461. *The Degradation of Carbohydrates by Alkali. Part I. α-Alkoxy-ketones.*

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A study of the oxidation and hydrolysis of α-alkoxy-ketones under alkaline conditions leads to the conclusion that the former, but not the latter, is satisfactorily comparable with the behaviour of oxycelluloses.

ONE group, termed oxycelluloses, of the somewhat indefinite products resulting from the oxidation of cellulose is characterised by a pronounced liability to degradation by, for example, cold dilute sodium carbonate solution, and by reducing properties such as are usually regarded as typical of aldehydes. The latter might be attributable to the ·CH(OH)·CO· grouping which could well result from oxidation of cellulose. But depolymerisation by alkali must involve the glycoside linkages connecting the anhydroglucose units, and we are thus led to consider the behaviour of simple α-alkoxy-ketones. Their reducing properties have been repeatedly recorded (Grimaux and Lefevre, *Bull. Soc. chim.*, 1899, **1**, 12; Leonardi and de Franchis, *Gazzetta*, 1903, **33**, 319; Henry, *Compt. rend.*, 1904, **138**, 971; Gauthier, *Ann. Chim. Phys.*, 1909, **16**, 319), and the inference that these arise from a preliminary enolisation is supported by Hlasiwetz and Habermann's observation (*Annalen*, 1875, **246**, 340) that benzoquinone is formed when quinol monomethyl ether is boiled with ammoniacal silver nitrate; similarly, guaiacol exhibits reducing properties. Again, Irvine and Patterson surmised enolisation of 1 : 3 : 4 : 5-tetramethyl fructose from its degradation by cold alkaline potassium permanganate solution (*J.*, 1922, 2696).

A more detailed study of simple α-alkoxy-carbonyl compounds in this respect is therefore now presented. A comparative estimate of the extent of their enolisation in water

was obtained by direct titration against barium hydroxide (cf. Seidel, Thier, Uber, and Dittmer, *Ber.*, 1936, **69**, 650). The results (Table 1) illustrate the relative $-I$ effects of

TABLE 1. *Enolisation of substituted propan-2-ones in water (duplicate determinations).*

Propan-2-one derivative	Enolisation, %	Propan-2-one derivative	Enolisation, %
1-Methoxy-	1·12, 1·12	1 : 3-Di*iso*propoxy-	1·56, 1·57
1 : 3-Dimethoxy-	6·20, 6·18	1 : 3-Dibenzyloxy-	6·93, 7·00
1 : 3-Diethoxy-	2·82, 2·80	1-Hydroxy-3-methoxy-	3·41, 3·26
1 : 3-Di-*n*-propoxy-	2·13, 2·09	1 : 3-Dihydroxy-	0·09, 0·07
		Methoxyacetaldehyde	3·22, 3·14

hydroxyl and alkoxyl groups in promoting the removal of proton requisite for enolisation, but it seems that symmetry also asserts itself as a factor in resonance.

Ultra-violet absorption measurements in this series indicated that enolisation occurred smoothly and rendered possible a determination of the time taken to attain equilibrium in 0·05N-sodium hydroxide (see Table 2).

TABLE 2. *Ultra-violet absorption of substituted propan-2-ones.*

	In water		In 0·05N-NaOH, equil. state		Time (hr.)
Propan-2-one derivative	$\lambda_{max.}$, Å	ε	$\lambda_{max.}$, Å	ε	reqd. for equil.
1-Methoxy-	2660	13·5	2530	39·2	>9
1 : 3-Dimethoxy-	2750	18·4	2490	156	5·0
1 : 3-Dihydroxy-	2700	22·5	2940	872	1·5
1-Hydroxy-3-methoxy-	2810	94·4	3060	452	1·0
Fructose	2780	0·6	2980	199	>9

With 1 : 3-dihydroxy- and 1-hydroxy-3-methoxy-propan-2-one, aldol condensation could follow enolisation and, in accord with this, an equilibrated solution of fructose in the same alkali showed a similar absorption spectrum. The same tendency to condensation limits the yield of each of the products of oxidation of 1 : 3-dimethoxypropan-2-one at the ordinary temperature by silver oxide in presence of sodium hydroxide to about 25% in each case, but the reaction proceeds smoothly and follows a course of which the following would appear a reasonable representation :

$$\mathrm{MeO{\cdot}CH_2{\cdot}\overset{\displaystyle CH_2{\cdot}OMe}{\overset{|}{C}}O} \overset{OH^-}{\rightleftharpoons} \mathrm{MeO{\cdot}CH_2{\cdot}\overset{\displaystyle CH{\cdot}OMe}{\overset{||}{C}}{\cdot}O^-} \overset{Ag^+}{\longrightarrow}$$

$$\mathrm{MeO{\cdot}CH_2{\cdot}\overset{\displaystyle CH{\cdot}OMe}{\overset{||}{C}}{\cdot}O{\cdot}} \longleftrightarrow \mathrm{MeO{\cdot}CH_2{\cdot}\overset{\displaystyle -CH{\cdot}OMe}{\overset{|}{C}}O} \overset{Ag^+}{\longrightarrow} \mathrm{MeO{\cdot}CH_2{\cdot}\overset{\displaystyle {}^+CH{\cdot}OMe}{\overset{|}{C}}O} \overset{OH^-}{\longrightarrow} \mathrm{MeO{\cdot}CH_2{\cdot}\overset{\displaystyle HO{\cdot}CH{\cdot}OMe}{\overset{|}{C}}O} \longrightarrow$$

$$\mathrm{MeOH + MeO{\cdot}CH_2{\cdot}CO{\cdot}CHO \longrightarrow MeO{\cdot}CH_2{\cdot}CO_2H + H{\cdot}CO_2H}$$

The second stage of the oxidation could clearly be achieved more directly with the aid of hydroxyl radicals available in alkaline potassium permanganate solution (Duke, *J. Amer. Chem. Soc.*, 1948, **70**, 3975), as used by Irvine and Patterson (*loc. cit.*). The limitation of acid yields by condensation is demonstrated by the results expressed in Tables 3 and 4,

TABLE 3. *Qualitative oxidations with silver oxide in* N-*sodium hydroxide.*

Compound	Products	Recovery (%)	Compound	Products	Recovery (%)
$MeO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OMe$	MeOH	26·8	$HO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OH$	$H{\cdot}CO_2H$	75·0
	$H{\cdot}CO_2H$	26·9		$HO{\cdot}CH_2{\cdot}CO_2H$	72·0
	$MeO{\cdot}CH_2{\cdot}CO_2H$	26·8			
$HO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OMe$	MeOH	49·8	$MeO{\cdot}CH_2{\cdot}CHO$	MeOH	7·4
	$H{\cdot}CO_2H$	24·9		$H{\cdot}CO_2H$	18·8
	$HO{\cdot}CH_2{\cdot}CO_2H$	27·5		$MeO{\cdot}CH_2{\cdot}CO_2H$	72·7
	$MeO{\cdot}CH_2{\cdot}CO_2H$	11·9			

TABLE 4. *Quantitative oxidations with silver oxide in* 0·1N-*sodium hydroxide.*

Compound	Equil. time (min.)	Yield of acids (equiv./mole)	Compound	Equil. time (min.)	Yield of acids (equiv./mole)
$MeO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OMe$	230	1·61	$HO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OH$	<5	2·03
$HO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OMe$	30	1·66	$MeO{\cdot}CH_2{\cdot}CHO$	<5	1·11

whence it is evident that if the oxidation proceeds rapidly little condensation occurs and the yields of acid approach the theoretical. For example, 1 : 3-dihydroxypropan-2-one is oxidised exothermally under the conditions described with the formation of approximately equivalent amounts of formic and glycollic acids. The yields are about three times as great as those obtained from 1 : 3-dimethoxypropan-2-one, oxidation of which under the same conditions required almost 4 hr.

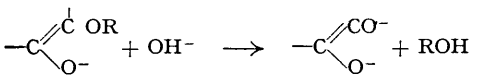
The alternative modes of enolisation of 1-hydroxy-3-methoxypropan-2-one are reflected in two sets of oxidation products, in which glycollic is definitely preponderant over methoxyacetic acid :

$$HO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}OMe \begin{cases} \longrightarrow HO{\cdot}CH_2{\cdot}C(OH){:}CH{\cdot}OMe \longrightarrow HO{\cdot}CH_2{\cdot}CO_2H + H{\cdot}CO_2H + MeOH \\ \longrightarrow HO{\cdot}CH{:}C(OH){\cdot}CH_2{\cdot}OMe \longrightarrow MeO{\cdot}CH_2{\cdot}CO_2H + H{\cdot}CO_2H \end{cases}$$

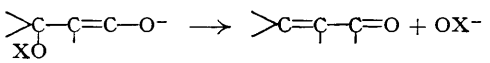
Methoxyacetaldehyde also is evidently subject to enolisation since it furnished on oxidation almost 20% of formic acid together with 73% of methoxyacetic acid :

$$MeO{\cdot}CH_2{\cdot}CO_2H \longleftarrow MeO{\cdot}CH_2{\cdot}CHO \longrightarrow 2H{\cdot}CO_2H + MeOH$$

The α-alkoxy-carbonyl compounds were also found to undergo hydrolysis in boiling 0·5N-sodium hydroxide, with liberation of the corresponding alcohol identified in the form of its triphenylmethyl ether (cf. Table 6, p. 2244). As might be expected, much resinification occurred, apart from the hydrolysis. Furthermore, the latter does not at all correspond in facility with the degradation of oxycelluloses by weak alkali at the ordinary temperature, presumably because it involves the genesis of a doubly charged anion from a singly charged one :



In subsequent papers of this series evidence will be adduced for the belief that the behaviour of oxycelluloses involves the transition from a singly charged anion to a neutral product by extrusion of anion from the β-position :



Experimental

Materials.—1-Methoxypropan-2-one, prepared by the method of Gauthier (*loc. cit.*), exhibited the properties recorded by Mariella and Leech (*J. Amer. Chem. Soc.*, 1949, **71**, 3558).

1-Ethoxypropan-2-one, prepared from the corresponding secondary alcohol (compare Mariella and Leech, *loc. cit.*), exhibited the properties recorded by Henze and Rigler (*J. Amer. Chem. Soc.*, 1934, **56**, 1350) and was further characterised by its 2 : 4-*dinitrophenylhydrazone*, m. p. 160—161·5° (Found : C, 46·9; H, 5·0; N, 19·7. $C_{11}H_{14}O_5N_4$ requires C, 46·8; H, 5·0; N, 19·9%). The ketone gradually developed acidity, apparently owing to photo-oxidation.

1 : 3-*Dialkoxypropan-2-ones.*—Henze and Rogers' procedure (*J. Amer. Chem. Soc.*, 1939, **61**, 433) for the oxidation of 1 : 3-dimethoxypropan-2-ol furnished a product which, whilst being apparently homogeneous, gave only a 30% yield of the 2 : 4-dinitrophenylhydrazone. The following modification proved satisfactory : The alcohol (1 mole) was stirred with water (100 ml.) and sodium dichromate (1 mole) while concentrated sulphuric acid (195 ml.), diluted with water (400 ml.), was added at a rate sufficient to keep the mixture at 30—35° with the aid of cooling in ice-water. After 18 hr.' stirring at room temperature the solution was extracted with ether, and the extracts were shaken with anhydrous potassium carbonate until no longer acid. Since washing the ethereal solution with water entailed considerable loss of the ketone, the extract was shaken with an excess of anhydrous calcium sulphate for 1 hr., filtered, and fractionated. The ketones prepared in this way gave an almost theoretical yield of the corresponding 2 : 4-dinitrophenylhydrazones. Table 5 summarises the results.

The 2 : 4-*dinitrophenylhydrazones* of the following ketones were new (nos. as in Table 5) : (2), m. p. 85° (Found : C, 47·7; H, 5·5; N, 17·4. $C_{13}H_{18}O_6N_4$ requires C, 47·8; H, 5·6; N, 17·2%); (3), m. p. 39—39·5° (Found : C, 50·8; H, 6·3; N, 16·1. $C_{15}H_{22}O_6N_4$ requires C, 50·8; H,

6·3; N, 15·8%); (4), m. p. 77—78° (Found: C, 50·8; H, 6·4; N, 16·0%); (5), m. p. 87·5° (Found: C, 61·5; H, 4·9; N, 12·6. $C_{23}H_{22}O_6N_4$ requires C, 61·3; H, 4·9; N, 12·4%).

TABLE 5. *Substituted propan-2-ones.*

No.	Compound	B. p./mm.	n_D	Yield (%) (>90% purity)
1	1 : 3-Dimethoxypropan-2-one	71—71·5°/16	1·4189 (18°)	35·5
2	1 : 3-Diethoxypropan-2-one	90—92°/14	1·4192 (16°)	33·1
3	1 : 3-Di-*n*-propoxypropan-2-one	116—118°/21	1·4207 (25°)	43·0
4	1 : 3-Di*iso*propoxypropan-2-one	98—98·5°/13	1·4175 (22°)	34·0
5	1 : 3-Dibenzyloxypropan-2-one	208—212°/0·04	1·5483 (25°)	19·4

1 : 3-*Dibenzyloxypropan*-2-*one*, prepared according to the above procedure, suffers some oxidation during distillation, unless air is replaced by nitrogen (compare the case of dibenzyl ether, Eichel, U.S.P. 2,561,350) (Found: C, 75·6; H, 6·7. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). The *semicarbazone* has m. p. 83° (Found: C, 66·2; H, 6·7; N, 13·0. $C_{18}H_{21}O_3N_3$ requires C, 66·0; H, 6·5; N, 12·8%).

1-*Hydroxy*-3-*methoxypropan*-2-*one*.—A solution of methoxyacetyl chloride (12 g.) in anhydrous ether (50 ml.) was gradually added to an ethereal solution (750 ml.) of diazomethane (10 g.) at 0°. After 20 hr. at the ordinary temperature and subsequent removal of solvent, sulphuric acid (0·5N; 50 ml.) was added to the residual yellow oil. The solution remaining after stirring of the mixture at the ordinary temperature until cessation of gas evolution (4 hr.) was saturated with sodium acetate and, after a further 20 hr.' storage, followed by exhaustive extraction with ether in the presence of barium carbonate, the extract was dried ($CaSO_4$). On distillation it furnished a fraction (3·1 g.; b. p. 40—85°/21 mm.) containing pyruvaldehyde, whose 2 : 4-dinitrophenylhydrazone, precipitated instantaneously at room temperature, showed m. p. and mixed m. p. 205°. 1-*Hydroxy*-3-*methoxypropan*-2-*one* (4·0 g., 35%) distilled at 89—90°/21 mm. and showed n_D^{23} 1·4507 (Found: C, 46·1; H, 7·5. $C_4H_8O_3$ requires C, 46·1; H, 7·7%). It reduced Fehling's solution and ammoniacal silver nitrate solution instantaneously at room temperature. The 2 : 4-dinitrophenylhydrazone had m. p. 175° (Found: N, 19·5; OMe, 10·7. Calc. for $C_{10}H_{12}O_6N_4$: N, 19·7; OMe, 10·9%) (Neuberg, *Biochem. Z.*, 1931, **238**, 459, and Fischer and Baer, *Ber.*, 1932, **65**, 345, found m. p. 175°).

Measurement of Enolisation (see Table 1).—A magnetically stirred solution of the carbonyl derivative (10^{-3} mole) in cold, boiled water (10 ml.) in a conical flask, closed by a stopper carrying a burette and a soda–lime tube, was titrated by dropwise addition of 0·01N-barium hydroxide until the phenolphthalein end-point persisted for at least 4 sec.

Ultra-violet Absorption (see Table 2).—Measurements were performed on solutions of each carbonyl derivative in 0·05N-sodium hydroxide solution (oxygen-free) in stoppered cells because an immediate decay in absorption followed access of air at any stage. In the first place a solution of the carbonyl derivative was examined after being left overnight to attain equilibrium; then solutions were examined at varying times after preparation to determine the period needed to attain constancy of absorption.

Oxidation of 1 : 3-*Dihydroxypropan*-2-*one and Related Compounds in Alkaline Solutions*.—1 : 3-*Dimethoxypropan*-2-*one*. (*a*) Quantitalive method (see Table 4). To a solution of the ketone (0·504 g.) in oxygen-free water (100 ml.) was added freshly precipitated, air-dried silver oxide (from 7·2 g. of silver nitrate), immediately followed by oxygen-free 0·2N-sodium hydroxide (100 ml.). The mixture was stirred vigorously at room temperature in nitrogen, whilst at intervals aliquot portions were withdrawn through a sintered-glass filter and run into an equal volume of 0·1N-sulphuric acid. The acid produced was titrated directly with sodium hydroxide solution. Equilibrium was attained smoothly in 230 min. at 20° and the final solution was yellow. The results of quantitative oxidations of this and of other ketones are summarised.

(*b*) Qualitative method (cf. Table 3). An aqueous solution (900 ml.) of the ketone (2·1 g.), freed from oxygen, was successively treated with freshly precipitated, well-washed silver oxide (from 30 g. of silver nitrate), and oxygen-free aq. N-sodium hydroxide (100 ml.). After agitation for 4 hr. in nitrogen at room temperature, the mixture was filtered into phosphoric acid (2M; 50 ml.). Methyl alcohol (with some formic acid) was removed by slow distillation, and identified by treatment of an aliquot portion with triphenylmethyl chloride in pyridine. The crude product was dried (P_2O_5) and extracted with a mixture of ether (15 ml.) and light petroleum (20 ml.; b. p. 60—80°), and the solution transferred to a column of alumina and eluted with light petroleum. Methyl triphenylmethyl ether, m. p. and mixed m. p. 82—83°, was then obtained in 26·8% yield. Formic acid was separated by repeated addition of water

and distillation of the acid liquor to dryness under reduced pressure and determined by reduction with mercuric oxide (Evans and Hass, *J. Amer. Chem. Soc.*, 1926, **48**, 2705). A small residual acidity in the distillate was due to methoxyacetic acid, of which the main proportion remained in the residue from the distillation. It was removed by extraction with ether, determined by titration (26·8% yield), and identified as the 4-*bromophenacyl* ester, plates, m. p. and mixed m. p. 76—77° (Found: C, 46·0; H, 3·8; OMe, 10·6. $C_{11}H_{11}O_4Br$ requires C, 46·0; H, 3·9; OMe, 10·8%).

1-*Hydroxy*-3-*methoxypropan*-2-*one*. Oxidation of this ketone as described above was complete in 30 min. (cf. Table 3). Methanol was identified as the triphenylmethyl ether. Formic acid in the acidic distillate was accompanied by a larger proportion of other acid than in the previous case. From this, after removal of formic acid, 4-bromophenacyl glycollate, m. p. and mixed m. p. 137—139°, was prepared and purified by repeated crystallisation from aqueous alcohol. Glycollic and methoxyacetic acids were also separated by paper chromatography of their sodium salts (Brown, *Biochem. J.*, 1950, **47**, 598). The respective R_F values were 0·085 and 0·164 (for $H{\cdot}CO_2^-$, 0·14), with butanol (4 vol.), 3N-ammonia (5 vol.), and ethanol (1 vol.) as eluant, the papers being eluted for several days at room temperature. The yields cited were based on determination of the methoxyl contents of salts and total acidity.

1 : 3-*Dihydroxypropan*-2-*one*. Formic acid was removed in steam but was accompanied by a small proportion of glycollic acid. The main proportion of the latter, remaining in the residue from the distillation, was extracted by ether and identified chromatographically and by conversion into its 4-bromophenacyl ester.

Methoxyacetaldehyde. Methoxyacetic acid, formic acid, and methyl alcohol were identified and estimated as above.

Action of Alkali on α-Alkoxy-carbonyl Derivatives.—Solutions of the ketones (*ca.* 5 g.) in oxygen-free 0·5N-sodium hydroxide (90 ml.) were heated in a slow stream of nitrogen for 1 hr. at 100°, 3·5 hr. at 105°, and 0·5 hr. at 110°, so that any distillate could be collected. After removal of any ketone as 2 : 4-dinitrophenylhydrazone, the distillate was redistilled and made up to 25 ml. for determination of its density, and hence its content of methyl or ether alcohol. The presence of this was confirmed by preparation of the corresponding triphenylmethyl ether, m. p. and mixed m. p. 82—83° or 83·5—84·5° respectively. The results obtained are in Table 6. Other products were not determined because the conditions employed obviously favoured extensive condensation and resinification occurred.

TABLE 6.

Propan-2-one derivative	Heating conditions	Yield of alcohol (%)
1 : 3-Dimethoxy-	As described above	50
1 : 3-Diethoxy-	,, ,,	26
1 : 3-Di-*n*-propoxy-	,, ,,	9
1-Hydroxy-3-methoxy-	,, ,,	49
1-Ethoxy-	Refluxing for 5 hr. and subsequent distilln.	16
Methoxyacetaldehyde	Refluxing for 1 hr. and subsequent distilln.	78

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