Synthesis of 5,6-Dihydropyran-3(4*H*)-one

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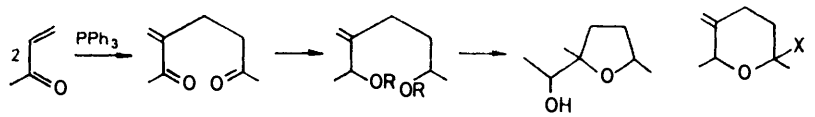
The synthesis and oxidation of the title compound (8b) are described. Attempted cyclization of 3-methyleneheptane-2,6-diol (2a) and 2,6-diacetoxyheptan-3-one (5) afforded furan derivatives (3) and (7), respectively. 6,6-Ethylenedioxy-3-methyleneheptan-2-ol (10) was successively cyclized, methoxylated, and ozonized to give 5,6-dihydropyran-3(4*H*)-one (8b), which yielded 6-methylmaltol (13) on treatment with selenium dioxide.

In the course of our studies on the synthesis of 3-hydroxy-4*H*-pyran-4-ones, potent flavouring materials, we previously reported the preparation of these compounds from tetrahydro-4*H*-pyran-4-ones.[1] 5,6-Dihydropyran-3(4*H*)-ones (8) are also considered to be good precursors of 3-hydroxy-4*H*-pyran-4-ones, but little attention has been paid to their oxidation. Moreover, they have previously been synthesized from materials obtainable only with difficulty, *viz.* carbohydrates,[2] 3,4-dihydro-2*H*-pyrans,[3] or furfuryl alcohols.[4] We now report the preparation of the the title compound from the readily available 3-methyleneheptane-2,6-dione and also report its oxidation to 3-hydroxy-4*H*-pyran-4-one.

As a likely precursor to (8) cyclization of 3-methyleneheptane-2,6-diol (2a) by dehydration and intramolecular acetalization of 6-ethylenedioxy-3-methyleneheptan-2-ol (10) were undertaken.

Dimerization of methyl vinyl ketone in the presence of triphenylphosphine afforded the known[5] diketone (1) which was converted into the diol (2a) upon treatment with sodium borohydride in methanol. Compound (2a) was converted into its acetoxy-derivative (2b) by treatment with acetic anhydride in the presence of sodium acetate. When (2a) and a catalytic amount of toluene-*p*-sulphonic acid or dicyclohexylcarbodi-imide–toluene-*p*-sulphonic acid[6] on toluene was refluxed for 9 h, 2-(1-hydroxyethyl)-2,5-dimethyltetrahydrofuran (3) was obtained as the sole product.



(1) (2) (3) (4)

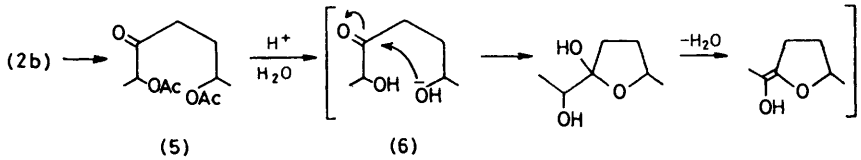
a; R = H
b; R = COMe

a; X = H
b; X = OH
c; X = OMe

To date, all efforts to convert the diol (2a) into the heterocycle (4a) by direct dehydration have proven unsuccessful. Numerous procedures have been attempted which result in either recovered starting material[7,8] or a multitude of intractable products.[9]

A solution of the diol (2b) in methylene chloride was ozonized at −50 °C and, after decomposition of the ozonide with zinc powder–acetic acid, 2,6-diacetoxyheptan-3-one (5) was isolated in excellent yield.

Hydrolysis of the diacetate (5) in 2M-hydrochloric



(5) (6)

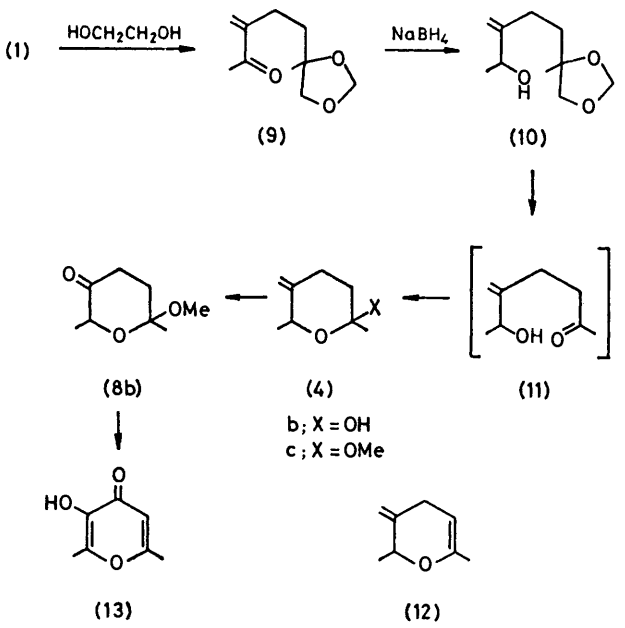
(7) (8)

a; X = H
b; X = OMe

Scheme

acid at 70 °C for 1 h afforded 2-acetyl-5-methyltetrahydrofuran (7) in 67% yield but none of the expected diol (6) could be isolated. The formation of the tetrahydrofuran (7) can be rationalized as shown in the Scheme: the hydrolysed product (6) formed in the first stage undergoes intramolecular acetalization to produce a furandiol, which gives the product (7) on subsequent dehydration, which occurs spontaneously under the conditions employed. Thus, attempted cyclization of compounds (2a, b) gave the furan derivatives (3) and (7) without any formation of the pyran derivatives (4a) and (8a).

We next examined the synthesis of 5,6-dihydropyran-3(4*H*)-ones (8) by means of intramolecular acetalization of 6-hydroxy-5-methyleneheptan-2-one (11). 6,6-Ethylenedioxy-3-methyleneheptan-2-one (9) was easily prepared by refluxing (1) with ethylene glycol in benzene in the presence of toluene-*p*-sulphonic acid.[5] Reduction of (9) with sodium borohydride in methanol at −25 °C



afforded 6,6-ethylenedioxy-3-methyleneheptan-2-ol (10) in high yield. A two-phase solution containing the acetal (10) in benzene and 1M-sulphuric acid at room temperature for 30 h provided 2-hydroxy-2,6-dimethyl-5-methylene-3,4,5,6-tetrahydro-2*H*-pyran (4b) instead of the hydroxy-ketone (11). However, treatment of (10) in the presence of toluene-*p*-sulphonic acid in methanol–methyl orthoformate at room temperature for 6 h afforded 2-methoxy-2,6-dimethyl-5-methylene-3,4,5,-6-tetrahydro-2*H*-pyran (4c) in 56% yield. As compound (4c) readily underwent elimination of methanol to give 2,6-dimethyl-3-methylene-3,4-dihydro-2*H*-pyran (12) on distillation over 100 °C and 6-methoxy-2,6-dimethyl-5,6-dihydropyran-3(4*H*)-one (8b) was expected to be easily isolable by the oxidation used in the next step, the reaction mixture was used without isolation of the product (4c).

A solution of compound (4c) in methanol was ozonized at −50 °C and after decomposition of the ozonide with dimethyl sulphide, the tetrahydropyranone (8b) was isolated in a pure state [35% from (10)]. The structure (8b) was assigned on the basis of i.r., n.m.r., and mass spectra, and by elemental analysis.

Finally, we examined the oxidation of compound (8b). 3-Hydroxy-2,6-dimethyl-4*H*-pyran-4-one (13), the odour of which has been described as raspberry-like,[10] could be obtained by refluxing (8b) with selenium dioxide in 95% ethanol. The i.r. and n.m.r. spectra of the pyranone (13) were identical with those of an authentic sample.[11]

EXPERIMENTAL

I.r. spectra were determined with a Hitachi 215 spectrophotometer, n.m.r. spectra with a JEOL C-60 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi RMU-6E spectrometer. Column chromatography was carried out with Wakogel C-100. 3-Methyleneheptane-2,6-dione (1) was prepared by the reported method; b.p. 80.5—82.0 °C at 4 mmHg (lit.,[5] 82—83 °C at 4 mmHg).

3-Methyleneheptane-2,6-diol (2a).—To a mixture of 3-methyleneheptane-2,6-dione (1) [5] (50.0 g, 0.35 mol) in methanol (170 ml) was added a solution of sodium borohydride (12.0 g, 0.32 mol) in methanol (120 ml) at −25 °C and the mixture was stirred for 1 h. The excess of sodium borohydride was destroyed by addition of saturated ammonium chloride solution and methanol was removed *in vacuo*. Precipitated sodium chloride was filtered off and the filtrate was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The resulting oil was distilled to give the diol (2a) (37.8 g, 74%), b.p. 86.5—88.0 °C at 0.25 mmHg; $\nu_{max.}$ (neat) 3 350 (OH) and 905 cm^{-1} (C=CH_2); δ(CCl_4) 1.20 (3 H, d, *J* 6.0 Hz), 1.29 (3 H, d, *J* 6.0 Hz), 1.59 (4 H, m), 3.22 (2 H, s), 3.52 (1 H, m), 3.80 (1 H, q, *J* 6.0 Hz), 4.79 (1 H, s), and 5.00 (1 H, s).

2-(1-Hydroxyethyl)-2,5-dimethyltetrahydrofuran (3).—A mixture of the diol (2a) (3.0 g), a trace of toluene-*p*-sulphonic acid monohydrate, and benzene (67 ml) was refluxed, while the water was removed with a Dean-and-Stark trap, for 9 h. Removal of the solvent and distillation of the residue gave recovered diol (2a) (0.84 g) and the *furan* (3) (1.14 g, 38%), b.p. 51—52 °C at 30 mmHg; $\nu_{max.}$ (neat) 3 430 (OH) and 1 085 cm^{-1} (C–O–C); δ(CCl_4) 1.15 (3 H, s), 1.19 (6 H, m), 1.83 (4 H, m), 2.77 (1 H, s), 3.60 (1 H, m), and 4.08 (1 H, m) (Found: C, 66.7; H, 11.1. $C_8H_{16}O_2$ requires C, 66.6; H, 11.2%).

2,6-Diacetoxy-3-methyleneheptane (2b).—Acetylation of (2a) (8.4 g) with acetic anhydride (100 ml) and sodium acetate (1.8 g) at 60 °C for 8 h and distillation gave the *acetate* (2b) (12.2 g, 92%), b.p. 74—75 °C at 0.27 mmHg; $\nu_{max.}$ (neat) 1 730 (C=O), 1 643 (C=C), 1 246 (C–O–C), and 906 cm^{-1} (C=CH_2); δ(CCl_4) 1.23 (3 H, d, *J* 6.0 Hz), 1.33 (3 H, d, *J* 6.0 Hz), 1.91 (4 H, m), 2.04 (6 H, s), 4.98 (1 H, s), 5.17 (1 H, s), and 5.35 (2 H, m) (Found: C, 63.05; H, 9.1. $C_{12}H_{20}O_4$ requires C, 63.15; H, 8.85%).

2,6-Diacetoxyheptan-3-one (5).—A solution of (2b) (1.70 g) in methylene chloride (32 ml) was placed in 100 ml flask equipped with an ozone inlet, and a gas outlet. Ozone was produced by electric discharge from an ozonator and bubbled through the solution at −50 °C for 20 min; excess of ozone was then removed by flushing with oxygen. Acetic acid (9.5 ml), water (4 ml), and zinc powder (32 g) was then

added to the ozonolysis mixture, which was stirred at 46 °C for 1 h. When the ozonide had been completely decomposed, the inorganic materials were filtered off and the filtrate was dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was distilled to give the *ketone* (5) (1.59 g, 93%), b.p. 93—94 °C at 0.23 mmHg; $\nu_{max.}$ (neat) 1 733 (C=O), 1 371, and 1 244 cm^{-1} (C–O–C); $\delta(CCl_4)$ 1.22 (3 H, d, *J* 6.0 Hz), 1.37 (3 H, d, *J* 7.5 Hz), 1.77 (2 H, m), 2.01 (3 H, s), 2.12 (3 H, s), 2.51 (2 H, m), 4.89 (1 H, m), and 5.08 (1 H, q, *J* 7.5 Hz) (Found: C, 57.4; H, 8.2. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%).

2-*Acetyl*-5-*methyltetrahydrofuran* (7).—A mixture of the ketone (5) (2.20 g) and 2M-hydrochloric acid (22 ml) was heated at 70 °C for 1 h. The cooled mixture was neutralized with sodium hydrogen carbonate, extracted with ether, and the ethereal extract was washed with water and then dried ($MgSO_4$). After removal of the solvent, the resulting oil was distilled to afford the tetrahydrofuran (7) (0.82 g, 67%), b.p. 60—61 °C at 20 mmHg; $\nu_{max.}$ (neat) 1 717 (C=O), 1 355, and 1 090 cm^{-1} (C–O–C); $\delta(CCl_4)$ 1.26 (3 H, d, *J* 6.0 Hz), 2.10 (4 H, m), 2.16 (3 H, s), 4.10 (1 H, m), and 4.25 (1 H, m); *m/e* 128 (M^+) and 85 (M^+ — Ac).

6,6-*Ethylenedioxy*-3-*methyleneheptan*-2-*ol* (10).—To a mixture of 6,6-ethylenedioxy-3-methyleneheptan-2-one [2] (78.5 g) in methanol (400 ml) was added a solution of sodium borohydride (8.1 g) in methanol (100 ml) at −25 °C and the mixture was stirred for a further 1 h at −25 °C. Excess of sodium borohydride was destroyed by addition of saturated ammonium chloride solution, and methanol was removed *in vacuo*. Precipitated sodium chloride was filtered off and the filtrate was extracted with ether. The extract was washed with water, dried, and evaporated. The resulting oil was distilled to give the alcohol (10) (68.3 g, 86%), b.p. 93—96 °C at 1.2 mmHg; $\nu_{max.}$ (neat) 3 420 (OH), 1 640 (C=C), 1 050 (C–O–C), and 900 cm^{-1} ($C=CH_2$); $\delta(CCl_4)$, 1.21 (3 H, d, *J* 6.0 Hz), 1.28 (3 H, s), 1.97 (4 H, m), 2.97br (1 H, s), 3.89 (4 H, s), 4.20 (1 H, q, *J* 6.0 Hz), 4.74 (1 H, s), and 4.97 (1 H, s); *m/e* 186 (M^+).

2,6-*Dimethyl*-5-*methylene*-3,4,5,6-*tetrahydro*-2H-*pyran*-2-*ol* (4b).—A mixture of the alcohol (10) (220 mg), benzene (3 ml), and 1M-sulphuric acid (0.5 ml) was stirred at room temperature for 30 h. The separated organic layer was washed with aqueous sodium hydrogencarbonate and water, and then dried. Removal of the solvent left a clear oil, which was chromatographed on silica gel [eluant hexane–ethyl acetate (10 : 1 v/v)] to give the tetrahydropyran (4b) (65 mg, 38%); $\nu_{max.}$ (neat) 3 350 (OH), 1 645 (C=C), 1 080 (C–O–C), and 900 cm^{-1} ($C=CH_2$); $\delta(CCl_4)$ 1.26 (3 H, d, *J* 7.0 Hz), 1.37 (3 H, s), 1.92 (4 H, m), 3.70 (1 H, s), 3.75 (1 H, m), and 4.75br (2 H, s); *m/e* 141 (M^+ — H) and 125 (M^+ — OH).

2-*Methoxy*-2,6-*dimethyl*-5-*methylene*-3,4,5,6-*tetrahydro*-2H-*pyran* (4c).—A mixture of the alcohol (10) (5.0 g), methanol (50 ml), methyl orthoformate (5.6 g), and toluene-*p*-sulphonic acid monohydrate (52.6 mg) was stirred at room temperature for 6 h. The resulting mixture was then poured into aqueous sodium carbonate and extracted with ether. The ethereal extract was then well washed with water, dried with sodium sulphate, and evaporated. The residual oil was distilled (bath temperature below 100 °C) to give the *tetrahydropyran* (4c) (2.33 g, 56%), b.p. 85—87 °C at 70 mmHg, n_D^{20} 1.448 9; $\nu_{max.}$ (neat) 1 650 (C=C), 1 095, 1 060 (C–O–C), and 900 cm^{-1} ($C=CH_2$); $\delta(CCl_4)$ 1.21 (3 H, s), 1.21 (3 H, d, *J* 7.0 Hz), 1.98 (4 H, m), 3.21 (3 H, s), 4.05 (1 H, q, *J* 7.0 Hz), and 4.70br (2 H, s); *m/e* 125 (M^+ — MeO) and 124 (M^+ — MeOH) (Found: C, 69.4; H, 10.4. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%).

When this distillation was carried out at over 100 °C, elimination of methanol occurred to give 2,6-*dimethyl*-3-*methylene*-3,4-*dihydro*-2H-*pyran* (12), b.p. 60—65 °C at 65 mmHg; $\nu_{max.}$ (neat) 1 670 (C=C), 1 045 (C–O–C), and 895 cm^{-1} ($C=CH_2$); $\delta(CCl_4)$ 1.33 (3 H, d, *J* 7.0 Hz), 1.63 (3 H, s), 2.70 (2 H, m), 4.30 (1 H, m), 4.35 (1 H, q, *J* 7.0 Hz), and 4.88br (2 H, s); *m/e* 124 (M^+).

6-*Methoxy*-2,6-*dimethyl*-5,6-*dihydropyran*-3(4H)-*one* (8b).—A mixture of the alcohol (10) (5.0 g), methanol (50 ml), methyl orthoformate (5.6 g), and toluene-*p*-sulphonic acid monohydrate (52.6 mg) was stirred at room temperature for 6 h. To this reaction mixture anhydrous sodium carbonate (29.6 mg) was added with stirring, and then ozone was bubbled through over a period of 2 h at −50 °C. Excess of ozone was removed by flushing with oxygen for 15 min and further flushing with nitrogen for 30 min. Dimethyl sulphide (5 ml) was then added to the ozonolysis mixture, which was stirred for 1 h at −10 °C and for an additional 1.5 h at room temperature. The resulting mixture was poured into water and extracted with water and the extracts were dried over sodium sulphate. Removal of the solvent under reduced pressure and chromatography of the residue [silica gel, pentane–diethyl ether (5 : 1 v/v) as eluant] gave the *ketone* (8b) (1.50 g, 35%), n_D^{20} 1.442 5; $\nu_{max.}$ (neat) 1 722 (C=O), 1 080, and 1 055 (C–O–C); $\delta(CCl_4)$ 1.13 (3 H, d, *J* 7.0 Hz), 1.31 (3 H, s), 2.21 (4 H, m), 3.22 (3 H, s), and 3.95 (1 H, q, *J* 7.0 Hz); *m/e* 158 (M^+), 127 (M^+ — MeO) (Found: C, 60.4; H, 8.6. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%).

3-*Hydroxy*-2,6-*dimethyl*-4H-*pyran*-4-*one* (13).—To a mixture of the ketone (8b) (750 mg) in 95% ethanol (8 ml) was added a solution of selenium dioxide (1.8 g) in 95% ethanol (16 ml) over 20 min under reflux. The mixture was refluxed for 4 h, and then the precipitated selenium was filtered off. The filtrate was concentrated and the residue was then chromatographed on silica gel using benzene–ethanol (20 : 1 v/v) as eluant to give the crude product. Sublimation of the crude crystals and recrystallization from methylene chloride–pentane (1 : 1 v/v) afforded a pure sample of the pyranone (13) (196 mg, 30%), m.p. 161—162 °C (lit.,[12] 162.5 °C). A mixed-melting point determination with an authentic sample [11] indicated no depression.

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