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Synthesis of Linear Pyranocoumarins: Xanthoxyletin, 4-Methylxanthyletin, and 4-Phenylxanthyletin

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A convenient synthesis of linear pyranocoumarins (2*H*,8*H*-benzo[1,2-b: 5,4-b′]dipyran-2-ones), *viz.*, xanthoxyletin, 4-methylxanthyletin and 4-phenylxanthyletin is described which uses blocking the 8-position of appropriate 7-hydroxycoumarin derivatives with iodine and 1,1-dimethyl-2-propynylation followed by cyclisation.

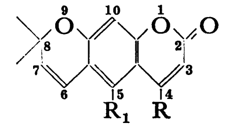
The occurrence of linear pyranocoumarins (2*H*,8*H*-benzo[1,2-b: 5,4-b′]dipyran-2-one derivatives), *viz.*, xanthyletin,[1-3] xanthoxyletin,[3-5] luvangetin,[1] dentatin,[6] roubustic acid,[7-10] robustin,[10] their methyl ethers,[10] lonchocarpic acid[9,11-13] and lonchocarpen[13] prompted us to devise a convenient method for their synthesis. A few syntheses of these coumarins are known[14-17] but these involve a number of steps and the overall yield is poor.

It has been shown[16,18,19] that 7-hydroxycoumarin derivatives react with 3-chloro-3-methyl-1-butyne in acetone to yield the 7-(1,1-dimethyl-2-propynyl) ethers, which on heating with *N*,*N*-dimethylaniline resulted[17-19] in the formation of angular pyrano coumarins (2*H*,8*H*-benzo[1,2-b: 3,4-b′]dipyran-2-one derivatives) *i.e.* cyclization takes place at more reactive 8-position due to fixation of double bond. But if 8-position is substituted,[15,16] the cyclization takes place at 6-position and the corresponding 8-substituted linear pyranocoumarins are obtained. Thus linear pyranocoumarins having 8-position free could not be prepared by this method. However these coumarins have been synthesized by very tedious methods.[14-17] A convenient method has now been developed for the synthesis of linear pyranocoumarins by blocking the 8-position with an easily introducable and removable group like iodine, which is knocked out on heating with *N*,*N*-dimethylaniline and cyclization takes place at 6-position. The required intermediate 7-(1,1-dimethyl-2-propynyloxy)-8-iodocoumarin derivatives were prepared by iodination of corresponding 7-hydroxycoumarin with iodine and periodic acid, followed by reaction with 3-chloro-3-methyl-1-butyne in acetone in presence of potassium carbonate.

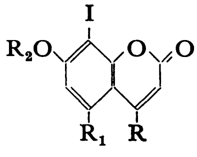
Using the above method, the synthesis of 5-methoxy-8,8-dimethyl-2*H*,8*H*-benzo[1,2-b: 5,4-b′]dipyran-2-one (xanthoxyletin) (**1**), 4,8,8-trimethyl-2*H*,8*H*-benzo[1,2-b: 5,4-b′]dipyran-2-one (4-methylxanthyletin) (**2**) and 8,8-dimethyl-4-phenyl-2*H*,8*H*-benzo[1,2-b: 5,4-b′]dipyran-2-one (4-phenylxanthyletin) (**3**) has been carried out. The synthesis of **1** was effected as follows. Iodination of 7-hydroxy-5-methoxycoumarin[20] with iodine/periodic acid gave 7-hydroxy-8-iodo-5-methoxycoumarin (**4**), the structure of which was confirmed by the ^{1}H NMR spectrum of its acetate. Etherification of **4** with 3-chloro-3-methyl-1-butyne in acetone/K_2CO_3 yielded 7-(1,1-dimethyl-2-propynyloxy)-8-iodo-5-methoxycoumarin (**5**), which on heating with *N*,*N*-dimethylaniline afforded **1**. That the cyclization takes place at 6-position and iodine was knocked out in above reaction was shown by its NMR spectral data, and its disagreement with angular isomer, *viz.*, 5-methoxy-8,8-dimethyl-2*H*,8*H*-benzo[1,2-b: 3,4-b′]dipyran-2-one.[21]

Similarly, iodination of 7-hydroxy-4-methylcoumarin[22] with iodine/periodic acid gave 7-hydroxy-8-iodo-4-methylcoumarin (**6**). Its structure was confirmed by the NMR spectral data of its acetate, which showed the presence of two doublets (J=9.5 Hz) for ortho-coupled H5 and H6 protons. Etherification of **6** with 3-chloro-3-methyl-1-butyne in acetone/K_2CO_3 yielded 7-(1,1-dimethyl-2-propynyloxy)-8-iodo-4-methylcoumarin (**7**), which on heating with *N*,*N*-dimethylaniline afforded **2**. Its structure was in agreement with the NMR spectral data which showed the presence of two singlets for para-coupled H5 and H10 protons, along with other usual signals.

Using the above method, 4-phenylxanthyletin (**3**) has also been synthesized starting from 7-(1,1-dimethyl-2-propynyloxy)-8-iodo-4-phenylcoumarin (**8**), which was prepared by the iodination of 7-hydroxy-4-phenylcoumarin[23] with iodine and periodic acid to 7-hydroxy-8-iodo-4-phenylcoumarin (**9**), followed by etherification with 3-chloro-3-methyl-1-butyne in acetone in presence of potassium carbonate. Compound **8** on heating with *N*,*N*-dimethylaniline yielded **3**. Its structure was in agreement with its ^{1}H-NMR spectral data.



(**1**) R=H; R_1=OCH_3
(**2**) R=CH_3; R_1=H
(**3**) R=C_6H_5; R_1=H



(**4**) R=R_2=H; R_1=OCH_3
(**5**) R=H; R_1=OCH_3; R_2=-$C(CH_3)_2C{\equiv}CH$
(**6**) R=CH_3; R_1=R_2=H
(**7**) R=CH_3; R_1=H; R_2=-$C(CH_3)_2C{\equiv}CH$
(**8**) R=C_6H_5; R_1=H; R_2=-$C(CH_3)_2C{\equiv}CH$
(**9**) R=C_6H_5; R_1=R_2=H

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infra-cord spectrometer. The NMR spectra were recorded on Perkin Elmer R-32 instrument with TMS as internal standard.

*5-Methoxy-8,8-dimethyl-2*H*,8*H*-benzo[1,2-b: 5,4-b′]dipyran-2-one (Xanthoxyletin) (1).* *(a) 7-Hydroxy-8-iodo-5-methoxycoumarin (4)*: 7-Hydroxy-5-methoxycoumarin[20] (2 g, 10.4 mmol) was dissolved in minimum amount of ethanol and to this solution iodine (2.1 g) and periodic acid (0.5 g in water) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give the coumarin (**4**) (2.2 g, 6.91 mmol) (66.7%). It crystallized from ethanol as yellow needles mp 235—237 °C. Found: C, 37.6; H, 2.1%. Calcd for $C_{10}H_7O_4I$: C, 37.7; H, 2.2%. Its acetate (prepared by acetic anhydride–pyridine) melted at 205—207 °C. NMR (DMSO-d_6): δ 2.20 (s, 3H, 7-OAc); 3.75 (s, 3H, 5-OCH_3); 6.25 (d, 1H, J_0=9.5 Hz, H3); 6.85 (s, 1H, H6); 7.88 (d, 1H, J_0=9.5 Hz, H4).

(b) 7-(1,1-Dimethyl-2-propynyloxy)-8-iodo-5-methoxycoumarin (5): A solution of (**4**) (1 g, 3.14 mmol) in dry acetone (75 ml) was refluxed with 3-chloro-3-methyl-1-butyne (4 ml, 38.9 mmol) in presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (1.9 g) for 24 h. The solvent was distilled off and the residue was treated with ice. The separated solid was filtered, washed with a dilute solution of sodium carbonate and water and crystallized from benzene–petroleum ether to give (**5**) (0.62 g, 1.61 mmol) (51.7%) as yellow needles mp 178—179 °C. Found: C, 46.9; H, 3.5%. Calcd for $C_{15}H_{13}O_4I$: C, 46.8; H, 3.6%. NMR ($CDCl_3$) δ 1.62 (s, 6H, $-C(CH_3)_2$); 2.58 (s, 1H, $-C\equiv CH$); 3.82 (s, 3H, 5-OCH_3); 6.09 (d, 1H, J_0=9.5 Hz, H3); 6.88 (s, 1H, H6); 7.91 (d, 1H, J_0=9.5 Hz, H4).

*(c) 5-Methoxy-8,8-dimethyl-2*H,*8*H-*benzo[1,2-b: 5,4-b′]dipyran-2-one (Xanthoxyetin) (1)*: The above 1,1-dimethyl-2-propynyl ether (**5**) (0.1 g, 0.26 mmol), was refluxed with *N,N*-dimethylaniline (3 ml) for 12 h. The cooled reaction mixture was poured over ice-cold hydrochloric acid. The solution was extracted thrice with ethyl acetate (150 ml), washed with 5% HCl, 5% NaOH and finally with water and dried (Na_2SO_4). Distillation of ethyl acetate yielded **1** (50 mg, 0.19 mmol) (74.6%) which crystallized from benzene–petroleum ether as yellow needles, mp 132—133 °C (lit,[5] mp 132—133 °C). Found: C, 69.6; H, 5.5%. Calcd for $C_{15}H_{14}O_4$: C, 69.7; H, 5.4%. NMR ($CDCl_3$) δ 1.76 (s, 6H, $-C(CH_3)_2$); 4.16 (s, 3H, 5-OCH_3); 5.85 (d, 1H, J_0=9.5 Hz, H3); 6.32 (d, 1H, $J_{6,7}$=10 Hz, H6); 6.5 (s, 1H, H10); 7.08 (d, 1H, $J_{6,7}$=10 Hz, H7); 8.2 (d, 1H, J_0=9.5 Hz, H4). IR ν_{max} (KBr) (cm^{-1}) 1710 (C=O); 1610 and 1600 (C=C); 1350 and 1360 ($-C(CH_3)_2$).

*4,8,8-Trimethyl-2*H,*8*H-*benzo[1,2-b: 5,4-b′]dipyran-2-one (4-Methylxanthyletin) (2). (a) 7-Hydroxy-8-iodo-4-methylcoumarin (6)*: 7-Hydroxy-4-methylcoumarin[22] (2 g, 11.3 mmol) was dissolved in minimum amount of ethanol and to this solution iodine (2.31 g) and periodic acid (0.52 g in water) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give **6** (2.5 g, 8.27 mmol) (73.3%). It crystallized from ethanol as light yellow needles, mp 219—220 °C. Found: C, 39.6; H, 2.3%. Calcd for $C_{10}H_7O_3I$: C, 39.7; H, 2.3%. Its acetate (acetic anhydride-pyridine) melted at 180—181 °C. NMR ($CDCl_3$) δ 2.5 (bs, 6H, 4-CH_3 and 7-OAc); 6.48 (s, 1H, H3); 7.34 (d, 1H, J_0=9.5 Hz, H6); 7.85 (d, 1H, J_0=9.5 Hz, H5).

(b) 7-(1,1-Dimethyl-2-propynyloxy)-8-iodo-4-methylcoumarin (7): A solution of **6** (1 g, 3.31 mmol) in dry acetone (75 ml) was refluxed with 3-chloro-3-methyl-1-butyne (4 ml, 38.9 mmol) in presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (2.06 g) for 24 h. Working up of the reaction mixture yielded **7** (0.65 g, 1.76 mmol) (54.2%). It crystallized from benzene–petroleum ether as yellow needles, mp 185—186 °C. Found: C, 48.8; H, 3.4%. Calcd for $C_{15}H_{13}O_3I$: C, 48.9; H, 3.5%. NMR ($CDCl_3$) δ 1.81 (s, 6H, $-C(CH_3)_2$); 2.42 (s, 3H, 4-CH_3); 2.7 (s, 1H, $-C\equiv CH$); 6.15 (s, 1H, H3); 7.3 (d, 1H, J_0=9.5 Hz, H6); 7.55 (d, 1H, J_0=9.5 Hz, H5).

*(c) 4,8,8-Trimethyl-2*H,*8*H-*benzo[1,2-b: 5,4-b′]dipyran-2-one (4-Methylxanthyletin) (2)*: The above 1,1-dimethyl-2-propynyl ether (0.1 g, 0.27 mmol) was refluxed with *N,N*-dimethylaniline (3 ml) for 12 h. The cooled reaction mixture was poured over ice cold hydrochloric acid, worked up (as in the case of **1**) to yield **2** (50 mg, 0.20 mmol) (76.9%), which crystallized from benzene–petroleum ether as yellow needles, mp 237—238 °C. Found: C, 74.2; H, 5.8%. Calcd for $C_{15}H_{14}O_3$: C, 74.3; H, 5.7%. NMR ($CDCl_3$) δ 1.49 (s, 6H, $-C(CH_3)_2$); 2.35 (s, 3H, 4-CH_3); 5.65 (d, 1H, $J_{6,7}$=10 Hz, H6); 6.05 (s, 1H, H3); 6.26 (d, 1H, $J_{6,7}$=10 Hz, H7); 7.09 (s, 1H, H10); 7.22 (s, 1H, H5). IR ν_{max} (KBr) (cm^{-1}) 1710 (C=O); 1610 and 1600 (C=C); 1345 and 1360 ($-C(CH_3)_2$).

*8,8-Dimethyl-4-phenyl-2*H,*8*H-*benzo[1,2-b: 5,4-b′]dipyran-2-one (4-Phenylxanthyletin) (3). (a) 7-Hydroxy-8-iodo-4-phenylcoumarin (9)*: 7-Hydroxy-4-phenylcoumarin[23] (2 g, 8.40 mmol) was dissolved in minimum amount of ethanol and to this solution iodine (1.71 g) and periodic acid (0.39 g in water) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give coumarin (**9**) (2.5 g, 6.86 mmol) (80%). It crystallized from ethanol as light yellowish needles, mp 263—264 °C. Found: C, 49.3; H, 2.4%. Calcd for $C_{15}H_9O_3I$: C, 49.4; H, 2.5%. Its acetate (acetic anhydride–pyridine) melted at 178—179 °C. NMR ($CDCl_3$) δ 2.44 (s, 3H, 7-OAc); 6.38 (s, 1H, H3); 7.05 (d, 1H, J_0=9.5 Hz, H6); 7.32 (d, 1H, J_0=9.5 Hz, H5); 7.4 (bs, 5H, 4-Ph).

(b) 7-(1,1-Dimethyl-2-propynyloxy)-8-iodo-4-phenylcoumarin (8): A solution of **9** (1 g, 2.80 mmol) in dry acetone (75 ml) was refluxed with 3-chloro-3-methyl-1-butyne (4 ml, 38.9 mmol) in presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (1.5 g) for 24 h. Working up of the reaction mixture yielded (**8**) (0.7 g, 1.62 mmol) (63.6%) which crystallized from benzene–petroleum ether as brown needles mp 261—262 °C (Found: C, 55.7; H, 3.5%. Calcd for $C_{20}H_{15}O_3I$: C, 55.8; H, 3.4%). NMR ($CDCl_3$): δ 1.9 (s, 6H, $-C(CH_3)_2$); 2.76 (s, 1H, $-C\equiv CH$); 6.32 (s, 1H, H3); 7.32 (d, 1H, J_0=9.5 Hz, H6); 7.56 (s, 5H, 4-Ph); 7.66 (d, 1H, J_0=9.5 Hz, H5).

*(c) 8,8-Dimethyl-4-phenyl-2*H,*8*H-*benzo[1,2-b: 5,4-b′]dipyran-2-one (4-Phenylxanthyletin) (3).* The above 1,1-dimethyl-2-propynyl ether (**8**) (0.1 g, 0.23 mmol) was refluxed with *N,N*-dimethylaniline (3 ml) for 6 h. The cooled reaction mixture was poured over ice cold hydrochloric acid and worked up (as in case of **1**) to yield **3** (45 mg, 0.14 mmol) (63.9%). It crystallized from benzene–petroleum ether as yellow needles, mp 181—182 °C. Found: C, 78.8; H, 5.3%. Calcd for $C_{20}H_{16}O_3$: C, 78.9; H, 5.2%. NMR ($CDCl_3$) δ 1.52 (s, 6H, $-C(CH_3)_2$); 5.62 (d, 1H, $J_{6,7}$=10 Hz, H6); 6.08 (s, 1H, H3); 6.18 (d, 1H, $J_{6,7}$=10 Hz, H7); 6.96 (s, 1H, H10); 7.3 (s, 5H, 4-Ph); 7.45 (s, 1H, H5). IR ν_{max} (KBr) (cm^{-1}) 1715 (C=O); 1615 and 1600 (C=C); 1345 and 1360 ($-C(CH_3)_2$).

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