J. Indian Chem. Soc.,
Vol. 72, March 1995, pp. 209-210

NOTE

Reaction of 7-Hydroxycoumarins with activated DMSO and Dibromomethane : Formation of Dicoumarols

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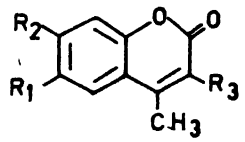
Manuscript received 17 August 1993, revised 3 November 1993, accepted 19 November 1993

Dicoumarols are long known for their use in hemorrahagis disease in cattle[1]. The reaction of 4-hydroxycoumarin with dimethyl sulphoxide and acetic anhydride produces dicoumarol under specific reaction conditions[2]. The reaction of 4-hydroxycoumarin derivatives with activated DMSO was also studied later[3]. On the basis of the mechanism stated for this reaction, it was thought that the study of the reaction of activated DMSO with 7-hydroxycoumarin derivatives would be of interest, as the corresponding dicoumarols are expected to be formed in this case as well.

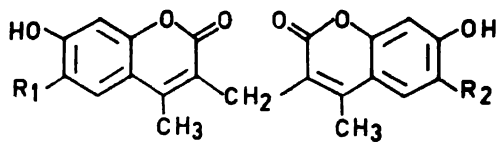
Like activated DMSO, dibromomethane had been reported much earlier to produce dicoumarols from 4-hydroxycoumarins[4]. It was, therefore, thought pertinent to extend this reaction to 7-hydroxycoumarins. To check the necessity of the presence of hydroxyl group at C-4 and/or C-7, two substrates having no OH group were also used.

The coumarins (**1–4**) were prepared by condensing phenols with ethyl acetoacetate using 75% sulphuric acid as condensing agent[5]. The 7-hydroxycoumarins (**1** and **2**) on reaction with activated DMSO at room temperature for a week gave the respective dicoumarols (**7** and **8**), as identified by the elemental analyses and spectral data. However, the coumarins **3** and **4** were recovered unchanged when allowed to react with activated DMSO under similar conditions.

Dibromomethane reacted with the coumarins **1** and **2** by refluxing in dry acetone in presence of anhydrous potassium carbonate to obtain again the dicoumarols **7** and **8**. The coumarins **3** and **4** remained unchanged with dibromomethane under similar conditions. Thus, the presence of a OH group at C-4 or C-7 seems to be the driving force behind the formation of dicoumarols. The reaction of activated DMSO with 7-hydroxycoumarins presumably follows the same mechanistic pathway which is operative for this reaction with 4-hydroxycoumarins.



1-4



7, 8

Dibromomethane gives dicoumarol because of the activation of C_3-H due to 4-OH or 7-OH group in the coumarins. 4-Methyl-7-methoxycoumarin (**5**)[7] and 3-bromo-4-methyl-7-hydroxycoumarin (**6**)[8] do not react with activated DMSO or CH_2Br_2. Thus, coumarins without C-4 or C-7 hydroxyl substituent or protected hydroxyl group (by methylation) do not give dicoumarols either by activated DMSO-Ac_2O or dibromomethane method. Even if the 3-position of hydroxy-

coumarins is substituted (by bromine) there is no formation of dicoumarol (as 3-position is the linkage position). These results also confirm the position of linkage in dicoumarol. While the activated DMSO method for dicoumarol requires a week's time, the dibromomethane method requires only 4 h. The yield of dicoumarol is the same in both the methods, i.e. nearly 50%.

Experimental

The coumarins (**1–4**) : The respective phenol (0.1 mol) and ethyl acetoacetate (0.1 mol) were dissolved in sulphuric acid (75%; 20 ml). The mixture was stirred well and kept overnight. It was then diluted with ice-cold water and the solid obtained was crystallised from aqueous ethanol to give coumarins **1–4** : **1** (R_1 = R_3 = H, R_2=OH), yield 90%, m.p. 184° (lit[5]. 185°); **2** (R_1 = Cl, R_2 = OH, R_3 = H), 80%, 280° (280°[6]); **3** (R_1 = R_3 = H, R_2 = CH_3), 70%, 134° (134°[5]); **4** (R_1 = CH_3, R_2 = R_3 = H), 50%, 148° (148°[5]); **5** (R_1 = R_3 = H, R_2 = OCH_3), 60%, 159° (159°[7]); **6** (R_1 = H, R_2 = OH, R_3 = Br), 40%, 213° (213°[8]); **1** ν_{max} 3 500 (OH), 1 680 (CO), 1 600 (benzene ring), 1 380, 1 280, 990 and 820 cm^{-1}; λ_{max} 322 and 220 nm.

Reaction of activated DMSO on coumarins (**1, 2**) : A mixture of DMSO (16 ml) and acetic anhydride (8 ml) was heated at about 80° for 2 h. Then 7-hydroxycoumarin (**1** or **2**; 10 g) was added to it and left at room temperature for a week. The solid that separated washed with benzene, dried and identified as the dicoumarol (**7** or **8**).

Reaction of dibromomethane with coumarins (**1, 2**) : A mixture of 7-hydroxycoumarin (0.02 mol), dibromomethane (0.01 mol) and anhydrous potassium carbonate (5 g) was refluxed in dry acetone (30 ml) for 4 h. The mixture was then filtered hot and after evaporating acetone the resulting solid was washed with dilute NaOH and crystallised from acetic acid to get colourless dicoumarol (**7** or **8**). The m.p.s, yields as follows : **7** (R_1 = R_2 = H), 50% m.p. 175°; ν_{max} 3 550 (OH), 1 680 (C=O), 1 600 (benzene), 1 390, 1 275, 1 080, 840 and 600 cm^{-1}; λ_{max} 322 and 220 nm; δ ($CDCl_3$/DMSO-d_6; TMS) 2.35 (6H, s, 2 × CH_3), 1.2 (2H, s, CH_2), 6.5–7.7 (6H, m, ArH) (peaks at δ 6.15 absent, indicating linkage of C_3 by CH_2) and 10 (2H, s, OH).

Acknowledgement

The authors thank R.S.I.C., Lucknow, and R.S.I.C., I.I.T., Pawai, Bombay, for elemental analysis and spectral data, and also thank U.G.C., New Delhi, for financial assistance.

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