A Rapid and Convenient Technique for converting Ketones into their Ethylenedioxy- or Trimethylenedioxy-derivatives, and for making Acetonides

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The ethylenedioxy-derivatives (ethylene acetals) of unhindered steroid, triterpene, and other ketones can be prepared by running a mixture of the ketone and ethylene glycol in tetrahydrofuran through an acid ion-exchange column and isolating the derivative from the eluate. This technique is particularly appropriate where such compounds are to be subjected to mass spectrometry but can also be used on a larger scale in synthetic sequences where protection of the carbonyl group is desired. The homologous (cyclic trimethylenedioxy-)derivatives, better for the latter purpose in certain cases, can be prepared in the same way, as can the acetonides of 1,3-dihydroxy-compounds.

SINCE steroid and triterpene ketones themselves give complex and rather unhelpful electron-impact mass spectra, they are usually first converted into their ethylenedioxy-derivatives, the $>C(OCH_2)_2$ function leading to the preferential cleavage of particular C–C bonds and hence to simpler and more meaningful fragmentation patterns.[1-3] It then becomes possible to infer the presence of methyl substituents, or double bonds, up to five carbon atoms away from the derivatised carbonyl function.[1] Thus, for example, the ethylenedioxy-derivatives of steroid-3-ones give fragments at *m/e* 99 (100%), 112 (~10%), and 125 (~45%); of 4-monomethyl compounds (in which the pathway leading to the 99 fragment is enhanced) at 99 (100%), 112 (negligible), and at 139 (125 + CH_2; ~4%); and of 4,4-dimethyl compounds (where lack of a C-4-proton prevents formation of the 112 and 125 fragments) at 99 only.[1]

In connection with recent structure-elucidation work carried out here on such compounds, we needed an efficient but mild method of effecting this derivatisation. The traditional procedures seemed to us rather tedious, requiring prolonged heating of the parent ketone in, typically, benzene containing an acid catalyst and either ethylene glycol [with Dean–Stark [4] (Salmi method) or chemical [5] removal of the liberated water] or an ethylenedioxy-exchange reagent.[6] In addition they are not particularly amenable to small-scale work.

A fortuitous observation of dimethyl acetal formation occurring from a ketone–methanol mixture on an acid-resin column suggested that such a method might also be used to effect ethylene acetal formation; this has proved to be the case, one of the acid ion-exchange resins designed to be unaffected by organic solvents proving to be effective and stable as well as being well suited to column operation. It was hoped to find a single solvent capable of dissolving both ethylene glycol and reactant; a cyclic ether seemed the obvious choice. In the event, it was found that either dioxan or tetrahydrofuran (THF) could be used but, as dioxan has been reported to be carcinogenic,[7] THF was preferred; its greater volatility is also an advantage.

The method involves running a solution of the ketone in ethylene glycol–THF (1 : 2) through a column of the resin (at a flow-rate depending on the reactivity of the ketone), collecting the eluate, and subjecting it to a simple work-up to isolate the derivative. Table 1 summarises the results obtained with representative ketones. The reaction proceeds quickly with unhindered cyclic ketones with, in particular, steroid-3-ones typically giving an 80—90% yield of derivative following a 5 minute pass through the column (in contrast to several hours at 80 °C using the Salmi method); and by using slower flow rates steroid-12- and 17-ones and triterpene-3-ones can also be derivatised satisfactorily. Varying carbonyl reactivity allows selectivity in, *e.g.*, compounds (11) and (13). The technique succeeds for compounds (6) and (16), difficult to derivatise by the Salmi method,[8,9] and is generally mild: t-hydroxy, acetate, and cyclopropane functions all survive. While this technique was mainly designed for small-scale work, it has also been used successfully for larger-scale (0.5 g) runs.

Derivatisation by the ethylenedioxy-group is frequently used in synthetic sequences to protect the carbonyl function (and its α-protons), particularly in the steroid series.[10] However, Heathcock *et al.*[11] have found that this method is inadequate when an alkyl-lithium is to be used as the reagent, since it simultaneously attacks the ethylenedioxy ring; for such reactions protection by the homologous (trimethylenedioxy) derivative is preferable. We have therefore confirmed (Table 2) that these derivatives can also be made using this technique, by substituting propane-1,3-diol for ethylene glycol. Rather slower flow rates usually have to be used but this is in line with Newman and Harper's finding [12] that preparation of such derivatives by the Salmi method requires longer reaction times and more catalyst than for the ethylenedioxy-derivatives.

Finally, we have shown that the derivatisation of a 1,3-dihydroxy compound by acetone, with the formation of the corresponding acetonide, can also be effected in this way. Here the procedure is particularly simple since the acetone serves as both solvent and reagent.

Others [13] have independently reported the formation of ethylenedioxy-derivatives from ethylene glycol and certain carbonyl compounds when kept in contact with acid ion-exchange resins. However, they variously stirred or heated the reactants together, only worked with aldehydes, did not employ a resin of the type used by us (which was found to be far superior for the present

purpose to the traditional, aqueous-solvent resins), and did not translate the procedure into a routine, column operation.

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. N.m.r. spectra were recorded at 60 MHz for solutions in deuteriochloroform with tetramethylsilane as internal reference and i.r. spectra were run in carbon tetrachloride. The resin was Rohm and Haas ' Amberlyst 15,' (BDH), one of the acidic (sulphonated polystyrene) ion-exchange resins stable to organic solvents. A slurry of the resin in ethylene glycol–tetrahydrofuran (from a recently opened bottle) (1 : 2 v/v) was poured into a standard chromatography column fitted with an ungreased tap. Heat was evolved when the slurry was prepared on a large scale. If the reaction was to be monitored by observing the disappearance of the C=O band in the i.r. spectrum, the THF was first run through a short column of active alumina and then distilled from lithium aluminium hydride or sodium to remove a carbonyl impurity which otherwise interfered (this was also done for any large-scale runs to ensure freedom from peroxides).

TABLE 1

Preparation of ethylenedioxy-derivatives (1,3-dioxolans)

	Ketone	Flow rate	% Reaction [a]	Isolated yield [b] (%)	B.p. or m.p. of derivative (°C) (mmHg) [c]
(1)	Cyclohexanone	Std. condns.[d]	100	71	178—179 (760)
(2)	2-Methylcyclohexanone	Std. condns.	97	73	185—186 (760)
(3)	2,6-Dimethylcyclohexanone	1/20th std. rate [e]	89 [f]	66 [f]	204—206 (760) *
(4)	Cyclopentanone	Std. condns.	88	50 [g]	150—153 (760)
(5)	Heptan-2-one	1/10th std. rate	83	60	184—186 (760)
(6)	Ethyl 4-oxopentanoate (laevulate)	1/10th std. rate	80	64	122—124 (25)
(7)	5α-Cholestan-3-one	Std. condns.	>98	90	114—115
(8)	Cholest-5-en-3-one	Std. condns.	55	*h*	129—131
(9)	5α-Androstan-3-one	Std. condns.	95	82	114—115
(10)	17β-Hydroxy-5α-androstan-3-one	Std. condns.	95	78	172—174
(11)	5α-Androstane-3,17-dione	Std. condns.		40 (3-acetal) 50 (bis-acetal) [i]	156 163
(12)	3α-Hydroxy-5α-androstan-17-one	1/10th std. rate	*ca.* 30	not isolated	
(13)	5α-Pregnane-3,11,20-trione	Std. condns.	not measured	65 (3-acetal) [j]	156—157 *
(14)	3β-Hydroxy-5α-spirostan-12-one (hecogenin)	1/10th std. rate	95	78	230—231
(15)	Urs-12-en-3-one (α-amyrenone)	1/20th std. rate [e]	75	55	182—184
(16)	4α,14-Dimethyl-9,19-cyclo-5α,9β-ergost-24(28)-en-3-one (cyclo-eucalenone)	1/10th std. rate [e]	not measured	75	87—88 *
(17)	24-Methylene-9,19-cyclo-5α,9β-lanostan-3-one (24-methylene-cycloartanone)	1/20th std. rate [e]	not measured	50	136—138 *

[a] As determined by g.l.c. (for liquids) and n.m.r. or i.r. (for solids). [b] Of distilled liquid or once-crystallised solid, and of >95% purity by g.l.c. or t.l.c. [c] Structures confirmed spectrally, by comparison of physical properties with those of authentic samples, *etc.*: see text for details. Those derivatives marked * were new compounds whose structures were additionally checked by C, H analyses derived from accurate M^+ values. [d] The ' standard conditions ' are those given in the Experimental section. [e] When such preparations are carried out on the 5—10 mg scale, the problem of maintaining a very slow column flow rate can be overcome by using a longer column and a correspondingly faster flow rate (and collecting more eluate). [f] After *two* passes through the column with a brief intermediate work-up. [g] Some product probably lost to aqueous phase during work-up. [h] Gave 55% (Δ^5-) derivative and 45% Δ^4-3-one after one pass through the column; increased to a total yield of 81% derivative by twice recycling the first pass mother liquors from crystallisation. [i] Reaction mixture resolved into 3-mono- and 3,17-bis-acetal by chromatography on active alumina using 40% ether in light petroleum for the bis- and pure ether for the mono-acetal (fractions monitored by i.r. spectroscopy). [j] No reaction detectable at 11- or 20-positions even with a flow rate 1/20th of standard.

TABLE 2

Preparation of trimethylenedioxy-derivatives (1,3-dioxanes) †

	Ketone	Flow rate	% Reaction [a]	Isolated yield [b] (%)	B.p. or m.p. of derivative (°C) (mmHg) [c]
(18)	Cyclohexanone	1/10th std. rate	85	68	196—198(760) 94—97 (20)
(19)	Cyclopentanone	Std. condns.[d]	95	50 [g]	195—197 (760)
(20)	5α-Cholestan-3-one	1/30th std. rate [e]	85	68	114 *
(21)	5α-Androstan-3-one	1/30th std. rate [e]	85	60	96—97

Under the ' standard conditions ' [d] compounds (18) and (21) gave 75 and 65% reaction respectively. † Same footnotes as Table 1.

10 × 1 cm Columns were used for those runs involving 10 mg or less of ketone, and 15 × 2.5 cm columns for the larger-scale (0.5 g) preparations. Columns were allowed to stand for at least an hour before use and then 25 or 200 ml, respectively, of the above-mentioned mixture was run through to remove brownish material leached from the resin.

To prepare an ethylenedioxy-derivative, the ketone, dissolved in the minimum quantity of ethylene glycol–THF, was run on to the top of the column and then washed through by adding further reagent mixture (15 ml for 10 mg ketone on a 10 × 1 column; 100 ml for 0.5 g on a 15 × 2.5 cm column) to the column and allowing it to percolate through at a rate dependent on the type of ketone and size of column. The *standard conditions* for unhindered cyclic ketones involved a flow rate of *ca.* 1.5 ml min^{-1} for the small column and 10 ml min^{-1} for the large—equivalent to a residence time of ~5 min in each case. The (slower) flow rates variously required for the other ketones were inferred from trial runs using i.r. spectroscopy (replacement of C=O by C–O bands), g.l.c. (Pye 104 instrument with flame ionization detector; 3% SE 30 on Chromosorb W; N_2 carrier), or t.l.c. (silica gel; ether–hexane; I_2 as detector; R_F derivative $>R_F$ ketone) to monitor the reaction.

To isolate the derivative from a 10 mg run, the eluate was diluted with water (30 ml) (preferably after first evaporating the bulk of the THF under reduced pressure at ≤ 30 °C) and extracted with dichloromethane (2 × 5 ml); the combined extracts were then washed with water (2 × 10 ml), dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. If the reaction went to >90—95% completion (i.r., g.l.c., or t.l.c.) the crude derivative was usually suitable, without further treatment, for mass spectrometry, any unchanged ketone giving insignificant peaks at that concentration. Otherwise, it was purified by distillation or by crystallisation from methanol or hexane, or, if necessary, by chromatography on alumina deactivated with 10% water (10 × 2 cm; hexane–ether; derivative eluted first). That the desired derivative had been obtained was demonstrated by n.m.r. [τ *ca.* 6.1 (4 H, s, O·CH_2·CH_2·O), as expected;[14] for steroid-3-ones, change in position of the C-19 methyl peak[15]], comparison of physical properties (b.p. and g.l.c. retention time for liquids; m.p. for solids) and i.r.–n.m.r. spectra with those found for samples prepared by the Salmi method,[4] or by mass spectrometry (M^+; and ions at *m/e* 99 *etc.*).

On the 0.5 g scale, the eluate was diluted with water (200 ml), and corresponding quantities of dichloromethane, *etc.*, were used.

The trimethylenedioxy-derivatives were prepared analogously except that propane-1,3-diol was used instead of ethylene glycol. A similar work-up procedure was used except that, due to the lower water solubility of propane-1,3-diol, the product was washed more thoroughly with water or else the crude product was run through a short column of alumina (deactivated with 10% water) using 2% ether in hexane as solvent, the excess of glycol being retained on the column. Care was taken during crystallisation to avoid exposure to water or acid, the trimethylenedioxy being more sensitive than the ethylenedioxy ring to hydrolysis.[12]

Structures were confirmed in the same way as for the ethylenedioxy-derivatives: τ *ca.* 6.2 (4 H, t or q, '*J*' *ca.* 5 Hz, O·CH_2·CH_2·CH_2·O), as found for other freely inverting 1,3-dioxanes;[16] the mass spectrum included fragments analogous to those seen at 99, *etc.*, for the ethylenedioxy-derivatives but, as expected,[3] at +14 a.m.u. (additional CH_2 (group); *viz.* at 113, 126 (weak), and 139 for the derivatives of compounds (20) and (21), and at 113 only for the derivatives of (18) and (19).

Columns could be used repeatedly with different ketones without noticeable deterioration in efficacy and could be left ready for use as required, providing they were kept covered with the solvent mixture and washed briefly with it before use.

The acetonide of the methyl ester of diploclisolic acid (a β-amyrin derivative containing a 1,3-diol grouping)[17] was prepared by running a solution of the compound (0.5 g) in acetone (125 ml) through a column of Amberlyst-15 (15 × 2.5 cm; previously washed with acetone). On standing, the eluate deposited the acetonide as needles (350 mg, 65%), m.p. 296—300 °C, τ 8.58 (6 H, s, $OCMe_2O$), M^+ 570.

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REFERENCES

[1] Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 3722.
[2] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Elucidation of Natural Products by Mass Spectrometry,' Holden–Day, San Francisco, 1964, Vol. 2, pp. 25, 64.
[3] H. Audier, J. Bottin, A. Diara, M. Fetizon, P. Foy, M. Golfier, and W. Vetter, *Bull. Soc. chim. France*, 1964, 2292.
[4] E. J. Salmi, *Chem. Ber.*, 1938, **71**, 1803.
[5] A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouennes, and J. Jacques, *Bull. Soc. chim. France*, 1961, 1822.
[6] Cf. H. J. Dauben, B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1954, **76**, 1359.
[7] L. N. Ferguson, *Chem. Soc. Rev.*, 1975, **4**, 289.
[8] C. K. Warren and B. C. L. Weedon, *J. Chem. Soc.*, 1958, 3972.
[9] M. J. Nagler, unpublished results.
[10] For reviews, see, *e.g.*, refs. 5 and 13 in ref. 6 or 'Steroid Reactions', ed. C. Djerassi, Holden–Day, San Francisco, 1963.
[11] C. H. Heathcock, J. E. Ellis, and R. A. Badger, *J. Heterocyclic Chem.*, 1969, **6**, 139.
[12] M. S. Newman and R. J. Harper, *J. Amer. Chem. Soc.*, 1958, **80**, 6350; S. W. Smith and M. S. Newman, *ibid.*, 1968, **90**, 1249.
[13] P. Mastagli, Z. Zafiriadis, and G. Lagrange, *Compt. rend.*, 1953, **237**, 187; M. J. Astle, J. A. Zaslowsky, and P. G. Lafyatis, *Ind. and Eng. Chem.*, 1954, **46**, 787; B.P. 739,022/1955 (*Chem. Abs.*, 1956, **50**, 15592f); V. I. Stenberg, G. F. Vesley, and D. Kubic, *J. Org. Chem.*, 1971, **36**, 2550.
[14] M. S. Heller, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 1962, **45**, 1261.
[15] R. F. Zürcher, *Helv. Chim. Acta*, 1961, **44**, 1380.
[16] V. I. P. Jones and J. A. Ladd, *J. Chem. Soc.* (*B*), 1971, 567; J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, 1966, **62** 39; H. Friebolin, H. G. Schmid, S. Kabuss, and W. Faisst, *Org. Magnetic Resonance*, 1969, **1**, 67 (Spectrum no. 0035).
[17] R. D. Coker, Ph.D. thesis, City University, 1976.