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Synthesis and antileishmanial activity of some chromon-8-ylalkanoic acids and their methyl esters

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Some new 2-(2-aryl – 6-methylchromon-8-yl)alkanoic acids **7** and their methyl esters **6** have been synthesized from appropriate 8-alkanoylflavones **5** by 1,2-aryl migration of flavone ring using iodobenzene diacetate (IBD). Some of the compounds have been assayed for their *in vitro* antileishmanial activity on *Leishmania donovam* strain UR-6. Compound **7c** has been found to possess promising activity.

Arylalkanoic acids as well as chromon-6-ylalkanoic acids[1-4] have been shown to possess immense biological activity. This prompted us to evolve a facile procedure for the synthesis of some new chromon-8-ylalkanoic acids[5], which are otherwise difficult to synthesize.

In the previous two communications[3,4] we have reported the synthesis of chromon-6-ylalkanoic acids from 6-acylchromones using hypervalent iodine reagents. In continuation of this work and as a part of our programme for the synthesis of biologically active chromones and flavones, we report in this paper a facile transformation of 8-alkanoaylchromones **5** to 2-(chromon-8-yl)-alkanoic acids **7** and their methyl esters **6** using the versatile IBD reagent (Scheme I) with a view to evaluate their biological activity[6].

The acids **7** were synthesized in six steps commencing with 2-hydroxy-5-methylacetophenone according to the procedures described in the literature. Friedel-Crafts propionylation and butyrylation[7] of **1** afforded **2** in 90-95% yields. Compounds **2** upon esterification with benzoyl chloride in the presence of pyridine or appropriate aromatic acids and $POCl_3$ also in the presence of pyridine afforded **3** (90-95% yield). Compounds **3** underwent Baker-Venkataraman rearrangement[7,8] upon treatment with powdered KOH in pyridine to give **4** in 90-92% yields. A look at the ^1H NMR spectra of **4** reveaaled that they exhibit keto-enol tautomerism[9] with enol form predominating. The 90 MHz ^1H NMR spectrum ($CDCl_3$) of **4a**, for instance, displayed signals at δ 4.60 (methylene protons) and 7.25 (olefinic proton) which were assigned to keto and enol forms, respectively.

Compounds **4** on treatment with conc. H_2SO_4 in glacial acetic acid underwent cyclization to give **5** in 85-90% yields. Treatment of **5** with two moles of iodobenzene diacetate (IBD)[10,11] in the presence of conc. H_2SO_4 in trimethyl orthoformate (TMOF) at 50-60°C for 3-5 hr, furnished methyl 2-(2-aryl-6-methylchromon-8-yl)alkanoates **6** in 90-95% yields. Finally, hydrolysis of **6** with 30% aqueous $HClO_4$ in acetone afforded 2-(2-aryl-6-methylchromon-8-yl)alkanoic acids **7** in 78-85% yields.

The structures of **7** have been established on the basis of their elemental analyses and spectral characteristics. These compounds in their IR spectra exhibited three characteristic stretching vibrations: 3440-2470 (νOH, bonded, acid), 1725-

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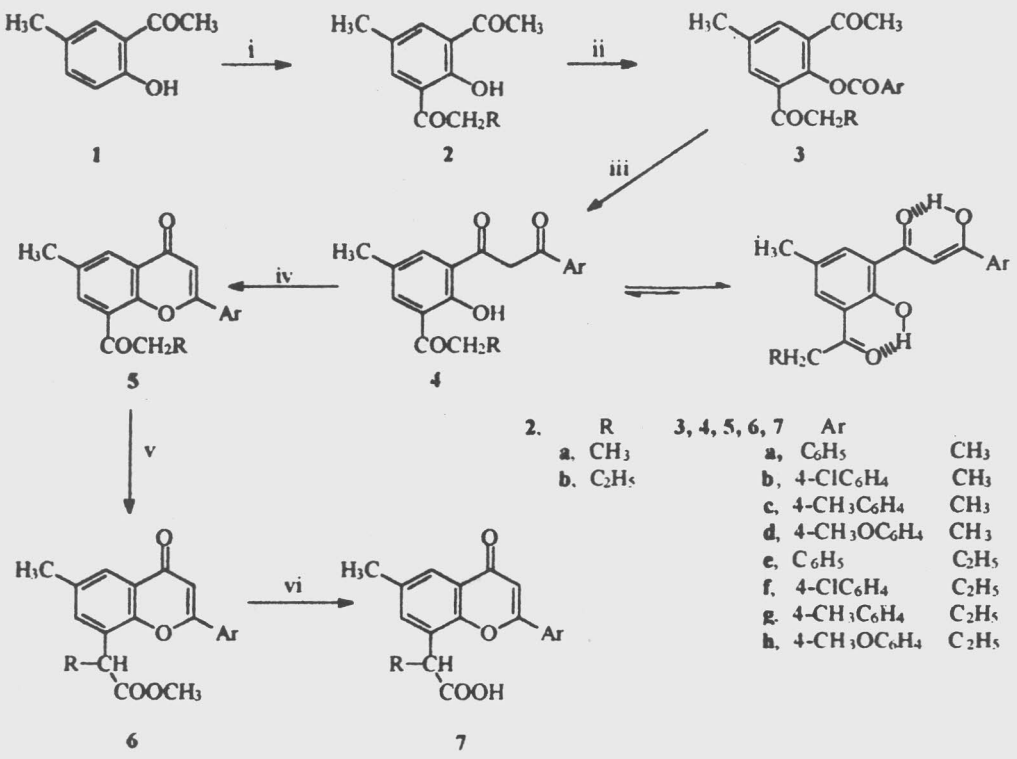

i. $CH_3CH_2COCl/CH_3CH_2CH_2COCl$, $AlCl_3$ in CS_2; ***ii.*** C_6H_5COCl in pyridine/ArCOOH, $POCl_3$ in pyridine; ***iii.*** KOH in pyridine; ***iv.*** H_2SO_4 in glacial acetic acid; ***v.*** $PhI(OAc)_2$, H_2SO_4 in $CH(OMe)_3$; ***vi.*** 30% aqueous $HClO_4$ in acetone

Scheme I

1710 (νCO, acid), and 1645-1620 cm^{-1} (νCO, chromone). The 90 MHz ^1H NMR ($CDCl_3$-TFA) spectrum of **7a**, a typical compound, exhibited signals due to various protons at δ 1.58, [3H, d, CH (CH_3)COOH], 2.38 (3H, s, C_6-CH_3), 4.22 [1H, q, CH(CH_3)COOH], 6.79 (1H, s, C_3-H), 7.38-7.58 (4H, m, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, C_7-H), 7.75 (1H, d, c_5-H, J=2.5 Hz) and 7.85-8.08 (2H, m, $C_{2'}$-H, $C_{6'}$-H).

Structures of all other compounds, including the intermediates, which have been synthesized for the first time during the course of the present work, were consistent with their elemental analyses and spectral data (*vide infra*).

In vitro Antileishmanial Activity. Compound **6a, 6b, 6c, 6d, 7a, 7b, 7c** and **7d** were screened for their *in vitro* antileishmanial activity[12]. These compounds varied in their activity (Table I), with compound **7c** exhibiting highest antileishmanial activity of 95 compared to the standard value of 100 for pentamidine.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer-842 spectrophotometer in nujol mulls. ^1H NMR spectra were scanned on a Perkin-Elmer R-32, 90 MHz machine using $CDCl_3$, $CDCl_3$/TFA as solvents and TMS as internal standard.

6-Acetyl-4-methyl-2-propionylphenol 2a. A

Table I — Characterization data and antileishmanial activity of various compounds synthesized

Compd*	Ar	R	Cryst Solvent	Yield (%)	m.p. °C	Mol formula (M^+, m/z)	Antileishmanial† activity mortality inhibition (%)
Pentamidine (standard)	—	—	—	—	—	—	100.00
2a	—	CH_3	Pet .ether	95	51.52	$C_{12}H_{14}O_3$	—
2b	—	C_2H_5	Pet .ether	90	53-.55	$C_{13}H_{16}O_3$	—
3a	C_6H_5	CH_3	Aq ethanol	90	74	$C_{19}H_{18}O_4$	—
3b	4-Cl.C_6H_4	CH_3	Aq ethanol	95	91-92	$C_{19}H_{17}ClO_4$	—
3c	4-CH_3.C_6H_4	CH_3	Aq ethanol	95	109-110	$C_{20}H_{20}O_4$	—
3d	4-CH_3O.C_6H_4	CH_3	Aq ethanol	95	110-11	$C_{20}H_{20}O_5$	—
3e	C_6H_5	C_2H_5	Aq ethanol	95	90-91	$C_{20}H_{20}O_4$	—
3f	4-Cl.C_6H_4	C_2H_5	Aq ethanol	90	101-02	$C_{20}H_{19}ClO_4$	—
3g	4-CH_3.C_6H_4	C_2H_5	Aq ethanol	95	65-66	$C_{21}H_{22}O_4$	—
3h	4-CH_3O.C_6H_4	C_2H_5	Aq ethanol	95	73-75	$C_{21}H_{22}O_5$	—
4a	C_6H_5	CH_3	Aq ethanol	90	121-22	$C_{19}H_{18}O_4$	—
4b	4-Cl.C_6H_4	CH_3	Aq ethanol	92	129-30	$C_{19}H_{17}ClO_4$	—
4c	4-CH_3.C_6H_4	CH_3	Aq ethanol	90	123-26	$C_{20}H_{20}O_4$	—
4d	4-CH_3O.C_6H_4	CH_3	Aq ethanol	90	118-19	$C_{20}H_{20}O_5$	—
4e	C_6H_5	C_2H_5	Aq ethanol	80	115-16	$C_{20}H_{20}O_4$	—
4f	4-Cl.C_6H_4	C_2H_5	Aq ethanol	81	126-27	$C_{20}H_{19}ClO_4$	—
4g	4-CH_3.C_6H_4	C_2H_5	Aq ethanol	82	134-35	$C_{21}H_{22}O_4$	—
4h	4-CH_3O.C_6H_4	C_2H_5	Aq ethanol	78	118-19	$C_{21}H_{22}O_5$	—
5a	C_6H_5	CH_3	Aq ethanol	89	137-38	$C_{19}H_{16}O_3$	—
5b	4-Cl.C_6H_4	CH_3	Aq ethanol	85	181-82	$C_{19}H_{15}ClO_3$	—
5c	4-CH_3.C_6H_4	CH_3	Aq ethanol	85	139-40	$C_{20}H_{18}O_3$	—
5d	4-CH_3O.C_6H_4	CH_3	Aq ethanol	90	143-44	$C_{20}H_{18}O_4$	—
5e	C_6H_5	C_2H_5	Aq ethanol	80	122-23	$C_{20}H_{18}O_3$	—
5f	4-Cl.C_6H_4	C_2H_5	Aq ethanol	80	168-70	$C_{20}H_{17}ClO_3$	—
5g	4-CH_3.C_6H_4	C_2H_5	Aq ethanol	80	120-23	$C_{21}H_{20}O_3$	—
5h	4-CH_3O.C_6H_4	C_2H_5	Aq ethanol	82	143-44	$C_{21}H_{20}O_4$	—
6a	C_6H_5	CH_3	Pet ether	95	179-80	$C_{20}H_{18}O_4$	44.00±2.00
6b	4-Cl.C_6H_4	CH_3	Pet ether	95	187-88	$C_{20}H_{17}ClO_4$	50.00±4.00
6c	4-CH_3.C_6H_4	CH_3	Pet ether	90	145-46	$C_{21}H_{20}O_4$	55.00±3.00
6d	4-CH_3O.C_6H_4	CH_3	Pet ether	90	153-54	$C_{21}H_{20}O_5$	30.00±3.00
6e	C_6H_5	C_2H_5	Pet ether	90	105-06	$C_{21}H_{20}O_4$	—
6f	4-Cl.C_6H_4	C_2H_5	Pet ether	90	130-32	$C_{21}H_{19}ClO_4$	—
6g	4-CH_3.C_6H_4	C_2H_5	Pet ether	90	109-10	$C_{22}H_{22}O_4$	—
6h	4-CH_3O.C_6H_4	C_2H_5	Pet ether	90	140-41	$C_{22}H_{22}O_5$	—
7a	C_6H_5	CH_3	Aq. Acetone	85	237-38	$C_{19}H_{16}O_4$	50.00±5.00
7b	4-Cl.C_6H_4	CH_3	Aq. Acetone	80	265-66	$C_{19}H_{15}ClO_4$	56.00±4.00
7c	4-CH_3.C_6H_4	CH_3	Aq. Acetone	80	257-58	$C_{20}H_{18}O_4$	95.00±5.00
7d	4-CH_3O.C_6H_4	CH_3	Aq. Acetone	80	220-21	$C_{20}H_{18}O_5$	40.00±1.00
7e	C_6H_5	C_2H_5	Aq. Acetone	80	228-30	$C_{20}H_{18}O_4$	—
7f	4-Cl.C_6H_4	C_2H_5	Aq. Acetone	80	226-27	$C_{20}H_{17}ClO_4$	—
7g	4-CH_3.C_6H_4	C_2H_5	Aq. Acetone	78	201-02	$C_{21}H_{20}O_4$	—
7h	4-CH_3O.C_6H_4	C_2H_5	Aq. Acetone	78	185-86	$C_{21}H_{20}O_5$	—

* Structures of all compounds were in conformity with their IR and ^1H NMR spectral data. Satisfactory analyses were obtained for all the compounds

The data are the mean ± S.D. of triplicate determinations from three experiments.

mixture of 2-hydroxy-5-methylacetophenone **1** (30.0 g, 0.2 mole) and propionyl chloride (30 mL) was added, dropwise, to a suspension of anhydrous $AlCl_3$ (100 g) in CS_2 (200 mL) at room temperature during 1 hr with constant stirring. The solvent was then distilled off and the residue added to ice-HCl mixture keeping the temperature below 15°C. The solid so obtained was filtered, washed with water, dried and crystallized from pet. ether, yield 39 g (95%), m.p. 51-52°; Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8 . Found : C, 69.8; H, 6.6%; IR (Nujol): 3420 (νOH, chelated), 1660 (νCO, $-COCH_3$), 1640 cm^{-1} (νCO, COC_2H_5); ^1H NMR ($CDCl_3$): δ 1.14 (3H, t, $COCH_2$-CH_3), 2.26 (3H, s, C_4-CH_3), 2.57 (3H, s, $COCH_3$), 3.00 (2H, q, $-CHCH_2CH_3$), 7.67 (2H, s, C_3-H, C_5-H) and 13.00 (1H, bs, C_1-OH, exchangeable with D_2O).

6-Acetyl-4-methyl-2-*n*-butyrylphenol 2b. The compound **2b** was prepared by treating **1** with *n*-butyryl chloride according to the procedure described above. The mixture after usual work-up afforded **2b**, which was crystallized from pet. Ether, yield 90, m.p. 53.55°. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.7; H, 7.3 . Found : C, 70.7; H, 7.1%; IR (Nujol): 3345 (νOH, chelated), 1670 (νCO, $COCH_3$), 1645 cm^{-1} (νCO, COC_3H_7); ^1H NMR ($CDCl_3$): δ 0.93 (3H, t, $COCH_2CH_2CH_3$), 1.46-1.86 (2H, m, $COCH_2CH_2$-CH_3), 2.25(3H,s,C_4-CH_3),2.53 (3H, s, $COCH_3$), 2.89 (2H, t, $CHCH_2$ CH_2CH_3), 7.59 (2H, s, C_3-H, C_5-H) and 12.99 (1H, bs, C_1-OH, exchangeable with D_2O).

6-Acetyl-4-methyl-2-propionylphenyl benzoate 3a. To 10.3 g of **2** (0.05 mole) in 50 mL of pyridine, was added dropwise 6 mL of benzoyl chloride with constant stirring. The mixture was further stirred for 5 hr and then poured into ice cold water. The solid so obtained was filtered, washed with water and crystallized from aqueous ethanol, yield 14 g (90%), m.p. 74% Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8 . Found : C, 73.3; H, 5.7%; IR (Nujol): 1740 (νOH, ester), 1690 (νCO, $-COCH_3$), 1680 cm^{-1} (νCO, $-COC_2H_5$); ^1H NMR ($CDCl_3$): δ 0.99 (3H, t, $COCH_2CH_3$), 2.36 (6H, s, C_4-CH_3, $COCH_3$), 2.72 (2H, q, $-COCH_2CH_3$), 7.40-7.54 (5H, m, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, C_3-H, C_5-H) and 7.98-8.08 (2H, m, $C_{2'}$H, $C_{6'}$-H).

Compounds **3b-h** were prepared by treating 4-substituted benzoic acids with $POCl_3$ in pyridine as described in the literature. Their characterization data are given in Table I.

α-Benzoyl-2-hydroxy-5-methyl-3-propionyl-acetophenone 4a. To 5.0 g of **3a** (0.16 mole) in 50 mL of pyridine was added 3 g of powdered KOH while stirring. The stirring was further continued for 2 hr. The mixture was then poured into ice cold water and neutralized with dil. Acetic acid. The solid so obtained was filtered, washed with water and crystallized from aqueous ethanol, yield 4.5 g (90%), m.p. 121-22° . Anal. Calcd for $C_{19}H_{18}O_4$:C, 73.5; H, 5.8 . Found : C, 73.3; H, 5.6%; IR (Nujol): 3440-3100 (νOH, bonded), 1650 (νCO, COC_2H_5), 1595 cm^{-1}[νCO, COCH=C(OH)-]; ^1H NMR ($CDCl_3$): δ 1.17 (3H, t, $COCH_2$-CH_3), 2.28 (3H, s, C_5-CH_3), 2.94 (2H, q, $-CHCH_2CH_3$), 4.60 (2 squares, s, $COCH_2CO$, keto form) 7.25 [9 squares, s, COCH=C(OH), enol form], 7.30-7.43 (3H, m, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H), 7.53 (1H, d, C4-H), 7.77-7.98 (3H, m, $C_{2'}$H, $C_{6'}$-H, C_6-H), 13.02 (1H, bs, C_2-OH, exchangeable with D_2O) and 13.32 (9 squares, bs, COCH=C(OH), exchangeable with D_2O).

Compounds **4b-h** were prepared following the same procedure. Their characterization data are given in Table I.

2-Phenyl-6-methyl-8-propionylchromone 5a. To 6.2 g (0.02 mole) of **4a** in 50 mL glacial acetic acid was added 2mL on conc. H_2SO_4 while stirring. The contents were heated on a water-bath with intermittent shaking for 4 hr. After cooling the reaction mixture was poured onto the crushed ice with vigorous shaking. The solid so obtained was filtered, washed with water and crystallized from aqueous ethanol, yield 5.2 g (89%), m.p. 137-38° Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.1, H, 5.5. Found :C, 78.1; H, 5.3% IR (Nujol): 1670 (νOH, $-COC_2H_5$), 1640 cm^{-1} (νCO, chromone); ^1H NMR ($CDCl_3$): δ 1.19 (3H, t, $COCH_2CH_3$), 2.41 (3H, s, C_6-CH_3), 3.07 (2H, q, $-CHCH_2CH_3$), 6.62 (1H, d, C_3-H), 7.36-7.52(3H, m, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H), 7.70 (1H, d, C_7-H, J=2.5Hz), and 7.80 -7.98 (3H, m, $C_{2'}$-H, $C_{6'}$-H, C_5-H).

Compounds **5b-h** were prepared in the same fashion and their characterization data are given in Table 1.

Methyl 2-(2-phenyl-6-methylchromon-8-yl)propanoate 6a. To an ice cold solution of **5a**

(1.46 g, 0.005 mole) and IBD (3.23 g, 0.01 mole) in TMOF (10 mL) was added cone. H_2SO_4 (0.05 mL), dropwise, with constant stirring. The mixture was warmed on a water-bath at 50-60°C for 3 hr and then poured into a saturated solution of $NaHCO_3$. in water The resulting gummy mass was extracted with chloroform. The solvent was removed under reduced pressure and the residue triturated with pet. Ether to afford **6a**, yield 1.25 g (95%) m.p. 179-80°. Anal. Calcd for $C_{20}H_{18}O_4$:C, 74.5, H, 5.6. Found : C, 74.3; H, 5.3% IR (Nujol): 1730 (νCO, ester), 1640 cm^{-1} (νCO, chromone); ^1H NMR ($CDCl_3$): δ 1.60 [3H, d, CH(CH_3) $COOCH_3$], 2.40 (3H, s, C_6-CH_3). 3.60 (3H, s, $COOCH_3$) 4.29 [1H, q, -CH(CH_3) $COOCH_3$], 6.75 (1H, s, C_3-H) 7.33-7.53 (4H, m, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, C_7-H)and 7.74-7.92 (3H, m, $C_{2'}$-H, $C_{6'}$-H, C_5-H).

Compounds **6b-h** were synthesized following the same procedure. Their characterization data are given in Table I.

2-(2-Phenyl-6-methylchromon-8-yl) propanoic acid 7a. To 1.61 g (0.005 mole) of **6a** in acetone (50 mL) was added 10 mL of 30% aqueous $HClO_4$. The contents were refluxed on a water-bath for 8 hr. The solvent was distilled off and the contents were poured into a saturated solution of $NaHCO_3$ in water and filtered. The filtrate on acidification with dil. HCl afforded **7a** as solid, which was filtered and crystallized from aqueous acetone, yield 1.31 g (85%), m.p. 237-38°. Anal. Calcd for $C_{19}H_{16}O_4$.: C,74.0; H,5.2. Found: C, 73.8; H, 5.1%. IR (Nujol): 3400-2500 (νOH, acid), 1715 (νCO, acid), 1635 cm^{-1}(νCO, chromone).

Compounds **7b-h** were prepared by the same method. Their characterization data are given in Table I.

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