action mixtures, again probably because of its effect in increasing the *p*H. The condensation product (I) takes up a slight amount of hydrochloric acid, probably because of partial dissociation under the conditions of titration, but the value is so low that it may be concluded that no free amino group is present in the compound.

Remarks on the Use of the Linderstrøm-Lang Method in the Presence of Cysteine.—In a private communication Dr. Linderstrøm-Lang of the Carlsberg Laboratories, Copenhagen, informed us that he was able to confirm, qualitatively, these results on the titration of cysteine provided that our procedure was followed (addition of all the acetone first, then titration with hydrochloric acid). However he pointed out that the original directions for the method called for the addition of most of the required hydrochloric acid before adding the acetone, then completing the titration in acetone. When this is done, cysteine, both in the presence and absence of glycine, gives very nearly the theoretical values. Apparently when most of the acid is added first, the *p*H of the mixture is depressed to a point where the reaction between cysteine and acetone occurs only very slowly. The reason assigned, in the original description of the method, for adding the hydrochloric acid first was to avoid precipitation of any of the amino acids by the acetone before titration has been completed; the hydrochlorides as a rule are more soluble than the free amino acids in the acetone–water mixtures. Since in our work no such precipitation was ever observed, we used the procedure, frequently employed by others, of adding the entire amount of acetone before titration. From the present work a second reason is apparent for following the original instructions as to order of additions, namely, the obviation of low titrations which might result due to the condensation with the acetone of any cysteine present.

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Summary

Cysteine reacts with acetone with loss of water to form 2,2-dimethylthiazolidine-4-carboxylic acid (I), which is unstable in aqueous solution, decomposing into the original constituents. Polarimetric data indicate the existence of an equilibrium, cysteine + acetone $\leftrightharpoons$ (I) + H_2O, the point of equilibrium depending on the acetone concentration and the *p*H. Because of the occurrence of this reaction, it is essential, in applying the Linderstrøm-Lang amino acid titration method in the presence of cysteine, to follow exactly the original directions with respect to order of addition of the reagents.

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Replacement Series of Alkyl Groups as Determined by Alcoholysis of Esters. II

BY GEORGE BATES HATCH AND HOMER ADKINS

A comparison of the relative replacing power of alkyl groups in the type reaction

$$AcOR + R'OH \longleftrightarrow AcOR' + ROH$$

has been extended using the methods previously reported.[1] This involves allowing an equimolecular mixture of an alcohol and an acetate, of relatively widely different volatilities, to react in a steel vessel at 200° for seventy hours under hydrogen in the presence of a few drops of water. The more volatile alcohol and ester are then removed by distillation, and the amount of the less volatile ester determined by saponification. In most cases the volume of the reactants was approximately 70 ml., although a smaller reaction vessel[2] containing only 20 ml. gave equally good results in the cases in which it was used. The comparisons reported for the first time in this paper were all made by reaction of: (a) the alcohol with ethyl acetate, and (b) ethanol with the acetate of the alcohol, equilibrium being established from both directions.

A summary of the relative replacing power of twenty-seven alcohols is given in Table I. The figures in the column headed "Replacement Values" represent the moles of the alkyl acetate per mole of methyl acetate which would be found at equilibrium in a system which before reaction contained equimolecular amounts of the alcohol and methyl acetate. For the purpose of tabulation and comparison the results are given as though the comparisons were made with methanol. If the comparisons were actually made against ethanol, then the replacement value so calculated (AcOR/AcOEt) was multiplied by 0.81, the value for ethanol in terms of methanol.

(1) Fehlandt and Adkins, THIS JOURNAL, **57**, 193 (1935).
(2) Adkins, *ibid.*, **55**, 4272 (1933).

TABLE I

SUMMARY OF REPLACEMENT VALUES

Alcohol	Replacement values $\frac{AcOr}{AcOMe}$	Equilibrium constant $\frac{AcOR \times MeOH}{AcOMe \times ROH}$
Methanol[a]	1.00	1.00
Ethanol[a]	0.81 ± 2	0.66
Propanol-1[a]	.79 ± 3	.62
Butanol-1[a]	.80 ± 4	.64
Pentanol-1	.98 ± 1	.95
Hexanol-1	.88 ± 1	.77
Heptanol-1[a]	.88 ± 1	.77
Octanol-1	.85 ± 2	.72
Nonanol-1	.88 ± 1	.77
Decanol-1	.88 ± 4	.77
Dodecanol-1[a]	.84 ± 1	.71
Propanol-2[a]	.55 ± 1	.30
Butanol-2[a]	.53 ± 1	.28
Pentanol-2	.80 ± 1	.64
Hexanol-2	.72 ± 2	.52
Heptanol-2	.71 ± 1	.50
Octanol-2[a]	.68 ± 2	.46
Nonanol-2	.63 ± 2	.40
2-Methylpropanol-1[a]	.66 ± 1	.44
2-Ethylbutanol-1	.92 ± 2	.85
2-Ethylhexanol-1	1.01 ± 2	1.02
4-Methylpentanol-2	0.72 ± 1	0.52
Cyclohexanol[a]	.57 ± 1	.32
Allyl alcohol[a]	.62 ± 2	.38
Benzyl alcohol[a]	.59 ± 3	.35
2-Phenylethanol[a]	.65 ± 2	.42
3-Phenylpropanol-1[a]	.83 ± 2	.69

[a] These alcohols were measured by Fehlandt.

Some of the more significant facts to be seen in Table I are the following:

(1) In a series of primary straight chain alcohols containing from one to twelve carbon atoms, methanol and pentanol-1 are nearly identical in replacement value, and considerably higher than are the other alcohols of the series. Ethanol, propanol-1, and butanol-1 are nearly identical in reactivity, and about twenty points lower than methanol. Hexanol-1, heptanol-1, nonanol-1, and decanol-1 have the same reactivity, *i. e.*, twelve points below methanol. Octanol-1 and dodecanol-1 are fifteen to sixteen points lower than methanol.

(2) In a series of straight chain secondary alcohols (the methylcarbinols), pentanol-2 has the highest replacement value. Propanol-2 and butanol-2 are about twenty-six points lower than pentanol-2, while four members of the series above pentanol-2 have replacement values of eight to seventeen points less than that alcohol.

(3) A comparison of the series of primary alcohols with the series of secondary alcohols shows that, with a given carbon content, the secondary alcohol is sixteen to twenty-five points lower in replacement value than the primary alcohol.

(4) In the two cases measured, substitution of a methyl group in the 2-position with respect to the hydroxyl (2-methylpropanol-1, and 4-methylpentanol-2) lowers reactivity eight to thirteen points as compared with that of the parent substance (propanol-1 or pentanol-2). However, the substitution of an ethyl group in the 2-position (2-ethylbutanol-1 and 2-ethylhexanol-1) increases the reactivity twelve or thirteen points as compared with the parent substances (butanol-1 or hexanol-1).

(5) Introduction of unsaturation, as in allyl alcohol, reduces reactivity seventeen points in comparison with the saturated propanol-1. Similarly, introduction of an unsaturated cycle causes a fall in reactivity in benzyl alcohol (forty-one points below methanol), and in 2-phenylethanol (fifteen points below ethanol); but the effect is perhaps reversed when the unsaturation is at a greater distance from the functional group as in 3-phenylpropanol-1.

The data show very clearly that in neither of the two homologous series studied does the replacement value change progressively as the series is ascended. This conclusion is in accord with various other measurements as reviewed by W. B. Lee.[3]

The outstanding anomalies in Table I are: (a) the high values of pentanol-1 and pentanol-2 as compared with those of the alcohols preceding and following them in their respective homologous series; (b) the high replacement values of 2-ethylbutanol-1, and especially of 2-ethylhexanol-1 as compared with butanol-1 and hexanol-1; (c) the higher values of the alcohols above as compared with those below the pentanols.

All of these anomalous values are rationalized if the assumption is made that the effect of a methyl (or methylene) group may be transferred directly as well as through the chain. The four alcohols having the highest replacement values are methanol, 1.00, pentanol-1, 0.98, 2-ethylhexanol-1, 1.01, and 2-ethylbutanol-1, 0.92. In methanol the methyl group is connected by a primary linkage to the hydroxyl and so acts directly. The methyl group in pentanol-1 may from stereochemical considerations also be near to the hydroxyl. In 2-ethylbutanol-1 a methyl group may be near the hydroxyl. Similarly, in

(3) W. B. Lee, *Trans. Faraday Soc.*, **23**, 630–640 (1927).

2-ethylhexanol, *two* methyl groups may be near the hydroxyl group; thus it is understandable why this alcohol has the highest replacement value among the alcohols studied.

The higher values for the alcohols above pentanol-1 and -2 as compared with those below them in their respective series may be rationalized in a similar fashion, that is, by ascribing the higher values to the effect of the methyl or methylene groups which for stereochemical reasons are probably near the oxygen. This is clearly suggested by a comparison of the values for hexanol-2 and cyclohexanol. The former has a value of 0.72, while the latter is 0.57. In cyclohexanol none of the methylene groups can be near the oxygen while in hexanol-2 there is every reason to believe that the chain is coiled, bringing a methylene in juxtaposition to the oxygen, and thus giving the higher replacement value to hexanol-2.

A comparison of the extent of alcoholysis by ethanol of hexanol-1 and nonanol-1 acetates indicated that the concentration of ethyl acetate at equilibrium was about 0.6% higher at 230° than at 140°.

Experimental Section

In order to compare the technique used in this study with that of Fehlandt, the concentrations of ester at equilibrium for two systems were redetermined. Fehlandt found the concentrations of benzyl acetate at equilibrium to be 42.1 mole per cent., while in this study the value 42.6% was found when the equilibrium was approached from one direction and 42.5% when from the other direction. Fehlandt found the concentration of octanol-2 acetate at equilibrium to be 45.8%, while in this study the values 45.9% and 45.3% were obtained by approaching the equilibrium from the two directions. The technique of analysis was such that the amount of high boiling ester (benzyl acetate) found was within 0.2 to 0.3% that known to be present in synthetic mixtures.

Pentanol-1, octanol-1 and decanol-1 were made by the Grignard synthesis using ethylene oxide.[4] Nonanol-1 was prepared by the hydrogenation of ethyl pelargonate over copper–chromium oxide at 250° by the standard procedure.[5] The ester was prepared from heptaldehyde and malonic ester.[6] Pentanol-2, hexanol-2, heptanol-2 and nonanol-2 were made by the hydrogenation of the corresponding ketones over copper–chromium oxide at 150°. The ketones were made from acetoacetic ester by standard procedures. Octanol-2 was prepared by the hydrogenation of a commercial product containing a mixture of octanone-2, and octanol-2. 4-Methylpentanol-2 was made by the hydrogenation of methyl isobutyl ketone. The other alcohols used were purified from commercial products.

The acetates, except ethyl acetate, were made from the alcohols with acetic anhydride. Mallinckrodt "absolute grade" ethyl acetate was dried over successive portions of phosphoric anhydride and twice distilled. All alcohols and esters were carefully fractionated through an electrically heated Widmer column.

TABLE II

PHYSICAL CONSTANTS OF ALCOHOLS AND ESTERS

	Boiling range, °C.[a]	$n^{25}D$	Sap. equiv.	Mol. wt.
Ethanol	78	1.3593		
Acetate	77	1.3695	88	88.1
Pentanol-1	136–137	1.4081		
Acetate	147.0–147.5	1.4000	130	130.1
Hexanol-1	155.5–156.0	1.4162		
Acetate	169.0–169.5	1.4068	143	144.1
Octanol-1	193–194	1.4260		
Acetate	209–210	1.4157	171	172.2
Nonanol-1	86 (2 mm.)	1.4312		
Acetate	223.6–224.3	1.4208	187.5	186.2
Decanol-1 (m. p. 7°)	225–231	1.4341		
Acetate	242–244	1.4245	197	200.2
Pentanol-2	116–118	1.4030		
Acetate	133–135	1.3937	130	130.1
Hexanol-2	140–141	1.4118		
Acetate	153.0–154.6	1.4014	144	144.1
Heptanol-2	157–158	1.4185		
Acetate	173.0–174.6	1.4072	160	158.1
Octanol-2	178–179	1.4236		
Acetate	193–194	1.4122	172	172.2
Nonanol-2	195.6–196.0	1.4275		
Acetate	208–211	1.4168	185	185.2
2-Ethylbutanol-1	148.5–149.0	1.4200		
Acetate	162–163	1.4083	144	144.1
2-Ethylhexanol-1	182.5–183.0	1.4292		
Acetate	197.5–198.0	1.4173	172	172.2
4-Methylpentanol-2	131.0–131.5	1.4083		
Acetate	146.0–146.5	1.3987	144	144.1
Benzyl alcohol	93–94 (8 mm.)	1.5364		
Acetate	74–75 (4 mm.)	1.4995	149	150.1

[a] These values were taken in a fractionating column so that they offer no evidence of purity.

Summary

Numerical values have been assigned to the relative replacing power of twenty-seven alcohols in the alcoholysis of esters. In general unsaturation or substitution of a methyl group for a hydrogen atom decreases the replacement value. However, if the stereo relations are such that a methyl group (or less effectively, a methylene) may be near in space to the oxygen, then the replacement value becomes higher and the alcohol, even though branched, may have a value at least as high as methanol itself.

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(4) "Organic Syntheses," Coll. Vol., John Wiley and Sons, Inc., New York, 1932, p. 299.

(5) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 97.

(6) Wojcik and Adkins, THIS JOURNAL, **56**, 2424 (1934).