A Convenient Method for the Synthesis of Dihydropyranobenzopyrandiones and Their Sulfur Analogs

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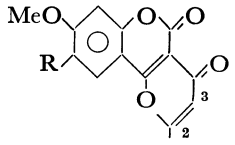
A general and convenient synthesis is described of a number of 2,3-dihydro-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4,5-diones and 2,3-dihydro-4*H*,5*H*-pyrano[2,3-*b*][1]benzothiopyran-4,5-diones. It involves the condensation of 4-hydroxycoumarin derivatives and their thioanalogs with different α,β-unsaturated acids in the presence of PPA. Assignments of the structures in both the cases are based on analytical and spectroscopic evidence.

The well-known anticoagulant activity of dicoumarol has led to the synthesis of large number of 4-hydroxycoumarin derivatives. Recently, a number of 3-[3-(*p*-substituted phenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarins have been reported, many of which show outstanding activity against both warfarin sensitive and warfarin resistant rats.[1)]

A major degradation product of the fungal metabolite citromycetin has also a 4-hydroxycoumarin skeleton.[2)]



I R=OMe
II R=H; 2,3-dihydro

One of the common methods for the synthesis of such type of compounds is to treat the appropriate 4-hydroxycoumarin derivative with ethyl acetoacetate.[3)] Also, in connection with the synthesis of radicinin and (±)-dihydroradicinin, Kato and coworkers[4)] have reported the formation of similar types of compounds from the reaction of 4-hydroxy-2-pyranone and crotonoyl chloride in the presence of titanium tetrachloride in 1,1,2,2-tetrachloroethane. Using the same method, Whalley and coworkers[5)] have synthesised di-*O*-methylcitromycinone (I).

The synthetic method described in the present work is a new route to a variety of 2,3-dihydro-4*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-4,5-diones which involves the reaction of 4-hydroxycoumarin derivatives with α,β-unsaturated acids in the presence of polyphosphoric acid. Besides acrylic acid other acids such as methcrylic, crotonic, β,β-dimethylacrylic and cinnamic acids could be used. Generally, the products were separated after quenching the reaction mixture with water, but in some cases, extraction with chloroform becomes necessary. Mechanistically the reaction follows a Friedel-Crafts acylation route. The reaction conditions used are compatible with a variety of substituents. The yields of the diones range from 35 to 40%. Hydroxycoumarins could be recoverred to the extent of 20 to 25%. In this context it is pertinent to mention that the cyanoethylation of 4-hydroxycoumarin derivative with acrylonitrile does not take place either in the presence of acidic or basic catalyst.

The structures of the compounds **1**—**17** were established on the basis of spectral and analytical data. In general dihydropyranobenzopyrandiones exhibit characteristic UV bands at λ_{max}^{MeOH} 215, 220, 280—290 (>C=O, lactonic), 315 nm (>C=O chromanone). The IR (Nujol or CH_2Cl_2) spectra of these compounds showed two bands: 1720—1740, 1660—1680. In the ^1H NMR spectra in $CDCl_3$ the aromatic protons appeared in the region δ 7.3—7.8 but in trifluoroacetic acid they were observed at δ 8.0.

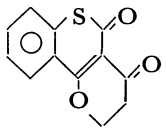
Further, all of them readily gave 2,4-dinitrophenylhydrazones, which rule out the possibility of the acryloyloxy derivatives. As a model compound for the synthesis of I, 4-hydroxy-7-methoxycoumarin was reacted with crotonic acid in the presence of PPA to yield a crystalline solid (II) which readily gave 2,4-dinitrophenylhydrazone (mp 264 °C) and was found to be identical (mmp) with the compound previously reported.[5)]

The above reaction was extended to 4-hydroxythiocoumarin and its derivatives. The chemistry of the latter is of interest since they also show the same pharmacological properties as the oxygen analogs. The activity of the sulfur analog of dicoumarol is 1/10th that of parent compound but the sulfur analog of warfarin has the same activity as that of dicoumarol.[6)]

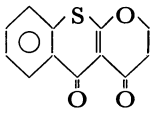
When 4-hydroxy(thiocoumarin) was allowed to reacted with α,β-unsaturated acids in the presence of polyphosphoric acid, the dihydropyranobenzothiopyrandiones were obtained in good yields (55—70%). However, the spectral data of these compounds revealed that they are not the expected 2,3-dihydro-4*H*,5*H*-pyrano[3,2-*c*][1]benzothiopyran-4,5-diones (III) but rather the isomeric chromanones (IV) as follows:

Firstly, their UV_{max}^{MeOH} showed only two principal bands namely at λ 225—230 nm and λ 305—315 nm indicating that absorption due to carbonyl group of the coumarin is absent.

The IR (CH_2Cl_2) of some typical compounds of this type showed bands at 1680 and 1610 cm^{-1} corresponding to CO frequencies at 4 and 5 positions.



III



IV

Additional and convincing proof of the above structures was deduced from their NMR spectra.

In the latter, the aromatic protons were shifted much downfield to δ 8.7—9.1 whereas in the expected dihydropyrano[3,2-*c*][1]benzothiopyrandiones the signals for aromatic protons would have come to δ 7.4—7.8.

It would be expected that the hydrogen nucleus proximate to the carbonyl group *i.e.* at the position 6,

would be the most pertubed of aromatic hydrogen atoms of the 2,3-dihydro-4*H*,5*H*-pyrano[2,3-*b*][1]-benzothiopyran-4,5-diones. These aromatic protons constitute a complex system wherein the proton at position '6' produces a quartet at unusually low field. In contrast the aromatic protons of the angular 2,3-dihydro-4*H*,5*H*-pyrano[3,2-*c*][1]benzothiopyran-4,5-diones would absorb around δ 7.4—7.8 as observed by us as well as by Berndt and Holzer[7] in their work on the Beckmann rearrangement of oximes of thiochromanones.

This difference helps in distinguishing angular and linear pyranobenzothiopyrandione structures.

The general applicability of this reaction was demonstrated by reacting 4-hydroxy-8-methyl, 7-methyl; 6-methylcoumarins as well as thiocoumarins with α,β-unsaturated acids in presence of PPA.

Experimental

^{1}H NMR spectra were recorded for solutions in deuteriochloroform and trifluoroacetic acid with a Varian A-60 instrument (tetramethylsilane as an internal reference). IR spectra were measured for Nujol mulls and for solutions in dichloromethane with a Perkin-Elmer spectrophotometer. UV spectra were measured for solutions in methanol with a Hilger instrument. Melting points were determined in a sulfuric acid bath. Purity of compounds was tested by TLC in all cases.

General procedure for the condensation of 4-hydroxycoumarin or thiocoumarin with α,β-unsaturated acids.

To a freshly prepared mixture of phosphorus pentaoxide (20 g) and phosphoric acid (10 ml) preheated to 100° for 30 min, 4-hydroxycoumarin or thiocoumarin (0.01 mol) and α,β-unsaturated acid (0.01 mol) were added. Temperature of the reaction mixture was maintained at 120 °C for 5 h. Reaction mixture was then cooled and cold water added and it was kept overnight. The product that separated was collected by filtration and washed well with sodium hydrogencarbonate solution to remove unreacted hydroxycoumarin and then with water, dried and crystallized from appropriate solvents. In cases of extraction with chloroform, the solvent layer was thoroughly washed with sodium hydrogen carbonate solution, water and dried. Evaporation of the solvent yielded a solid in most cases, crystallised from suitable solvent.

a) From 4-Hydroxycoumarin:

1 Mp 196—197 °C (ethanol), brown needles. UV λ_{max} (MeOH) 215, 295 and 315 nm. NMR ($CDCl_3$+DMSO-d_6) δ: 2.9 (2H, t, CH_2 next to C=O, J=3 Hz); 4.95 (2H, t, CH_2 next to O, J=3 Hz); 7—8 (4H, m, ar.). Found: C, 66.5; H, 3.4%. Calcd for $C_{12}H_8O_4$: C, 66.7; H, 3.1%. 2,4-DNP, mp 258—260 °C. Found: N, 14.2%. Calcd for $C_{18}H_{12}N_4O_7$: N, 14.2%. Yield: 800 mg.

2 Mp 213—214 °C (methanol-acetone); brown plates. UV λ_{max} (MeOH) 215, 295, and 320 nm. IR (Nujol) cm^{-1}: 1750 (>C=O, coumarin); 1675 (>C=O, chromanone); 1600, 1550, and 1500 (ar.). NMR ($CDCl_3$+DMSO-d_6) δ: 1.2 (3H, d, CH_3, J=3.5 Hz); 2.8 (1H, m, <CH); 4.6—4.8 (2H, d, O-CH_2-, J=3 Hz); 7—8 (4H, m,ar.). Found: C, 67.5; H, 4.5%. Calcd for $C_{13}H_{10}O_4$: C, 67.8; H, 4.3%. 2,4-DNP, mp 254—255 °C. Found: 14.0%. Calcd for $C_{19}H_{14}N_4O_7$: N, 13.7%. Yield: 830 mg.

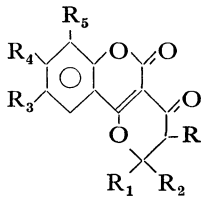
3 Mp 209—210 °C (ethanol), yellow plates. IR(Nujol) cm^{-1}: 1740 (>C=O, counarim); 1660 (>C=O, chromanone); 1600, 1550, 1500 (ar.). NMR (CF_3CO_2H) δ: 1.83 (3H, d, CH_3, J=6 Hz), 3.0 (2H, broad s, CH_2); 5.1—5.4 (1H, broad, m, >CH); 7.4—8.4 (4H, m, ar.). MS: *m/e* 230, 215 (M−15). Found: C, 67.8; H, 4.6%. Calcd for $C_{13}H_{10}O_4$: C, 67.8; H, 4.3%. 2,4-DNP, mp 264—265 °C. Found: N, 13.8%. Calcd for $C_{19}H_{14}N_4O_7$: N, 13.7%. Yield: 740 mg.

4 Mp 184—185 °C (ethanol), pale yellow needles. Found: C, 68.6; H, 5.1%. Calcd for $C_{14}H_{12}O_4$ C, 68.9; H, 4.9%. 2,4-DNP, mp 249—251 °C. Found: N, 13.5%. Calcd for $C_{20}H_{16}N_4O_7$: N, 13.7%. Yield: 840 mg.

5 Mp 258—260 °C (ethanol-chloroform), brown plates. Found: C, 73.9; H, 4.2%. Calcd for $C_{18}H_{12}O_4$: C, 74.0; H, 4.1%. Yield: 860 mg.

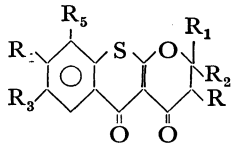
6 Mp 203—204 °C (acetic acid-water); brown needles. Found: C, 68.1; H, 4.0%. Calcd for $C_{13}H_{10}O_4$: C, 67.8; H, 4.3%. Yield: 835 mg.

7 Mp 209—210 °C (ethanol), brown needles. Found:



2,3-Dihydro-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4,5-diones.

1 R=R$_1$=R$_2$=R$_3$=R$_4$=R$_5$=H
2 R=Me; R$_2$=R$_5$=H
3 R=H; R$_1$=Me; R$_2$—R$_5$=H
4 R=H; R$_1$=R$_2$=Me; R$_3$—R$_5$=H
5 R=H; R$_1$=Ph; R$_2$—R$_5$=H
6 R=R$_1$=R$_2$=R$_4$=R$_5$=H; R$_3$=Me
7 R=R$_3$=Me; R$_1$=R$_2$=R$_4$=R$_5$=H
8 R$_1$=R$_3$=Me; R=R$_2$=R$_4$=R$_5$=H
9 R$_1$=R$_2$=R$_3$=Me; R=R$_4$=R$_5$=H
10 R=R$_1$=R$_2$=R$_3$=R$_5$=H; R$_4$=Me
11 R=R$_4$=Me; R$_1$=R$_2$=R$_3$=R$_5$=H
12 R$_1$=R$_4$=Me; R=R$_2$=R$_3$=R$_5$=H
13 R$_1$=R$_2$=R$_4$=Me; R=R$_3$=R$_5$=H
14 R=R$_1$=R$_2$=R$_3$=R$_4$=H; R$_5$=Me
15 R=R$_5$=Me; R$_1$=R$_2$=R$_3$=R$_4$=H
16 R$_1$=R$_5$=Me; R=R$_2$=R$_3$=R$_4$=H
17 R$_1$=R$_2$=R$_5$=Me; R=R$_3$=R$_4$=H



2,3-Dihydro-4*H*,5*H*-pyrano[2,3-*b*][1]benzothiopyran-4,5-diones.

18 R—R$_5$=H
19 R=Me; R$_1$—R$_5$=H
20 R$_1$=Me; R=R$_2$=R$_5$=H
21 R$_1$=R$_2$=Me; R=R$_2$—R$_5$=H
22 R$_3$=Me; R=R$_1$=R$_2$=R$_4$=R$_5$=H
23 R=R$_3$=Me; R$_1$=R$_2$=R$_4$=R$_5$=H
24 R$_2$=R$_3$=Me; R=R$_1$=R$_4$=R$_5$=H
25 R$_1$=R$_2$=R$_3$=Me; R=R$_4$=R$_5$=H
26 R$_1$=R$_4$=Me; R=R$_2$=R$_3$=R$_5$=H
27 R$_1$=R$_2$=R$_4$=Me; R=R$_3$=R$_5$=H
28 R—R$_4$=H; R$_5$=Me
29 R=R$_5$=Me; R$_1$—R$_4$=H
30 R$_1$=R$_5$=Me; R=R$_2$—R$_4$=H
31 R$_1$=R$_2$=R$_5$=Me; R=R$_3$=R$_4$=H

C, 68.7; H, 5.1%. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%. 2,4-DNP, mp >280 °C. Found: N, 14.3%. Calcd for $C_{20}H_{16}N_4O_7$: N, 14.2%. Yield: 810 mg.

8 Mp 192—194 °C (benzene–acetone), brown cubes. IR (CH_2Cl_2) cm^{-1}: 1760 (>C=O, coumarin); 1650 (>C=O, chromanone); 1600, 1550, and 1500 (ar.). NMR ($CDCl_3$) δ: 1.7 (3H, d, CH-CH_3; J=6.5 Hz); 2.5 (3H, s, CH_3); 2.8 (2H, d, CH_2, J=7 Hz); 4.9—5.2 (1H, m, CH-); 7.2—7.8 (3H, m, ar.). Found: C, 69.1; H, 4.9%. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%. Yield: 850 mg.

9 Mp 199—201 °C (ethanol), yellowish brown needles. Found: C, 69.6; H, 5.5%. Calcd for $C_{15}H_{14}O_4$: C, 69.8; H, 5.4%. 2,4-DNP, mp 268—270 °C. Found: N, 12.6%. Calcd for $C_{21}H_{18}N_4O_7$: N, 12.8%. Yield: 820 mg.

10 Mp 168 °C (ethanol–chloroform), brown needles. Found: C, 67.9; H, 4.4%. Calcd for $C_{13}H_{10}O_4$: C, 67.8; H, 4.3%. Yield: 790 mg.

11 Mp 183—185 °C (ethanol), pale brown needles. Found: C, 68.6; H, 5.2%. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%. 2,4-DNP, mp —320 °C. Found: N, 14.2%. Calcd for $C_{20}H_{18}N_4O_7$: N, 14.2%. Yield: 800 mg.

12 Mp 170—171 °C (aqueous ethanol), yellow prisms. Found: C, 69.2; H, 4.9%. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%. 2,4-DNP, mp 265—266 °C. Found: N, 14.4%. Calcd for $C_{20}H_{16}N_4O_7$: N, 14.2%. Yield: 780 mg.

13 Mp 158—160 °C (ethyl acetate–petroleum ether), yellow needles. IR (KBr) cm^{-1}: 1725 (>C=O, coumarin); 1680 (>C=O, chromanone) 1600, 1550, and 1500 (ar.). NMR ($CDCl_3$) δ: 1.63 (6H, s, $C(CH_3)_2$); 2.8 (2H, s, CH_2); 7.1—7.8 (3H, m, ar.). Found: C, 69.6; H, 5.6%. Calcd for $C_{15}H_{14}O_4$: C, 69.8; H, 5.4%. 2,4-DNP, mp 274—275 °C. Found: N, 15.9%; Calcd for $C_{21}H_{18}N_4O_7$: N, 15.7%. Yield: 720 mg.

14 Mp 221—223 °C (ethanol–chloroform), pale yellow needles. Found: C, 68.1; H, 4.2%. Calcd for $C_{13}H_{10}O_4$: C, 67.8; H, 3.9%. Yield: 680 mg.

15 Mp 225—227 °C (ethanol–chloroform), pale orange needles. Found: C, 69.2; H, 4.7%. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%. 2,4-DNP, mp >290 °C. Found: N, 14.4%. Calcd for $C_{20}H_{16}N_4O_7$: N, 14.2%. Yield: 790 mg.

16 Mp 170—172 °C (ethanol–chloroform), brown needles. Found: C, 69.1; H, 5.2%. Calcd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%. Yield: 900 mg.

17 Mp 165—167 °C (ethyl acetate–petroleum ether), brown prisms. Found: C, 69.6; H, 5.5%. Calcd for $C_{15}H_{14}O_4$: C, 69.8; H, 5.4%. 2,4-DNP, mp 279—280 °C. Found: N, 12.9%. Calcd for $C_{21}H_{18}N_4O_7$: N, 12.8%. Yield: 750 mg.

b) From 4-Hydroxy(thiocoumarin):

18 Mp 178—180 °C (ethanol–chloroform), pale yellow needles. UV (MeOH) λ_{max}: 230 and 315 nm. IR (CH_2Cl_2) cm^{-1}: 1710 (>C=O, chromanone); 1615 (>C=O, chromone), 1600, 1500 (ar.). NMR (CF_3CO_2H) δ: 3.9 (2H, t, CH_2 next to >C=O); 5.15 (2H, t, CH_2– next to –O–), 8.1—8.5 (3H, m, ar.), 8.83—9.1 (1H, m, ar.); MS: *m/e* 232, 204 (M−CO). Found: C, 62.4; H, 3.8%. Calcd for $C_{12}H_8O_3S$: C, 62.1; H, 3.5%. 2,4-DNP, mp 254—256 °C. Found: N, 13.4%. Calcd for $C_{18}H_{12}O_4$: N, 13.6%. Yield: 900 mg.

19 Mp 199—201 °C (ethanol), brown prisms. UV (MeOH) λ_{max} 230, 305 nm. Found: C, 63.3; H, 4.3%. Calcd for $C_{13}H_{10}O_3S$: C, 63.4; H, 4.1%. 2,4-DNP, mp 275—277 °C. Found: N, 13.1%. Calcd for $C_{19}H_{14}O_6N_4S$: N, 13.1%. Yield: 1.1 g.

20 Mp 203—205 °C (methanol), yellow prisms. IR (Nujol) cm^{-1}; 1700 (>C=O, chromanone); 1610 (>C=O, chromone), 1600, 1500 (ar.). NMR (CF_3CO_2H) δ: 1.9 (3H, d, CH_3, J=5 Hz); 3.2 (2H, broad t, CH_2– next to >C=O); 5.4 (2H, broad t, CH_2– next to –O–); 8.0 (3H, broad s, ar.); 8.75 (1H, broad d, ar. J=10 Hz). Yield: 1.3 g.

21 Bp 180—190 °C/2.5 mmHg, yellow oil. Found: C, 64.9; H, 4.7%. Calcd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6%. 2,4-DNP, mp 220—221 °C. Found: N, 12.9%. Calcd for $C_{20}H_{16}N_4O_6S$: N, 12.7%). Yield: 900 mg.

22 Mp 194—195 °C (aqueous ethanol), brown prisms. Found: C, 63.6; H, 4.4%. Calcd for $C_{13}H_{10}O_3S$: C, 63.4; H, 4.1%. 2,4-DNP, mp 264—265 °C. Found: N, 13.6%. Calcd for $C_{19}H_{14}N_4O_6S$: N, 13.8%. Yield: 1.32 g.

23 Yellow oil. Found: C, 64.5; H, 4.8%. Calcd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6%. 2,4-DNP, mp 205—207 °C. Found: N, 12.8%. Calcd for $C_{20}H_{16}N_4O_6S$: N, 12.7%. Yield: 1.1 g.

24 Mp 159—161 °C (aqueous ethanol), yellow prisms. Found: C, 64.4; H, 4.7%. Calcd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6%. 2,4-DNP, mp 268—270 °C. Found: N, 12.8%. Calcd for $C_{20}H_{16}N_4O_6S$: N, 12.7%. Yield: 1.45 g.

25 Yellow oil. Found: C, 65.9; H, 5.4%. Calcd for $C_{15}H_{14}O_3S$: C, 65.7; H, 5.1%. 2,4-DNP, mp 260—261 °C. Found: N, 12.2%. Calcd for $C_{21}H_{18}N_4O_5S$: N, 12.3%. Yield: 1.2 g.

26 Mp 164—165 °C (benzene–petroleum ether), pale yellow needles. Found: C, 64.9; H, 4.8%. Calcd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6%. Yield: 1.43 g.

27 Yellow oil. Found: C, 65.5; H, 4.9%. Calcd for $C_{15}H_{14}O_3S$: C, 65.7; H, 5.1%. 2,4-DNP, mp 205—207 °C. Found: N, 12.5%. Calcd for $C_{21}H_{18}N_4O_6S$: N, 12.3%. Yield: 1.2 g.

28 Mp 214—215 °C (acetic acid), pale yellow prisms. Found: C, 63.6; H, 4.3%. Calcd for $C_{13}H_{10}O_3S$: C, 63.4; H, 4.1%. Yield: 1.38 g.

29 Mp 226—228 °C (acetic acid), pale black needles. Found: C, 64.7; H, 4.9%. Calcd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6%. Yield: 1.25 g.

30 Mp 203—204 °C (ethanol), pale brown needles. Found: C, 64.3; H, 4.5%. Calcd for $C_{14}H_{12}O_3S$: C, 64.6; H, 4.6%. Yield: 1.47 g.

31 Yellow oil. Found: C, 65.5; H, 5.1%. Calcd for $C_{15}H_{14}O_3S$: C, 65.7; H, 5.1%. Yield: 1.3 g.

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