Regioselective Oxidation of Unactivated Methylene and Methine Groups by Dry Ozonation: Similarity to Microbiological Oxidation

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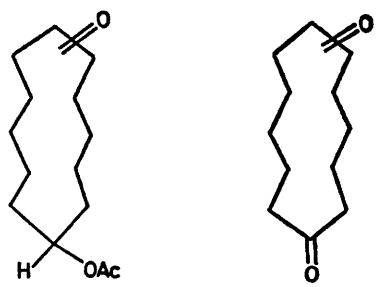
Summary Ozonation of cyclododecyl acetate or dodecyl acetate, adsorbed on silica-gel affords keto-acetates by regioselective oxidation of methylene groups remote from the binding sites; ozonation of 6-*exo*-acetoxy-*endo*,*exo*,-*endo*-3a,4,4a,5,6,7,8,8a,9,9a-decahydro-4,9:5,8-dimethano-1*H*-benz[*f*]indane (**3b**) or the related ketone (**3c**) gives hydroxylation products similar to those obtained by microbiological hydroxylation of (**3a**) or (**3c**).

WE have suggested previously[1] that reactions of substrates adsorbed as monolayers on suitable solid supports might accomplish the selective functionalization of positions remote from the binding sites. In order to test further this hypothesis we have examined the reactions of ozone with adsorbed samples of cyclododecyl acetate, and dodecyl acetate, and two derivatives, (**3b**) and (**3c**), of cyclopentadiene trimer.

The reaction of ozone with C-H bonds either in solution[2] or by the 'dry ozonation' method[1,3] exhibits marked preference for attack at tertiary positions. In solution methylene groups undergo slow oxidation[2] but the conversion of CH_2 groups into C=O by dry ozonation appears not to have been observed except in the special case of cyclopropane compounds when cyclopropyl ketones are formed.[4] We now report that dry ozonation can introduce the carbonyl group at positions remote from functional groups.

When a sample of silica-gel bearing 10% of its weight of adsorbed cyclododecyl acetate was mixed with a nine-fold excess of pure silica-gel and exposed to ozone at −78 °C in the usual way the substrate was converted into a mixture of oxidation products which was shown by g.l.c. to contain only three keto-acetates, *viz.* (**1a**), (**1b**), and (**1c**) in yields of 15, 27, and 9%, respectively. Hydrolysis of the crude product followed by oxidation afforded pure samples of the known diketones (**2a**), (**2b**), and (**2c**).[5]



(1) (2)

a, 5-CO
b, 6-CO
c, 7-CO

Repetition of the reaction at lower substrate loadings gave increased yields of unidentified polar materials, but the relative yields of the keto-acetates (**1a**), (**1b**), and (**1c**) were essentially unchanged. The fact that this reaction, like hydroxylation of cyclododecanone by incubation with various fungal cultures,[5] is confined to the 5-, 6-, and 7-positions, demonstrates an interesting similarity between dry ozonation and microbiological oxidation.

Dry ozonation of dodecyl acetate gave a complex mixture of keto-acetates which could not be completely analysed by g.l.c. Accordingly, the mixture was subjected to Baeyer–Villiger oxidation, and the saturated acids produced were estimated quantitatively. The yields given in the Table

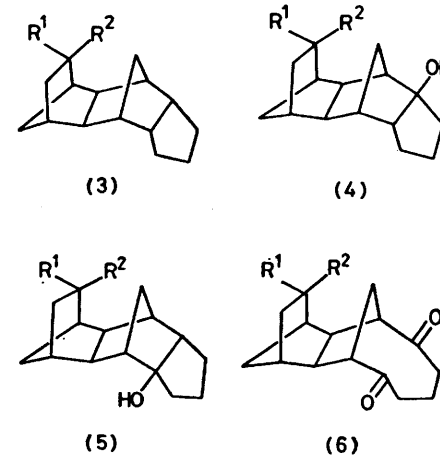
TABLE. Dry ozonation of docecyl acetate

		Relative yield (%) of *x*-keto-acetate						
		x						
% Loading	% Yield	5-	6-	7-	8-	9-	10-	11-
1	20	4	18	41	18	10	4	5
5[a]	38	9	16	15	15	11	9	25
10[a]	45	6	14	10	10	9	9	42

[a] Adsorbed sample mixed with sufficient silica-gel to give a mean substrate loading of 1%.

are based on the assumption that the relative yields of acids produced from the various keto-acetates will be approximately the same as those observed for suitable model compounds (octanones).

The data clearly show that the regioselectivity of the ozonation reaction is related to the substrate loading. At 1% loading, when presumably the chain can fold back towards the adsorbent, attack occurs preferentially at positions 6, 7, and 8, and the reaction is thus similar to that of cyclododecyl acetate. However, when the substrate loading is sufficient (10%) to cause formation of a close-packed adsorbed monolayer a marked preference is observed for reaction at the penultimate position.



(3) (4)

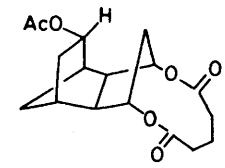
(5) (6)

a, R^1 = OH, R^2 = H
b, R^1 = OAc, R^2 = H
c, R^1R^2 = =O

Dry ozonation of the acetate (**3b**) derived from cyclopentadiene trimer[6] gave a mixture of three major components which were estimated by v.p.c. and separated by column chromatography. The two main products (35 and 25%) were identified as the hydroxy-acetates (**4b**), m.p. 128—130 °C, and (**5b**), m.p. 150—151 °C. On hydrolysis they gave the diols (**4a**) and (**5a**), identical (i.r., ^1H and ^{13}C n.m.r.) with the products of microbiological hydroxylation of the alcohol (**3a**) by *Rhizopus nigricans*.[7]

The third major product (20%), m.p. 145—147 °C, was the diketo-acetate (**6b**). On hydrolysis it gave the diketo-alcohol (**6a**), m.p. 155—156 °C, which was readily oxidized to the triketone (**6c**), m.p. 165—167 °C. The structure of the latter rests on its ^{13}C n.m.r. spectrum, and on the oxidation of (**6b**) under Baeyer–Villiger conditions to the dilactone (**7**), m.p. 158—159 °C. Reduction of (**7**) with $LiAlH_4$ afforded pentane-1,5-diol.

Dry ozonation of the ketone (**3c**) for 6 h afforded a mixture of the ketols (**4c**) (18%) and (**5c**) (12%) previously identified as the major products of the incubation of (**3c**) with *Rhizopus* species.[7] The ozonation also afforded the triketone (**6c**) (18%).



(7)

The results described above, and particularly the high regioselectivity of the reaction, are consistent with the view[4] that dry ozonation involves attack by gaseous ozone at positions remote from the binding site on substrate adsorbed as a monolayer. The remarkable similarity between the results of dry ozonation and biological oxidation indicates that ozonation may have considerable utility for the synthesis of a variety of natural products.

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