164. *Tetrahydropyran-3 : 4-diol and Tetrahydro-2 : 2 : 5 : 5-tetramethylfuran-3 : 4-diol.*

By Oscar Heuberger and L. N. Owen.

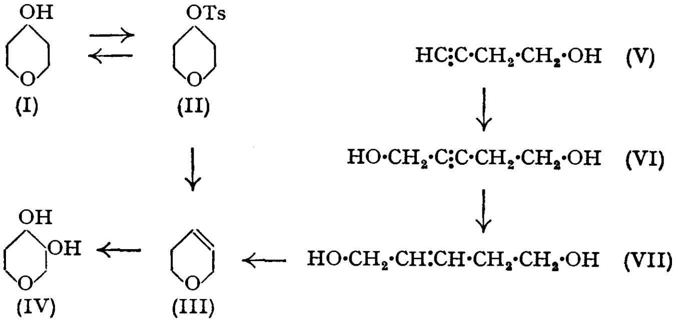
The sulphonyloxy-group in the toluene-*p*-sulphonate of tetrahydropyran-4-ol undergoes replacement by iodine, acetoxy-, etc., much more readily than in the alicyclic series.

A convenient synthesis of 2 : 3-dihydro-6-pyran, from acetylenic precursors, is described.

The *cis*- and the *trans*-form of each of the diols mentioned in the title has been prepared by hydroxylation of the corresponding unsaturated compound with neutral potassium permanganate or performic acid. The isolation and properties of 3 : 4-epoxytetrahydro-2 : 2 : 5 : 5-tetramethylfuran (IX) are recorded.

In connection with studies on alicyclic glycols (Clarke and Owen, *J.*, 1950, 2108, and earlier papers), an extension into the field of heterocyclic glycols is envisaged, and, as a simple analogue of *cyclo*hexane-1 : 2-diol, the preparation of tetrahydropyran-3 : 4-diol (IV) has been investigated. The *trans*-form was briefly described by Paul and Tchelitcheff (*Compt. rend.*, 1947, **224**, 1722, where it is incorrectly named 2 : 3-dihydroxytetrahydropyran) as obtained by hydrolysis of the 3 : 4-epoxide derived by oxidation of 5 : 6-dihydro-2-pyran (III) with perbenzoic acid, but it is evident that by the use of the appropriate hydroxylation methods it should be possible to prepare both the *cis*- and the *trans*-diol directly from the unsaturated compound (III). The latter was obtained by Paul and Tchelitcheff (*loc. cit.*) by dehydrobromination of 4-bromotetrahydropyran, but an alternative method appeared to be the elimination of toluene-*p*-sulphonic acid from the ester (II), particularly since *cyclo*hexyl toluene-*p*-sulphonate gives *cyclo*hexene, and no *cyclo*hexanol, when treated with alkali (Hückel and Frank, *Annalen*, 1930, **477**, 143).

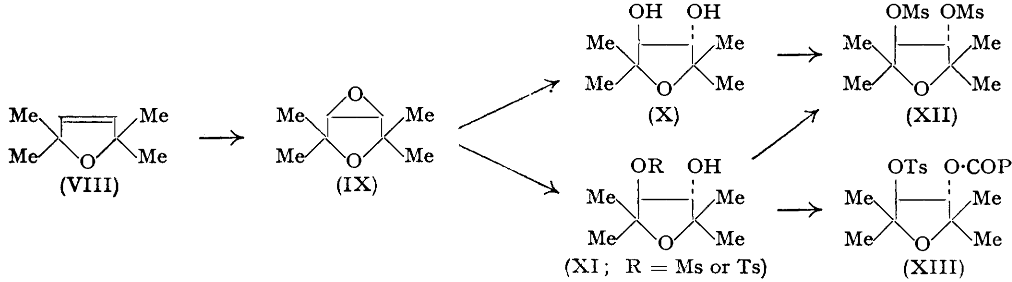
Tetrahydropyran-4-ol (I) readily formed a crystalline toluene-*p*-sulphonate (II), but when this was heated with aqueous potassium hydroxide it not only gave the dihydropyran (III) but also underwent simple hydrolysis and regenerated a considerable proportion of (I); replacement, at the expense of elimination, therefore occurs more readily than with the alicyclic analogue. This was also shown in the reactions of (II) with alcoholic potassium acetate, alcoholic lithium chloride, and sodium iodide in acetone (cf. Clarke and Owen, *loc. cit.*), the corresponding acetate, chloride (together with some ethyl ether), and iodide being formed as well as the unsaturated product. The replacement with iodine occurred particularly readily, and gave a 67% yield of distilled tetrahydro-4-iodopyran, in marked contrast to the similar reaction with *cyclo*hexyl toluene-*p*-sulphonate (cf. Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133).



These results, coupled with the inaccessibility of tetrahydro-4-hydroxypyran itself, made it necessary to devise a new synthesis of the dihydropyran, and the following method was found to be suitable. But-3-yn-1-ol (V), prepared by condensation of acetylene and ethylene oxide in liquid ammonia (cf. Macallum, U.S.P. 2 125 384), was converted into pent-2-yne-1 : 5-diol (VI) by reaction with formaldehyde in the presence of the cuprous hydroxide catalyst described by Heilbron, Jones, and Sondheimer (*J.*, 1947, 1586); an alternative procedure, involving the interaction of gaseous formaldehyde with the Grignard compound of but-3-yn-1-ol gave a smaller yield of the desired product. Quantitative hydrogenation of the pentynediol over a palladium catalyst deposited on charcoal, calcium carbonate, or barium sulphate, gave no indication of a change of rate after the absorption of 1 mol. of hydrogen, but by interruption of the hydrogenation at that point a product was obtained which contained the required pent-2-ene-1 : 5-diol (VII) since when heated under reduced pressure with sulphuric acid it gave 5 : 6-dihydro-2-pyran (III) in 34% yield; this could probably be improved by further study of the semihydrogenation conditions.

The *cis*- and the *trans*-tetrahydropyran-3 : 4-diol were readily prepared by hydroxylation of the dihydropyran with neutral permanganate and performic acid, respectively. Both were oils, but they were characterised as the crystalline ditoluene-*p*-sulphonates.

An unusual result was obtained in the hydroxylation of 2 : 5-dihydro-2 : 2 : 5 : 5-tetramethylfuran (VIII). With neutral permanganate it gave the expected *cis*-tetrahydro-2 : 2 : 5 : 5-tetramethylfuran-3 : 4-diol, but with performic acid not only the *trans*-diol (X) but also the epoxide (IX) was obtained. Both stereoisomers of the diol were solid, and they were further characterised by conversion into crystalline disulphonates. Epoxides are considered to be intermediates in the hydroxylation of olefins with performic acid (cf. Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786), but normally do not survive the strongly acidic conditions; the present instance appears to be the first case of the isolation of the epoxide, which suggests that the ethylene oxide ring in (IX) is more stable than usual. Nevertheless, the oxide was hydrolysed to the *trans*-diol (X) when heated with sulphuric acid in aqueous dioxan, and reacted readily with methanesulphonic acid and with toluene-*p*-sulphonic acid to give the monosulphonates (XI) of the *trans*-diol; these were liquids, but they were characterised by conversion into the crystalline *trans*-dimethanesulphonate (XII) and *trans*-benzoate toluene-*p*-sulphonate (XIII).



EXPERIMENTAL

γ-Pyrone was prepared by decarboxylation of chelidonic acid (*Org. Synth.*, Coll. Vol. II, p. 126) by heating it at 250—260°, in batches of 10 g., with copper powder (20 g.) and 20-mesh pumice (10 g.). The organic layer from the distillate was taken up in ether, dried, evaporated, and distilled to give γ-pyrone, b. p. 97°/12 mm. The average yield was 64% (cf. Willstätter and Pummerer, *Ber.*, 1904, **37**, 3745).

Tetrahydropyran-4-ol.—γ-Pyrone (22 g.) in ethanol (250 c.c.) was hydrogenated at 100° and 60 atm. during 8 hours by use of Raney nickel catalyst (5 g.). The product, isolated by evaporation of the filtered solution, was dissolved in ether and dried (Na_2SO_4). Distillation gave tetrahydropyran-4-ol (17·5 g., 79%), b. p. 84—85°/12 mm., n_D^{20} 1·4580.

*Toluene-*p*-sulphonate.* A solution of toluene-*p*-sulphonyl chloride (32 g.) in dry pyridine (50 c.c.) was added during 1 hour to a stirred solution of tetrahydropyran-4-ol (17·2 g.) in dry pyridine (50 c.c.) at 0°; the mixture was set aside at 0° overnight. The *toluene-*p*-sulphonate* (27 g., 63%) was precipitated by addition of ice, and crystallised from aqueous ethanol in colourless needles, m. p. 56° (Found: S, 12·3. $C_{12}H_{16}O_4S$ requires S, 12·5%).

Methanesulphonate. Tetrahydropyran-4-ol (2·86 g.) was treated with methanesulphonyl chloride (3·2 g.) in pyridine (10 c.c.). After 12 hours at 0°, the reaction mixture was diluted with chloroform (50 c.c.), washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The *methanesulphonate* (1·75 g., 35%) crystallised from ethanol in needles, m. p. 49—50° (Found : C, 40·3; H, 6·7; S, 17·5. $C_6H_{12}O_4S$ requires C, 40·0; H, 6·7; S, 17·8%).

Reactions of the Toluene-p-*sulphonate*.—(a) *With aqueous alkali*. The toluene-*p*-sulphonate (12·4 g.) was heated under reflux with 5% aqueous potassium hydroxide (100 c.c.) for 2 hours. After being cooled and saturated with salt, the reaction mixture was continuously extracted with ether for 2 days. Fractionation of the dried ethereal solution gave two main fractions : 5 : 6-dihydro-2-pyran (1·16 g., 28·6%), b. p. 92—100°, n_D^{24} 1·4438, and tetrahydropyran-4-ol (1·37 g., 27·8%), b. p. 88—90°/14 mm., n_D^{24} 1·4553. The latter was further identified as its toluene-*p*-sulphonate, m. p. and mixed m. p. 56°.

(b) *With sodium iodide*. The toluene-*p*-sulphonate (2 g.) and sodium iodide (3 g., 2·5 equiv.) in acetone (30 c.c.) were refluxed for 24 hours. The dark brown solution was filtered from sodium toluene-*p*-sulphonate (1·4 g., 92·5%) and was concentrated through a Fenske column to small bulk, the distillate being unsaturated. The semi-solid residue was diluted with water (10 c.c.) and extracted with ether (200 c.c.). The extracts were washed with aqueous sodium thiosulphate and water to remove free iodine, dried (Na_2SO_4), and evaporated under reduced pressure to a pale yellow oil, which on distillation gave *tetrahydro*-4-*iodopyran* (1·1 g., 67%), b. p. 79—80°/12 mm., n_D^{21} 1·5471 (Found : I, 59·85. C_5H_9OI requires I, 59·9%). The same product was also obtained (yield, 36%) by similar treatment of the methanesulphonate.

(c) *With potassium acetate*. The toluene-*p*-sulphonate (5 g.) and potassium acetate (5 g.) in ethanol (60 c.c.) were refluxed for 20 hours. The potassium toluene-*p*-sulphonate (3·5 g., 85%) was filtered off and an aliquot part of the filtrate was titrated with sodium hydroxide (phenolphthalein); the acidity corresponded to the formation of 42% of acetic acid. The mixture was concentrated to small bulk, the distillate being unsaturated. The solid residue was dissolved in water (10 c.c.) and extracted with ether (200 c.c.). The dried extracts, on fractional distillation, gave the acetate of tetrahydropyran-4-ol (0·8 g., 29%) as a colourless oil, b. p. 75—76°/12 mm., n_D^{22} 1·4368 (Found : C, 58·5; H, 8·7. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·4%). Baker (*J.*, 1944, 296) gives b. p. 47·5°/1 mm.

(d) *With lithium chloride*. A solution of the toluene-*p*-sulphonate (4 g.) and lithium chloride (2 g.) in ethanol (70 c.c.) was refluxed for 16 hours and then concentrated to small bulk, the distillate being unsaturated. The residue was diluted with water (20 c.c.) and extracted with ether (250 c.c.). The dried (Na_2SO_4) extracts were evaporated to an oil (0·37 g.), b. p. 44—45°/12 mm., n_D^{25} 1·4492, which was a mixture of 4-chloro- and 4-ethoxy-tetrahydropyran (Found : C, 54·7; H, 8·7; Cl, 19·6. Calc. for a mixture of 67% C_5H_9OCl and 33% $C_7H_{14}O_2$: C, 54·7; H, 8·6; Cl, 19·7%).

Pent-2-*yne*-1 : 5-*diol*.—(i) A cuprous hydroxide catalyst (Heilbron, Jones, and Sondheimer, *loc. cit.*) was prepared by treatment of cuprous chloride (12 g.) in 12% hydrochloric acid (180 c.c.) with 40% aqueous potassium hydroxide (180 c.c.). The precipitate was collected and washed with water; it was then transferred, while still moist, to a mixture of but-3-yn-1-ol (52 g.), 40% formaldehyde (80 g.), water (24 c.c.), and calcium carbonate (0·8 g.), which was stirred on a steam-bath for 4 days under nitrogen. The semi-solid product was collected on a filter and washed with aqueous ethanol (1 : 1) (500 c.c.). The filtrate and washings were concentrated and distilled, to give *pent*-2-*yne*-1 : 5-*diol* (48·8 g., 66%) as a colourless oil, b. p. 120°/0·5 mm., n_D^{24} 1·4890 (Found : C, 60·1; H, 7·9. $C_5H_8O_2$ requires C, 60·0; H, 8·05%).

(ii) A solution of methylmagnesium bromide was prepared from methyl bromide (172 g.) and magnesium (32·4 g.) in dry ether (800 c.c.). The ether was removed by distillation, dry benzene (1000 c.c.) being simultaneously added, and to the resulting solution but-3-yn-1-ol (40 g.) dissolved in dry benzene (50 c.c.) was slowly added, with stirring, during 2½ hours. Formaldehyde gas, generated by heating paraformaldehyde (60 g.), was introduced during a further 2 hours, stirring being maintained for several hours afterwards (cf. Raphael and Sondheimer, *J.*, 1950, 2100). The resulting complex was decomposed in the usual way with ammonium chloride solution, and the product on distillation afforded pent-2-yne-1 : 5-diol (8·75 g., 18%), b. p. 90—95°/0·03 mm., n_D^{21} 1·4895.

5 : 6-*Dihydro*-2-*pyran*.—A solution of pent-2-yne-1 : 5-diol (47·4 g.) in ethanol (250 c.c.) was hydrogenated at room temperature and pressure with a 5% palladium–charcoal catalyst (5 g.). When 1 mol. of hydrogen had been absorbed (4 hours) the reaction was stopped. Evaporation of the filtered solution then gave pent-2-ene-1 : 5-diol (39·3 g.), b. p. 91—92°/0·5 mm., n_D^{21} 1·4759. This material (18 g.), with 20% sulphuric acid (1 c.c.), was heated in nitrogen at

120°/12 mm., the distillate being collected in a receiver cooled in liquid air. After 4 hours the end of the reaction was indicated by a sudden frothing of the dark viscous residue. The distillate was allowed to melt, and the organic layer was removed, dried (Na_2SO_4), and distilled to give 5 : 6-dihydro-2-pyran (5·1 g., 34%), b. p. 94—95°, n_D^{15} 1·4480. Paul and Tchelitcheff (*loc. cit.*) give b. p. 93—94°, n_D^{19} 1·4477.

cis-*Tetrahydropyran*-3 : 4-*diol*.—A solution of potassium permanganate (10 g.) and magnesium sulphate (7·5 g.) in water (200 c.c.) was added dropwise with vigorous stirring to a solution of 5 : 6-dihydro-2-pyran (6·6 g.) in ethanol (150 c.c.) during 2½ hours, the temperature being kept between −15° and −20°. The manganese dioxide was filtered off and thoroughly washed with boiling water (400 c.c.) and the combined filtrates were filtered again through kieselguhr and concentrated under reduced pressure to small bulk. The residue was saturated with salt and continuously extracted with ether, to yield *cis*-tetrahydropyran-3 : 4-diol as a colourless viscous oil (1·6 g.), b. p. 84—87°/0·3 mm., n_D^{21} 1·4875. On treatment with toluene-*p*-sulphonyl chloride in pyridine it gave the cis-*ditoluene*-p-*sulphonate*, which crystallised from ethanol in needles, m. p. 131—132° (Found : C, 53·3; H, 5·2; S, 15·0. $C_{19}H_{22}O_7S_2$ requires C, 53·5; H, 5·2; S, 15·0%).

trans-*Tetrahydropyran*-3 : 4-*diol*.—5 : 6-Dihydro-2-pyran (6·9 g.) was added to pure formic acid (90 g.) and 30% hydrogen peroxide (11 g.) with vigorous stirring. The temperature rose to 45° and was so maintained by external cooling and later by heating in a water-bath during 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue heated on the steam-bath with 10% sodium hydroxide (100 c.c.) for an hour and again concentrated to small bulk. The residue was continuously extracted with ether and furnished *trans*-tetrahydropyran-3 : 4-diol (5·95 g.) as a colourless oil, b. p. 100—102°/0·5 mm., n_D^{23} 1·4861. Paul and Tchelitcheff (*loc. cit.*) give b. p. 158—159°/9 mm., n_D^{18} 1·4873. Reaction with toluene-*p*-sulphonyl chloride in pyridine gave the trans-*ditoluene*-p-*sulphonate*, which crystallised from ethanol in needles, m. p. 161—162° (Found : C, 53·8; H, 5·5; S, 14·8%).

Reaction of 2 : 5-*Dihydro*-2 : 2 : 5 : 5-*tetramethylfuran with Performic Acid*.—The dihydrotetramethylfuran (Johnson and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 2615) (7·9 g.), pure formic acid (68 g.), and 30% hydrogen peroxide (8·4 g.) were stirred at 40° for 3½ hours. Formic acid was then distilled off, and the dark brown residue was basified with sodium hydroxide, heated under reflux for an hour, and distilled under reduced pressure. The distillate was saturated with salt and extracted with ether; the extracts were dried (Na_2SO_4) and concentrated to give 3 : 4-*epoxytetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran* (2·3 g., 25%) as a colourless, camphoraceous oil, b. p. 90—91°/100 mm., n_D^{22} 1·4190, which solidified below 20° (Found : C, 67·3; H, 10·2. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). The alkaline residue from the distillation was dissolved in water and extracted with ether (400 c.c.); evaporation of the dried (Na_2SO_4) extracts gave trans-*tetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*-3 : 4-*diol* (0·6 g.) which crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 158—159° (Found : C, 60·2; H, 10·15. $C_8H_{16}O_3$ requires C, 60·0; H, 10·1%). The *dimethanesulphonate*, prepared by treatment of the diol with excess of methanesulphonyl chloride in pyridine, crystallised from methanol in plates, m. p. 104° (Found : C, 37·95; H, 6·3; S, 19·9. $C_{10}H_{20}O_7S_2$ requires C, 37·95; H, 6·4; S, 20·3%).

Ring-fission of 3 : 4-*Epoxytetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*.—(i) The epoxide (0·15 g.) was heated for 1½ hours at 100° with dioxan (1·5 c.c.) and N-sulphuric acid (3 c.c.). The solution was then neutralised with barium carbonate, filtered, and evaporated to a solid residue of *trans*-tetrahydro-2 : 2 : 5 : 5-tetramethylfuran-3 : 4-diol (0·1 g.), m. p. and mixed m. p. 158—159° after recrystallisation from light petroleum (b. p. 80—100°).

(ii) A solution of the epoxide (1 g.) and toluene-*p*-sulphonic acid (1·2 g.) in dry ether (80 c.c.) was set aside at 0° for 24 hours, then washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to an oil. A portion of this crude monotoluene-*p*-sulphonate was treated with benzoyl chloride in pyridine at 0° overnight, and gave the *benzoate toluene*-p-*sulphonate* of the *trans*-diol, which crystallised from ethanol in needles, m. p. 141—142° (Found : C, 62·8; H, 6·3. $C_{22}H_{26}O_6S$ requires C, 63·1; H, 6·3%).

(iii) Freshly distilled methanesulphonic acid (0·45 g.) was added to the epoxide (0·6 g.). The mixture became hot and viscous. The crude monomethanesulphonate thus obtained failed to crystallise; on treatment in pyridine solution with methanesulphonyl chloride it gave, in good yield, the *trans*-dimethanesulphonate, m. p. and mixed m. p. 104°.

cis-*Tetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*-3 : 4-*diol*.—A solution of potassium permanganate (6·25 g.) and anydrous magnesium sulphate (4·7 g.) in water (125 c.c.) was added dropwise with vigorous stirring to a solution of crude dihydrotetramethylfuran (6·3 g., b. p. 84—100°) in ethanol (150 c.c.) during 2 hours, the temperature being kept at 0°; manganese dioxide was then filtered off and washed with ethanol. The filtrates were evaporated under reduced pressure to a solid residue, which was extracted with ether, dried (Na_2SO_4), concentrated, and distilled to yield cis-*tetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*-3 : 4-*diol*, which crystallised from light petroleum (b. p. 40—60°) in needles (0·6 g.), m. p. 93—94° (Found: C, 60·2; H, 10·3. $C_8H_{16}O_3$ requires C, 60·0; H, 10·1%). Treatment of the diol with toluene-*p*-sulphonyl chloride in pyridine gave the *ditoluene*-p-*sulphonate*, which crystallised from methanol in flattened needles, m. p. 131—132° (Found: C, 56·5; H, 6·0; S, 13·6. $C_{22}H_{28}O_7S_2$ requires C, 56·4; H, 6·0; S, 13·7%).

The authors thank Professor R. P. Linstead, C.B.E., F.R.S., for his interest. Analyses were carried out in the Microanalytical Laboratory of this Department (Mr. F. H. Oliver).

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[*Received, November* 21*st*, 1951.]