Reaction of Ninhydrin with β-Dicarbonyl Compounds

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Received March 18, 1994
Revised August 10, 1994

The reactions of ninhydrin (**1**) with β-ketoesters and β-diketones were studied. Two kinds of products were observed, which were either simple adducts of the dicarbonyl compounds to the center carbonyl group of ninhydrin, or tricyclic indeno[1,2-*b*]furans. Treatment of methyl 3-aminocrotonate (**2**) with ninhydrin led in analogous fashion to an indeno[1,2-*b*]pyrrole (**3**) which was reduced to a complex tetracyclic dihydropyridine **12**. A mechanism for the production of **12** is presented. Structures for the novel heterocycles are supported by high resolution nmr studies and X-ray crystallography.

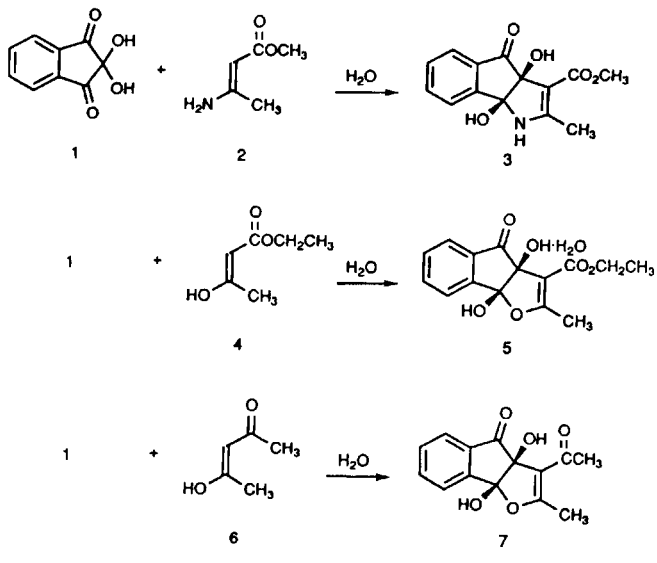
J. Heterocyclic Chem., **32**, 33 (1995).

Reactions of 1,2,3-tricarbonyl compounds with compounds having two nucleophilic centers produce interesting and complex fused polyheterocyclic systems. Quinolinobenzoxazines and quinolinobenzoxazepines have been prepared from arylamines and 2,3,4-trioxo-1-phenyl-1,2,3,4-tetrahydroquinoline [1], whereas the latter tricarbonyl compound and anthranilic acid gave spirolactones which thermally rearranged to fused benzoxazines [2]. Ninhydrin (**1**, 1,2,3-indanetrione) has been shown to react with cytosine, cytidine and cytidine nucleotides to give fused heterocycles in which the amino group of the cytosine formed a bond with the 2-position of **1** and the 5-position of the cytosine formed a bond with the 1-position of **1** [3]. Ureas and **1** were shown to produce indenoimidazolediones [4].

Interestingly, enamines have also been shown to interact with **1** to produce fused systems. Thus, 6-aminopyrimidine-2,4-diones [4], methyl 3-aminocrotonate [5], 3-aminocrotonitrile [5] and 2-aminopent-2-ene-4-one [5] have all been treated with **1** to produce indeno[1,2-*b*]-pyrroles [6]. These reports prompted us to investigate the reaction of β-dicarbonyl compounds with **1**, since we reasoned that highly enolized β-dicarbonyl compounds should be isosteric with enamines and similarly reactive.

In Scheme I are shown reactions of **1** with methyl 3-aminocrotonate (**2**) [5], ethyl acetoacetate (**4**) and acetylacetone (**6**). All of these reactions were performed in water as the only solvent and all reactions produced fused systems in which the vinyl carbon atom bearing the hydrogen atom in compounds **2**, **4** and **6**, which is probably the most nucleophilic atom in these building blocks, has done a 1,2-addition across the central carbonyl group of **1**, and the amino or hydroxy group has done a 1,2-addition across an adjacent carbonyl group from the same face. The structures of the tricyclic compounds were established based on nmr spectroscopy. Thus, for **3**, NOE

Scheme I

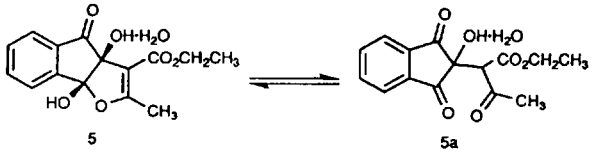


correlations were observed between the NH and 2-CH_3, 8b-OH, and H-8. The correlations are only consistent with the tricyclic structure **3**. Analysis of the ^{13}C and APT (attached proton test) data were also consistent with structure **3** (see Experimental). Key observations included the two quaternary carbons observed at 91.5 and 85.2 ppm for the two aliphatic bridgehead carbons C-8b and C-3a, and a single ketone-carbonyl observed at 198.9 ppm.

The nmr spectra of the oxygen analogues were more complicated. In both deuteriochloroform and dimethyl sulfoxide-d_6 the ^1H nmr spectra showed an *ca.* 85/15 mixture of components for **5**. In addition, broadened signals were observed for some signals in the ^{13}C nmr spectrum consistent with a slow equilibration on the nmr time scale between two solution structures. The signals attributed to

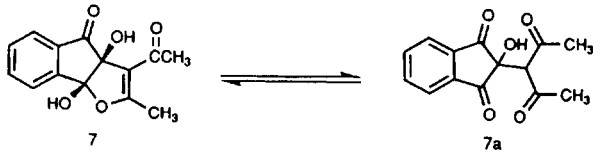
the major species are consistent with the tricyclic structure shown. Important observations included two exchangeable protons (-OH's) in the ^1H spectrum and two downfield aliphatic bridgehead carbons at 109.5 and 104.7 in the ^{13}C nmr spectrum. Signals assigned to the minor component included three keto-carbonyl signals (202.2, 197.8 and 197.2 ppm), an aliphatic quaternary carbon at 73.1 ppm, a methine carbon at 62.5 ppm, and a methyl signal at 31.2 ppm. These are consistent with the ring-open structure **5a** shown in Scheme II.

Scheme II



For **7** a single solution species is indicated in both the ^1H and ^{13}C nmr spectra (slighly broad signals were observed for some signals). Interestingly, however, in a phase-sensitive NOESY spectrum a negative correlation was observed between the two methyl signals indicative of chemical exchange. This is explained by the fast (on the nmr time-scale) equilibrium shown in Scheme III where the ring-open form **7a** can lead to exchange of the two methyls in the tricyclic structure.

Scheme III



A positional isomer of **7** has been recently presented by Yalpani and Wilke [8]. They showed that the trimethylsilyl enol ether of 2,4-pentanedione [9] adds to ninhydrin (**1**) to give a bis-*O*-trimethylsilyl adduct which, after treatment with boron trifluoride etherate, produced compound **7** or the isomeric structure in which the addition of **6** to **1** had occurred in the other possible manner. Both of these structures were presented and the identity of the compound produced by this sequence was not established.

The solid-state structure of the fused compound produced from ninhydrin (**1**) and 2,4-pentanedione (**6**) was unequivocally established by X-ray crystallography. In Figure I is shown the ORTEP view of this adduct, namely, (3a-*cis*)-3-acetyl-3a,8b-dihydro-3a,8b-dihydroxy-2-methyl-4*H*-indeno[1,2-*b*]furan-4-one (**7**). We were also able to obtain a single crystal X-ray structure for the adduct of **1** with ethyl acetoacetate (**4**), which confirmed the same mode of addition. In Figure II is shown an ORTEP view of (3a-*cis*)-3a,8b-dihydro-3a,8b-dihydroxy-2-methyl-4-oxo-4*H*-indeno[1,2-*b*]furan-3-carboxylic acid ethyl ester monohydrate (**5**). Crystal and refinement data for **7** and **5** are shown in Table I. In Tables II-V are shown bond lengths and angles for these structures.

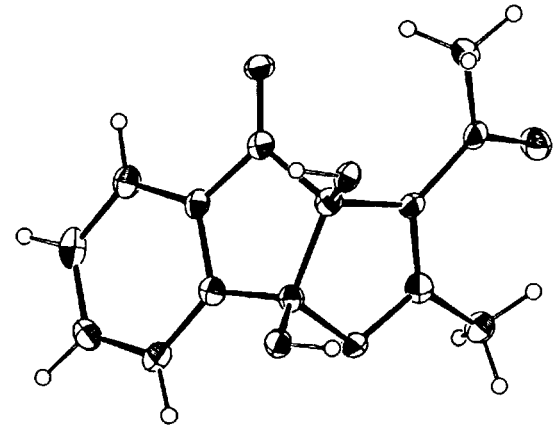


Figure I. ORTEP drawing of (3a-*cis*)-3-acetyl-3a,8b-dihydro-3a,8b-dihydroxy-2-methyl-4*H*-indeno[1,2-*b*]furan-4-one (**7**).

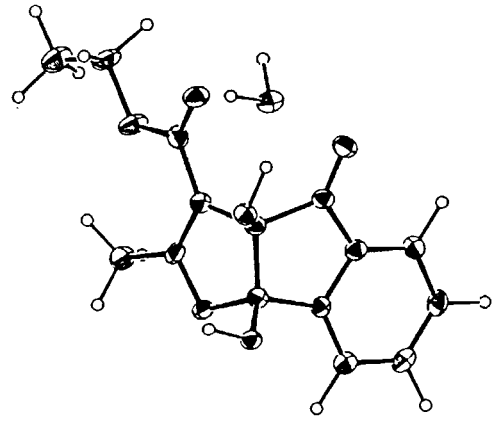


Figure II. ORTEP drawing of (3a-*cis*)-3a,8b-dihydro-3a,8b-dihydroxy-2-methyl-4-oxo-4*H*-indeno[1,2-*b*]furan-3-carboxylic acid ethyl ester monohydrate (**5**).

When a bulkier β-ketoester and cyclic β-diketones were condensed with ninhydrin, the solution structures of the adducts formed were predominantly the ring-open structures

Scheme IV

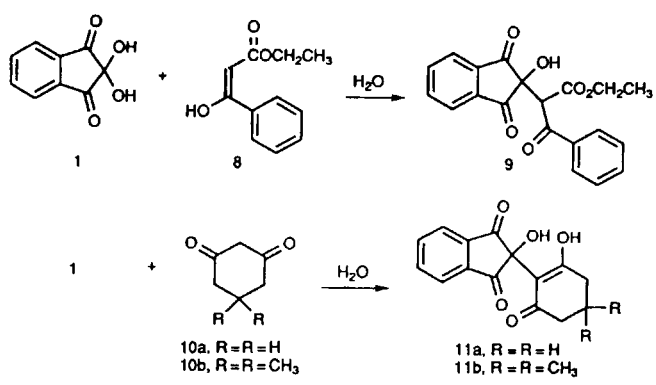


Table I

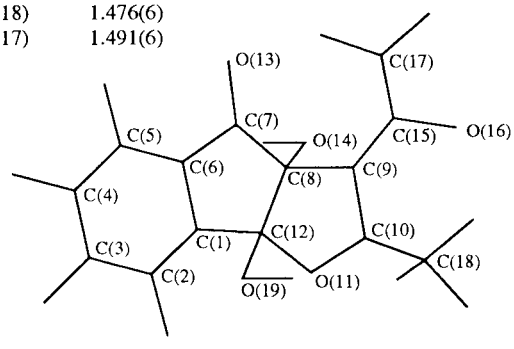
Crystal and Refinement Data

	Cpd **7**	Cpd **5**	Cpd **12**
formula	$C_{14}H_{12}O_5$	$C_{15}H_{14}O_6 H_2O$	$C_{18}H_{17}NO_5$
color	colorless	colorless	colorless
dimensions	.25 x .25 x .25	.25 x .25 x .25	.35 x .35 x .35
space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
a, Å	12.266 (5)	7.922 (3)	11.965 (3)
b, Å	7.672 (3)	16.529 (6)	9.329 (2)
c,	13.705 (5)	11.033 (4)	14.012 (3)
beta, deg.	114.91 (1)	99.20 (2)	109.81 (1)
Z	4	4	4
volume	1169.65	1426.20	1471.46
calcd dens	1.478	1.436	1.478
wavelength	.71069	.71069	.71069
form weight	260.25	308.29	327.34
lin abs coef	1.057	1.075	1.015
scan speed, deg/min	4.0	6.0	4.0
scan width, deg	2.0 + disp	1.8 + disp	2.0 + disp
total refl	1701	1997	4146
unique data	1532	1876	1911
no. F>0.0	1412	1739	1641
no. F>2.33 σ (F)	1262	1575	1310
R for avg	.051	.052	.067
R (F)	.0534	.0427	.0489
Rw (F)	.0557	.0476	.0455
goodness/fit	1.308	1.105	.839
max δ/σ	.23	.05	.32

Table II

Bond Distances for Compound **7**

A	B	Distance	A	B	Distance
O(11)	C(10)	1.354(5)	O(14)	H(5)	0.93(6)
O(11)	C(12)	1.469(4)	O(19)	H(12)	1.01(5)
O(13)	C(7)	1.214(5)	C(2)	H(1)	0.95(4)
O(14)	C(8)	1.419(5)	C(3)	H(2)	1.00(4)
O(16)	C(15)	1.231(5)	C(4)	H(3)	0.96(4)
O(19)	C(12)	1.368(4)	C(5)	H(4)	0.97(4)
C(1)	C(2)	1.387(6)	C(17)	H(6)	1.00(4)
C(1)	C(6)	1.393(6)	C(17)	H(7)	0.99(5)
C(1)	C(12)	1.501(5)	C(17)	H(8)	0.94(5)
C(2)	C(3)	1.384(6)	C(18)	H(9)	1.02(6)
C(3)	C(4)	1.397(6)	C(18)	H(10)	1.00(5)
C(4)	C(5)	1.374(6)	C(18)	H(11)	0.93(5)
C(5)	C(6)	1.394(6)			
C(6)	C(7)	1.479(5)			
C(7)	C(8)	1.544(5)			
C(8)	C(9)	1.509(5)			
C(8)	C(12)	1.569(5)			
C(9)	C(10)	1.358(5)			
C(9)	C(15)	1.469(5)			
C(10)	C(18)	1.476(6)			
C(15)	C(17)	1.491(6)			



shown in Scheme IV. Thus, ethyl benzoylacetate (**8**) gave adduct **9**, which arises from the normal addition of an enolized ketone to the central carbonyl group of ninhydrin (**1**). In dimethyl sulfoxide-d_6 the ^1H nmr showed a *ca.* 90/10 mixture of two solution species. The major component was characterized by a singlet at 7.10 ppm which underwent rapid deuterium exchange upon the addition of deuterium oxide to the sample solution, thus assigned as the hydroxy proton of **9**. By contrast, a singlet was observed at 5.24 ppm which underwent slow exchange over several hours. This is consistent with the methine proton which slowly exchanges due to tautomerism. The minor component had two fast exchanging protons at 6.39 and 8.23 ppm consistent with the two hydroxy protons of the tricyclic structure. In deuteriochloroform only one species is observed. Analysis of the ^{13}C and APT spectra of this solution showed three keto-carbonyl signals at 196.6, 195.8, and 193.6 ppm, assigned as the two diasteriotopic carbonyls of the dioxo-indene and the benzoyl carbonyl. In the aliphatic region important resonances included a quaternary carbon observed at 74.4 ppm and a methine carbon at 56.0 ppm, consistent with **9**. The assignment of **9** as the addition product to the central carbonyl of ninhydrin and not the 1-carbonyl was made based on the absence of an NOE correlation between either the hydroxy or methine proton and the indene-aromatic protons. The solution structures of the adducts **11a** and **11b** formed by the addition of 1,3-cyclohexanedione (**10a**) and its 4,4-dimethyl derivative **10b** to ninhydrin were similarly characterized. In dimethyl sulfoxide-d_6 very broad signals were

observed in the ^1H nmr spectra. By contrast, at high temperature (125°) or in deuteriochloroform at 25° a single solution species was observed. These were assigned as the ring-open adducts shown based on the observed equivalence of the appropriate signals in the symmetrical cyclohexanedione. It is very unlikely these signals would be equivalent in both solvents in the tricyclic species.

Reduction studies were initiated on compound **3** in an attempt to produce a fully unsaturated pyrrole. The process we envisioned proceeded by reduction of an imine, produced by dehydration, followed by a subsequent dehydration. While this transformation did not occur when we treated a slurry of **3** in methanol and acetic acid with a palladium catalyst and hydrogen gas, an alternate and remarkable conversion did take place. The structure of the product which we isolated from this reaction is dihydropyridine **12**, which is shown in Scheme V. The key analytical data for structure elucidation of **12** were as follows. The mass spectrum (molecular ion m/z 327) and elemental analysis indicated a molecular formula of $C_{18}H_{17}NO_5$. The ^1H and ^{13}C nmr data indicated the absence of the keto-carbonyl and the presence of one aromatic ring, two aliphatic methines (87.3 and

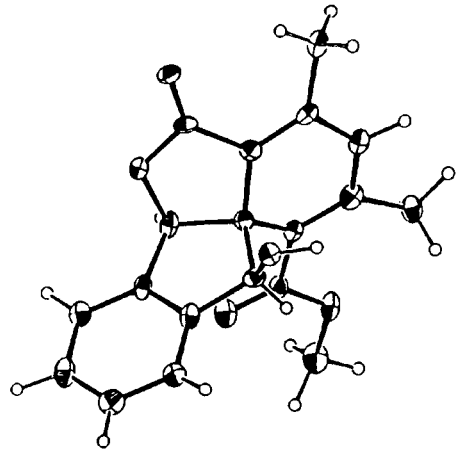


Figure III. ORTEP drawing of [6a-(6aα,11β,11a]-3,5,6a,11-tetrahydro-11-hydroxy-2,4-dimethyl-5-oxoindeno[2′,1′:4,5]furo[3,4-*c*]pyridine-1-carboxylic acid methyl ester (**12**).

Scheme V

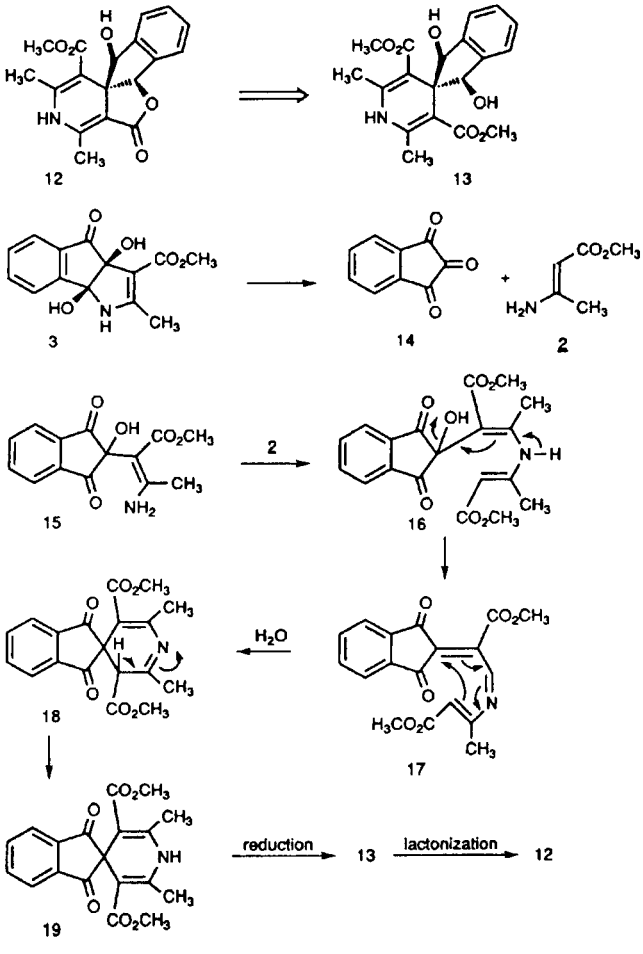


Table III

Bond Angles for Compound **7**

A	B	C	Angle	A	B	C	Angle
C(10)	O(11)	C(12)	108.9(3)	C(8)	O(14)	H(5)	109(3)
C(2)	C(1)	C(6)	120.5(4)	C(12)	O(19)	H(12)	112(3)
C(2)	C(1)	C(12)	128.2(4)	C(1)	C(2)	H(1)	118.9(23)
C(6)	C(1)	C(12)	111.3(3)	C(3)	C(2)	H(1)	122.9(23)
C(1)	C(2)	C(3)	118.2(4)	C(2)	C(3)	H(2)	123.2(24)
C(2)	C(3)	C(4)	121.2(4)	C(4)	C(3)	H(2)	115.5(24)
C(3)	C(4)	C(5)	120.9(4)	C(3)	C(4)	H(3)	117.8(24)
C(4)	C(5)	C(6)	118.0(4)	C(5)	C(4)	H(3)	121.4(24)
C(1)	C(6)	C(5)	121.2(4)	C(4)	C(5)	H(4)	123.2(24)
C(1)	C(6)	C(7)	110.1(3)	C(6)	C(5)	H(4)	118.7(24)
C(5)	C(6)	C(7)	128.6(4)	C(15)	C(17)	H(6)	110.3(24)
O(13)	C(7)	C(6)	126.5(4)	C(15)	C(17)	H(7)	108.6(27)
O(13)	C(7)	C(8)	125.5(4)	C(15)	C(17)	H(8)	112.6(27)
C(6)	C(7)	C(8)	108.0(3)	H(6)	C(17)	H(7)	115.0(4)
O(14)	C(8)	C(7)	112.6(3)	H(6)	C(17)	H(8)	106.0(3)
O(14)	C(8)	C(9)	111.4(3)	H(7)	C(17)	H(8)	105.0(4)
O(14)	C(8)	C(12)	113.8(3)	C(10)	C(18)	H(9)	110.0(3)
C(7)	C(8)	C(9)	112.1(3)	C(10)	C(18)	H(10)	111.9(26)
C(7)	C(8)	C(12)	103.8(3)	C(10)	C(18)	H(11)	114.0(3)
C(9)	C(8)	C(12)	102.4(3)	H(9)	C(18)	H(10)	105.0(4)
C(8)	C(9)	C(10)	108.9(3)	H(9)	C(18)	H(11)	107.0(4)
C(8)	C(9)	C(15)	126.8(3)	H(10)	C(18)	H(11)	108.0(4)
C(10)	C(9)	C(15)	124.3(3)				
O(11)	C(10)	C(9)	114.4(3)				
O(11)	C(10)	C(18)	112.9(4)				
C(9)	C(10)	C(18)	132.7(4)				
O(11)	C(12)	O(19)	108.8(3)				
O(11)	C(12)	C(1)	107.4(3)				
O(11)	C(12)	C(8)	105.25(27)				
O(19)	C(12)	C(1)	112.6(3)				
O(19)	C(12)	C(8)	116.4(3)				
C(1)	C(12)	C(8)	105.9(3)				
O(16)	C(15)	C(9)	121.2(4)				
O(16)	C(15)	C(17)	120.1(4)				
C(9)	C(15)	C(17)	118.4(3)				

Table IV

Bond Distances for Compound **5**

A	B	Distance	A	B	Distance
O(8)	C(7)	1.478(4)	O(14)	H(5)	0.93(4)
O(8)	C(9)	1.358(4)	O(21)	H(14)	0.93(5)
O(13)	C(12)	1.215(4)	O(22)	H(15)	0.95(5)
O(14)	C(7)	1.377(3)	O(22)	H(16)	0.91(4)
O(17)	C(16)	1.222(4)	C(2)	H(1)	0.92(3)
O(18)	C(16)	1.344(4)	C(3)	H(2)	0.95(3)
O(18)	C(19)	1.463(4)	C(4)	H(3)	0.98(4)
O(21)	C(11)	1.422(4)	C(5)	H(4)	0.97(3)
C(1)	C(2)	1.390(4)	C(15)	H(6)	0.90(4)
C(1)	C(6)	1.394(4)	C(15)	H(7)	0.96(5)
C(1)	C(12)	1.473(4)	C(15)	H(8)	0.99(5)
C(2)	C(3)	1.380(5)	C(19)	H(9)	1.02(4)
C(3)	C(4)	1.398(5)	C(19)	H(10)	1.00(4)
C(4)	C(5)	1.384(5)	C(20)	H(11)	0.98(4)
C(5)	C(6)	1.387(4)	C(20)	H(12)	1.00(4)
C(6)	C(7)	1.511(4)	C(20)	H(13)	1.00(5)
C(7)	C(11)	1.566(4)			
C(9)	C(10)	1.346(4)			
C(9)	C(15)	1.495(5)			
C(10)	C(11)	1.507(4)			
C(10)	C(16)	1.457(4)			
C(11)	C(12)	1.542(4)			
C(19)	C(20)	1.494(5)			

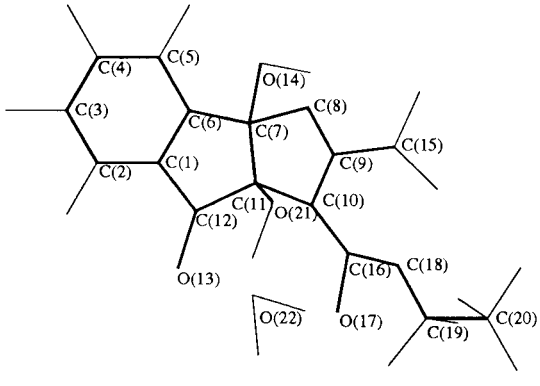


Table V

Bond Angles for Compound **5**

A	B	C	Angle
C(7)	O(14)	H(5)	111.8(22)
C(11)	O(21)	H(14)	112.0(3)
H(15)	O(22)	H(16)	102.0(3)
C(1)	C(2)	H(1)	119.8(19)
C(3)	C(2)	H(1)	121.9(19)
C(2)	C(3)	H(2)	118.4(18)
C(4)	C(3)	H(2)	120.9(18)
C(3)	C(4)	H(3)	117.2(20)
C(5)	C(4)	H(3)	121.3(20)
C(4)	C(5)	H(4)	122.6(18)
C(6)	C(5)	H(4)	119.9(18)
C(9)	C(15)	H(6)	112.0(25)
C(9)	C(15)	H(7)	110.2(25)
C(9)	C(15)	H(8)	112.3(26)
H(6)	C(15)	H(7)	110.0(3)
H(6)	C(15)	H(8)	102.0(3)
H(7)	C(15)	H(8)	111.0(3)

Table V (continued)

A	B	C	Angle
O(18)	C(19)	H(9)	103.9(19)
O(18)	C(19)	H(10)	106.7(22)
C(20)	C(19)	H(9)	109.8(20)
C(20)	C(19)	H(10)	114.9(22)
H(9)	C(19)	H(10)	115.0(3)
C(19)	C(20)	H(11)	107.8(20)
C(19)	C(20)	H(12)	109.1(20)
C(19)	C(20)	H(13)	112.0(26)
H(11)	C(20)	H(12)	111.0(3)
H(11)	C(20)	H(13)	113.0(3)
H(12)	C(20)	H(13)	104.0(3)

Table VI

Bond Distances for Compound **12**

A	B	Distance	A	B	Distance
O(1)	C(2)	1.431(5)	O(1)	H(1)	0.90(6)
O(10)	C(9)	1.476(5)	N(14)	H(8)	0.90(4)
O(10)	C(11)	1.359(5)	C(2)	H(2)	0.96(4)
O(18)	C(11)	1.225(5)	C(4)	H(3)	0.94(5)
O(22)	C(21)	1.205(5)	C(5)	H(4)	1.00(5)
O(23)	C(21)	1.351(5)	C(6)	H(5)	1.00(4)
O(23)	C(24)	1.451(6)	C(7)	H(6)	0.99(4)
N(14)	C(13)	1.373(5)	C(9)	H(7)	0.99(4)
N(14)	C(15)	1.392(6)	C(19)	H(9)	0.89(5)
C(2)	C(3)	1.505(6)	C(19)	H(10)	0.99(5)
C(2)	C(17)	1.599(6)	C(19)	H(11)	0.99(5)
C(3)	C(4)	1.389(6)	C(20)	H(12)	1.00(6)
C(3)	C(8)	1.389(6)	C(20)	H(13)	0.98(6)
C(4)	C(5)	1.382(7)	C(20)	H(14)	0.96(5)
C(5)	C(6)	1.388(7)	C(24)	H(15)	1.05(6)
C(6)	C(7)	1.389(6)	C(24)	H(16)	0.93(5)
C(7)	C(8)	1.388(6)	C(24)	H(17)	0.96(5)
C(8)	C(9)	1.493(6)			
C(9)	C(17)	1.550(6)			
C(11)	C(12)	1.450(6)			
C(12)	C(13)	1.347(6)			
C(12)	C(17)	1.496(6)			
C(13)	C(19)	1.486(6)			
C(15)	C(16)	1.351(6)			
C(15)	C(20)	1.495(7)			
C(16)	C(17)	1.522(6)			
C(16)	C(21)	1.480(6)			

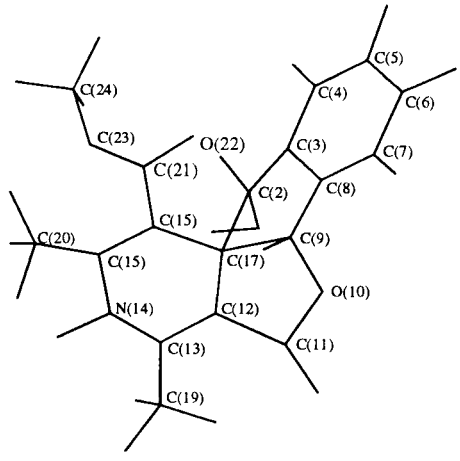


Table VII

Bond Angles for Compound **12**

A	B	C	Angle	A	B	C	Angle
C(9)	O(10)	C(11)	111.0(3)	C(2)	O(1)	H(1)	111.0(4)
C(21)	O(23)	C(24)	114.8(4)	C(13)	N(14)	H(8)	116.7(24)
C(13)	N(14)	C(15)	123.2(4)	C(15)	N(14)	H(8)	119.7(24)
O(1)	C(2)	C(3)	110.2(4)	O(1)	C(2)	H(2)	107.7(23)
O(1)	C(2)	C(17)	114.4(3)	C(3)	C(2)	H(2)	108.4(23)
C(3)	C(2)	C(17)	105.1(4)	C(17)	C(2)	H(2)	110.9(23)
C(2)	C(3)	C(4)	128.2(4)	C(3)	C(4)	H(3)	117.2(27)
C(2)	C(3)	C(8)	111.5(4)	C(5)	C(4)	H(3)	123.7(28)
C(4)	C(3)	C(8)	120.2(4)	C(4)	C(5)	H(4)	120.0(3)
C(3)	C(4)	C(5)	119.0(5)	C(6)	C(5)	H(4)	119.0(3)
C(4)	C(5)	C(6)	120.7(5)	C(5)	C(6)	H(5)	120.3(24)
C(5)	C(6)	C(7)	120.6(5)	C(7)	C(6)	H(5)	119.1(24)
C(6)	C(7)	C(8)	118.5(4)	C(6)	C(7)	H(6)	121.4(23)
C(3)	C(8)	C(7)	120.9(4)	C(8)	C(7)	H(6)	120.0(23)
C(3)	C(8)	C(9)	111.3(4)	O(10)	C(9)	H(7)	109.7(20)
C(7)	C(8)	C(9)	127.8(4)	C(8)	C(9)	H(7)	115.4(20)
O(10)	C(9)	C(8)	107.0(4)	C(17)	C(9)	H(7)	111.6(20)
O(10)	C(9)	C(17)	105.7(3)	C(13)	C(19)	H(9)	108.0(3)
C(8)	C(9)	C(17)	106.9(4)	C(13)	C(19)	H(10)	111.5(28)
O(10)	C(11)	O(18)	119.7(4)	C(13)	C(19)	H(11)	112.6(27)
O(10)	C(11)	C(12)	108.9(4)	H(9)	C(19)	H(10)	111.0(4)
O(18)	C(11)	C(12)	131.4(4)	H(9)	C(19)	H(11)	109.0(4)
C(11)	C(12)	C(13)	126.3(4)	H(10)	C(19)	H(11)	105.0(4)
C(11)	C(12)	C(17)	109.8(4)	C(15)	C(20)	H(12)	111.0(3)
C(13)	C(12)	C(17)	122.9(4)	C(15)	C(20)	H(13)	116.0(3)
N(14)	C(13)	C(12)	117.2(4)	C(15)	C(20)	H(14)	109.3(27)
N(14)	C(13)	C(19)	116.7(4)	H(12)	C(20)	H(13)	110.5(5)
C(12)	C(13)	C(19)	125.9(4)	H(12)	C(20)	H(14)	103.0(4)
N(14)	C(15)	C(16)	119.7(4)	H(13)	C(20)	H(14)	107.0(4)
N(14)	C(15)	C(20)	112.7(4)	O(23)	C(24)	H(15)	114.0(28)
C(16)	C(15)	C(20)	127.7(4)	O(23)	C(24)	H(16)	113.0(3)
C(15)	C(16)	C(17)	118.7(4)	O(23)	C(24)	H(17)	107.0(3)
C(15)	C(16)	C(21)	124.6(4)	H(15)	C(24)	H(16)	106.0(4)
C(17)	C(16)	C(21)	115.9(4)	H(15)	C(24)	H(17)	109.0(4)
C(2)	C(17)	C(9)	104.1(3)	H(16)	C(24)	H(17)	108.0(4)
C(2)	C(17)	C(12)	115.2(4)				
C(2)	C(17)	C(16)	107.6(4)				
C(9)	C(17)	C(12)	101.4(4)				
C(9)	C(17)	C(16)	118.8(3)				
C(12)	C(17)	C(16)	109.9(4)				
O(22)	C(21)	O(23)	122.0(4)				
O(22)	C(21)	C(16)	123.7(4)				
O(23)	C(21)	C(16)	114.2(4)				

85.9 ppm), one aliphatic quaternary carbon (52.0 ppm), one methyl ester (50.1 ppm), and two upfield methyls (18.4 and 14.5 ppm). The upfield methine was part of a CH-OH spin system in the ^{1}H nmr while the other methine was a singlet. Each methine proton had an NOE correlation to a different aromatic proton and the NH proton had NOE correlations to both methyls. These data are all consistent with **12**.

The mechanism which we propose for the production of **12** from **3** is also shown in Scheme V. This mechanism involves discreet processes of dissociation, recondensation of the starting materials with different stoichiometry, reduction of the ketones to alcohols and subsequent lactonization by interaction of a newly formed alcohol with an ester. Thus, dissociation of **3** to ninhydrin and methyl 3-aminocrotonate (**2**) followed by recondensation of ninhydrin with two equivalents of **2** could lead to divinyl amine **16**, which could then dehydrate to produce intermediate **17**. Cyclization of **17** as shown would give dihydropyridine **19**, after tautomerization. Reduction of both carbonyl groups in **19** from the same face of the indanedione ring would give diol **13**, which would lactonize to give **12**.

The ORTEP drawing of **12** is shown in Figure III. The two oxygen functionalities on the spiroindanediol ring are clearly shown to be on the same face, one as a hydroxyl group and the other as the ether oxygen atom of the lactone. Crystal and refinement data for **12** are shown in Table I. In Tables VI and

VII are shown bond lengths and angles for **12**.

In summary, we have investigated the interactions of ninhydrin (**1**) with enamine **2** and 1,3-dicarbonyl compounds and found two kinds of products. Treatment of the adduct of **1** and methyl 3-aminocrotonate (**2**) with hydrogen gas in the presence of a palladium catalyst gave a complex dihydropyridine (**12**). Structural assignments were made on the basis of high field nmr analysis and confirmed by single crystal X-ray analysis on key structures. The chemistry described here provided complex and unusual compounds for biological evaluation [10].

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses (tlc) were performed with Merck DC-F254 or Analtech GHLF silica gel plates, with visualization by iodine, alkaline permanganate, or uv irradiation. Flash chromatography was performed with Merck silica gel 60 (0.040-0.063 mm). The nmr spectra were recorded on Varian VXR 300, Unity 300, or Unity 400 spectrometers at 25° except where noted. The ^1H and ^{13}C nmr signals are reported in ppm from tetramethylsilane, and coupling constants are reported in Hertz (Hz). Where appropriate additional nmr spectra were obtained to aid in structural assignments. These included APT spectra (D_2 = 7 or 4 msec), COSY, NOESY (mix time = 1 sec), and HETCOR spectra. These were obtained using the Varian supplied pulse sequences and the minimal sweep widths required to observe all appropriate resonances. The ir spectra were recorded on a Perkin-Elmer Model 1800 or Mattson Galaxy 5020 FT-IR spectrophotometer. Mass spectral data were collected at 70 eV on a Finnigan MAT 4600, MAT TSQ-700 or VG Analytical Limited ZAB2-SE mass spectrophotometer and computerized peak matching with perfluorokerosene as the reference was utilized for hrms. Combustion analysis was obtained on a Perkin-Elmer Model 2400 elemental analyzer and fell within ± 0.4% of the calculated values. All reactions were run under an inert atmosphere. The organic extracts were dried over anhydrous magnesium sulfate or sodium sulfate prior to solvent removal on a rotary evaporator.

Crystal Data.

Compound **7**, $C_{14}H_{12}O_5$, has a monoclinic space group $P2_1/c$, a = 12.266 (5), b = 7.672 (3), c = 13.705 (5), β = 114.91 (1), V = 1169.65 A^3, Z = 4, D_c = 1.478 gm/cc. There were 1532 unique intensities from 1701 total reflections collected. Final residues were R = 0.0534 and R_n = 0.0557.

Compound **5**, $C_{15}H_{14}O_6 \cdot H_2O$, has a monoclinic space group $P2_1/c$, a = 7.922 (3), b = 16.529 (6), c = 11.033 (4), β = 99.20 (2), V = 1426.20 A^3, Z = 4, D_c = 1.436 gm/cc. There were 1876 unique intensities from 1997 total reflections collected. Final residues were R = 0.0427 and R_w = 0.0476.

Compound **12**, $C_{18}H_{17}NO_5$, has a monoclinic space group $P2_1/n$, a = 11.965 (3), b = 9.329 (2), c = 14.012 (3), β = 109.81 (1), V = 1471.46 A^3, Z = 4, D_c = 1.478 gm/cc. There were 1911 unique intensities from 4146 total reflections collected. Final residues were R = 0.0489 and R_w = 0.0455.

Reflections were collected with a Picker goniostat using graphite-monochromatized molybdenum radiation. The diffractometer, data-handling techniques, and general procedure have been described previously [11]. Structures were solved by direct methods and refined by full-matrix squares. Atomic coordinates for this work are available on request from the Director of Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EN, England. Any request should be accompanied by a full literature citation of this article. Complete crystallographic details are also available in microfiche form from the Chemistry Library, Indiana University, Bloomington, Indiana, 47405. For compound **5** request MSC Report No. 88701; for compound **7** request MSC Report No. 91706; and for compound **12** request MSC Report No. 91703.

(3a-*cis*)-1,3a,4,8b-Tetrahydro-3a,8b-dihydroxy-2-methyl-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylic Acid Methyl Ester (**3**).

A solution of 23.0 g (0.200 mole) of methyl 3-aminocrotonate (**2**) in 550 ml of warm water and a solution of 35.6 g (0.200 mole) of ninhydrin in 750 ml of water were both added to a flask with filtration, and the resulting red solution soon began to deposit a crystalline material. After 15 hours the off-white prisms were collected and air-dried to give 51.9 g (94%) of **3**, mp 193-196° (lit [5] mp 201-202°); ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 8.83 (bs, 1H, exchangeable, NH), 7.82-7.75 (m, 2H, H-7 and H-8), 7.67 (dm, 1H, J = 7.8 Hz, H-5), 7.54 (ddd, 1H, J = 2.6, 5.3 and 7.8 Hz, H-6), 6.38 (s, 1H, exchangeable, 8b-OH), 5.43 (s, 1H, exchangeable, 3a-OH), 3.52 (s, 3H, $-OCH_3$), 2.06 (s, 3H, 2-CH_3); ^{13}C nmr (75 MHz, dimethyl sulfoxide-d_6): δ 198.9 (C-4), 165.6 (3-CO), 160.0 (C-2), 149.7 (C-8a), 135.4 (Ar), 134.7 (C-4a), 129.8 (Ar), 124.7 (Ar), 122.6 (Ar), 94.8 (C-3), 91.5 (C-8b), 85.2 (C-3a), 49.6 (OCH_3), 14.5 (2-CH_3); ir (potassium bromide): 1712, 1636, 1486 cm^{-1}; ms: (EI, 70 eV m/z (relative intensity) 275 (10), 243 (85), 225 (100).

(3a-*cis*)-3a,8b-Dihydro-3a,8b-dihydroxy-2-methyl-4-oxo-4*H*-indeno[1,2-*b*]furan-3-carboxylic Acid Ethyl Ester Monohydrate (**5**).

A solution of 26.0 g (0.200 mole) of ethyl acetoacetate (**4**) in 550 ml of warm water and a solution of 35.6 g (0.200 mole) of ninhydrin in 750 ml of warm water were both filtered into a common flask. After 15 hours, the white prisms which had formed were collected and air-dried to give 57.4 g (93%) of **5**, mp 93-103°; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): *ca.* 90/10 mixture of tautomers): 8.07-7.32 (m, 5H, Ar and OH), 6.13 (br s, 1H, OH), 4.16-3.83 (m, 2H, CH_2), 2.42 (s, 0.3H, minor 2-CH_3), 2.14 (s, 2.7H, major 2-CH_3), 1.21 (t, 2.7H, J = 7.1 Hz, major ester-CH_3), 0.95 (t, 0.3H, J = 7.1 Hz, minor ester-CH_3); ^1H nmr (300 MHz, deuteriochloroform, *ca.* 85/15 mixture of tautomers): 8.09-7.51 (m, 4H, Ar), 4.53 (vb s, 2H, OH's), 4.40-4.21 (m, 2H, CH_2), 2.36 (s, 0.5H, minor 2-CH_3), 2.24 (s, 2.5H, major 2-CH_3), 1.35 (t, 2.5H, J = 7.1 Hz, major ester-CH_3), 1.32 (t, 0.5H, minor ester-CH_3); ^{13}C nmr (100 MHz, dimethyl sulfoxide-d_6): major tautomer δ 197.4 (C-4), 169.0 (C-2), 163.8 (3-carbonyl), 146.9 (C-8a), 136.0 (Ar CH), 134.3 (C-4a), 131.2 (Ar CH), 124.7 (Ar CH), 122.8 (Ar CH), 109.6 (C-8b), 104.7 (C-3), 84.2 (C-3a), 59.0 (CH_2), 14.9 (2-CH_3), 14.2 (ester-CH_3); minor tautomer 202.2, 197.8, and 197.2 (keto-carbonyls), 167.5 (ester-carbonyl), 140.6 and 139.9 (Ar C), 136.7, 136.6, 123.8, 123.6 (Ar CH), 73.1 (C-2), 62.5 (CH), 61.1 (CH_2), 31.2 (acetyl-CH_3), 13.4 (ester-CH_3); ms: (EI, 70 eV), m/z (relative intensity) 290 (31), 248 (49), 244 (64), 202 (82), 43 (100).

Anal. Calcd. for $C_{15}H_{14}O_6 \cdot H_2O$: C, 58.44; H, 5.23. Found: C,

58.40; H, 5.33.

(3a-*cis*)-3-Acetyl-3a,8b-dihydro-3a,8b-dihydroxy-2-methyl-4*H*-indeno[1,2-*b*]furan-4-one (**7**).

To a solution of 2.00 g (20.0 mmoles) of acetylacetone (**6**) in 50 ml of warm water was added a solution of 3.56 g (20.0 mmoles) of ninhydrin (**1**) in 55 ml of warm water. A white solid soon began to precipitate. After 19 hours of stirring the solid was collected, washed with water and air-dried to give 4.97 g (96%) of **7**. Recrystallization (ethyl acetate-hexane) gave 4.50 g (86%) of pure **7** as clear, flat prisms, mp 169-173° [12]; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 8.21 (s, 1H, exchangeable, 8b-OH), 7.92-7.86 (m, 2H, H-7 and H-8), 7.77 (dm, 1H, J = 7.8 Hz, H-10), 7.67 (m, 1H, H-6), 6.50 (s, 1H, exchangeable, 3a-OH), 2.40 (s, 3H, acetyl-CH_3), 2.12 (s, 3H, 2-CH_3); ^{13}C nmr (75 MHz, dimethyl sulfoxide-d_6): δ 199.4 (C-4), 195.3 (3-CO), 168.6 (C-2), 147.6 (C-8a), 136.6 (C-7), 133.9 (C-4a), 131.3 (C-6), 125.0 (C-8), 123.2 (C-5), 112.6 (C-3), 109.6 (C-8b), 84.3 (C-3a), 29.7 (acetyl-CH_3), 15.4 (2-CH_3); ms: (EI, 70 eV) m/z (relative intensity) 260 (45), 242 (100), 176 (50).

Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.46; H, 4.57.

α-Benzoyl-2,3-dihydro-2-hydroxy-1,3-dioxo-1*H*-indene-2-acetic Acid Ethyl Ester (**9**).

To a mixture of 3.84 g (20.0 mmoles) of ethyl benzoylacetate (**8**) in 400 ml of water at 90° (most of **8** appeared to be in solution) was added a solution of 3.56 g (20.0 mmoles) of ninhydrin (**1**) in 55 ml of water. The mixture became cloudy, and was allowed to cool with stirring for 15 hours. The white solid was collected, washed with water and air-dried to give 6.16 g (88%) of **9**. Recrystallization (ethyl acetate-hexane) gave 5.08 g (72%) of **9** as white prisms, mp 115-117°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6, 90/10 mixture of tautomers): δ 8.23 (s, 0.1H, exchangeable, minor OH), 8.09-7.36 (m, 4H, Ar), 7.10 (s, 0.9H, exchangeable, major OH), 6.39 (s, 0.1H, exchangeable, minor OH), 5.24 (s, 0.9H, CH), 4.12-4.00 (m, 2H, CH_2), 1.10 (t, 0.3H, J = 7.1 Hz, minor CH_3), 1.05 (t, 2.7H, J = 7.1 Hz, major CH_3); ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.13-7.41 (m, 9H, Ar), 5.12 (s, 1H, 2-CH), 5.00 (s, 1H, exchangeable, 2-OH), 4.31 (q, 2H, J = 7.1 Hz, CH_2), 1.18 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C nmr (75 MHz, deuteriochloroform): δ (carbon type from APT spectra) 196.6 (C), 195.8 (C), 193.6 (C), 169.1 (C), 141.4 (C), 140.8 (C), 136.3 (CH), 135.8 (CH), 135.6 (C), 134.1 (CH), 128.8 (CH), 128.6 (CH), 124.3 (CH), 124.3 (CH), 74.4 (C), 63.0 (CH_2), 56.0 (CH), 13.7 (CH_3); ms: (DCI/CH4) m/z (relative intensity) 353 (75), 193 (95), 161 (100).

Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.21; H, 4.31.

2-Hydroxy-2-(2-hydroxy-6-oxo-1-cyclohexen-1-yl)-1*H*-indene-1,3(2*H*)-dione (**11a**).

A warm solution of 3.56 g (20.0 mmoles) of ninhydrin (**1**) was added to a solution of 2.35 g (21.0 mmoles) of 1,3-cyclohexanedione (**10a**) at ambient temperature. After 22 hours of vigorous stirring the white solid was collected, washed with water and air-dried to give 4.47 g (82%) of **11a**. Recrystallization (ethyl acetate-hexane) gave 3.66 g (67%) of **11a** as clear, flat prisms, mp 174-175° dec; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6, 25°): δ 8.34-7.55 (bm, 5.5H), 6.20 (bs, 0.5H), 2.60-1.70 (m, 6H); ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6, 125°): 7.86-7.78 (m, 4H), 2.29 (t, 4H, J = 6.4 Hz), 1.86 (m, 2H); ^{1}H nmr (300 MHz, deuteriochloroform, 25°): δ 7.90 (m, 2H), 7.73 (m, 2H), 5.51 (bs, 2H), 2.41 (m, 4H), 1.98 (m, 2H); ms: (EI, 70 eV) m/z (relative intensity) 272 (100), 254 (32), 230 (43), 216 (41).

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.42; H, 4.57.

2-Hydroxy-2-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-1*H*-indene-1,3(2*H*)-dione (**11b**).

A warm solution of 3.56 g (20.0 mmoles) of ninhydrin (**1**) in 55 ml of water was added to a solution of 2.80 g (20.0 mmoles) of dimedone (**10b**) in 300 ml of water which had been warmed to 60° on a hot plate. Heating was discontinued and after 15 minutes of stirring a white precipitate abruptly formed. The mixture was stirred at room temperature for 15 hours and the white solid was collected, washed with water and air-dried to give 5.75 g (96%) of **11b**. Recrystallization (ethyl acetate-hexane) gave 4.94 g (96%) of **11b** as a white solid. Recrystallization (ethyl acetate-hexane) gave 4.94 g (82%) of **11b** as white prisms, mp 208° dec; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6, 25°) δ 8.50-7.44 (bm, 5.5H), 6.28 (bs, 0.5H), 2.41-1.97 (bm, 4H), 1.22-0.76 (bm, 6H); ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6, 125°) 7.87 (s, 4H), 2.22 (s, 4H), 1.01 (s, 6H); ^{1}H nmr (300 MHz, deuteriochloroform, 25°) δ 7.94-7.87 (m, 2H), 7.77-7.70 (m, 2H), 2.27 (s, 4H), 1.04 (s, 6H); ms: (EI, 70 eV) m/z (relative intensity) 300 (85), 167 (35), 83 (100).

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.02; H, 5.31.

(6aα, 11β)-3,5,6a,11-Tetrahydro-11-hydroxy-2,4-dimethyl-5-oxoindeno[2',1':4,5]furo[3,4-*c*]pyridine-1-carboxylic Acid Methyl Ester (**12**).

A 13.8 g (50.0 mmoles) quantity of **3** was slurried with 200 ml of methanol, 50 ml of acetic acid and 0.5 g of 5% palladium on carbon and treated with hydrogen gas in a Parr shaker at 60 psi for 15 hours. A 0.5 g quantity of fresh catalyst was added and the reduction was continued for an additional 7 hours with a heating lamp aimed at the shaker. The resulting pale green solution with suspended catalyst was filtered through celite and the filtrate was concentrated. The residue was slurried with ether and filtration removed 4.77 g (29%) of crude **12** as a yellow solid. Recrystallization of this solid was effected by dissolution in 2 l of absolute ethanol and concentration to less than 500 ml. The white, microcrystalline solid was collected to give 1.30 g (8%) of pure **12**, mp 314-315°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 9.45 (bs, 1H, exchangeable, NH), 7.47-7.30 (m, 4H, Ar), 5.47 (s, 1H, H-6a), 5.32 (d, 1H, J = 6.7 Hz, exchangeable, OH), 4.47 (d, 1H, J = 6.7 Hz, H-11), 3.19 (s, 3H, OCH_3), 2.29 (s, 3H, 2-CH_3 or 4-CH_3), 2.26 (s, 3H, 2-CH_3 or 4-CH_3); ^{13}C nmr (75 MHz, dimethyl sulfoxide-d_6): δ 169.4 (C-5), 166.5 (ester carbonyl), 145.7 (C-6b), 145.4 (C-2 or C-4), 144.6 (C-2 or C-4), 141.4 (C-10a), 128.7 (Ar CH), 128.0 (Ar CH), 125.4 (Ar CH), 124.8 (Ar CH), 101.5 (C-1 or C-4a), 96.1 (C-1 or C-4a), 87.3 (C-6a), 85.9 (C-11), 52.0 (C-11a), 50.1 (OCH_3), 18.4 (2-CH_3 or 4-CH_3), 14.5 (2-CH_3 or 4-CH_3); ir (potassium bromide): 1710, 1678, 1492, 754 cm^{-1}; ms: (EI, 70 eV) m/z (relative intensity) 327 (30), 282 (50), 268 (100), 165 (39).

The following solvents (crystal forms) were employed to produce crystals suitable for X-ray crystallography: diglyme (fluffy white needles); 2-methoxyethanol, dilute (small prisms); 2-methoxyethanol, concentrated (small prisms and prism clusters); and methanol (large, clear prisms). The crystals from methanol,

mp 319-321°dec were chosen for X-ray crystallography.

Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.20; H, 5.33; N, 4.31.

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[12] Since Yalpani and Wilke [8] report an mp of 106-107° for their desilylated adduct of ninhydrin (**1**) with the *bis*-*O*-trimethylsilyl derivative of 2,4-pentanedione, we presume that their structure is isomeric with adduct **7**.