grateful to Dr. Stephen Billets, Research Institute of Pharmaceutical Sciences, School of Pharmacy, for determining the mass spectra.

**Registry No.**—(±)-**4**, 57236-56-3; **5**, 57196-56-2; **6**, 3937-16-4; **7**, 57196-57-3; **8**, 57237-60-2; **9**, 57196-58-4; **10**, 57196-59-5.

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# Revision of the Structure of the Bisindole Alkaloid 14',15'-Dihydropycnanthine. A Carbon-13 Nuclear Magnetic Resonance Study[1]

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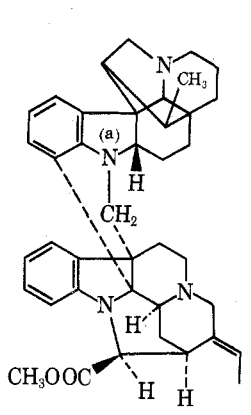
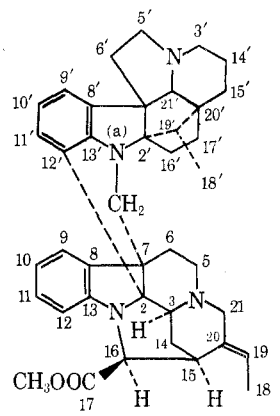
*Received July 15, 1975*

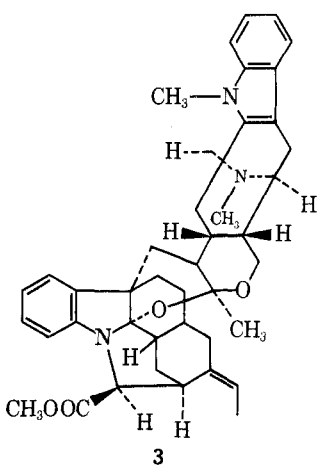
We wish to describe a $^{13}C$ nuclear magnetic resonance spectral analysis of the previously reported bisindole alkaloid 14',15'-dihydropycnanthine (1)[2] and present evidence for the necessity of structural revision to **2**.



1



2



3

From the leaves of *Gonioma malagasy* Mgf. et P. Bt.[3] has been isolated a bisindole alkaloid [mp 247°; $[\alpha]^{22}D$ +243° (*c* 1.4, $CHCl_3$); *m/e* 614] [lit. mp 250°; $[\alpha]^{25}D$ +274 ± 10° (*c* 0.442, $CHCl_3$)] whose spectral characteristics (mass, $^1H$ NMR, uv, and ir) have indicated that it was identical in every respect with 14',15'-dihydropycnanthine (1) having decarbomethoxy 14',15'-dihydrovindolinine and 2,7-dihydropleiocarpamine moieties.[2,4]

The structure of the decarbomethoxy 14',15'-dihydrovindolinine unit of 14',15-dihydropycnanthine (1) had been

Table I
$^{13}C$ Chemical Shifts

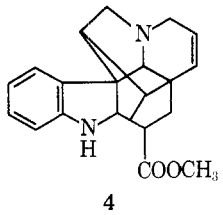
| Compd | C-2 | C-3 | C-5 | C-6 | C-7 | C-8 | C-9 | C-10 | C-11 | C-12 |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 67.6 | 52.1 | 53.9 | 27.5[a] | 46.3 | 135.8 | 121.0 | 117.7 | 126.6 | 108.8 |
| 3 | 92.2 | 51.5 | 53.1 | 28.6 | 44.2 | 132.9 | 120.9 | 118.1[a] | 126.5 | 109.3 |
| | C-13 | C-14 | C-15 | C-16 | C-17 | C-18 | C-19 | C-20 | C-21 | $COOCH_3$ |
| 2 | 147.1 | 28.1 | 31.1 | 58.0 | 170.5 | 12.3 | 117.2 | 135.8 | 47.8 | 51.7 |
| 3 | 147.0 | 28.9 | 31.9 | 57.8 | 170.8 | 12.2 | 118.4[a] | 136.4 | 47.5 | 51.9 |

| | C-2′ | C-3′ | C-5′ | C-6′ | C-7′ | C-8′ | C-9′ | C-10′ | C-11′ | C-12′ | C-13′ | C-14′ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 80.1 | 54.5 | 48.4 | 36.8 | 58.0 | 137.1 | 120.6 | 116.5 | 128.9 | 120.6 | 149.0 | 20.1 |
| 5 | 81.4 | 58.0 | 50.3 | 36.3 | 59.8 | 139.8 | 123.6 | 121.0 | 127.2 | 112.0 | 149.4 | 128.5 |
| 6 | 80.6 | 55.0 | 48.1 | 37.3 | 60.3 | 140.1 | 123.6 | 121.1 | 127.2 | 112.7 | 149.5 | 20.7 |
| 7 | 84.4 | 58.0 | 50.0 | 36.0 | 58.8 | 135.5 | 123.0 | 117.8 | 127.7 | 105.6 | 150.2 | 127.7 |
| 8 | 80.4 | 57.5 | 49.8 | 37.2 | 58.4 | 139.0 | 123.1 | 121.2 | 127.0 | 111.8 | 149.2 | 128.1 |

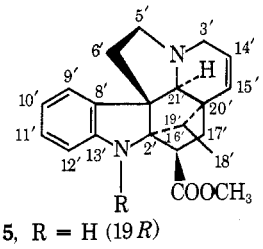
| | C-15′ | C-16′ | C-17′ | C-18′ | C-19′ | C-20′ | C-21′ | N′$CH_2$′ | ′$COOCH_3$ | $COOCH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | a | | |
| 2 | 32.4 | 27.0[a] | 22.1 | 11.0 | 54.1 | 45.1 | 74.5 | 41.4 | | |
| 5 | 130.7 | 39.2 | 29.1 | 7.4 | 48.4 | 46.2 | 78.0 | | 174.2 | 51.8 |
| 6 | 31.2 | 40.2 | 29.0 | 7.5 | 51.0 | 44.5 | 78.8 | | 175.0 | 52.0 |
| 7 | 130.8 | 37.0 | 28.0 | 9.0 | 47.0 | 45.6 | 77.0 $NCH_3$ | 30.0 | 174.0 | 52.0 |
| 8 | 131.0 | 42.7 | 31.4 | 10.1 | 51.2 | 44.2 | 74.2 | | 172.8 | 51.2 |

[a] Assignments within the same compounds may be reversed.

proposed[2] by analogy with that of vindolinine (4) on the basis of their similar mass spectral fragmentation pattern.[5] However, a recent $^{13}C$ NMR analysis has led to the revision of the plane structure of vindolinine,[6] whose stereostructure 5[7] and absolute configuration[8] were later established. As a consequence, a reinvestigation of the structure of 14′,15′-dihydropycnanthine (1) became advisable.




4




5, R = H (19*R*)
6, 14′,15′-dihydro-**5** (19*R*)
7, R = $CH_3$ (19*R*)
8, 19′-epi-**5** (19*S*)

Recently, complete signal assignments have been carried out in the $^{13}C$ NMR spectrum of villalstonine (3),[9] a 2,7-dihydropleiocarpamine unit containing bisindole alkaloid. Therefore, correlation of 14′,15′-dihydropycnanthine (1) with villalstonine (3), (19*R*)-vindolinine (5), and (19*S*)-vindolinine (8)[8] was sought through a study of their $^{13}C$ NMR spectra.

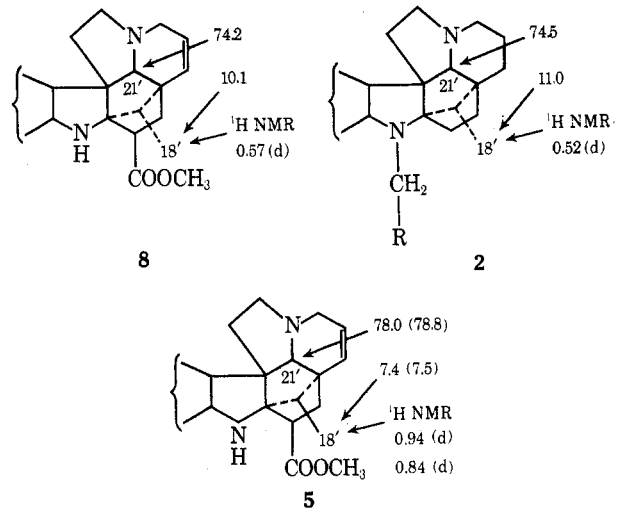
Noise, single-frequency, and noise off-resonance decoupled $^{13}C$ NMR spectra[10] of 14′,15′-dihydropycnanthine exhibited 12 nonprotonated carbons, 13 methines, 12 methylenes, and three methyl groups, suggesting that both of its indole nitrogens are substituted. Comparison of the $^{13}C$ NMR data of 14′,15′-dihydropycnanthine and villalstonine (3) afforded evidence (Table I) for the occurrence of a 2,7-dihydropleiocarpamine unit also in the former compound, substituted at C-2 and C-7 by carbon atoms and not as in 3 by an oxygen and by a carbon atom, respectively. The common fragment of the two bisindole alkaloids exhibited carbon signals identical both from the point of view of chemical shift and single-frequency decoupled multiplicity, except as expected, for the quaternary sites C-2, C-7, and C-8.

Thus by a substractive process, the signals representing the second moiety of 14′,15′-dihydropycnanthine could be easily deduced and their analysis could be undertaken. The three nonprotonated carbon signals at 80.1 (C-2′), 58.0 (C-7′), and 45.1 ppm (C-20′) indicated a vindolinine-like skeleton.[6] This interpretation was also in agreement with the chemical shift and single-frequency decoupled multiplicity of the remaining resonances, taking into account a decarbomethoxy 14′,15′-dihydro-(19*S*)-vindolinine unit. Signal assignments were based on our previous work[6] on the spectrum of (19*S*)-vindolinine (8) as well as on chemical shift rules.[11] As expected, C-16′ and C-17′ were strongly shielded in the spectrum of 14′,15′-dihydropycnanthine (2) with respect to the corresponding resonances of 8 as a result of the loss of $\alpha$ and $\beta$ effects due to a carboxyl group.

The stereochemistry of the C-18′ methyl group of 14′,15′-dihydropycnanthine (2) is clearly of (19*S*)-vindolinine type. This interpretation was based on the chemical shift comparison of C-18′ and C-21′ of 14′,15′-dihydropycnanthine (2) and the corresponding signals of 5 and 8 as well as on the high-field resonance positions of the doublets due to the methyl protons in the $^1H$ NMR spectra of 2 and 8 (Chart I).[12]

The $^{13}C$ NMR data presented in Table I for 14′,15′-dihydropycnanthine (2) support well the previously suggested type of linkage for its monomeric units.[2] It is well known

Chart I[a]




[a] Chemical shifts in parentheses are those of 14′,15′-dihydro-(19*R*)-vindolinine (6).

that in the spectra of $N_a$-methyldihydroindole alkaloids the highest field aromatic carbon signal at 107 ± 2 ppm represents C-12.[6,14] By analogy with methyl substitution effects on simple indole models[15] a C-12′ linkage as depicted in **2** should strongly deshield this carbon and slightly shield C-9′ while not significantly influencing the other aromatic sites. The shift contrast between the aromatic carbon signals of the decarbomethoxy 14′,15′-dihydro-(19*S*)-vindolinine part of **2** and those of $N'_a$-methyl-(19*R*)-vindolinine (**7**) was in perfect agreement with a C-12′ attachment of the monomers. The second site of linkage is of course through the $N'_a$-$CH'_2$ carbon of the alkaloid. Two possibilities had then to be considered. The close shifts of C-7 of villalstonine (**3**)[9] and C-7 of **2** strongly suggested similar environments for this carbon in both compounds and was in consonance with previous conclusions.[2] The stereochemistry of this cis linkage could not be ascertained by NMR spectroscopy and has been put forward by analogy with all other related bisindole alkaloids having 2,7-dihydropleiocarpamine as a constituent part.[16] Based on the arguments presented above, structure **2** is proposed for 14′,15′-dihydropycnanthine.

**Registry No.**—2, 21400-49-7.

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(12) Inspection of the data presented in Table I shows practically identical resonance positions for C-21′ of **2** and **8**. This can be rationalized in view of the strained piperideine system in **8**. The absence of any significant homoallylic endocyclic effect[13] was already demonstrated on the C-21′ shift of (19*R*)-vindolinine (**5**) compared to the resonance of the same carbon in 14′,15′-dihydro-(19*R*)-vindolinine (**6**).[6]
(13) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).
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## The Dianion of Adipoin. A Model Study for the C Ring of Phorbol


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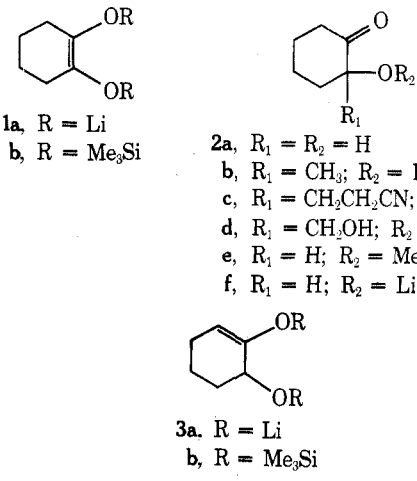
*Received June 30, 1975*

The acyloin condensation is a valuable method for ring formation and has been the subject of a recent reinvestigation[1] and review.[2] Although some details of the mechanism may be in question, enediolate **1a** is generally accepted as the stable species which on protonation gives adipoin **2a** or on silylation[3] gives bis silyl ether **1b**. The reverse reaction, however, i.e., treatment of an acyloin with base (**2a** → **1a**), is not so well known.

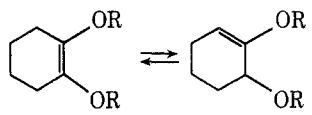



**1a**, R = Li
**b**, R = $Me_3Si$

**2a**, $R_1 = R_2 = H$
**b**, $R_1 = CH_3$; $R_2 = H$
**c**, $R_1 = CH_2CH_2CN$; $R_2 = H$
**d**, $R_1 = CH_2OH$; $R_2 = H$
**e**, $R_1 = H$; $R_2 = Me_3Si$
**f**, $R_1 = H$; $R_2 = Li$




**3a**. R = Li
**b**, R = $Me_3Si$




**1a,b** **2a,b**

A number of groups have reported the alkylation[4a-h] of acyloins on carbon (e.g., **2a** → **2b**), Michael addition[5a-c] (e.g., **2a** → **2c**), and aldol condensations[6] (e.g., **2a** → **2d**).

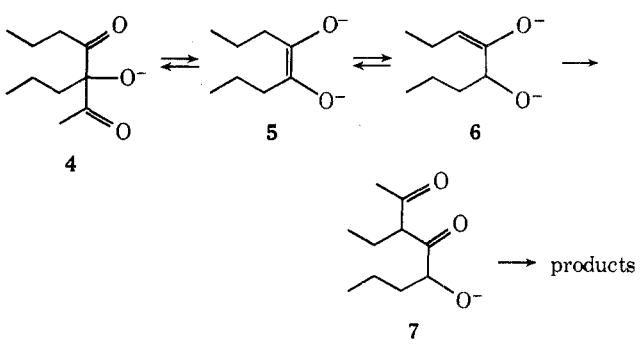
All published reports thus far on acyloin dianions, with one exception[7] (vida infra), however, evoke the structure of the well-known enediolate **1a**. We have determined that **1a** is in fact the "thermodynamic" enolate dianion and that compound **3a** is a readily accessible "kinetic" enolate dianion.[8]

When a THF solution of freshly distilled monomeric[9] adipoin **2a** is added dropwise to an excess of 2 equiv of lithium diisopropyl amide or 2,2,6,6-tetramethylpiperidide, a dianion is formed which on silylation gives predominantly the kinetic enolate cyclohexene-2,3-diol bis(trimethylsilyl) ether[13,14] (**3b**) in 73% yield (see Table I). This compound possesses the expected vinyl proton multiplet at δ 4.88 and methine adjacent to oxygen at δ 3.95.

If adipoin **2a** is refluxed in DMF with $Me_3SiCl$–$Et_3N$, conditions under which a "thermodynamic" mixture is to be expected,[15] the more stable bis silyl ether **1b** is the predominant bis silyl ether formed. These results are consistent with the observed site of reaction of acyloins which were conducted under equilibrating conditions.[4,5,6]

The observation[7] that enediolate **5**, obtained from acyloin condensation of ethyl butyrate, condenses with ethyl acetate to give a product derived from **7** can be best explained by the equilibrium in Scheme I. Condensation with

Scheme I




4 5 6 7