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REACTIONS OF POTASSIUM tert.-BUTOXIDE IN DIMETHYLSULFOXIDE.

III. HYDROLYSIS OF HINDERED CARBOXYLIC ESTERS.

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In a previous study (1) of elimination reactions of potassium tert.-butoxide in dimethylsulfoxide (KtBD)[1] on derivatives of bile acid esters, at 25° hydrolysis of the ester function was found to be instantaneous. This observation, coupled with an earlier finding (2) that KtBD apparently cleaves the sulfur-oxygen bond of a methanesulfonate group, suggested that the reagent might be effective for hydrolyzing esters of hindered acids through alkyl-oxygen fission under conditions less drastic or less restrictive than those employed in existing methods (3).

Our experiments demonstrate that KtBD does indeed hydrolyze hindered esters, with required reaction temperatures corresponding roughly to the apparent degree of hindrance. Thus, in comparison studies, methyl dehydroabietate is

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[1] "KtBD" was proposed (1) as an abbreviation for potassium tert.-butoxide in dimethylsulfoxide.

completely hydrolyzed in less than one hour at room temperature ; methyl O-methylpodocarpate requires two hours at a temperature of 56°; and methyl triisopropylacetate, incompletely hydrolyzed in twenty hours at 56°, requires about four hours at 100° for complete hydrolysis.[2]

In contrast to the methyl ester, triisopropylacetamide resisted hydrolysis by KtBD even with prolonged heating at 100°. This resistance may be taken as supporting evidence of alkyl-oxygen cleavage in the ester; apparently because the amide is inaccessible to an analogous attack, it is not hydrolyzed.[3]

KtBD has been shown (4) to consist of an equilibrium mixture containing both t-butoxide and methylsulfinyl (dimsyl) ions, and whether the compounds t-butyl methyl ether and ethyl methyl sulfoxide are present among the hydrolysis products is pertinent to the mechanism of the reaction. In a preliminary experiment we have isolated and identified t-butyl methyl ether (GLC, IR) from the hydrolysis of methyl triisopropylacetate, and estimate the yield to be at least 50%.

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[2] It is known that the carboxylate group of methyl O-methylpodocarpate being axial and subject to further non-bonded interaction with the axial angular methyl group, is more hindered than the epimeric (equatorial) carboxylate of methyl dehydroabietate; and according to its ionization constant and other evidence, triisopropylacetic acid appears to be one of the most highly hindered acids studied [M. S. Newman and T. Fukunaga, *J. Am. Chem. Soc.*, **85**, 1176 (1963); G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955); M. S. Newman, *ibid.*, **72**, 4735 (1950)].

[3] Hindered acid amides are hydrolyzed with marked difficulty in the usual basic and acidic media [J. Cason and W. J. Wolfhagen, *J. Org. Chem.*, **14**, 155 (1949); N. Sperber, D. Papa and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948); L. Tsai, T. Miwa and M. S. Newman, *J. Am. Chem. Soc.*, **85**, 1176 (1963)].

This result indicates that the main reaction involves butoxide ion, and is evidence for the alkyl-oxygen fission.

One hundred mg. (0.32 mmole) of methyl dehydroabietate (5) was treated with 5 ml. of 1N KtBD at room temperature, and the reaction was monitored by thin-layer chromatography (TLC). Hydrolysis was judged complete in less than one hour. The reaction mixture was poured on ice and water and acidified to give 90 mg. (94%) of the acid. Recrystallization from aqueous ethanol (after charcoal treatment) gave regular transparent plates, m.p. 168.0-170.6°, [lit. (5): 172-173°], shown to be dehydroabietic acid (5) by TLC, infrared spectrum, and mixture melting point comparison with an authentic sample of the acid.

Methyl O-methyl podocarpate (3a), when treated identically, showed only traces of hydrolysis even after 24 hours at room temperature, but was completely hydrolyzed in 2 hours at 56°. Processed similarly, the product gave O-methyl podocarpic acid (3a), m.p. 151-157°, in 97% yield. Recrystallization from ligroin (charcoal) gave regular transparent plates, m.p. 158.0-161.2° [lit. (3a): 157-158°]. Treatment with diazomethane afforded methyl O-methylpodocarpate, shown to be identical with the starting ester by TLC, IR and mixture m.p.

Methyl triisopropylacetate (6) at 56° was not completely hydrolyzed after 20 hours, but after less than 4 hours at 100° had been completely converted to acid in nearly quantitative yield. The recrystallized acid, m.p. 150.1-151.5° [lit. (6):

148-149°], was identical with triisopropylacetic acid (6) according to m.m.p., TLC and IR comparisons.

In an experiment in which 401 mg. of methyl triisopropylacetate was completely hydrolyzed, the reaction mixture was diluted with ice-water and extracted with n-butyl ether. t-Butyl methyl ether, separated from this extract (after washing and drying) by gas chromatography, was identified by retention time and infrared comparisons with authentic material. The same extract was also used for estimation of t-butyl methyl ether content by gas chromatographic peak analysis, giving an estimated[4] yield of 50%, based on starting ester.

Triisopropylacetamide (6), after heating with KtBD at 100° for 12 hours showed no reaction (TLC) and was recovered unchanged.

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[4] The actual calculated yield from GLC was 46%, but since the experiment was performed on a relatively small scale, we feel that a 4% loss during processing would be minimal. Larger scale quantitative experiments now in progress will be reported in a full paper; additionally, we hope to report regarding the possible product, ethyl methyl sulfoxide.

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