SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME OCTAHYDROXANTHEN-1, 8-DIONE DERIVATIVES

BY

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ABSTRACT

Nine octahydroxanthen-1,8-dione derivatives together with their corresponding bisdimedone intermediates were designed and synthesized. The total synthesis was designed from the appropriate disconnections of the target molecules. An aldehyde was first condensed with dimedone to form the bisdimedone derivative, which was then cyclized to form the 9-substituted-1,8-diketo octahydro xanthenes. The structures of the intermediates and the final products were confirmed by UV, IR, ^{1}H and ^{13}C-NMR studies. The corresponding hydrazones and oximes were prepared. Possible mechanistic explanation of the different synthetic routes together with their retrosynthetic analysis were dealt with.

The intermediates and the final products were scanned for their antibacterial activity against *S. aureus*, *E. coli* and *P. aeruginosa.* The compounds were found to possess some antimicrobial activity. The com-pounds were assayed for their antifungal activity against *C. albicans.*

الملخص:

تم تخليق تسعة من مشتقات أوكتاهيدروزانسين–8.1– دايون إضافة إلى وسيطاتها. تم التخطيط للتخليق الكامل باستخدام مفهوم تحليل تخليق الضديد للمركبات المطلوبة.

تم تكثيف الدايميدون مع الألدهيدات المقابلة لتكوين وسيطات مشتقات البيسدايميدون والتي تم حوئعتها لتكوين تسعة مشتق –8.1– داي كيتو أوكتا هييدروزانسين. البنيان التركيبي للوسيطات والنواتج النهائية تم التعرف عليها عن طريق تقنيات الطيف ونوع طيف الأشعة فوق البنفسجية، الأشعة تحت الحمراء، الرنين النووي المغناطيسي للبروتون والكربون 13.

تم تحضير الهيدرازونات والأوكسيمات المقابلة. تم أيضاً توضيح مختلف آليات التفاعلات ومفاهيم تخليق الضديد المتبع. وجد أن المركبات المصغرة تمتلك فعالية ضد بعض أنواع البكتريا العيارية والفطريات.

INTRODUCTION

Xanthene the parent compound of a number of naturally occuring substances and some synthetic dyes is 2,3,5,6-dibenzoylpyron. Xanthhy-drol, xanthylium and the carbonyl compound xanthone are derived from xanthene.

Xanthenes are important because of their use in medicine and they possess biological activities [1]. Xanthene dyes were reported to possess antifungal activity[2], suppressing oriental fruit fly populations[3,4]. A group of xanthene deriva-tives were reported as anthelmintics specifically with antischistosomal activity[5]. Ehretianone, a quinonoid xanthene was reported to possess antisnake venom activity[6]. Toxicity of xanthene dyes has been reviewed[7,8].

The synthon- disconnection is the nowadays the powerful technique in proceeding with organic synthesis. The present paper makes use of this approach by which on disconnecting the titled compounds- the target molecules - one can be back again to dimedone and aldehyde as the most simple synthetic equivalents for preparing the required compounds.

MATERIALS AND METHODS

Experimental: Ultraviolet-visible spectroscopy (UV-visible) was carried out at the Univeristy of Khartoum, using a Perkin Elmer-2 instrument. Infra Red spectroscopy (IR) was carried out at custom laboratories, Khartoum, using Thermoline and at Amipharma labs. Using Perkin Elmer FT-IR instrument with KBr disc. Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) was carried out at Sultan Gabbos University, Oman, using dpx 400 instruments. TLC was carried out using silica gel 60 GF 254 (Merck Germany) precoated plates or coated over glass with different mobile phases. Melting points were measure-ed using Gallenkamp apparatus and were uncorrected. All the reagents used were GPR and were used without purification.

Preparation of Bis-(1, 3-diketo-5, 5-dimethyl-2-cyclohexyl)-alkyl and aryl derivatives (II, IV, VI, VIII, X, XII, XIV, XVI, and XVIII): Dimedone (1.4gm, 0.1mole) in aqueous ethanol (50%, 20ml) was stirred for 5 minutes at room temperature using a reflux condenser. The required aliphatic aldehyde (0.05mole) and piperidine (5drops) were added. The reaction mixture was refluxed for (5-15) minutes. After cooling to room temperature, water was added drop-wise till the reaction mixture became cloudy, then it was chilled in ice to precipitate the required product.

For reaction conditions, physical, chemical and spectral data see (Tables 1,3,5,7,9,11 and 13).

Preparation of 3,3,6,6-tetramethyl–9-substituted-1,2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione (III, V, VII, IX, XI, XIII, XV, XVII, and XIX).

0.1 mole of the required Bis (1,3-diketo-5,5-dimethyl-2-cyclohexyl)-alkyl or aryl derivative (II, IV, VI, VIII, X, XII, XIV, XVI, and XVIII), 40 ml of 80% ethanol and 10 drops of concentrated hydrochloric acid (37% w/v) were heated under reflux for (20-30) minutes. After cooling to room temperature, water was added in order to precipitate the required product. For reaction conditions, physical, chemical and spectral data see (Tables 2, 4,6,8,10,12 and 14).

Table (1): Chemical Names of the Bisdimedone Derivatives

Comp.No	
II	***Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)-ethane***
IV	□,□ Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)- α, α, α trichloro-ethane.
VI	Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)- methane.
VIII	α, α Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)- acetaldehyde.
X	Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)- methyl-benzene.
XII	o-(Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)-methyl-phenol.
XIV	*p*-(Bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)-methyl-N,N-dimethyl-aniline
XVI	*p*-(bis-(1,3- diketo-5,5-dimethyl-2-cyclohexyl)- methyl-o- methoxy-phenol.
XVIII	2-(Bis -(1,3- diketo-5,5-dimethyl-2-cyclohexyl)-methyl -furan.

Table (2): Chemical Names of the Octahydro Xanthene Derivatives

Comp.No.	
III	3,3,6,6,9-pentamethyl-1, 2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione.
V	3,3,6,6-tetramethyl-9-trichloromethyl-1, 2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione
VII	3,3,6,6-tetramethyl-1, 2,3,4,5,6,7,8,9-octahydro-xanthen-1,8-dione
IX	3,3,6,6-tetramethyl- 1,8-diketo-1, 2,3,4,5,6,7,8-octahydro-xanthen- 9- aldehyde.
X1	3,3,6,6-tetramethyl-9- phenyl-1, 2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione.
XIII	3,3,6,6-tetramethyl-9- (o-hydroxy phenyl) 1,2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione.
XV	3,3,6,6-tetramethyl-9- (p- N, N-dimethyl amino-phenyl) 1,2,3,4,5,6,7,8-octahydro-xanthen-1, 8-dione
XVII	3,3,6,6-tetramethyl-9- (p-hydroxy-m-methoxy phenyl) 1,2,3,4,5,6,7,8-octahydro-

	xanthen-1,8-dione
XIX	3,3,6,6-tetramethyl-9- (2-furyl)-1,2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione

Table (3): Reaction Conditions for the Synthesis of Bisdimedone Derivatives

Compound No.	Aldehyde used	Reaction Time(min.)	Recrystallization solvent	Yield %.	m.p °C
II	Acetaldehyde	10	50%EtOH	55	170-171
IV	Chloral hydrate	10	MeOH	50	119-120
VI	Formaldehyde	10	MeOH	95	195-196
VIII	Glyoxal	10	MeOH	75	168-169
X	Benzaldehyde	15	MeOH	70	194-195
XII	Salicylaldehyde	15	50%EtOH	95	170-171
XIV	p-N,N-dimethyl amino benzaldehyde	15	MeOH	95	168-169
XVI	Vanillin	15	50% EtOH	85	130-131
XVIII	Furalaldehyde	15	MeOH	80	145-146

Table (4): Reaction Conditions for the Synthesis of Octahydro Xanthene Derivatives

Comp. No.	Aldehyde used	Reaction Time (min)	Recrystallization Solvent	Yield %	m.p °C
III	Acetaldehyde	10	EtOH	95	156-157
V	Chloral hydrate	10	MeOH	60	120 – 121
VII	Formaldehyde	10	MeOH	90	196 –197
IX	Glyoxal	10	MeOH	95	138 – 139
XI	Benzaldehyde	15	MeOH	85	210 – 211
XIII	Salicylaldehyde	15	EtOH	80	194 – 195
XV	P-N,N-dimethyl amino benzaldehyde	15	MeOH	80	200 –201
XVII	Vanillin	15	50% EtOH	80	230 –231
XIX	Furalaldehyde	15	MeOH	80	160 -161

Table (5): IR. Data of the Bisdimedone Derivatives

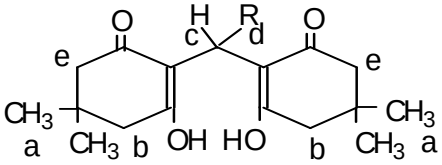
Comp. No	O-H st.vib	C-O st.vib	>C=O st.vib	C-H st.vib	C-H bend -CH_3	C-H bend- CH_2.	C=C st.vib	Others
II	3350-2600	1155	1560	2960,2870	1370	1450	1610	-
IV	3400-2400	1150	1570	2960,2875	1375	1450	1620	-
VI	3500-3100	1150	1550	2960,2870	1380	1450	1620	-
VIII	3350-2100	1151	1590	2961,2875	1382	1456	1600	1610, 2720 (CHO)
X	3400-2400	1165	1592	2962,2877	1374	1450	1615	1510 ring
XII	3450-2500	1160	1590	2960,2880	1375	1450	1615	1515, ring
XIV	3300-2400	1159	1594	2950	1370	1450	1620	1520,ring, 811 p-sub.
XVI	3400-2200	1150,1113	1589	2961,2876	1380	1452	1640	747,659
XVIII	3500-2600	1167	1620	2956,2870	1376	1440	1620	804

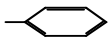
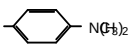
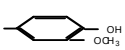
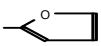
Table (6): IR. Data of the Octahydro Xanthene Derivatives

Comp. No	O-H st.vib	C-O st.vib	>C=O st.vib	C-H st.vib	C-H bend -CH_3	C-H bend - CH_2.	C=C st.vib	Others

I	3500-2400	1160	1665	2958	1380	1460			
V	-	1143	1654	2960, 2872	1379	1459			
IX	-	1153	1607 (overlap)	2956, 2870	1373	1451	1620	2700	
XI	-	1196	1664	2960, 2876	1360	1462	1623	800,700	3025
XIII	3350-3090	1185, 1235	1622	2959, 2872	1378	1487	1615	1577	764
XV	-	1197	1660	2958	1362	1465	1614	1517	832
XVII	3450-3100	1272,1196,1141	1668	2959,2875	1363	1461	1619	3023	1513, 757, 676

Table (7): ^{1}H-NMR Data of the Bisdimedone Derivatives. ($CDCl_3$)

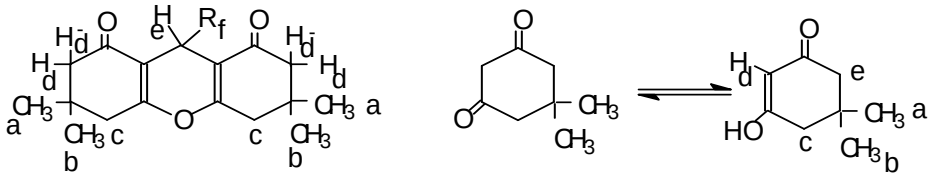


Comp. No	R	Chemical shift-δ-value-ppm-(intensity, multiplicity) a	c	d	b	e
II	$-CH_3$	1.10 (12,S)	3.51(1,q,j =7.0 Hz)	1.03 (3,d,j = 6.5 Hz)	2.21(2,d,j=14.0 Hz) 2.28 (2,d,j =14.5 Hz)	2.41(2,d,j=15.5 Hz) 2.48 (2,d,j=15 Hz)
IV	CCl_3	1.05 (12,S)	5.30(1,S)	-	2.22(4,S)	2.57(2,s), 2.29-2.39(2,m)
V1	-H	1.07 (12,S)	3.15 (2,S)		2.35 (8,S)	
X		1.15 (12,S)	5.52 (1,S)	7.14-7.27 (5,m)	2.41 (8,S)	
X11		1.12 (12,S)	5.32 (1,S)	6.92-7.18 (4,m).	2.38 (8,S)	
XIV		1.15 (12,S)	5.41 (1,S)	6.65(2,d,j=1.0 Hz) 6.95(2,d,j=1.0 Hz) 2.83)6, s)	2.38 (8,S)	
XVI		1.09 (6,S); 1.22 (6,S)	5.53 (1,S)	6.58-7.85(3,m) 3.72(3,s); 12.1 (1,bs)	2.43 8,m)	
XVIII		1.11 (12,S)	5.62 (1,S)	6.25-7.45(3,m)	2.38 (4,S)	2.66 (4,s)

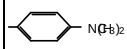
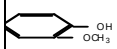
S= singlet; d=doublet; t = triplet; q quartet, m = multiplet.

Preparation of 2,4-Dinitrophenyl Hydrazones: 0.25gm of 2,4-dinitrophenyl hydra-zine were dissolved in 5ml of concentrated sulphuric acid. The warm solution was filtered and 0.1gm of the required compound Bis - (1,3-diketo-5,5-dimethyl-2-cyclohexyl)-alkyl or aryl derivatives (II, IV, VI, VIII, X, XII, XIV, XVI, and XVIII) or 3,3,6,6-tetramethyl-9-substituted-1,2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione (III, V, VII, IX, XI, XIII, XV, XVII, and XIX) in small volume of methanol was added. The required hydrazone precipitated within a period of 10 minutes or after addition of dilute solution of sulphuric acid. For melting points of these derivatives see (Tables 15 and 16).

Table (8): ^{1}H-NMR Data of the Octahydro Xanthene Derivatives. ($CDCl_3$):



Comp. No.	R	Chemical shift-δ-value-ppm-(intensity, multiplicity)

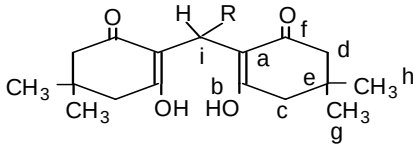
	-	a	b	c.	d	-	e	f
I	-	0.99(3,S)	1.05 (3,S)	2.19 (2,S)	3.32 (1,S)	-	2.55 (2,S)	-
VII	-H	1:07 (12,S)		2.35 (8,S)			3.15 (2,S)	
IX	-CHO	1.05 (12,S)		2.29 (5,S)+e	2.85 (2,m)	**1.48(1,d,j =11.0Hz)** 1.30(1,d,j =11.5Hz)	overlap (c)	out range
XI		0.98(6,S)	1.10 (6,S)	2.53 (2,dj =14.5Hz) 2.60 (2,d,j=14.0 Hz)	2.23 (2,d,j =15.5 Hz)	2.12(2,d,j =15.0Hz)	4.67 (1,S)	7.05-7.28 (5,S)
XV		0.98(6,S)	1.10 (6,S)	2.58 (2,d,j =16.5Hz) 2.51 (2,dj =16.0Hz)	2.24 (2,d,j =17.0 Hz)	2.10 (2d,j =17.0Hz)	4.65 (1,S)	6.57 (2,d,j =1.2Hz); 7.06 (2,d,j=1.1Hz), 2.81 (6,S)
XVII		0.98(6,S)	1.10 (6,S)	2.58 (4,S)	2.22 (2,S)	2.15(2,S)	4.62 (1,S)	6.65-6.78 (3,m); 3.80 (3,S)

S= singlet; d=doublet; t = triplet; q quartet, m = multiplet.

Preparation of Oxime Derivatives: A mixture of 0.1 gm of the required compound Bis (1,3-diketo-5,5-dimethyl-2-cyclo hexyl)-alkyl or aryl derivatives (II, IV, VI, VIII, X, XII, XIV, XVI, and XVIII) or 3,3,6,6-tetramethyl-9-substituted-1,2,3,4,5,6,7,8-octahydro-xanthen-1,8-dione (III, V, VII, IX, XI, XIII, XV, XVII, and XIX), 0.5 gm of hydroxylamine hydrochloride, 5 ml water and 1.5 gm of sodium acetate were shaken at room temperature for few minutes and allowed to stand in order to precipitate the product. The reaction may be accelerated by warming the mixture on a water bath for a few minutes.

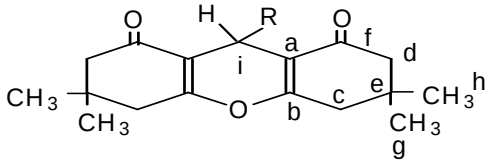
For melting points of the derivatives see (Tables 15 and 16).

Table (9): ^{13}C-NMR- Data of the Bisdimedone Derivatives ($CDCl_3$)



		(δppm)									
Comp.	**R**	**a**	**b**	**c**	**D**	**e**	**f**	**h**	**g**	**i**	**r**
II	$-CH_3$	163.7	117	51.4	41.1	30.5	197.97	32.76	30.90	32.7	21.7
X		160.00	140.19	47.76	34.10	32.82	190.98	30.98	30.78	31.18	129.45,128.28,126.94, 116.63
XIV		166.00	148.8	46.3	39.8	31.7	190.00	30.95	30.70	31.2	127.40,126.00,115.5,112. 4,28.3

Table (10): ^{13}C-NMR- Data of the Octahydro Xanthene Derivatives ($CDCl_3$)



		δ (ppm)									
Comp. No.	-	**a**	**b**	**c**	**d**	**e**	**f**	**h**	**e**	**i**	**R**
IX	-CHO	165.00	118.20	51.45	46.98	32.40	190.00	29.64	28.30	74.60	196.00
XI		163.56	145.70	51.24	41.16	31.78	196.37	29.23	27.28	31.37	129.41, 128.67, 127.04,

											116.09
XV		162.01	148.00	50.32	40.16	31.76	195.39	29.68	29.49	30.40	132-78, 1228-85, 115.54,111 .93, 26.34
XVII		164.22, 163.76	148.21, 146.46	56.82, 51.93	47.55, 43.77	32.44, 33.18	196.61, 190.61	30.79, 30.60	27.62, 25.04	30.99	137.78, 122.12, 118.79, 116.82, 115.79, 113.92

Table (11): Ultraviolet Data of the Bisdimedone Derivatives

Compounds No.	Solvent Used	λmax (nm)
II	Acetone	328,316,300
IV	Acetone	330,309,296
VI	Acetone	383,328,313,299,286
VIII	Acetone	330,306,292
X	Acetone	328,313,299
XII	Acetone	330 ,295
XIV	Acetone	365,329,320,311,298
XVI	Acetone	365,329,311,296
XVIII	Acetone	329,314,299

Table (12): Ultraviolet Data of the Octahydro Xanthene Derivatives

Compounds No.	Solvent Used	λmax (nm)
I	Acetone	329,318,301,287
III	Acetone	365,327,316,297
V	Acetone	383,328,313,299,286
VII	Acetone	330,306,292
IX	Acetone	335,328,321,314,298
XI	Acetone	328,312,297
XIII	Acetone	329,319,298
XV	Acetone	329,310,296
XVII	Acetone	383,364,327,318,305,298
XIX	Acetone	329,313,297,286

Table (13): Thin Layer Chromatographic Data of the Bisdimedone Derivatives

Compound No.	Solvent system	R_f value
II	EtOAc: pet-ether (3:7)	0.30
IV	EtOAc: pet-ether (3:7)	0.83
VI	EtOAc: pet-ether (1:1)	0.42
VIII	EtOAc: pet-ether (1:1)	0.90
X	EtOAc: pet-ether (1:9)	0.83
XII	EtOAc: pet-ether (1:1)	0.53
XIV	EtOAc: pet-ether (1:1)	0.87
XVI	EtOAc: pet-ether (3:7)	0.94
XVIII	EtOAc: pet-ether (3:7)	0.63

Table (14): Thin Layer Chromatographic Data of the Octahydro Xanthene Derivatives

Compound No.	Solvent System	R_f value
I	EtOAc: pet-ether (3:7) EtOAc: pet.ether (1:1)	0.12 0.24
III	EtOAc: pet-ether (3:7)	0.40
V	EtOAc: pet-ether (3:7)	0.83

VII	EtOAc: pet-ether (1:1)	0.42
IX	EtOAc: pet-ether (1:1)	0.80
XI	EtOAc: pet-ether (1:9)	0.60
XIII	EtOAc: pet-ether (1:1)	0.63
XV	EtOAc: pet-ether (1:1)	0.56
XVII	EtOAc: pet-ether (1:7)	0.26
XIX	EtOAc: pet-ether (1:7)	0.50

Table (15): Melting Points of Hydrazones and Oximes (Bis Dimedone Derivatives) in °C.

Compound No.	Hydrozones	Oximes
II	130-131	70 –71
IV	84-86	36-37
VI	260-262	180-181
VIII	174-175	52 53
X	238-239	188-189
XII	160-161	130-131
XIV	196-197	120-121
XVI	260-261	80-81
XVIII	70-72	280-281

Table (16): Melting Points of Hydrozones and Oximes (Xanthene Derivatives) in °C

Compound No.	Hydrozones	Oximes
I	-	-
III	174-176	110-111
V	84-85	36-37
VII	260-261	180-181
IX	119-120	60-61
XI	250-251	140-141
XIII	116-117	210-211
XV	230-231	162-163
XVII	274-275	110-111
XIX	116-117	280-281

Table (17): Sodium Hydroxide and Ferric Chloride Tests of the Bisdimedone Derivatives

Comp. No.	FeCl	NaOH
II	+	+
IV	+	+
VI	+	+
VIII	+	+
X	+	+
XII	+	+
XIV	+	+
XVI	+	+
XVIII	+	+

Table (18): Sodium Hydroxide and Ferric Chloride Tests of the Octahydro Xanthene Derivatives

Comp. No.	$FeCl_3$	NaOH
III	-	-
V	-	-
VII	+	+
IX	-	-
XI	-	-
XIII	+	+

XV	-	-
XVII	+	+
XIX	-	-

RESULTS

Testing Antimicrobial Activity:

Preparation of Standard Bacterial Suspensions: One ml aliquots of a 24 hours broth culture of the testing organisms were aseptically transferred to nutrient agar slopes and incubated at 37 °C for 24 hours. The bacterial growth was washed off with sterile normal saline. The harvested growth was suspended in small volume of normal saline and adjusted to standard.

Preparation of Standard Fungal Suspension: The fungal cultures were maintain-ed on Subouraud dextrose agar incubated at 25 °C for seven days. The fungus was harvested and washed with sterile normal saline and finally suspended in 100ml of sterile bottle and stored in the refrigerator till used.

Testing for Antibacterial Activity: 2 ml of standardised bacterial stock were thoroughly mixed with 250 ml of sterile melted nutrient agar, which was maintained at 45°C.

20ml aliquots of the incubated nutrient agar were distributed into sterile Petri dishes. The agar was left to solidify .A sterile cork borer (No. 4) was used to bunch and the agar discs were removed. Alternate cups were filled with 0.1 ml samples of each of the derivatives. The plates were lift on the bench at room temperature for two hours. During this period diffusion take place. The plates were then incubated, in the up right position, at 37 °C for 22 hours. After incubation period the diameters of the inhibition zones were mea-sured in (mm). The average of the mean values was tabulated in (Table 19).

Testing for Antifungal Activity: The same method described for antibacterial activity, was adopted. Instead of nutrient agar, Sabouroud dextrose agar was used. The incubated medium was incubated at 25°C for one day; results were given in (Table 20).

Table (19): Antibacterial Activity of the prepared Compounds Expressed as Mean Inhibition Zone Diameter (mm)

Compound No.	S. aureus	E. coli	P. aeruginosa
I	10	16	12
II	10	18	12
III	11	20	10
IV	11	14	14
V	13	31	12
VI	12	16	13
VII	12	16	13
VIII	10	12	10
IX	14	10	14
X	10	20	12
XI	10	14	10
XII	11	10	11
XIII	11	14	11
XIV	13	18	12
XV	11	18	12
XVI	12	16	12
XVII	10	14	10
XVIII	11	12	10
XIX	12	16	13

Solvent: polyethylene glycol concentration 5mg/ml.

Table (20): Antifungal Activity of the Prepared Compounds

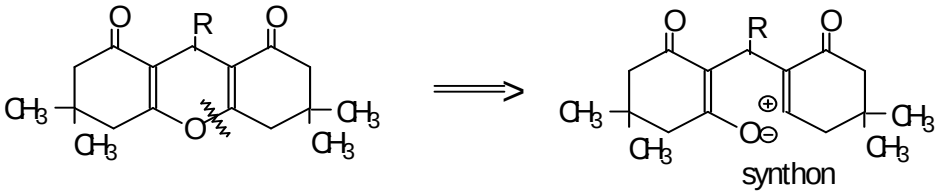
Compound No.	Mean inhibition Zone Diameter (mm) *C. albicans*
I	12
II	14
III	12
IV	20
V	-
VI	13
VII	13
VIII	19
IX	16

X	31
XI	32
XII	14
XIII	13
XIV	14
XV	13
XVI	16
XVII	17

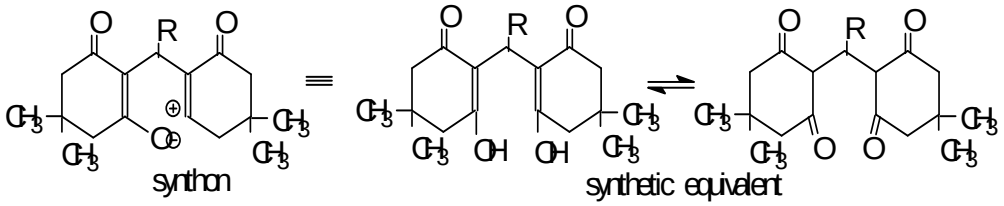
DISCUSSION

The synthetic strategies followed in the courses of this work have been constructed from the appropriate retrosynthetic analysis of the target molecules.

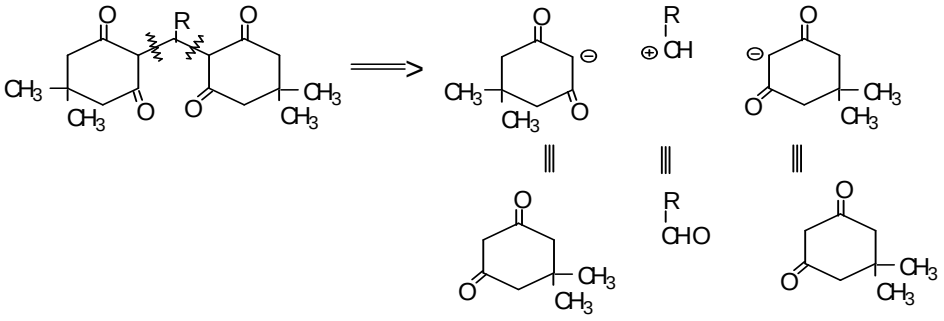
The basic octahydro xanthene ring structure can be disconnected at C-O bond as in any heterocyclic-oxygen containing compounds through ring opening [11,12]:



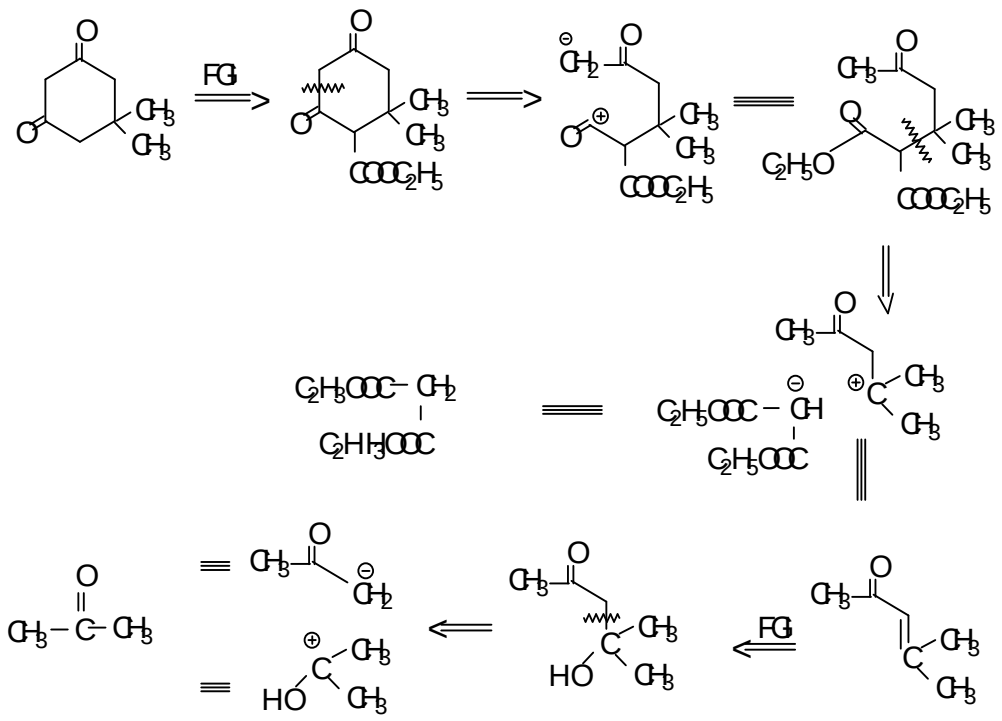
TheAppropriate Synthetic Equivalent of theProduced Synthon may be



This disconnection with the resulting synthetic equivalent can account for the formation of the octahydroxanthenes from the corresponding bis dimedone derivatives. The next step is the disconnection of the second produced target molecule; the bisdimedone derivatives:



The resulting synthetic equivalents were two molecules of dimedone and one molecule of an aldehyde. Furthermore, the dimedone structure can be disconnected in the following manner:

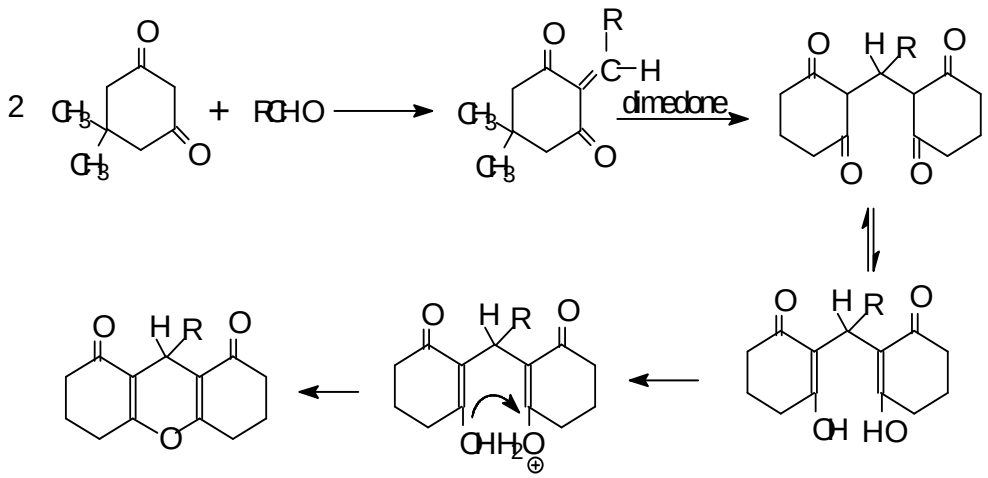


FGI =Functional Group Interconversion

Therefore, the overall synthetic strategy, and accordingly the mechanis-tic pathway of the total synthesis of the titled compounds can be illustrated as follows:

This first step is simply aldol condensation resulting in the formation of diacetonealcohol which is followed by dehydration to form the required α, β unsaturated compound, the mesityl oxide. The formation of dimedone from mesityl oxide and diethyl malonate can be worked with the a mechanism which illustrates simple intramolecular Claisen condens-ation, the first step seems to be Michael addition and the over all picture is Robinson annulation.

Two molecules of dimedone condense with the aldehyde to form the bisdimedone derivative followed by ring cyclization.



Ring closure can be achieved in acidic media to furnish the final product. The reaction of an aldehyde with dimedone forms bisdimedone derivatives. The derivatives of most aldehydes can be made to undergo cyclization to give octa hydroxanthenes. The usual method is to heat the derivative with alcohol containing small amount of hydrochloric acid. The cyclization usually occurs in 10 minutes, except in case of furfuraldehyde and salicyaldehyde, which need more time. The yields of the derivatives are nearly quantitative for most compounds prepared. The bisdimedone VI derive-ed from formaldehyde did not form octa hydroxanthene.

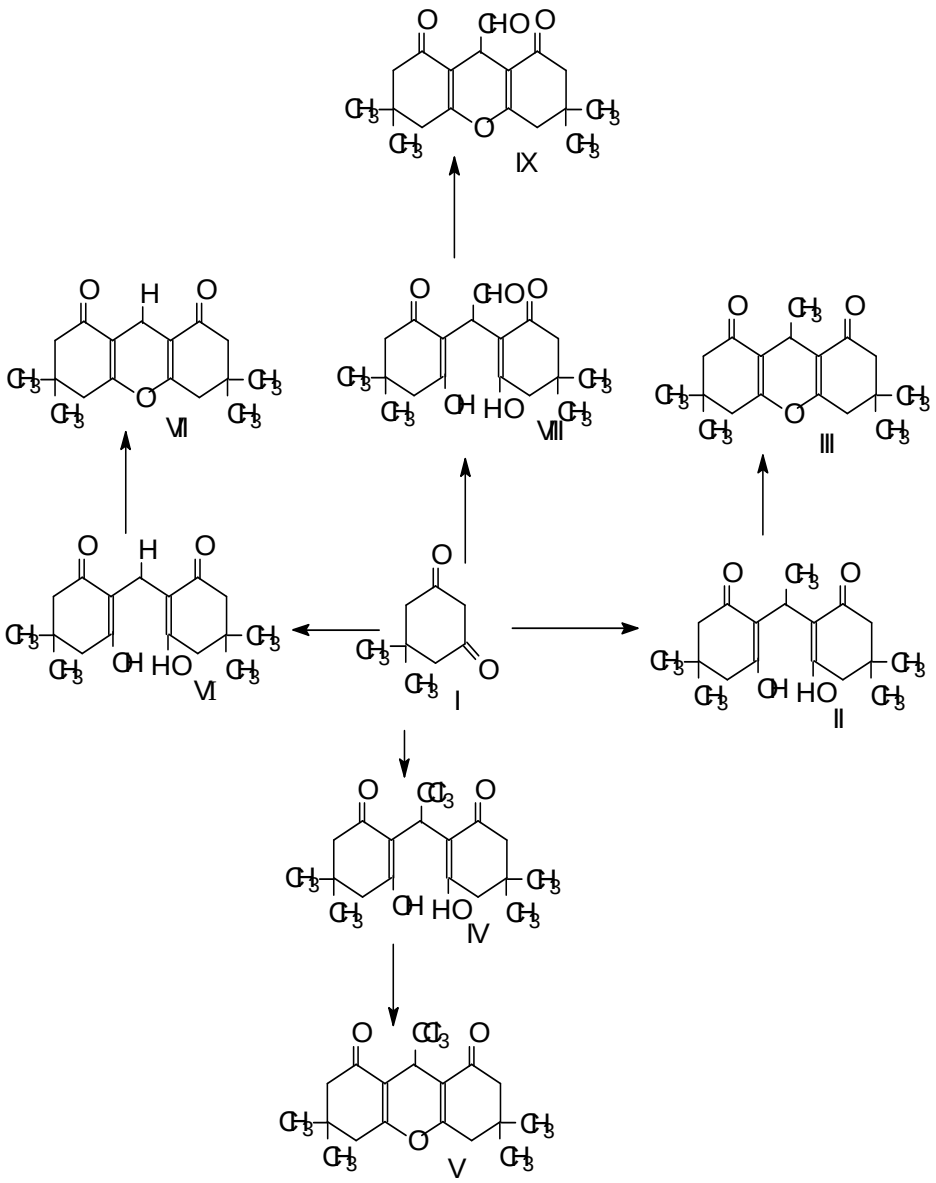
The prepared compounds in the two groups: the bisdimedone derivatives and the octahydroxanthenes, each shared characteristic spectral features.

In the IR. spectra of the present compounds the keto- enol tautomer-ism was clearly seen, in the spectra of dimedone and bisdimedone derivatives. The essential difference in the IR. spectra of the two groups of compounds is the consistent appearance of the O-H st. vib (enolic, H-bonded, 3400-2400 cm^{-1}) in the bisdimedones and disappearance of this absorption in the xanthenes group. The C=O st-vib appears at ≈ 1550cm^{-1} for those compounds exhibiting the keto – enol tautomerism and at 1650 for normal xanthene derivatives. In both cases the frequency of absorption was lowered due to conjugation and H-bonding (≈ 1590 cm^{-1}enolic). The C-O st.vib appears as strong absorption at ≈1150, C-H st-vib of the aliphatic part appears consistently at ≈ 2960 cm^{-1} and ≈ 2875 cm^{-1}. The ^{1}H-NMR spectra of these compounds shared common two doublets caused by coupling of protons b in bisdimedone and c in octahydroxanthenes. The four-methyl protons form one set of magnetically equivalent protons in the bis dimedone derivatives. They appear as a singlet of 12 protons. This fact may contradict with the observed ^{13}C-NMR. However in the octahydro xanthenes, ^{1}H and ^{13}C-NMR come to agreement. The four-methyl groups in this case form two sets of equivalent protons giving rise to two singlets each with six hydrogens. The ^{1}H-NMR of the prepared compounds provides an excellent proof of the identity of the prepared compounds. Due to the possibility of free rotation and conformational considerations, the four methyl groups become equivalent and appear as a singlet at δ 1.10.The two methylene protons in the four positions, are not equivalent, due to ring conformation. They are located as axial and equatorial; therefore they are non-equivalent and give rise to two doublets (δ 2.20, J = 14.0 Hz). The proton at the bridge between the two-dimedone rings is affected by its neighbouring substituents. In ^{13}C-NMR the two dimedone portions – carbon atoms were symmetrical and give rise to one signal for

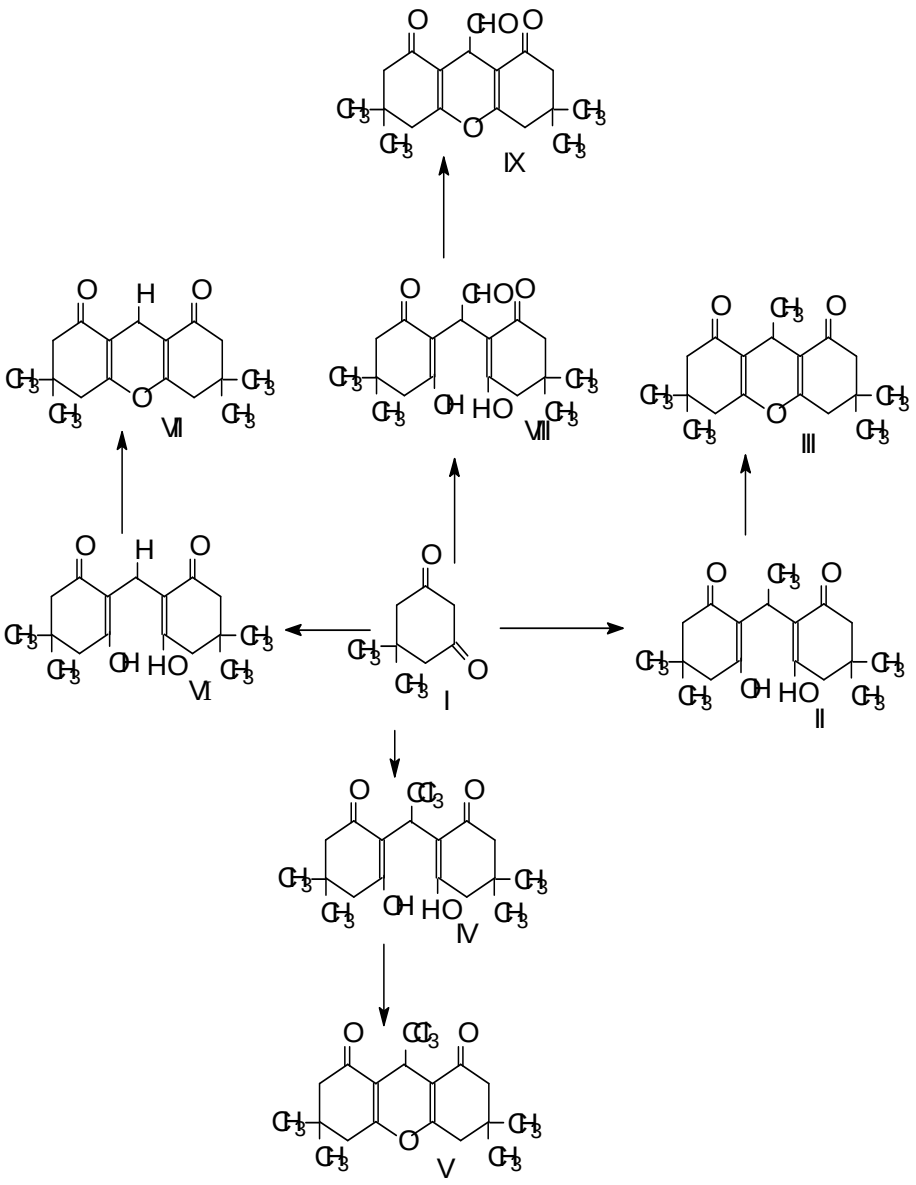
each set of carbons. Again the keto-enol tautomerism could be observed through the shift to higher δ values of carbons and b indicating enol form. The carbonyl group carbon appears consistently at δ 190 ppm. The four-methyl groups form two sets of axial and equatorial methyl, and hence appear differently. In the UV/VIS the mean U.V. peaks of both intermediates and the final products appear round 328 and 298 nm mainly. The one at the longer wavelength 328 nm can be attributed to n to π transition as it needs lower energy and appears with less intensity compared to that of 298, indicating lower energy value and therefore a forbidden transition. The band, which appears at wavelength 298 nm, can be attributed to π to π transition. This band is shifted to a higher wavelength due to the possible conjugation and the auxochrome effect causing a bathochromic shift [13].

Ferric chloride and sodium hydroxide tests provide vital information concerning the cyclization process. In most cases the bisdimedone derivatives give a positive test, which indicate the presence of C=C-OH enolic. The xanthenes family, with the exception of those bearing aromatic OH in the substituent part, result in a negative test for the two reagents, which indicate the occurrence of cyclization process.

2,4-dinitrophenylhydrazine and hydroxylamine were used to form the corresponding hydrazones and oximes respectively. The two reagents emphasized the presence of the carbonyl groups.



Scheme (1): Chemical Structures of the Prepared Compounds - Aliphatic



Scheme (2): Chemical structures of the prepared compounds - Aromatic

The bisdimedone derivatives were soluble in dilute alkali and gave color-ation with ferric chloride solution. On the other hand, the octahydroxanthenes derivatives are insoluble in dilute alkali and hence can easily be distinguished from the bisdimedone derivatives.

All the prepared compounds were found to posses a weak antibacter-ial activity. On average the bisdimedone seem to posses higher activity compared to their xanthene derivatives. This is clearly seen in the activity of some compou-nds against *E. coli*. The same fact can be observed for *S. aureus* and *P. aerugonsa*. Compounds with electron donating groups (CH_3, NM_2, *o*-MeO) exhibit the highest activity against the three test organisms.

The compounds were found to possess an antifungal activity. No clear difference between the bisdimedone derivatives and the xanthenes was observed with regard to the antifungal activity.

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