Synthetic Studies of Laurencin and Related Compounds. IV.[1] Synthesis of *cis*-2-Ethyl-8-formyl-3,4,7,8-dihydro-2*H*-oxocin-3-one 3-Ethylene Acetal and Related Compounds

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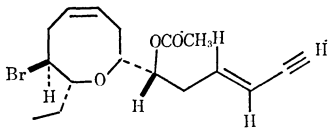
The synthesis of *cis*-2-ethyl-8-formyl-3, 4, 7, 8-dihydro-2*H*-oxocin-3-one and its derivatives, key intermediates for synthesis of laurencin, from methyl 2-ethyl-2,5-dihydro-2-furoates is described. The structure and configuration of these compounds and the synthetic intermediates are defined clearly on the basis of the chemical and spectral evidence.

Laurencin[2] (**1**) and related compounds are a group of naturally occurring halogeno compounds with (a) medium-sized ether ring(s) as well as an enyne moiety, and the structure and configuration have been established well.[3] In recent communications[1,4] we reported the synthesis of the title compound (**2**) and its transformation into (±)-laurencin. The present paper describes details of the synthesis of the key intermediate (**2**) and related compounds.



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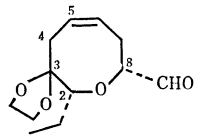

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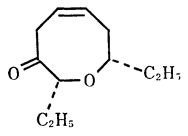
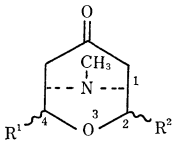
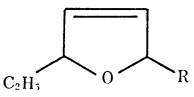


3a *cis*
3b *trans*

The synthesis of *cis*-2-ethyl-8-formylhydrooxocinone ethylene acetal (**2**) and related compounds was carried out in an analogous manner to that of the corresponding *cis*- and *trans*-2,8-diethylhydrooxocinones[5] (**3a** and **3b**), and hence required preparation of 4-ethyl-2-formyl-9-methyl-3-oxa-9-azabiocyclo[3.3.1]nonan-7-ones or their synthetic equivalents, *e.g.*, 2-acetoxymethyl-4-ethyloxaazabicyclononanones (**4**). These relevant intermediates were finally prepared by the Robinson-Schöpf condensation as described below.

The Birch reduction of 5-ethyl-2-furoic acid followed by esterification produced a 1:1 mixture of methyl *cis*- and *trans*-5-ethyl-2,5-dihydro-2-furoates[6] (**5**), which were reduced with lithium aluminium hydride to give the corresponding alcohols (**6**) in good yield. The alcohols (**6**) were submitted to ozonolysis at −70 °C in methanol, and the resulting dialdehyde mixture was immediately treated with methylamine and acetonedicarboxylic acid under the Robinson-Schöpf conditions (room temp, pH 5, 2 d). Total basic products were treated with acetic anhydride in pyridine and then purified by chromatography, giving a 3:2:1 mixture of the relevant oxaazabicyclononanones (**4a**, **4b**, and **4c**) in 7.8% yield from **6**. Further purification by column chromatography and subsequent preparative TLC effected isolation of each stereoisomer (**4a**), mp 76—78 °C, (**4b**), oil, and (**4c**), oil, in 2.2, 0.4, and 0.2% yields, respectively. In accordance with the assigned (planar) structure, each compound had the same molecular formula $C_{13}H_{21}O_4N$, and displayed ester and ketone carbonyl bands near 1730 and 1710 cm^{-1} and the same fragmentation peaks at *m/e* 225 (M^+), 196, 138, 111, and 110 in the IR and mass spectra. The configuration in question of these bicyclononanones was elucidated on the basis of the NMR spectra, which are summarized in Table 1 with those of the related compounds, 2-(acetoxymethyl)-oxaazabicyclononanones (**7a** and **7b**) (*cf.*, Experimental).





4a R^1=···C_2H_5, R^2=···CH_2OAc
4b R^1=···C_2H_5, R^2=—CH_2OAc
4c R^1=—C_2H_5, R^2=···CH_2OAc
7a R^1=H, R^2=···CH_2OAc
7a′ R^1=H, R^2=···CH_2OH
7b R^1=H, R^2=—CH_2OAc
7b′ R^1=H, R^2=—CH_2OH
8 R^1=R^2=H
9a R^1=R^3=···C_2H_5
9b R^1=···C_2H_5, R^2=—C_2H_5

5 R=$COOCH_3$ (*cis* and *trans*)
6 R=CH_2OH (*cis* and *trans*)

As shown in Table 1, all compounds (**4a—4c**, **7a** and **7b**) revealed the following coupling constants; $J_{1,8a}=J_{5,6a}=6$ Hz and $J_{1,8e}=J_{5,6e}\fallingdotseq 0$ Hz. These constants indicated that the dihedral angles between the proton at C_1 (C_5) and the equatorial and axial protons at C_8 (C_6) would be about 90 and 30°, respectively. Judging from these values as well as the previous result,[5,7] the piperidone ring would exist as a slightly deformed chair form. On the other hand, the coupling constants $J_{1,2e}$, $J_{1,2a}$, $J_{5,4e}$, and $J_{5,4a}$ were small for these compounds. Such constants were also observed in the NMR spectra of several 3-oxabi-

cyclo[3.3.1]nonane derivatives,[8] which also adopt a double-chair conformation. The spectral similarity between these compounds, coupled with our previous result on the conformation of 9-methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-one (**8**) and its 2,5-diethyl derivatives[5] (**9a** and **9b**), indicated that all the compounds would probably take a double-chair conformation. This assignment was confirmed by the X-ray crystallographic analysis of 2-acetoxymethyl-4-ethyloxaazabicyclononanone (**4a**),[9] one of the most important key compound; namely, in spite of the presence of 2,4-diaxial substitutents, the compound (**4a**) exists in the double-chair conformation, as illustrated in Fig. 1.

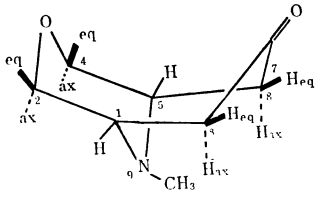


Fig. 1.

Stereochemistry of the substituent(s) at C_2 and/or C_4 in compounds **4b**, **4c**, **7a**, and **7b** was deduced from the chemical shift and signal pattern of the ethyl methylene and acetoxymethyl methylene protons. Signals due to the acetoxymethyl methylene protons of **4a**, **4b**, and **7a** were very similar each other; two double doublets (one with J=11 and 5—6 Hz and another with J=11 and 7.5—8 Hz, *cf*, Table 1) appeared at δ 4.38 and 4.18, at δ 4.69 and 4.22, and at δ 4.68 and 4.23, respectively. To the contrary, the corresponding protons of **4c** and **7b** were observed as broad singlets at higher field, δ 4.00 and 3.98, respectively. The striking difference in chemical shift and splitting pattern indicates that the acetoxymethyl methylene protons of the former three oxaazabicyclononanones (**4a**, **4b**, and **7a**) are disposed 1,3-diaxially with the nitrogen lone pair electrons[10] and free rotation of the acetoxymethyl group would be hindered. The same discussion holds for the ethyl groups of compounds **4a**—**4c**, **9a**, and **9b**; absorption peaks due to the ethyl methylene protons of **4a**, **4c**, and **9a** were observed at lower field than δ 1.58, while those of **4b** and **9b** at higher field than δ 1.40. In summary, all the compounds in Table 1 are represented by the respective assigned configurations and conformations, which would be interpreted well as the result of interaction between the ether oxygen and carbonyl carbon atoms.[11]

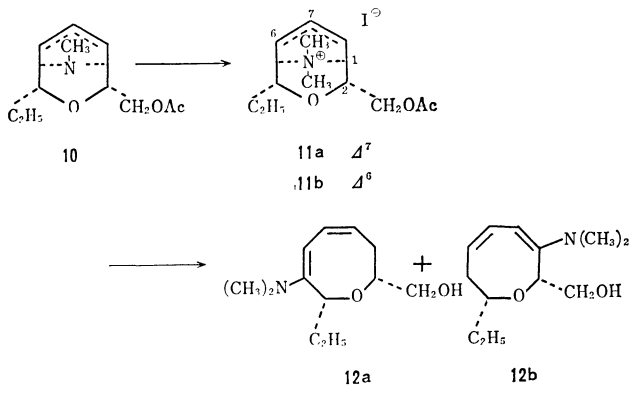
Treatment of *cis*-2-acetoxymethyl-4-ethyloxaazabicyclononanone (**4a**) with tosylhydrazine in acidic tetrahydrofuran under reflux and then with methyllithium in benzene and ether[12] produced olefinic alcohols (**10**), which were converted into a crystalline mixture of methiodides (**11a** and **11b**) in good yield. The methiodides, when eluted through Amberlite IRA-400 and then heated at 60—80 °C, underwent the Hofmann elimination with concurrent facile 1,5-sigmatropic hydrogen transfer to give a mixture of dienamines (**12a** and **12b**). The dienamine mixture, without isolation, was hydrolyzed in 7% fluoroboric acid under reflux to yield a mixture of keto alcohols (**13a** and **13b**), which were purified by column chromatography to give **13a** and **13b** in pure state in 32

TABLE 1. THE NMR SPECTRA OF 9-METHYL-3-OXA-9-AZABICYCLO[3.3.1]NONAN-7-ONES[a]

Proton	Chemical shifts (δ)[b] Compounds **4a**	**4b**	**4c**	**7a**	**7b**	J	Coupling constans (Hz)[c,d] Compounds **4a**	**4b**	**4c**	**7a**	**7b**
H_1	3.12 br d	3.06 br d	3.10 br d	3.08 br d	3.10 br d	$J_{1,2e}$	1.5	0.5	—	0.0	—
H_5	3.06 d	2.99 m	3.04 br d	3.08 br d	3.10 br d	$J_{5,4e}$	0.0	—	0.5	0.0	0.5
H_{2e}	3.69 br do d	3.83 br do d	—	3.80 do d	—	$J_{1,2a}$	—	—	1.0	—	0.5
H_{4e}	3.39 t	—	3.56 do d	3.51 d	3.78 br d	$J_{5,4a}$	—	1.0	—	2.0	1.0
H_{2a}	—	—	4.00 m	—	3.98 m	$J_{1,8e}$	0.0	0.5	0.0	0.0	0.0
H_{4a}	—	3.80 br m	—	4.03 br d	3.89 br d	$J_{5,6e}$	0.0	1.5	0.0	0.0	0.0
H_{6e}	2.18 d	2.23 d	2.19 d	2.20 d	2.16 br d	$J_{1,8a}$	6.0	6.0	6.0	6.0	6.0
H_{8e}	2.18 d	2.17 d	2.19 d	2.20 d	2.24 br d	$J_{5,6a}$	6.0	6.0	6.0	6.0	6.0
H_{6a}	2.80 do d	2.55 do d	2.75 do d	2.53 do d	2.72 do d	$J_{2,H}$	8	8	small	8	small
							5	6		5	
CH_3CH_2	1.70 qui	1.38 m	1.58	—	—	$J_{1,H}$	7		8		
							7		6	—	—
CH_2OAc	4.38 do d	4.69 do d	4.00 br s	4.68 do d	3.98 br s						
	4.18 do d	4.22 do d		4.23 do d							

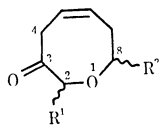
a) The spectra were measured in $CDCl_3$ at 100 MHz, and the abbreviations "H_{2e} and $J_{1,2e}$" refer to "equatorial proton at C_2 and coupling constant between H_1 and H_{2e}," respectively. b) The chemical shifts of N-CH_3 (s), acetoxyl methyl (s) and ethyl methyl protons (t, J=6.5—7.0 Hz) fell within δ 2.49—2.61, 2.02—2.05, and 0.85—0.93, respectively. c) The coupling constans were estimated by first-order approximations. d) The geminal couplings followed as: $J_{6a,6b}$ and $J_{8a,8e}$ were 15—16 Hz for all compounds, $J_{4a,4e}$ 11—11.5 Hz for **7a** and **7b**, and J_{AB} (CH_AH_BOAc) 11 Hz for **4a**, **4b**, and **7a**, respectively.

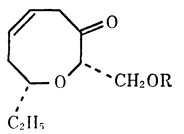
and 13% yields (from the total methiodides), respectively. The structure of these ketones was assigned on the basis of the spectral data.



10 11a Δ^7 11b Δ^6 12a 12b

Compound **13a**, $C_{10}H_{16}O_3$ [MS, *m/e* 184 (M^+)], exhibited absorption maxima at 294 nm (ε 147, sh), 303 (173), 312 (161), and 323 (84, sh) with enhanced intensity due to the n-π^* transition, characteristic for β,γ-unsaturated carbonyl chromophores, and those at 3480 (OH), 1720 (C=O), and 1645 (C=C) cm^{-1} in the UV and IR spectra, respectively. Compound **13b** also displayed essentially the same mass, UV, and IR spectra as **13a**, indicating both the compounds to be isomers. The NMR spectra, coupled with the spin decoupling studies, provided definite evidence for disposition of the carbonyl groups in both the compounds (**13a** and **13b**). In the spectrum of **13a**, a double doublet (J=5 and 7 Hz) at δ 3.82 [C_2H_5-CH(O)–] was simplified to a singlet on irradiation at δ 1.70 (CH_3CH_2–), but remained unchanged on that near δ 2.3 (–CH_2CH=CH–). On the other hand, a double double doublet (J=2, 6, and 12 Hz) at δ 3.40 [C_2H_5CH(O)–] in the spectrum of **13b** was collapsed to a broad doublet (J=6 Hz) and to a double doublet (J=6 and 12 Hz) on irradiation at δ 1.62 (CH_3CH_2–) and near δ 2.3 (–CH_2CH=CH–), respectively. The result reveals the presence of partial formulas $C_2H_5\overset{1}{C}H(-O-)C(=O)-$ and $C_2H_5\overset{1}{C}H-O-CH_2CH=CH-$ in **13a** and **13b**, respectively, confirming the assigned structures.



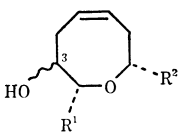


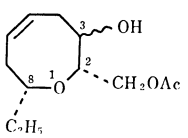
13a R^1=···C_2H_5, R^2=—CH_2OH
15a R^1=···C_2H_5, R^2=—CH_2OAc
13c R^1=—C_2H_5, R^2=···CH_2OH
14a R^1=R^2=···C_2H_5
14b R^1=···C_2H_5, R^2=—C_2H_5

13b R=H
15b R=Ac

Repetition of the aforementioned sequence on a 2:2:1 mixture of the oxaazabicyclononanones (**4a**, **4b**, and **4c**), free from pure **4a**, led to formation of a mixture of β,γ-unsaturated ketones, from which compounds **13a** and **13b** and a new compound (**13c**) were isolated in 6, 3, and 2% yields, respectively. The compound (**13c**) revealed essentially the same mass, UV, and IR spectra as **13a**, and also exhibited two characteristic double doublets (one with J=14 and 4 Hz and another with J=14 and 2 Hz) at δ 3.08 and 3.44 in the NMR spectrum. These signals are corresponding to the following peaks due to the C_4-protons of **13a**, *cis*- and *trans*-2,8-diethyltetrahydrooxocins[5] **14a** and **14b**: **13a**, δ 2.82 and 3.86 (each J=12 and 6 Hz); **14a**, δ 2.77 and 3.82 (each J=13 and 6 Hz); **14b**, δ 2.93 and 3.52 (J=16, 3 and 16, 2 Hz).[5] The spectral similarity indicated that the new compound (**13c**) would be a stereoisomer of **13a**. Indeed, compound **13c** was converted by treatment with base under mild conditions into **13a** quantitatively. The low yields of these unsaturated ketones would result from difficult separation of the products and also incomplete 1,5-hydrogen transfer in aminodienes (to dienamines corresponding to **12** derived from the *trans*-oxaazabicyclononanones (**4b** and **4c**).

Before proceeding with the synthesis, we examined the stereochemistry of reduction of the carbonyl group of the tetrahydrooxocinones. Compound **13a** was converted into the acetate (**15a**), which on treatment with sodium borohydride gave hydroxy acetate (**16**) in 60% yield as an isolable main product. The compound (**16**) showed a double doublet (J=12 and 8 Hz) at δ 2.62 in the NMR spectrum, which was attributed to one of the C_4-protons. In view of the different signal pattern due to the corresponding proton of laurencin (**1**) (δ 3.2, do do d, J=3, 7, and 13 Hz),[2] the alcohol (**16**) was suggested to possess all *cis*-configuration concerning the substituents at C_2, C_3, and C_8. In order to ascertain this assignment, the isomeric *cis*-2-hydroxymethyl-8-ethyltetrahydrooxocinone (**13b**) was likewise converted into the acetate (**15b**) and then reduced with the hydride reagent to give a 1:1 mixture of new hydroxy acetates (**17a** and **17b**), which could be isolated by column chromatography. The NMR spectrum of more polar alcohol (**17b**) revealed two characteristic peaks at δ 2.81 (do do d, J=3, 7, and 13 Hz) and 3.80 (do t, J=9, 3, and 3 Hz), which were ascribed to one of the C_4-protons and a proton on the carbon (C_3) bearing the hydroxyl group, respectively. These absorption patterns were practically the same as those of the corresponding protons (do do d, J=3, 7, and 13 Hz, and do t, J=9, 3, and 3 Hz)[2] of laurencin (**1**). On the other hand, the relevant proton at C_4 of less polar alcohol (**17a**) appeared at δ 2.64 as a double doublet (J=12 and 8 Hz) in the spectrum. All these splitting patterns, combined with the previous result [the C_4-proton in question of two reduction products, major (**18a**) and minor (**18b**), from *cis*-diethyltetrahydrooxocinone (**14a**) [δ 2.63 (do d, J=8 and 12 Hz) for **18a**, and δ 2.82 (do do d, J=3, 7, and 13 Hz) for **18b**][5] indicate that all-cis assignment to the three substituents at



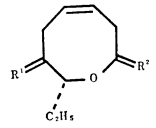


16 R^1=C_2H_5, R^2=CH_2OAc, 3α-OH
18a R^1=R^2=C_2H_5, 3α-OH
18b R^1=R^2=C_2H_5, 3β-OH

17a 3α-OH
17b 3β-OH

C_2, C_3, and C_8 of alcohol **16** is correct. The predominant formation of all-*cis*-substituted alcohol (**16**) would be convenient for substitution of the hydroxyl group to a bromine atom with the desired configuration by triphenylphosphine and carbon tetrabromide, because the bromination usually proceeds in S_N2 manner.[13]

Compound **13a** was transformed into several derivatives including the title compound (**2**). Acetalization of **13a** under usual conditions gave the ethylene acetal (**19**) in quantitative yield. The NMR spectrum revealed two double doublets (each J=13 and 8 Hz) due to the C_4-protons at δ 2.89, indicating that the double bond at C_5 and C_6 did not migrate during the reaction. Oxidation of **19** with chromium(VI) oxide and pyridine in dichloromethane[14] afforded crystalline aldehyde, the title compound (**2**), mp 73—74 °C, in quantitative yield, whose spectra were completely consistent with the assigned structure. On the other hand, treatment of **2** with 1 equiv of 1,2-ethanedithiol in the presence of boron trifluoride in dichloromethane resulted in thioacetalization with concomitant hydrolysis of the acetal group at C_3 to give monothioacetal (**20**), showing a β,γ-unsaturated carbonyl band at 1720 cm^{-1} in the IR spectrum. The compound (**20**) also exhibited two double doublets (each J=13 and 6 Hz) due to the relevant C_4-protons at δ 2.86 and 3.82, indicative of retention of the relative configuration of the substituents at C_2 and C_8.[5] The same treatment of **2** with 2 equiv of ethanedithiol led to formation of bis(dithioacetal) (**21**), while the mono(dithioacetal) (**20**) was converted into acetal dithioacetal (**22**), showing two double doublets (each, J=13 and 9 Hz) at δ 2.15 and 2.89 in the NMR spectrum. All these compounds (**2**, **20**—**22**) possess all functional groups convertible into those of laurencin (**1**), and hence the present result implies the synthesis of most appropriate intermediates leading to the natural product (**1**) as described in the following paper.



2 R^1=OCH_2CH_2O, R^2=—H, ···CHO
19 R^1=OCH_2CH_2O, R^2=—H, ···CH_2OH
20 R^1=O, R^2=—H, ···CH(S—)(S—)
21 R^1=SCH_2CH_2S, R=—H, ···CH(S—)(S—)
22 R^1=OCH_2CH_2O, R^2=—H, ···CH(S—)(S—)

Experimental

All the mps and bps were uncorrected. The homogeneity of each compound was always checked by TLC over silica gel (Wakogel B-5) and/or GLC (Hitachi K-53) over 10% SE-30. Column chromatography was carried out over silicic acid (Merck, Kieselgel 60, 70—230 mesh) and/or alumina (Merck, standard, Active I and II—III). The UV, IR, and NMR (100 MHz) spectra were measured in 2,2,4-trimethylpentane, in liquid state, and in chloroform-*d*, respectively, unless otherwise stated. The abbreviations "s, d, t, q, qui, m, br, do, and sh," in the NMR and IR spectra denote "singlet, doublet, triplet, quartet, quintet, multiplet, broad, double, and shoulder," respectively.

5-Ethyl-2,5-dihydrofurfuryl Alcohols (6). To a stirred slurry of lithium aluminum hydride (LAH, 6 g) in anhydrous ether (1.2 l) at 0 °C was added dropwise a solution of methyl 5-ethyl-2,5-dihydro-2-furoates[6] (**5**, 28 g) in ether (200 ml). The mixture was stirred at room temperature for 20 h, cooled, mixed with water (7.5 ml), 30% aq sodium hydroxide (7.5 ml) and then water (7.5 ml). The resulting inorganic salts were removed by filtration, and the filtrate was dried over anhydrous sodium sulfate and evaporated to leave oil, which was distilled to give **6** (11.3 g), bp 72—73 °C/15 Torr; MS, *m/e* 128 (M^+) and 99: IR (CCl_4), ν_{max} 3410, 1075, and 1030 cm^{-1}; NMR, δ 0.90 and 0.91 (total 3H, each t, J=7 Hz, CH_3CH_2), 1.57 (2H, qui, J=7 Hz, CH_3CH_2), 3.45 (1H, br, OH), 3.57 (2H, br s, CH_2OH), 4.85 (2H, m, 2H at C_2 and C_5), 5.78 and 5.91 (2H, ABq, J=6 Hz, 2H at C_3 and C_4). Found: C, 65.59; H, 9.47%. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44%.

(2R,4R)-, (2S,4R)-, and (2R,4S)-2-Acetoxymethyl-4-ethyl-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-ones (4a, 4b, and 4c). Into a solution of **6** (29 g) in methanol (300 ml) or dichloromethane (300 ml) containing three drops of pyridine, cooled at −70 °C in a Dry Ice-ethanol bath, was passed ozonized oxygen gas, until the reaction mixture became blue. The mixture, while still at −70——60 °C, was flushed with nitrogen for 10 min, when the blue color disappeared. After addition of dimethyl sulfide (20 ml) at the temperature, the mixture was stirred at −70——30 °C for 30 min, then at ice-bath temperature for 2 h, and finally at room temperature for 1 h, and evaporated below 45 °C to leave oily residue containing dimethyl sulfoxide, which was treated with 25% aq acetic acid (40 ml) under reflux for 45 min and cooled to room temperature. To the solution was immediately added an aqueous solution (300 ml) containing sodium monohydrogenphosphate (4.25 g) and potassium dihydrogenphosphate (2.43 g), acetonedicarboxylic acid (36 g) and methylamine hydrochloride (16 g). The whole solution was adjusted to pH 5 with 6 M aq sodium hydroxide and stirred at room temperature for 2 d, the pH being maintained at 5.0 by occasional addition of citric acid. The solution was concentrated under reduced pressure to one-half of the volume, made acidic strongly by addition of concd hydrochloric acid and washed with ether (2×200 ml). The acidic aqueous solution was then made strongly basic with concd aq potassium hydroxide and extracted with chloroform (4×300 ml). The chloroform solutions were combined, dried and evaporated to leave oil (17.3 g). The oil was passed through a short alumina column (Merck, Active II—III, 60 g, benzene) to give oil (11.8 g), which was treated with acetic anhydride (48 g) and pyridine (120 ml). The resulting acetate mixture (14 g) was again passed through a short alumina column (45 g) to give oily basic material (12.3 g), which was purified by chromatography over silica gel (Merck, 250 g, benzene : acetone = 10 : 1) to yield a 3 : 2 : 1 mixture (3.55 g) of **4a**, **4b**, and **4c** (estimated by measurement of the NMR signals due to the C_2-protons). The mixture was further chromatographed over silica gel to give crystalline base, which was recrystallized from ether to yield **4a** (1.0 g), mp 76—78 °C. This was recrystallized from ether for analysis, mp 77—78.5 °C; mass (the text); IR (Nujol), ν_{max} 1730, 1710, 1240, 1160, and 1038 cm^{-1}; NMR (Table 1). Found: C, 60.98; H,

8.36; N, 5.51%. Calcd for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29; N, 5.49%.

A part (700 mg) of the residual oil (a 2 : 2 : 1 mixture of **4a**, **4b**, and **4c**), free from pure **4a**, was separated into two fractions by repeated preparative TLC over silica gel (benzene : acetone = 9 : 1). Fractions (100 mg) with higher R_f value gave **4b** (95 mg), oil, showing a single spot; MS (the text), IR, ν_{max} 1730, 1710, 1240, 1160, and 1038 cm^{-1}; NMR (Table 1). Found: C, 61.28; H, 8.10; N, 5.31%. Calcd for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29; N, 5.49%. Fractions (520 mg) with lower R_f value were again purified by repeated preparative TLC (benzene : acetone = 9 : 1) to give **4c** (40 mg), oil, showing a single spot; MS (the text); IR, ν_{max} 1743, 1712, 1240, 1160, and 1038 cm^{-1}; NMR (Table 1). Found: C, 60.99; H, 8.32; N, 5.61%. Calcd for $C_{13}H_{21}O_4N_4$: C, 61.15; H, 8.29; N, 5.49%.

2,5-Dihydrofurfuryl Alcohol. To suspension of ether (1 l) and LAH (4.7 g) was added dropwise methyl 2,5-dihydro-2-furoate (20 g) in ether (100 ml). The mixture was allowed to stir overnight and then refluxed for 2 h. To the mixture were added water (5 ml), 30% aq sodium hydroxide (5 ml) solwly. After removal of the resulting inorganic salts by filtration, the filtrate was evaporated to leave oil, which was distilled to give the alcohol (11.3 g), bp 51—52 °C/15 Torr; MS, *m/e* 83 ($M^+ - CH_2OH$); IR (CCl_4), ν_{max} 3400, 1090, and 1040 cm^{-1}; NMR, δ 3.12 (1H, br s, OH), 3.45 (2H, m, CH_2OH), 4.56 (2H, m, H at C_5), 4.70 (1H, m, H at C_2), 5.74 and 5.90 (2H, ABq, J=6.5 Hz, 2H at C_3 and C_4). Found: C, 59.87; H, 8.00%. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05%.

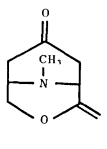
2-Acetoxymethyl-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-ones (7a and 7b). Into a solution of 2,5-dihydrofurfuryl alcohol (11.3 g) and two drops of pyridine in dichloromethane (400 ml), cooled at −60—−70 °C, was passed ozonized oxygen, and the resulting blue reaction mixture was flushed with nitrogen at the temperature for 15 min. After addition of dimethyl sulfide (10 ml) at −60 °C, the mixture was stirred at −10 °C for 1 h, then at ice-bath temperature for 1 h and, finally, at room temperature for 1 h, washed with water (2×50 ml) and dried over sodium sulfate. No reaction product was obtained after removal of the dichloromethane. The aqueous washings were mixed with an aqueous solution (1.8 l) containing sodium monohydrogenphosphate (25.6 g), potassium dihydrogenphosphate (15 g), methylamine hydrochloride (26.4 g) and acetonedicarboxylic acid (53.2 g). The whole solution was adjusted to pH 5 by addition of 40% aq sodium hydroxide, and then stirred at room temperature for 2 d, the pH being maintained at 5.0 by occasional addition of citric acid. After being concentrated to one-half of the volume, the solution was made strongly acidic by addition of concd hydrochloric acid and washed with ether 2×200 ml). The aqueous solution was then made basic strongly with concd aq potassium hydroxide and extracted continuously with chloroform (1.6 l) for 48 h. The chloroform solution was washed with water, dried and evaporated to give oily residue (34.1 g), showing several spots on TLC (benzene : acetone = 3 : 1). The residue was separated into two fractions by column chromatography over alumina (500 g, benzene : methanol = 60 : 5). Early fractions, eluted with benzene, gave 2-methylene-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (**23**, 9.3 g), oil, showing a single spot on TLC; MS, *m/e* 167 (M^+), 124, and 110; IR, ν_{max} 1710, 1660, 1130, 1070, 1020, and 915 cm^{-1}; NMR, δ 2.34 and 2.40 (each 1H, br d, J=16 Hz, H_{8e} and H_{6e}), 2.60 (3H, s, NCH_3), 2.78 and 2.82 (each 1H, do d, J=16 and 6 Hz, H_{6a} and H_{8a}), 3.12 and 3.48 (each 1H, br d, J=6 Hz, H_5 and H_1), 3.80 and 4.19 (each 1H, br d, J=11 Hz, 2H at C_4), 4.25 and 4.50 (each 1H, ABq, J=9 Hz, CH_2=C_2). Rechromatography of the oil under the same conditions afforded an analytical sample of **23**. Found: C, 64.65; H, 7.84; N, 7.83%. Calcd for $C_9H_{13}O_2N$: C, 64.85; H, 8.07; N, 7.03%.

Later fractions, showing two major spots on TLC (benzene : acetone = 3 : 1), gave oily substance (7.3 g), which was treated with acetic anhydride (30 ml) and pyridine (50 ml) at room temperature for 24 h. The acetates (7.8 g) were separated by chromatography over silica gel with benzene and acetone (9 : 1) to yield crystalline acetate (**7a**, 1.12 g), mp 105.5—108 °C, as an initial eluate. Recrystallization from hexane and ethanol gave an analytical sample of **7a**, mp 108—109 °C; MS, *m/e* 227 (M^+), 168, 124, and 110; IR ($CHCl_3$), ν_{max} 1730, 1710, and 1230 cm^{-1}; NMR (Table 1). Found: C, 57.83; H, 7.50; N, 6.14%. Calcd for $C_{11}H_{17}O_4N$: C, 58.13; H, 7.54; N, 6.16%. Oily acetate (**7b**), showing a single spot on TLC, was then eluted and purified by rechromatography to give an analytical sample of **7b**; MS, *m/e* 227 (M^+), 168, 124, and 110; IR ($CHCl_3$), ν_{max} 1730, 1710, and 1220 cm^{-1}; NMR (Table 1). Found: C, 57.83; H, 7.50; N, 6.14%. Calcd for $C_{11}H_{17}O_4$: C, 58.13; H, 7.54; N, 6.16%.

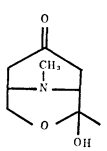
Acetates **7a** and **7b** were converted into the corresponding alcohols (**7a′** and **7b′**) by the method described below. To an ice-cooled solution of **7a** (280 mg) in ethanol (25 ml) was added sodium borohydride (NBH, 50 mg), and the mixture was stirred for 4 h at 0 °C. After addition of acetic acid (100 mg) and one drop of concd hydrochloric acid to decompose excess of NBH, the mixture was concentrated, made basic with aq sodium hydroxide and extracted with chloroform (2×40 ml). The chloroform solution was worked up as usual to give **7a′** (168 mg), which crystallized on trituration with ether and then recrystallized from ether to yield an analytical sample of **7a′**, mp 100—102 °C; MS, *m/e* 185 (M^+), 154, 128, and 110; IR ($CHCl_3$), ν_{max} 3330, 1710, 1100, and 1060 cm^{-1}; NMR, δ 2.26 (2H, d, J=15 Hz, H_{8e} and H_{6e}), 2.60 (3H, s, NCH_3), 2.75 and 2.80 (each 1H, do d, J=15 and 6 Hz, H_{6a} and H_{8a}), 3.58 (1H, d, J=11 Hz, H_{4e}), 3.65 (1H, do d, J=4 and 6 Hz, H_{2e}), 3.87 and 4.15 (each 1H, do d, J=4, 12 and 6, 12 Hz, CH_2OH), and 4.23 (1H, br d, J=11 Hz, H_{4a}). Found: C, 58.11; H, 8.23; N, 7.43%. Calcd for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56%.

The isomeric acetate (**7b**, 240 mg) was converted into the alcohol (**7b′**, 130 mg), oil, in the same manner as described above, and showed the following spectra; MS, *m/e* 185 (M^+), 154, 128, and 110; IR ($CHCl_3$), ν_{max} 3330, 1710, 1100, and 1060 cm^{-1}; NMR, δ 2.22 and 2.25 (each 1H, br d, J=15 Hz, H_{6e} and H_{8e}), 2.62 (3H, s, NCH_3), 2.67 and 2.71 (each 1H, do d, J=15 and 6 Hz, H_{6a} and H_{8a}), 3.13 (2H, br d, J=6 Hz, 2H at C_1 and C_5), 3.60 (3H, m, H_{2a} and CH_2OH), 3.79 and 3.93 (each 1H, br d, J=11 Hz, H_{4e} and H_{4a}).

2-Hydroxy-2,9-dimethyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one



23



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(24). This compound was isolated in one run of the preceding Robinson-Schöpf condensation experiments, and the structure was confirmed by the hydration of **23** described below. Compound **23** (90 mg) in chloroform (30 ml) was treated with concd hydrochloric acid (2 ml) at room temperature for 20 min. After removal of the chloroform and subsequent addition of water (5 ml), the resulting aqueous solution was made basic with 6 M aq sodium hydroxide and extracted with chloroform (2×20 ml). The chloroform solution was worked up as usual to give crystalline alcohol (**24**, 71 mg), mp 97—99 °C; MS, *m/e* 185 (M^+) and 142; IR ($CHCl_3$), ν_{max} 3420, 1715, 1070, 1020, and 915 cm^{-1}; NMR, δ 1.30, (3H, s, $C\underline{H}_3$ at C_2), 2.19 (2H, br d, J=15 Hz $\underline{H}_{8e}$ and $\underline{H}_{6e}$), 2.52 and 2.63 (each 1H, br do d, J=15 and 6 Hz, $\underline{H}_{6a}$ and $\underline{H}_{8a}$), 2.55 (3H, s, $NC\underline{H}_3$), 2.99 (1H, d, J=11 Hz, $\underline{H}_{4e}$), 4.12 (1H, do do d, J=1, 2.5, and 11 Hz, $\underline{H}_{4a}$), and 4.95 (1H, br, O$\underline{H}$). An analytical sample of **24** was prepared by recrystallization from ether and hexane, mp 100—101 °C. Found: C, 58.14; H, 8.19; N, 7.69%. Calcd for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56%.

cis-*3-Ethyl-2-hydroxymethyl-9-methyl-3-oxa-9-azabicyclo*[*3.3.1*]-*nonenes (10).* A solution of **4a** (2.98 g) and tosylhydrazine (3.64 g) in THF (70 ml) containing a few drops of concd hydrochloric acid was heated under reflux for 12 h in a three-necked flask, fitted with a condenser and a magnetic stirring bar. After addition of benzene (250 ml) and removal of the condenser, the solution was concentrated to 70—80 ml, when the temperature of distillates had became near 80 °C, and then cooled in an ice-bath. To the concentrated solution was slowly added a solution of methyllithium, prepared from lithium (2.0 g) and methyl iodide (13 ml), in ether (210 ml). The whole mixture was stirred at room temperature for 20 h, and then washed with water. The aqueous washings were extracted with chloroform. All the organic (ether, benzene, and chloroform) solutions were combined, dried and evaporated to leave crude olefinic alcohol (3.1 g), most of which was used for the next reaction without further purification. A part of the crude sample of **10** was purified by preparative TLC (benzene : acetone=1 : 1) to give an almost pure sample, showing the following spectra; ν_{max} 3395, 1120, 1092, 1054, and 1040 cm^{-1}; NMR, δ 0.96 (3H, t, J=7 Hz, $C\underline{H}_3$-CH_2), 1.62 (2H, m, $CH_3C\underline{H}_2$), 2.40 and 2.42 (total 3H, each s, $NC\underline{H}_3$), and 5.75 (2H, br m, W_H=7 Hz, C$\underline{H}$=C$\underline{H}$).

cis-*2-Ethyl-8-hydroxymethyl-* *and* cis-*8-Ethyl-2-hydroxymethyl-3,4,7,8-dihydro-2*H*-oxocin-3-ones (13a and 13b), and Their Acetates (15a and 15b).* 1) A solution of the crude olefinic alcohol (**10**, 3.0 g) in ethanol (80 ml) was refluxed with methyl iodide (62 ml) for 2 h and then evaporated to leave crystalline methiodides (3.65 g). Recrystallization from ethanol afforded a 1 : 8 mixture (crystals A, 1.33 g) of the methiodides (**11a** and **11b**), mp 213—124 °C, as the first crop; MS, *m/e* 197 (M^+-CH_3I), 142, 127, 108, and 94; IR (Nujol), ν_{max} 3330, 1200, 1172, 1140, 1108, 1045, and 995 cm^{-1}; NMR (D_2O), δ 1.28 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$), 2.05 (2H, m, $CH_3C\underline{H}_2$), 3.42 and 3.76 (each 3H, s, $2NC\underline{H}_3$), and 6.3 (2H, m, W_H=7 Hz, C$\underline{H}$=C$\underline{H}$). Found: C, 42.24; H, 6.56; N, 3.29; I, 37.19%. Calcd for $C_{12}H_{25}O_2NI$: C, 42.47; H, 6.48; N, 3.13; I, 37.45%.

An aqueous solution (20 ml) of crystals A (1.30 g) was passed through a column of Amberlite IRA-400 (basic form). The eluate was collected until it was no longer alkaline and evaporated under reduced pressure below 45 °C. The residual quaternary methohydroxides were decomposed by heating at 60—80 °C under reduced pressure for 45 min to give oil, which was extracted with ether (100 ml) and chloroform (100 ml). The solutions were combined, dried and evaporated to yield a 1 : 8 oily mixture (0.86 g) of *cis*-2-ethyl-8-hydroxymethyl-3-dimethylamino- and *cis*-8-ethyl-2-hydroxymethyl-3-dimethylamino-7,8-dihydro-2*H*-oxocins (**12a** and **12b**); IR, ν_{max} 3420, 1604 (dienamine), 1140, 1115, 1103, 1078, and 1043 cm^{-1}; NMR, δ 0.96 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$), 2.56 [6H, s, $N(C\underline{H}_3)_2$], 5.08 and 5.24 [total 1H (1 : 8), each d, J=4 Hz, $\underline{H}$ at C_4], 5.76 (1H, m, $\underline{H}$ at C_5), and 6.16 (1H, do d, J=4 and 10 Hz, $\underline{H}$ at C_6).

The mother liquors, obtained on removal of crystals A, were evaporated to give an 8 : 1 semi-crystalline mixture (crystals B, 2.20 g) of **11a** and **11b**, which was submitted to the same treatment as crystals A to yield an 8 : 1 oily mixtre (1.94 g) of **12a** and **12b**; IR, ν_{max} 3420, 1064 (dienamine), 1140, 1115, 1103, and 1078 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$), 1.72 (2H, m, $CH_3C\underline{H}_2$), 2.56 [6H, s, $2N(C\underline{H}_3)_2$], 5.08 and 5.24 [total 1H (8 : 1), each d, J=4 Hz, $\underline{H}$ at C_4], 5.70 (1H, m, $\underline{H}$ at C_5), and 6.18 (1H, do d, J=4 and 10 Hz, $\underline{H}$ at C_6).

2) An aqueous solution (7 ml) of the 1 : 8 mixture (0.85 g) of **12a** and **12b**, obtained from crystals A, was refluxed with 42% fluoroboric acid (1.5 ml) for 15 min. The reaction mixture was cooled, neutralized with saturated aq sodium hydrogencarbonate, and extracted with ether (2× 100 ml) and dichloromethene (2×200 ml). The combined organic solution was dried and evaporated to leave oil (601 mg), showing two spots on TLC (benzene : ethyl acetate=3 : 1). The oil was separated roughly into three fractions by column chromatography over silica gel (20 g, benzene : ethyl acetate=7 : 1). More mobile fractions gave **13b** (180 mg), oil, showing a single spots; MS, *m/e* 184 (M^+), 155, and 125; UV, λ_{max} 304 nm (ε 132) (sh), 312 (165), 321 (161), and 332 (95) (sh); IR; ν_{max} 3480, 1718, 1642, 1115, and 1055 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$), 1.62 (2H, m, $CH_3C\underline{H}_2$), 2.40 (3H, m, 2$\underline{H}$ at C_7 and O$\underline{H}$), 2.86 and 3.96 (each 1H, do d, J=12 and 6 Hz, 2$\underline{H}$ at C_4), 3.40 (1H, do do d, J=12, 6, and 2 Hz, $\underline{H}$ at C_8), 3.80 (2H, m, $C\underline{H}_2$OH), 4.00 (1H, do d, J=5 and 7 Hz, $\underline{H}$ at C_2), and 5.70 (2H, m, 2$\underline{H}$ at C_5 and C_6). An analytical sample of **13b** was obtained by rechromatography over silica gel. Found: C, 64.94; H, 8.65%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%. Middle fractions (99 mg) was found to be a 1 : 1 mixture of **13a** and **13b**. Less mobile fractions afforded **13a** (43 mg), showing a single spot, oil; MS, *m/e* 184 (M^+), 155, and 125; UV (the text); IR, ν_{max} 3480, 1720, 1645, 1115, 1095, and 1055 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$), 1.70 (2H, m, $CH_3C\underline{H}_2$), 2.30 (3H, m, 2$\underline{H}$ at C_3 and O$\underline{H}$), 2.82 and 3.86 (each 1H, do d, J=12 and 6 Hz, 2H at C_4), 3.62 (3H, m, $\underline{H}$ at C_8 and $CH_2O\underline{H}$), 3.82 (1H, do d, J=7 and 5 Hz, $\underline{H}$ at C_2), and 5.70 (2H, m, 2$\underline{H}$ at C_5 and C_6). The oil was rechromatographed over silica gel for analysis. Found: C, 65.33; H, 8.95%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

An aqueous solution (10 ml) of the 8 : 1 mixture (1.93 g), of **12a** and **12b**, obtained from crystals B, was likewise treated with 42% fluoroboric acid (2 ml) under reflux for 15 min. The reaction mixture was cooled, neutralized with saturated aq sodium hydrogencarbonate, and extracted with ether (2×200 ml) and then with chloroform (2×200 ml). The combined organic solution was worked up as usual to leave oil (954 mg), which was purified by repeated chromatography over silica gel (25 g) with benzene and ethyl acetate (8 : 1) to yield **13a** (181 mg) and **13b** (24 mg) in pure state with a 1 : 1 mixture (48 mg) of **13a** and **13b**.

3) Compound **13a** (62 mg) was treated with acetic an-

hydride (0.6 ml) and pyridine (1 ml) at room temperature overnight. The solution was poured into ice-water (5 ml) and extracted with ether (2×200 ml). The ether solutions were combined, washed with 2 M hydrochloric acid (2×10 ml) and water (2×10 ml), dried and evaporated to leave oil (15a, 69 mg), showing a single spot; IR, ν_{max} 1750, 1725, 1230, 1115, and 1040 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, CH_3CH_2), 1.64 (2H, m, CH_3CH_2), 2.10 (3H, s, $OCOCH_3$), 2.30 (2H, m, 2H at C_7), 2.80 (1H, do d, J= 12 and 6 Hz, H at C_3), 3.68 (1H, m, H at C_8), 3.76 (1H, do d, J=7 and 4 Hz, H at C_2), 3.84 (1H, do d, J=12 and 6 Hz, H at C_4), 4.15 (2H, m, CH_2OCOCH_3), and 5.75 (2H, m, 2H at C_5 and C_6).

Compound **13b** (104 mg) was likewise converted into the acetate (**15b**, 110 mg); IR, ν_{max} 1750, 1725, 1225, and 1115 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, CH_3CH_2), 1.56 (2H, m, CH_3CH_2), 2.05 (3H, s, $OCOCH_3$), 2.31 (2H, m, 2H at C_7), 2.84 (2H, do d, J=6 and 12 Hz, H at C_4), 3.34 (1H, m, H at C_8), 3.99 (1H, do d, J=6 and 12 Hz, H at C_4), 4.23 (3H, m, H at C_2 and CH_2OCOCH_3), and 5.78 (2H, m, 2H at C_5 and C_6).

*trans-2-Ethyl-8-hydroxymethyl-3,4,7,8-dihydro-2H-oxocin-3-one (**13c**).* The 2 : 2 : 1 mixture (16 g) of oxaazabicyclononanones **4a**, **4b**, and **4c**, described in the previous section, was transformed in almost the same manner as **4a** to give a mixture of tetrahydrooxocinones, from which **4a** (0.6 g), **4b** (0.3 g), and a new compound (**13c**, 0.2 g) were isolated by repeated chromatography. Compound **13c** showed the following spectra: MS, *m/e* 184 (M^+), 155, and 125; UV, λ_{max} 292 nm (ε 80), 303 (95), 313 (85), and 324 (40) (sh); IR, ν_{max} 3360, 1715, 1665, 1110, and 1050 cm^{-1}; NMR, δ 1.02 (3H, t, J=7 Hz, CH_3CH_2), 1.71 (2H, m, CH_3CH_2), 2.15 (3H, m, 2H at C_7 and OH), 3.08 and 3.44 (each 1H, do d, J=14, 5 and 14, 2 Hz, 2H at C_4), 3.52 and 3.76 (each 1H, do d and d, J=11, 7 and 11 Hz, CH_2OH), 3.93 (1H, m, H at C_8), 3.96 (1H, do d, J=5 and 7 Hz, H at C_2), and 5.65 (2H, m, 2H at C_5 and C_6). An analytical sample of **13c** was prepared by rechromatography over silica gel. Found: C, 64.92; H, 8.16%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

Compound **13c** (9 mg) was stirred with 5% potassium hydroxide in methanol (4 ml) at room temperature for 20 min. The solution was diluted with water (20 ml) and extracted with ether (2×30 ml). The ether solution, after being worked up as usual, afforded oil (8 mg), which was identical with **13a** in all respects (TLC, IR, and NMR).

*8-Acetoxymethyl-2-ethyl-3,4,7,8-tetrahydro-2H-oxocin-3-ol (**16**).* Compound **15a** (72 mg) in methanol (12 ml) was reduced with sodium borohydride (NBH, 50 mg) at 0 °C for 40 min. The solution was made acidic with 2 M hydrochloric acid, concentrated and extracted with ether. The ether solution, after usual work-up, left oil (65 mg), which was purified by chromatography over silica gel (2 g) with benzene and ethyl acetate (6 : 1) to give **16** (36 mg), oil, showing a single spot on TLC; MS, *m/e* 170, 168 (M^+—CH_3COOH), 125, and 116; IR, ν_{max} 3400, 1745, 2130, and 1035 cm^{-1}; NMR, δ 0.96 (3H, t, J=7 Hz, CH_3CH_2), 1.55 (2H, m, CH_3CH_2), 1.85 (1H, s, OH), 2.96 (3H, s, $OCOCH_3$), 2.29 (3H, br m, 3H at C_4 and C_7), 2.62 (1H, do d, J=12 and 8 Hz, H at C_4), 3.43 (1H, do do d, J= 8, 5, and 1.5 Hz, H at C_2), 3.67 (2H, m, 2H at C_3 and C_8), 4.08 (2H, m, CH_2OCOCH_3), and 5.78 (2H at C_5 and C_6). The sample was rechromatographed for analysis. Found: C, 63.25; H, 8.85%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

*2-Acetoxymethyl-8-ethyl-3,4,7,8-tetrahydro-2H-oxocin-3-ols (**17a** and **17b**).* Compound **15b** (120 mg) was reduced with NBH (68 mg) in methanol (15 ml) at 0 °C for 40 min. The reaction mixture was made acidic (pH 4—5) with 2 M hydrochloric acid, concentrated and extracted with ether (2×50 ml). The ether solution was worked up as usual to leave oil (114 mg), showing two spots on TLC, which was separated roughly into three fractions by column chromatography over silica gel (3 g, benzene : ethyl acetate =7 : 1). Fractions with higher R_f value gave **17b** (25 mg), oil, showing a single spot; MS, *m/e* 170, 168 (M^+—CH_3COOH), 125, and 116; IR, ν_{max} 3480, 1745, and 1235 cm^{-1}; NMR, δ 0.96 (3H, t, J=7 Hz, CH_3CH_2), 1.46 (2H, m, CH_3CH_2), 2.05 (3H, s, $OCOCH_3$), 2.06 (1H, s, OH), 2.26 (3H, br m, 3H at C_4 and C_7), 2.64 (1H, do d, J=12 and 8 Hz, H at C_4), 3.03 (1H, m, H at C_8), 3.78 (2H, m, 2H at C_2 and C_3), 4.16 (2H, m, CH_2OCOCH_3), and 5.76 (2H at C_5 and C_6). Rechromatography afforded an analytical sample of **17b**. Found: C, 62.91; H, 8.90%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%. Middle fractions (38 mg) were a 1 : 1 mixture of **17b** and **17a**.

Fractions (24 mg) with lower R_f value gave **17a** (24 mg), oil, showing a single spot: MS, *m/e* 170, 168 (M^+—CH_3COOH), 125, and 116; IR, ν_{max} 3480, 1740, and 1230 cm^{-1}; NMR, δ 0.96 (3H, t, J=7 Hz, CH_3CH_2), 1.47 (2H, m, CH_3CH_2), 2.07 (3H, s, $OCOCH_3$), 2.08 (1H, s, OH), 2.26 (3H, br m, 3H at C_4 and C_7), 2.81 (1H, do do d, J=3, 7, and 13 Hz, H at C_4), 3.30 (1H, m, H at C_8), 3.50 (1H, do d, J=4.5 and 9 Hz, H at C_2), 3.80 (1H, do t, J=9, 3, and 3 Hz, H at C_3), 4.24 (2H, d, J= 4.5 Hz, CH_2OCOCH_3), and 5.83 (2H, m, 2H at C_5 and C_6). An analytical sample of **17a** was prepared by rechromatography. Found: C, 63.25; H, 8.80%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

*cis-2-Ethyl-3,3-ethylenedioxy-8-hydroxymethyl-3,4,7,8-tetrahydro-2H-oxocin (**19**).* Compound **13a** (35 mg) in benzene (13 ml) was refluxed with ethylene glycol (30 mg) and *p*-toluenesulfonic acid (2 mg) for 18 h, water being removed by azeotropization. The solution was worked up as usual to give **19** (34 mg), oil; MS, *m/e* 228 (M^+), 130, and 125; IR, ν_{max} 3460, 1160, 1120, and 1022 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, CH_3CH_2), 1.46 (2H, m, CH_3CH_2), 2.00 (1H, do d, J=13 and 8 Hz, H at C_4), 2.32 (3H, m, 2H at C_7 and OH), 2.89 (1H, do d, J=13 and 8 Hz, H at C_4), 3.60 (2H, br s, CH_2OH), 3.63 (2H, m, 2H at C_2 and C_8), 3.98 (4H, m, W_H=10 Hz, OCH_2CH_2O), and 5.83 (2H, m, 2H at C_5 and C_6). An analytical sample was prepared by rechromatography. Found: C, 63.35; H, 8.75%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

*cis-2-Ethyl-3,3-ethylenedioxy-3,4,7,8-tetrahydro-2H-oxocin-8-carbaldehyde (**2**).* A viscous mixture, prepared by addition of chromium(VI) oxide (1.0 g) to anhydrous pyridine (1.6 g) in dichloromethane (25 ml) under stirring, was stirred at room temperature for 15 min. To the mixture was added a solution of **19** (0.40 g) in dichloromethane (5 ml), when a tarry black deposit separated immediately. The whole mixture was further stirred for 15 min at room temperature and then decanted. The supernatant solution thus obtained, was washed with 5% aq sodium hydroxide (3×10 ml) and 5% hydrochloric acid (20 ml), dried and evaporated to yield crystalline aldehyde (**2**, 0.39 g), mp 71—73 °C, which was recrystallized from ether and hexane to give **2** (0.35 g), mp 73—74 °C: MS, *m/e* 197 (M^+—CHO) and 168; IR (Nujol), ν_{max} 2820, 1735, 1160, 1140, 1110, and 1025 cm^{-1}; NMR, δ 0.99 (3H, t, J=7 Hz, CH_3CH_2), 1.55 (2H, m, CH_3CH_2), 2.20 and 2.88 (each 1H, do d, J=13, 6 and 13, 8 Hz, 2H at C_4), 2.41 (2H, m, 2H at C_7), 3.64 (1H, do d, J=8 and 5 Hz, H at C_2), 3.70 (1H, t, J=6 Hz, H at C_8), 3.99 (4H, m, OCH_2CH_2O), 5.83 (2H, m, 2H at

C_5 and C_6), and 9.76 (1H, s, CHO). Found: C, 63.88; H, 7.99%. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%.

*cis-2-Ethyl-8-(ethylenedioxymethyl)-3,4,7,8-tetrahydro-2H-oxocin-3-one (**20**), and Its 3,3-Ethylenedithio-(**21**) and 3,3-Ethylenedioxy-(**22**) Derivatives.* A solution of **2** (181 mg) and 1,2-ethanedithiol (74 mg, 1 equiv) in dichloromethane (30 ml) was treated with boron trifluoride etherate (74 mg) for 3 h at 0 °C, and then poured into 5% aq sodium hydrogencarbonate. The dichloromethane solution was washed with saturated brine (2×10 ml), dried and evaporated to leave oil, showing three spots on TLC. The oil was separated into three fractions by column chromatography over silica gel (5 g, benzene). Fractions with higher R_f value gave **21** (11 mg), oil, showing a single spot on TLC; MS, *m/e* 334 (M^+) and 305; IR, ν_{max} 1099, 1065, and 1025 cm^{-1}; NMR, δ 1.12 (3H, t, J=7 Hz, CH_3CH_2), 1.85 (2H, m, CH_3CH_2), 2.31 (1H, do d, J=12 and 8 Hz, H at C_4), 2.56 (2H, m, 2H at C_7), 3.24 and 3.28 (each 4H, br s, $2SCH_2CH_2S$), 3.31 (1H, do d, J=12 and 8 Hz, H at C_4), 3.51 (1H, m, H at C_8), 3.70 (1H, do d, J=9 and 2 Hz, H at C_2), 4.65 (1H, d, J=6 Hz, SCHS), and 5.88 (2H, m, 2H at C_5 and C_6). The compound was obtained from **2** in 80% yield, when 2 equiv of ethanedithiol was used.

Middle fractions gave **20** (122 mg), oil, showing a single spot on TLC; MS, *m/e* 258 (M^+) and 229; IR, ν_{max} 1720, 1645, 1100, and 1020 cm^{-1}; NMR, δ 1.00 (3H, t, J=7 Hz, CH_3CH_2), 1.70 (2H, qui, J=7 Hz, CH_3CH_2), 2.45 (2H, do d, J=7 and 4 Hz, 2H at C_7), 2.86 (1H, do d, J=13 and 6 Hz, H at C_4), 3.21 (4H, s, SCH_2CH_2S), 3.34 (1H, do d, J=7 and 4 Hz, H at C_8), 3.80 (1H, t, J=7 Hz, H at C_2), 3.82 (1H, do d, J=13 and 6 Hz, H at C_4), 4.58 (1H, d, J=8 Hz, SCHS), and 5.70 (2H, m, 2H at C_5 and C_6).

Fractions with lower R_f value afforded **22** (30 mg), oil, showing a single spot; MS, *m/e* 302 (M^+) and 273; IR, ν_{max} 1159, 1130, 1103, and 1020 cm^{-1}; NMR, δ 1.04 (3H, t, J=7 Hz, CH_3CH_2), 1.54 (2H, qui, J=7 Hz, CH_3CH_2), 2.15 (1H, do d, J=13 and 6 Hz, H at C_4), 2.45 (2H, m, 2H at C_7), 2.89 (1H, do d, J=13 and 9 Hz, H at C_4), 3.20 (4H, s, SCH_2CH_2S), 3.44 (1H, do do d, J=8, 6.5, and 3 Hz, H at C_8), 3.63 (1H, t, J=7 Hz, H at C_2), 3.95 (4H, m, OCH_2CH_2O), 4.62 (1H, d, J=7 Hz, SCHS), and 5.78 (2H, m, 2H at C_5 and C_6). The compound (**22**) was obtained from **20** in 65% yield by the procedure similar to that used for the conversion of **13a** into **19**.

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