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Acid Catalyzed Condensation of Isoprene with Orcinol: Synthesis of 2,2-Dimethylchromans and 5-Methylxanthyletin Derivatives

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Condensation of orcinol with 2-methylbuta-1,3-diene (isoprene) has been achieved in the presence of orthophosphoric acid as catalyst leading to the exclusive formation of 2,2-dimethylchromans in one step. A novel route for the synthesis of 5-methylxanthyletin derivatives is described.

(Keywords: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; 2,2-Dimethylchromans; 2-Methylbuta-1,3-diene; 5-Methylxanthyletin; Orcinol; Pechmann condensation)

Sauer katalysierte Kondensation von Isopren mit Orcin: Synthese von 2,2-Dimethylchroman- und 5-Methylxanthyletin-Derivaten

Kondensation von Orcin mit Isopren in Gegenwart von Orthophosphorsäure führt in einem Schritt zu 2,2-Dimethylchromanen. Außerdem wird ein neuer Weg für die Synthese von 5-Methylxanthyletinderivaten aufgezeigt.

Introduction

A frequently occurring arrangement[1] of the isoprenoid unit in natural phenolic products is either in the form of the 2,2-dimethylchromene ring or as 3,3-dimethylallyl unit. 2,2-Dimethylchromans occur rarely in plants; they are, however, obtained as degradative products during the structural elucidation of naturally occurring phenolic products bearing isoprenoid unit. The utility of these chromans as synthetic precursors for 2,2-dimethylchromenes[2] and pyranocoumarins[3] has been well demonstrated. In view of this, the condensation of

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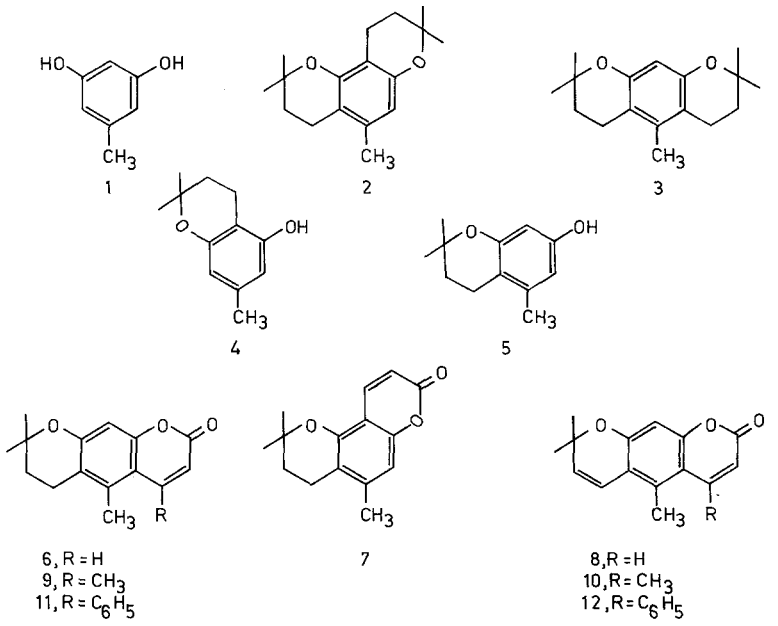
1,3-dihydroxy-5-methylbenzene (orcinol) (**1**) with 2-methylbuta-1,3-diene in the presence of an acid catalyst (orthophosphoric acid) has been studied which resulted in the exclusive formation of 2,2-dimethylchromans in good yields compared with earlier methods[4–6] for their synthesis. Further, the natural occurrence[7] of linear pyranocoumarins (xanthyletin derivatives) and their marked physiological activities[8,9] prompted us to devise a new and convenient route for their synthesis. In the present communication, the synthesis of 5-methylxanthyletin and its derivatives is reported.

Results and Discussion

The condensation of **1** with 2-methylbut-1,3-diene in presence of orthophosphoric acid gave a mixture of four products (**A**, **B**, **C** and **D**) in the ratio of 3:3:2:10 (overall yield: 70%). The separation of the mixture was achieved by column chromatography on silica gel with petroleum ether.

Compound **A** (the faster moving fraction) did not give the ferric reaction and its elemental analysis showed the introduction of two isoprene units. The ^{1}H-NMR spectrum of **A** showed a singlet of one proton at δ 6.20 ppm (aromatic proton), two singlets at 2.12 (methyl group) and 1.28 (gem. dimethyl groups), a triplet at 2.53 and a multiplet at 1.58–1.87 (each integrating for four protons), assigned to methylene groups. It was thus assigned the structure of 3,4,9,10-tetrahydro-2,2,5,8,8-pentamethyl-2*H*,8*H*-benzo[1,2-b:3,4-b']dipyran (**2**) (non symmetrical structure). Compound **B** was found to be an isomer of **2**. It was identified as 3,4,6,7-tetrahydro-2,2,5,8,8-pentamethyl-2*H*,8*H*-benzo[1,2-b:5,4-b']dipyran (**3**) on the basis of its elemental analysis and ^{1}H-NMR spectral data which showed two distinct triplets at 1.75 and 2.55 (each integrating for four protons, characteristic for chroman methylene groups) along with other usual signals.

Compounds **C** and **D** did not give ferric reaction and were found to be isomeric monochromans (elemental analysis). The ^{1}H-NMR spectra of **C** showed besides other signals two singlets of one aromatic proton each at 6.10 and 6.20 whereas that of **D** showed two singlets at 6.13 and 6.21. Hence, a clear distinction between the structures of compounds **C** and **D** were not possible and either of the compounds could be assigned the structure of 3,4-dihydro-5-hydroxy-2,2,7-trimethyl-2*H*-1-benzopyran (**4**) or 3,4-dihydro-7-hydroxy-2,2,5-trimethyl-2*H*-1-benzopyran (**5**). The structures of compounds **C** and **D** were confirmed as **4** and **5** by further reaction with 2-methylbut-1,3-



diene and orthophosphoric acid. **C** gave only one dichroman (**2**) while in the case of compound **D** a mixture of expected two dichromans **2** and **3** was obtained. The formation of the two dichromans (**2**, **3**) from **5** could be explained on the basis of the availability of two sites for 2-methylbuta-1,3-diene attack, followed by cyclization involving the 7-hydroxyl group.

Pechmann condensation of the monochroman **5** with malic acid in presence of concentrated sulphuric acid gave a product which could be assigned the structure of either 3,4-dihydro-2,2,5-trimethyl-2*H*,8*H*-benzo[1,2-b:5,4-b']dipyran-8-one (5-methyl-dihydroxanthyletin, **6**) or the isomeric 3,4-dihydro-2,2,5-trimethyl-2*H*,8*H*-benzo[1,2-b:3,4-b'] dipyran-8-one (**7**) on the basis of its ^{1}H-NMR spectral data, which showed a singlet at 6.60 for one aromatic proton along with other expected signals. The correct structure was confirmed as **6** by direct comparison (TLC, m.mp, ^{1}H-NMR) with an authentic sample[10]. Compound **6** on dehydrogenation with *DDQ* (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in anhydrous benzene afforded 2,2,5-trimethyl-2*H*,8*H*-benzo[1,2-b:5,4-b']dipyran-8-one (5-methylxanthyletin, **8**). Dehydrogenation of **6** could also be affected by the reaction with *NBS* (*N*-bromosuccinimide) in carbon tetrachloride. The structure of **8** was established on the basis of its ^{1}H-NMR spectral data.

Compound **5** on *Pechmann* condensation with ethyl acetoacetate in

absolute alcohol in presence of dry hydrogen chloride gas afforded 3,4-dihydro-2,2,5,6-tetramethyl-2*H*,8*H*-benzo[1,2-b:5,4-b']dipyran-8-one (4,5-dimethyldihydroxanthyletin, **9**), the structure of which was assigned on the basis of ^{1}H-NMR spectral data; the orientation was elucidated by analogy with the compound **6**, obtained in the previous case. Dehydrogenation of **9** either with *DDQ* or *NBS* gave 2,2,5,6-tetramethyl-2*H*,8*H*-benzo[1,2-b:5,4-b']dipyran-8-one (4,5-dimethylxanthyletin, **10**); its structure was confirmed on the basis of ^{1}H-NMR spectral data. Reaction of **5** with ethyl benzoylacetate in absolute alcohol in the presence of dry HCl gas gave 3,4-dihydro-2,2,5-trimethyl-6-phenyl-2*H*,8*H*-benzo[1,2-b:5,4-b']dipyran-8-one (5-methyl-4-phenyldihydroxanthyletin, **11**) which on dehydrogenation with *DDQ* or *NBS* furnished 2,2,5-trimethyl-6-phenyl-2*H*,8*H*-benzo[1,2-b:5,4-b'] dipyran-8-one (5-methyl-4-phenylxanthyletin, **12**). The structures of compounds **11** and **12** were in agreement with their ^{1}H-NMR spectral data.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. Silica gel (60–120 mesh) was used for all chromatographic separations. The experimental C,H-values for **2–6** and **9–11** were in full agreement with the given structures for these compounds.

Reaction of orcinol (**1**) *with 2-methylbuta-1,3-diene*

A solution of 2-methylbuta-1,3-diene (1.2 ml) in xylene (2 ml) was added to a mixture of **1** (1.0 g), orthophosphoric acid (85%, 1 ml) and xylene (3 ml) with constant stirring at 30–35° during 2 h. The stirring was continued for 4 h more and then the mixture neutralized with sodium bicarbonate solution (5%). It was extracted with ether, washed with water, dried (Na_2SO_4) and distilled to give a residue which was shown (TLC) to be a mixture of four products (**A**, **B**, **C** and **D**). These were separated by a column of silica gel while elution with petroleum ether gave the following four fractions successively.

Fraction **A**: *3,4,9,10-Tetrahydro-2,2,5,8,8-pentamethyl-2H,8H-benzo-[1,2-b:3,4-b']dipyran* (**2**)

Crystallized from petroleum ether as colourless shining elongated prisms (0.15 g), mp 74–75°. $C_{17}H_{24}O_2$.

^{1}H-NMR (δ, ppm): 1.28 [s, 12 H, 2 × $C(CH_3)_2$], 1.58–1.87 (m, 4 H, 3- and 9-CH_2—), 2.12 (s, 3 H, 5-CH_3), 2.53 (t, $J = 7$ Hz, 4 H, 4- and 10-CH_2—), 6.20 (s, 1 H, H-6).

Fraction **B**: *3,4,6,7-Tetrahydro-2,2,5,8,8-pentamethyl-2H,8H-benzo-[1,2-b:5,4-b']dipyran* (**3**)

Crystallized from petroleum ether as colourless shining needles (0.15 g), mp 120–121°. $C_{17}H_{24}O_2$.

^{1}H-NMR (δ): 1.27 [s, 12 H, 2 × $C(CH_3)_2$], 1.75 (t, $J = 7$ Hz, 4 H, 3- and 7-CH_2—), 2.55 (t, $J = 7$ Hz, 4 H, 4- and 6-CH_2—), 2.05 (s, 3 H, 5-CH_3), 6.08 (s, 1 H, H-10).

Fraction **C**: *3,4-Dihydro-5-hydroxy-2,2,7-trimethyl-2H-1-benzopyran* (**4**)

Crystallized from petroleum ether to give colourless shining prisms (0.1 g), mp 93–94°. $C_{12}H_{16}O_2$.

^{1}H-NMR (δ): 1.30 [s, 6 H, $C(CH_3)_2$], 1.74 and 2.58 (each t, $J = 7$ Hz, each 2 H, 3- and 4-CH_2— respectively), 6.10 and 6.20 (each s, each 1 H, H-6 and H-8 respectively).

Fraction **D**: *3,4-Dihydro-7-hydroxy-2,2,5-trimethyl-2H-1-benzopyran* (**5**)

Obtained as an oil (0.5 g). $C_{12}H_{16}O_2$.

^{1}H-NMR (δ): 1.27 [s, 6 H, $C(CH_3)_2$], 1.75 and 2.49 (each t, $J = 7$ Hz, each 2 H, 3- and 4-CH_2— respectively), 2.10 (s, 3 H, 5-CH_3), 6.13 and 6.21 (each s, each 1 H, H-6 and H-8 respectively).

Reaction of 2-methylbuta-1,3-diene with **4**

A solution of 2-methylbuta-1,3-diene (0.16 ml) in xylene (1 ml) was added to a mixture of the monochroman **4** (0.2 g), orthophosphoric acid (85%, 0.5 ml) and xylene (1 ml) with constant stirring at 30–35° during 2 h. The mixture was stirred for further 4 h and then the reaction worked up as in case of **1** to give the dichroman **2** (0.15 g), mp 74–75°. It was found to be identical (TLC, m.mp, ^{1}H-NMR) with the sample obtained above.

Reaction of 2-methylbuta-1,3-diene with **5**

A solution of 2-methylbuta-1,3-diene (0.39 ml) in xylene (1 ml) added to a mixture of **5** (0.5 g), orthophosphoric acid (85%, 0.5 ml) and xylene (1 ml) with constant stirring at 30–35° during 2 h. After stirring for further 4 h the reaction was worked up as in case of **1** to give a mixture of two compounds which were separated by preparative TLC to give the dichromans **2** (0.15 g) and **3** (0.3 g). These compounds were identical (TLC, m.mp, ^{1}H-NMR) with the samples obtained above.

3,4-Dihydro-2,2,5-trimethyl-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (**6**)

To a mixture of the monochroman **5** (1.0 g) and malic acid (1.2 g), conc. sulphuric acid (4 ml) was added. The contents were heated on an oil bath for 2 h at 120–125° and then the cooled reaction mixture was poured over crushed ice. The separated product was extracted with ether, the ether extract washed successively with aqueous sodium carbonate (5%, 20 × 10 ml), water, dried (Na_2SO_4) and distilled to give **6**. It was crystallized from benzene—petroleum ether as colourless needles (0.4 g), mp 164–165° (Lit.[10] mp 164–165°). $C_{15}H_{16}O_3$.

^{1}H-NMR (δ): 1.35 [s, 6 H, $C(CH_3)_2$], 1.80 and 2.70 (each t, $J = 7$ Hz, each 2 H, 3- and 4-CH_2— respectively), 2.35 (s, 3 H, 5-CH_3), 6.15 and 7.80 (each d, $J = 9.5$ Hz, each 1 H, H-7 and H-6 respectively), 6.60 (s, 1 H, H-10).

2,2,5-Trimethyl-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (**8**)

Method (i): The dihydropyranocoumarin **6** (0.1 g) was refluxed with *DDQ* (0.09 g) in anhydrous benzene (10 ml) for 72 h. The solution was filtered, washed

successively with 1% $NaHCO_3$ aq, water, dried (Na_2SO_4) and distilled. The residue, thus obtained on crystallisation from benzene—petroleum ether afforded **8** as colourless shining needles (0.08 g), mp 148–150°, (lit.[10] mp 148–150°).

^{1}H-NMR (δ): 1.50 [s, 6 H, $C(CH_3)_2$], 2.40 (s, 3 H, 5-CH_3), 5.70 and 6.35 (each d, $J = 10$ Hz, each 1 H, H-3 and H-4 respectively), 6.20 and 7.80 (each d, $J = 9.5$ Hz, each 1 H, H-7 and H-6 respectively), 6.60 (s, 1 H, H-10).

Method (ii): A solution of **6** (0.1 g), *NBS* (0.07 g) and benzoyl peroxide (0.005 g) in anhydrous carbon tetrachloride (10 ml) was refluxed for 36 h. The solution was filtered and solvent distilled off to give a product which on crystallization from benzene—petroleum ether furnished colourless shining crystals of **8** (0.05 g), mp 148–150°.

2,2,5,6-Tetramethyl-2 H,8 H-benzo[1,2-b:5,4-b']dipyran-8-one (**9**)

A stream of dry HCl gas was passed through a solution of **5** (0.5 g) and ethylacetoacetate (0.6 ml) in absolute ethanol (50 ml) for 6 h. After keeping for 2 days at room temperature, the solution was poured over crushed ice and the separated product was crystallized from alcohol to give **9** (0.5 g) as colourless shining needles, mp 125–126°. $C_{16}H_{18}O_3$.

^{1}H-NMR (δ): 1.37 [s, 6 H, $C(CH_3)_2$], 1.85 (t, $J = 7$ Hz, 2 H, 3-CH_2—), 2.26 (s, 3 H, 5-CH_3), 2.52–2.75 (m, 5 H, 4-CH_2— and 6-CH_3), 6.00 and 6.70 (each s, each 1 H, H-7 and H-10 respectively).

2,2,5,6-Tetramethyl-2 H,8 H-benzo[1,2-b:5,4-b']dipyran-8-one (**10**)

Method (i): The above dihydropyranocoumarin **8** (0.1 g) was refluxed with *DDQ* (0.098 g) in anhydrous benzene for 72 h. The reaction was worked up as in case of **8** (method i) to give a product which crystallized from benzene—petroleum ether as colourless shining needles of **10** (0.08 g), mp 91–92°. $C_{16}H_{16}O_3$.

^{1}H-NMR (δ): 1.50 [s, 6 H, $C(CH_3)_2$], 2.32 and 2.58 (each s, each 3 H, 5- and 6-CH_3 respectively), 5.60 and 6.45 (each d, $J = 10$ Hz, each 1 H, H-3 and H-4 respectively), 5.97 and 6.61 (each s, each 1 H, H-7 and H-10 respectively).

Method (ii): A solution of **8** (0.1 g), *NBS* (0.07 g) and benzoyl peroxide (0.005 g) was refluxed in anhydrous carbon tetrachloride (10 ml) for 30 h. Working up of the reaction mixture as in case of **8** (method ii) gave a product which crystallized from benzene—petroleum ether to give colourless shining crystals of **10** (0.04 g), mp 91–92°.

3,4-Dihydro-2,2,5-trimethyl-6-phenyl-2 H,8 H-benzo[1,2-b:5,4-b']dipyran-8-one (**11**)

Dry HCl gas was passed through a solution of **5** (0.5 g) and ethyl benzoyl acetate (0.6 ml) in absolute ethanol (50 ml) for 6 h. After keeping for two days at room temperature, the reaction was worked up as in case of **9** to give **11** which was crystallized from alcohol as colourless shining needles (0.70 g), mp 211–212°. $C_{21}H_{20}O_3$.

^{1}H-NMR (δ): 0.85 [s, 6 H, $C(CH_3)_2$], 1.65 and 2.57 (each t, $J = 7$ Hz, each 2 H, 3- and 4-CH_2— respectively), 2.30 (s, 3 H, 5-CH_3), 6.02 and 6.76 (each s, each 1 H, H-7 and H-10 respectively), 7.15–7.45 (m, 5 H, —C_6H_5).

2,2,5-Trimethyl-6-phenyl-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (**12**)

Method (i): The dihydropyranocoumarin **11** (0.1 g) was refluxed with *DDQ* (0.07 g) in dry benzene (10 ml) for 72 h. Working up of the reaction as usual gave a solid which crystallized from benzene—petroleum ether to give colourless shining needles of **12** (0.08 g), mp 169—170°. $C_{21}H_{18}O_3$.

^{1}H-NMR (δ): 0.92 [s, 6 H, $C(CH_3)_2$], 2.30 (s, 3 H, 5-CH_3), 5.35 and 6.31 (each d, $J = 10$ Hz, each 1 H, H-3 and H-4 respectively), 5.96 and 6.65 (each s, each 1 H, H-7 and H-10 respectively).

Method (ii): A solution of **11** (0.1 g), *NBS* (0.055 g) and benzoyl peroxide (0.005 g) in anhydrous carbon tetrachloride (10 ml) was refluxed for 36 h. The reaction on working up as usual gave **12** which crystallized from benzene—petroleum ether to give colourless shining needles (0.05 g), mp 169–170°.

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