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Synthesis and Biological Evaluation of 2-Arylidene-4-(4-methoxy-phenyl)but-3-en-4-olides

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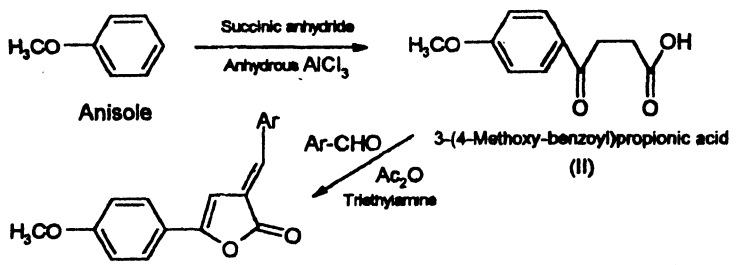
Fifteen new 2-arylidene-4-(4-methoxy-phenyl)but-3-en-4-olides have been synthesized by condensing 3-(4-methoxy benzoyl)propionic acid with appropriate aromatic aldehydes in presence of triethylamine. The compounds have been evaluated for their antimicrobial and antiinflammatory activities. Their structures were established on the basis of elemental analysis, IR and ^{1}H NMR spectral data.

Key Words: Butenolide, Antibacterial, Antiinflammatory activity.

INTRODUCTION

Butenolides consist of unsaturated γ-lactone ring which are also known as 2,3 and 2,5-dihydrofuran-2-ones. Some well-known lactones of natural origin are santonin, cardiac glycosides, sesquiterpene lactones and patulin (an antibiotic)[1–3]. Butenolides and their derivatives are known to possess numerous interesting biological properties[4–9], which include antiinflammatory, analgesic, antimicrobial, antitumour, cardiotonic, anticonvulsant, etc.

Research from our laboratories and elsewhere has shown that $\Delta^{\beta,\gamma}$-butenolides are associated with antimicrobial and anti inflammatory actions[10–13]. In continuation of these studies, the synthesis, antimicrobial and antiinflammatory activity of fifteen new 2-arylidene-4-(4-methoxy-phenyl)but-3-en-4-olides have been reported. The compounds were synthesized by following **Scheme-1** and their structures were established on the basis of elemental analysis, IR and ^{1}H NMR spectral data.



2-Arylidene-4-(4-methoxy-phenyl)but-3-en-4-olide (IIIa-o)

Scheme-1

EXPERIMENTAL

Melting points were recorded in open glass capillaries using paraffin bath and are uncorrected. Analytical data of C, H and N were within 10.4% of the theoretical values. Purity of the compounds was checked by TLC on silica gel plates and spots

were visualized by exposure to iodine vapours. The solvent system used for thin layer chromatography was toluene : ethyl acetate : formic acid in ratio of 5 : 4 : 1. ^{1}H NMR spectra were recorded on Bruker 300 MHz instrument in $CDCl_3$ using tetramethylsilane as internal standard. The IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer in potassium bromide pellets.

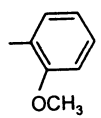
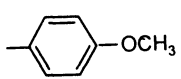
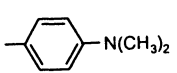
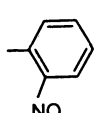
3-(4-Methoxy benzoyl)propionic acid (II): Succinic anhydride (0.1 mol) was condensed in presence of anhydrous aluminium chloride (0.1125 mol) with anisole (50 mL). The reaction mixture was refluxed for 4 h and excess solvent was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution (5% w/v), filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give **II**, m.p. 160°C, yield 63%, 1H NMR (ppm): 2.81 and 3.26 (t each, $2 \times CH_2$), 3.89 (s, 3H, OCH_3), 7.96 and 8.08 (d each, $2 \times A_2B_2$ *p*-substituted phenyl).

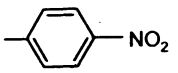
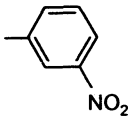
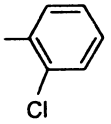
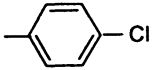
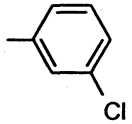
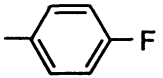
2-Arylidene-4-(4-methoxy-phenyl)but-3-en-4-olides (IIIa–o): To a solution of compound **II** (0.03 mol) and appropriate aromatic aldehyde (0.03 mol) in acetic anhydride (10 mL) was added triethylamine (3–4 drops) and the reaction mixture was refluxed for 4 h under anhydrous condition. After completion of reaction the mixture was poured onto crushed ice and a coloured solid mass, which separated out, was filtered, washed, dried and crystallized from methanol : chloroform mixture (1 : 1) to give **IIIa–o** (Table-1).

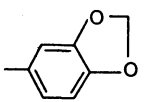
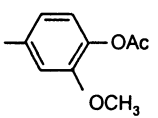
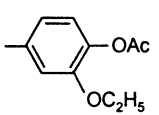
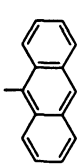
TABLE-1
PHYSICAL DATA AND BIOLOGICAL ACTIVITY OF THE COMPOUNDS

Compd.	m.p. (°C)	R_f value	Yield (%)	Anti-inflammatory activity (% Inhibition in edema)	Antibacterial activity (zone of inhibition, mm)	
					S. aureus	*E. coli*
IIIa	156	0.76	56	50.4	12	10
IIIb	138	0.71	60	52.6	–	05
IIIc	149	0.68	62	54.3	–	06
IIId	162	0.81	58	69.2	08	04
IIIe	216	0.70	56	44.4	12	10
IIIf	122	0.76	61	29.6	12	12
IIIg	170	0.74	58	38.5	12	12
IIIh	158	0.72	64	20.1	10	08
IIIi	176	0.70	65	44.1	08	10
IIIj	202	0.66	58	36.2	10	10
IIIk	180	0.68	55	69.8	16	14
IIIl	188	0.70	62	42.4	–	06
IIIm	162	0.71	54	49.7	10	12
IIIn	170	0.68	63	44.4	08	06
IIIo	205	0.65	56	49.7	10	11
Indomethacin				72.6		
Ofloxacin					29	24

TABLE-2
IR AND ^{1}H NMR DATA OF THE COMPOUNDS (**IIIa–o**)

Compd.		IR (KBr, cm^{-1})	^{1}H NMR (δ ppm)			
No.	Ar		βH (ring H)	Olefinic H	*p*-Methoxy phenyl protons	Ar protons
IIIa		1763 ν(C=O) 1621 ν(ArC=C), 835 ν(ArC—H)	6.81, s	7.26, s	3.87, s, 3H, OCH_3; 6.96, 7.71, d (e), 2x A_2B_2	7.47, m, 3H, H-3,4,5; 7.63, m, 2H, H-2,6
IIIb		1757 ν(C=O) 1603 ν(ArC=C), 827 ν(ArC—H)	6.76, s	7.26, s	3.86, s, 3H, OCH_3; 6.97, 7.73, d (e), 2x A_2B_2	3.89, s, 3H, OCH_3; 7.26, dd, 1H, H-3; 7.43, m, 2H, H-4,5; 7.61, dd, 1H, H-6
IIIc		1721 ν(C=O) 1597 ν(ArC=C), 846 ν(ArC—H)	6.78, s	7.33, s	3.86, s, 3H, OCH_3; 6.95, 7.69, d (e), 2x A_2B_2	3.88, s, 3H, OCH_3; 6.98, 7.6, d (e), 2x A_2B_2
IIId		1752 ν(C=O) 1583 ν(ArC=C), 813 ν(ArC—H)	6.74, s	7.32, s	3.85, s, 3H, OCH_3; 6.94, 7.68, d (e), 2x A_2B_2	3.07, s, 6H, -$N(CH_3)_2$; 6.72, 7.56, d (e), 2x A_2B_2.
IIIe		1777 ν(C=O) 1594 ν(ArC=C), 822 ν(ArC—H)	6.80, s	7.26, s	3.87, s, 3H, OCH_3; 6.93, 7.73, d (e), 2x A_2B_2	7.5, m, 1H, H-3; 7.68, m, 2H, H-4,5; 8.1, dd, 1H, H-6

Compd. No.	Ar	IR (KBr, cm^{-1})	^1H NMR (δ ppm) βH (ring H)	Olefinic H	*p*-Methoxy phenyl protons	Ar protons
IIIf		1775 ν(C=O) 1600 ν(ArC=C), 821 ν(ArC—H)	6.79, s	7.26, s	3.89, s, 3H, OCH_3; 6.99, 7.75, d (e), 2x A_2B_2	7.29, 8.31, d (e), 2x A_2B_2
IIIg		1766 ν(C=O) 1604 ν(ArC=C), 834 ν(ArC—H)	6.80, s	7.26, s	3.88, s, 3H, OCH_3; 7.01, 7.71, d (e), 2x A_2B_2	7.65, m, 1H, H-5; 7.88, dd, 1H, H-6; 8.24, dd, 1H, H-4; 8.47, d, 1H, H-2
IIIh		1776 ν(C=O) 1593 ν(ArC=C), 833 ν(ArC—H)	6.76, s	7.26, s	3.87, s, 3H, OCH_3; 6.98, 7.73, d (e), 2x A_2B_2	7.27, dd, 1H, H-3; 7.41, m, 2H, H-4,5; 7.61, dd, 1H, H-6
IIIi		1761 ν(C=O) 1603 ν(ArC=C), 832 ν(ArC—H)	6.74, s	7.26, s	3.86, s, 3H, OCH_3; 6.97, 7.77, d (e), 2x A_2B_2	7.42, 7.55, d (e), 2x A_2B_2
IIIj		1747 ν(C=O) 1589 ν(ArC=C), 819 ν(ArC—H)	6.85, s	7.28, s	3.84, s, 3H, OCH_3; 7.05, 7.81, d (e), 2x A_2B_2	7.62, m, 1H, H-5; 7.87, dd, 1H, H-6; 8.02, dd, 1H, H-4; 8.11, d, 1H, H-2
IIIk		1760 ν(C=O) 1626 ν(ArC=C), 827 ν(ArC—H)	6.75, s	7.32, s	3.87, s, 3H, OCH_3; 6.96, 7.70, d (e), 2x A_2B_2	7.16, 7.63, d (e), 2x A_2B_2

Compd.		IR (KBr, cm^{-1})	^1H NMR (δ ppm)			
No.	Ar		βH (ring H)	Olefinic H	*p*-Methoxy phenyl protons	Ar protons
IIIl		1747 ν(C=O) 1589 ν(ArC=C), 819 ν(ArC—H)	6.54, s	7.22, s	3.87, s, 3H, OCH_3; 6.88, 7.72, d (e), 2x A_2B_2	6.06, s, 2H, CH_2; 6.93, d, 1H, H-5; 7.19, m, 2H, H-2,6
IIIm		1773 ν(C=O, acetate) 1599 ν(ArC=C), 836 ν(ArC—H)	6.91, s	7.44, s	3.57, s, 3H, OCH_3; 6.74, 7.73, d (e), 2x A_2B_2	2.35, s, 3H, $OCOCH_3$; 3.91, s, 3H, OCH_3; 7.15, d, 1H, H-5; 7.16, d, 1H, H-2; 7.29, dd, 1H, H-6
IIIn		1772 ν(C=O, acetate) 1606 ν(ArC=C), 828 ν(ArC—H)	6.89, s	7.37, s	3.77, s, 3H, OCH_3; 6.84, 7.68, d (e), 2x A_2B_2	1.44, t, 3H, OCH_2CH_3; 4.10, q, 2H, OCH_2CH_3, 2.34, s, 3H, $OCOCH_3$; 7.12, m, 2H, H-2,5; 7.26, dd, 1H, H-6
IIIo		1777 ν(C=O) 1610 ν(ArC=C), 889 ν(ArC—H)	6.92, s	8.32, s	3.82, s, 3H, OCH_3; 6.87, 7.55, d (e), 2x A_2B_2	7.4, m, 4H, H-2,3,6,7; 8.1, m, 4H, H-1,4,5,8; 8.5, s, 1H, H-10.

s = singlet; d (e) = doublet each; dd= double doublet; t =triplet; q= quatret; m = multiplet

The synthesized butenolides were screened for antibacterial activity against gram-positive bacteria *S. aureus* and gram-negative bacteria *E. coli* by agar cup-plate method[14]. The testing was carried out using 100 μg/mL of sample in DMF. Sensitivity plates were seeded with bacterial innoculum of 1×10^6 CIU/mL and each cup (dia. 10 mm) was loaded with 0.1 mL of test solution. The zones of inhibition (mm) were recorded after incubation for 24 h. It was observed that all the compounds inhibit the growth of *E. coli*. However, 2-(4-fluoro-benzylidene)-4-(4-methoxy-phenyl)but-3-en-4-olide **(IIIk)** exhibited good activity against *S. aureus* and *E. coli* with zones of inhibition 16 and 14 mm respectively. The activity was compared with standard drug ofloxacin (Table-2).

Carrageenan induced rat paw edema method[15] was employed for evaluating the anti-inflammatory activity of the compounds at a dose level of 20 mg/kg b.w. in albino rats (weighing 100–120 g). In this test, the most active compounds were 2-(4-dimethylamino-benzylidene)-4-(4-methoxy-phenyl)but-3-en-4-olide **(IIId)** and 2-(4-fluoro-benzylidene)-4-(4-methoxy-phenyl)but-3-en-4-olide **(IIIk),** which showed 69.2 and 69.8% inhibition respectively and their activity was comparable with the standard drug indomethacin (72.6%) (Table-1).

REFERENCES

1. K.H. Lee, S.H. Kim and C. Piantadosi, *J. Pharm. Sci.*, **63**, 1163 (1976).
2. A. Gringuaz, Introduction to Medicinal Chemistry, Wiley-VCH, New York, U.S.A., p. 305 (1997).
3. A.A. Avetisyan and G.G. Tokmadzhyan, *Chem. Heterocycl. Compd.*, **23**, 595 (1987).
4. V.L. Gein, L.F. Gein, N.Y. Porseva, E.V. Voronina, M.I. Vakhrin, K.D. Kolla, L.P. Drovosekova, A.V. Milyutin, N.S. Schukalina and G.A. Veikhman, *Khim. Farm. Zh.*, **32,** 23 (1998); *Chem. Abstr.*, **130**, 153527e.
5. V.O. Kozminykh, N.M. Igidov, E.N. Kozminykh, Z.N. Semenova and Y. Andreichikov, *Die Pharmazie*, **47**, 261 (1992).
6. X. Caiding and N. Ei-Ichi, *Tetrahedron Lett.*, **40**, 431 (1999).
7. Y. Satomi, H. Nishino, A. Iwashima, M. Posrihara, Y. Tamai and M. Ito, *Anticancer Drug Des.*, **7**, 169 (1992).
8. E. Dacre and K. Staffan, *PCT Int. Appl. WO*, **01:43,** 739 (2001); *Chem. Abstr.*, **135**, 41008h (2001).
9. L. Eric, K. Derek, S. Harjit, M. Isidro, B. Adiba, A. Washington and J.T. Michael, *Pharm. Pharmacol. Lett.*, **11**, 5 (2001); *Chem. Abstr.*, **135,** 303735r (2001).
10. M.S.Y. Khan and A. Husain, *Die Pharmazie*, **57**, 448 (2002).
11. M.S.Y. Khan, A. Husain and S. Sharma, *Indian. J. Chem.*, **41B**, 2160 (2002).
12. S.M. El-Kousy, A.M. El-Torgoman, A.A. El-Basiounyl and A.I. Hashem, *Die Pharmazie*, **43**, 80 (1988).
13. C.K. Lau, C. Brideau, C.C. Chan, S. Charleson, W.A. Cromlish, D. Ethier, J.Y. Gauthier, R. Gordon, J. Guay, S. Kargman, C.S. Li, P. Prasit, D. Riendeau, M. Therien, D.M. Visco and L. Xu, *Biorg. Med. Chem. Lett.*, **15**, 3187 (1999).
14. A.L. Barry, in: Illus (Ed.), The Antimicrobial Susceptibility Test: Principles and Practices, Lea & Febiger, Philadelphia, Pa, USA, p. 180 (1976).
15. C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol.*, **111**, 544 (1962).

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