THE SYNTHESIS AND CHARACTERISATIONS OF RETINOIDAL 3(2H)-FURANONES

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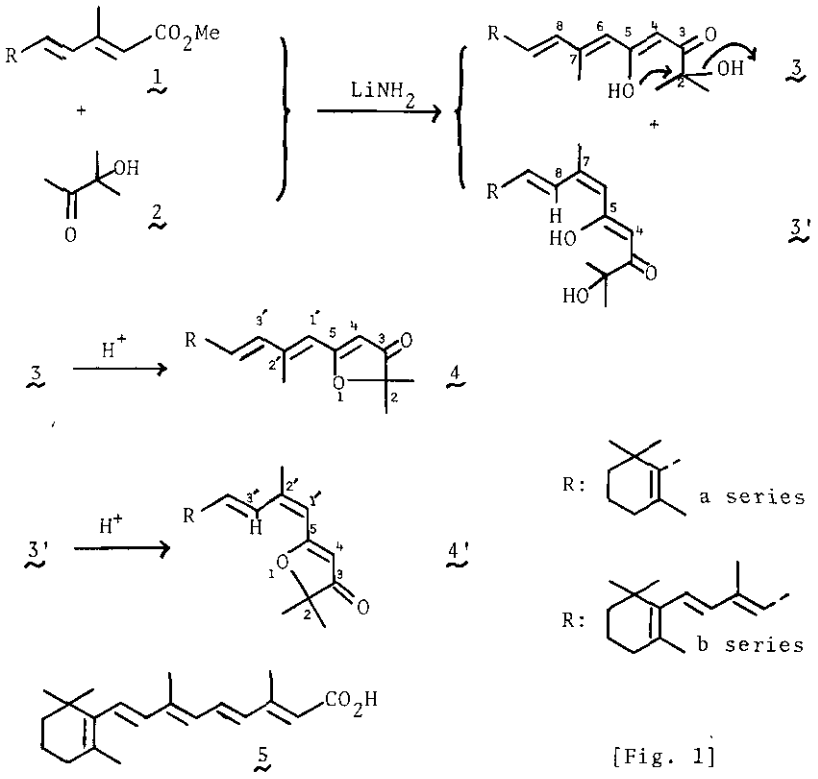
Abstract — Retinoidal 3(2H)-furanones [(4) and (4')] have been synthesised via a Claisen type condensation between the polyene ester (1) and the α-hydroxy methyl ketone (2) and their spectral characterisations have been reported.

The only few occurrences[1,2] of a 3(2H)-furanone system as natural heterocyclic products have been encountered before and their biological activities are therefore attractive ın relation to a 2(5H)-furanone system (butenolide), some of which are reported to have an antitumour activity.[3] In connection with the synthetic work of conjugated polyenes, we became interested in the preparation of a conjugated vinylogous lactone retinoıdal 3(2H)-furanone system (4). Because retinoic acid (vıtamin A acid) (5) and some of its related retinoids have recently been reported to prevent and inhibit the growth of epıthelial tumours.[4]

In this communıcation we wish to report the fırst method for the preparation of a retinoidal 3(2H)-furanone system (4) which involves a Claisen type condensation between the polyene ester (1) and the α-hydroxy methyl ketone (2) using $LiNH_2$ ın dry tetrahydrofuran (THF) followed by treatment of the resulting hydroxy polyconjugated enolic β-diketone (3) with dilute H_2SO_4 in ethanol [Fig. 1]. In addition, the spectral characterısations of furanones obtained are also described here.

A general preparative procedure is as follows: The conjugated polyene ester (1)[5] ıs refluxed in the presence of $LiNH_2$ with 3-hydroxy-3-methyl-2-butanone (2) [molar ratio; (1) : (2) : $LiNH_2$ = 1 : 10 : 20] ın dry THF for ca.20 hrs to afford a mixture of E (3) and Z (3') isomers of the hydroxy polyconjugated enolic β-diketone in 25-50% yield which is separated by preparative thin-layer chromatography (Merck

silica gel $60F_{254}$ precoated plate, 0.5mm thickness/ 20% acetone in n-hexane) to give the respective isomers in a pure state. Each isomer is treated with a few drops of 10% H_2SO_4 in ethanol for 2 hrs at room temperature to afford the corresponding retinoidal 3(2H)-furanone (4) and (4') in ca.50% yield, respectively.



[Fig. 1]

The compounds obtained are identified on the basis of the spectral data. Characteristic spectral data in each β-diketone isomer [(3a), (3'a), (3b) and (3'b)] are shown in Tables 1 and 2. The presence of a completely enolic β-diketone structure in the compounds [(3a), (3'a), (3b) and (3'b)] is revealed from the following evidences.

1) The presence of the enolic hydroxy proton and the lack of the methylene proton at C-4 in keto form of β-diketones in their NMR spectra.
2) The existence of the strongly chelated carbonyl group in the IR spectra (very broad band at 1640-1580 cm^{-1}).

A hypsochromic shift of the UV absorption maximum of each compound on addition of base (Table 2) is presumably a characteristic feature in a polyconjugated enolic

β-diketone, though a bathochromic shift is a general trend in a saturated acyclic β-diketone. The stereochemistry around the C-6,7 double bond in the β-diketone isomers is determined from the examination of the chemical shift of both the C-7-methyl and the C-8-olefinic proton resonances. The C-7-methyl signals of the E-compounds [(3a) and (3b)] are further downfield than the corresponding resonances of their Z-isomers [(3'a) and (3'b)] in which the protons at C-8 are deshielded[6] by enolic hydroxyl group.

Table 1 Characteristic NMR data of the hydroxy polyconjugated enolic β-diketones

Compounds*	δppm in $CDCl_3$ from TMS				
	C-4-H	enolic OH	C-2-OH	C-8-H	C-7-Me
(3a)	5.71 (s)	15.16	3.62	6.14 (d,J=16)	2.37
(3'a)	5.67 (s)	15.18	3.63	7.62 (d,J=16)	2.10
(3b)	5.73 (s)	15.17	3.61	#	2.39
(3'b)	5.71 (s)	15.29	3.63	7.81 (d,J=15)	2.18

* The mass spectrum of each compound is consistent with the assigned structure.[2]

\# This proton is observed between δ6.0 and δ6.5 overlapping with other protons.

Table 2 UV maxima of the hydroxy polyconjugated enolic β-diketones

Compounds	$\lambda_{max}(\varepsilon)$ in EtOH	in EtOH-NaOH
(3a)	358(25500)	340
(3'a)	361(25600)	340
(3b)	405(30000)	376
(3'b)	404(38000)	370

Characteristic spectral data of retinoidal 3(2H)-furanones are summarised in Tables 3 and 4. The IR spectra of non-conjugated 3(2H)-furanones have been reported to show a characteristic and very intense pair of bands at 1710 and 1610 cm^{-1}.[7] In the IR spectra of retinoidal 3(2H)-furanones, the distinctive and strong bands in the carbonyl and double bond absorption regions have also been observed as shown in Table 3. From the observed data (Table 3), the expected position of the absorption maximum in the polyconjugated 3(2H)-furanone system could be calculated as follows;

Parent value	260 nm[7]
Add for each substituents:	
a double bond (chain) extending the conjugation	27 nm
a double bond (ring) extending the conjugation	17 nm
each alkyl group or ring residue	5 nm

In the NMR data (Table 4) of retinoidal 3(2H)-furanones [(4) and (4')], the C-4 protons resonate at δca.5.5 as a slightly broadened singlet although the protons at the same carbon in the completely enolic β-diketone system exhibit a sharp peak (Table 1) at δca.5.7. The stereochemistry around C-1',2' double bond is determined from the fact that the C-2'-methyl signals of the E-isomers [(4a) and (4b)] and the proton signals at C-3' in the Z-isomers [(4'a) and (4'b)] are deshielded by enolic oxygen in the furanone ring.

Table 3 Characteristic IR and UV data of the retinoidal 3(2H)-furanones

Compounds*	ν_{max} cm^{-1} ($CHCl_3$)	$\lambda_{max}(\varepsilon)$ in EtOH
(4a)	1678, 1601	350(25000)
(4'a)	1678, 1601	350(23200)
(4b)	1670, 1605, 1570	408(44200)
(4'b)	1670, 1605, 1570	407(53000)

* New compounds described give satisfactory high resolution mass spectral analysis.

Table 4 Characteristic NMR data of the retinoidal 3(2H)-furanones (δppm in $CDCl_3$ from TMS)

Compounds	C-4-H	C-3'-H	C-2'-Me	C-2-gemMe
(4a)	5.52 (s)	6.19 (d,J=17)	2.26 (s)	1.41 (s)
(4'a)	5.44 (s)	7.31 (d,J=17)	2.12 (s)	1.40 (s)
(4b)	5.56 (s)	#	2.29 (s)	1.42 (s)
(4'b)	5.50 (s)	7.42 (d,J=15)	2.16 (s)	1.43 (s)

\# This proton is observed between δ6.0 and δ6.5 overlapping with other protons.

The present spectral characterisation in the retinoidal 3(2H)-furanones is the first case in the polyconjugated 3(2H)-furanones and could be applied to the other polyconjugated heterocyclic compounds. The preparative method described in this communication would be expected to have a wide applicability[8] in a synthesis of a more complicated compounds including a carotenoidal 3(2H)-furanone system. The biological activities of retinoidal 3(2H)-furanones obtained here are now under investigation.

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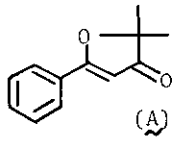
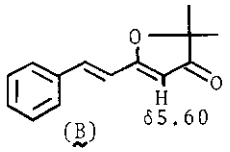
8. An application of this reaction to methyl benzoate and methyl cinnamate gave the corresponding furanones (A) (bullatenone) and (B) in reasonable yield.



(A)



(B) δ5.60

UV 334 nm (EtOH)

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