517. *The Esterification of Unstable Alcohols.*

By J. A. Mills.

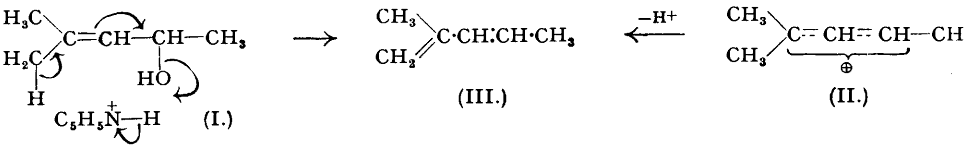
Poor yields of esters from the reaction of certain alcohols with acid chlorides in pyridine are probably due to decompositions catalysed by the pyridinium ion. Good yields may be obtained by avoiding an excess of pyridine and working in a solvent which precipitates pyridine hydrochloride as it is formed. The method is illustrated by the esterification of (±)-4-methylpent-3-en-2-ol with several acid chlorides.

The esterification of alcohols by reaction with the appropriate acid chlorides, pyridine being used as solvent and hydrogen chloride acceptor, sometimes gives unsatisfactory results. Blumann and Zeitschel (*Ber.*, 1913, **46**, 1178) reported a 50% yield of benzoate from verbenol, Read and Walker (*J.*, 1934, 308) only 13% of 3 : 5-dinitrobenzoate from a piperitol fraction, and Grubb and Read (*ibid.*, p. 242) did not isolate any ester from the product of the Meerwein–Ponndorf reduction of pulegone, although work in these laboratories (unpublished) indicates that the reduction product contains a considerable amount of pulegol. Attempts to prepare a *p*-nitrobenzoate from 4-methylpent-3-en-2-ol failed completely (Kenyon and Young, *J.*, 1940, 1547).

The alcohols which have given poor yields are all secondary alcohols containing an allylic system, being $\alpha\gamma\gamma$-trialkyl- or $\alpha\beta\gamma\gamma$-tetra-alkyl-allyl alcohols. These highly alkylated structures are known to be favourable for acid-catalysed reactions, such as dehydration or anionotropic rearrangement, and the acid-catalysed dehydration often produces dienes corresponding to "abnormal" or 1 : 4-elimination (Bacon and Farmer, *J.*, 1937, 1065; Dupont and Darmon, *Bull. Soc. chim.*, 1939, **6**, 1208; Kenyon and Young, *loc. cit.*; Read and Walker, *loc. cit.*). It is probable that esters of such alcohols will also undergo acid-catalysed decomposition to dienes at about the same rate as do the free alcohols (cf. Braude, *J.*, 1948, 794, on anionotropic rearrangements of alcohols and esters).

A probable explanation of the poor yields of esters in the usual method of preparation is the destruction of alcohol or ester, or both, by an acid-catalysed reaction initiated by the pyridinium ion which is present because of the appreciable solubility of pyridine hydrochloride in pyridine. The warming which is often applied in the conventional procedure is also an unfavourable factor. It is unimportant for the present purpose whether the diene formation from 4-methylpent-3-en-2-ol, for example, is truly a concerted 1 : 4-elimination, such as (I), or proceeds in two steps with the mesomeric carbonium ion (II) as intermediate; either route will lead to the diene (III) as the principal product, and removal of the pyridinium ion from solutions of the alcohol or ester should suppress the formation of (III).

These considerations, with an earlier observation (Gillespie, Macbeth, and Mills, *J.*, 1948, 996) that yields of nitrobenzoic esters from 4-*iso*propyl*cyclo*hex-2-en-1-ol were considerably improved when the reaction was carried out in benzene with only a moderate excess of pyridine, have suggested a successful general procedure for the esterification of such unstable alcohols. The alcohol and acid chloride are dissolved separately in benzene or light petroleum, according to their solubility, and allowed to react in the presence of a slight excess of pyridine. Pyridine hydrochloride crystallises out as it is formed, and the non-polar solvent suppresses the ionisation of any which remains in solution. Heating is avoided, and mineral acids are not used in working up the product.


(I.) (III.) (II.)

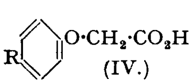
The esterification of 4-methylpent-3-en-2-ol by various acid chlorides was selected as a test case, and in every instance good yields of ester were obtained. Once isolated, the esters were quite stable, and could be recrystallised from polar solvents; the instability mentioned by Kenyon and Young (*loc. cit.*) should be ascribed more to the conditions of preparation than to the nature of the esters. The procedure described has been used successfully by other workers in these laboratories for the isolation of terpene alcohols, and the esterification of piperitol has been reported by Barnes, Jackman, and Macbeth (*J.*, 1951, 1848), with a preliminary description of the method used. Pulegol has also been esterified, but the investigation is incomplete. The isolation of the more unstable types of terpene alcohol now seems to be possible on a scale suitable for detailed examination.

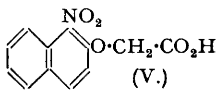
No novelty is claimed for the use of an inert diluent in esterifications with acid chlorides (see, *e.g.*, Reichstein, *Helv. Chim. Acta*, 1926, **9**, 799, 803; Friedman and Seligman, *J. Amer. Chem. Soc.*, 1950, **72**, 624), but it may not be generally realised that in certain cases it is essential to use this modification. In general, it is best to avoid the use of excess of pyridine as solvent in any reactions with acid chlorides if the primary product is susceptible to rearrangement, or to an exchange reaction with chloride ion (*e.g.*, some sulphonic esters).

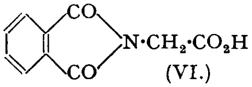
The method described may be combined with the procedure for preparation of acid chlorides in solution (Human and Mills, *J.*, 1949, S 77; *Nature*, 1946, **158**, 877); the acid is allowed to react with one mole each of thionyl chloride and pyridine, and the resulting solution of acid chloride is added to a solution of the alcohol containing an additional one mole of pyridine. This provides a method for esterifying labile alcohols with labile acid chlorides.

Kenyon and Young's work (*loc. cit.*) on 4-methylpent-3-en-2-ol provides additional evidence that acid-catalysed decomposition is the main factor preventing successful esterification. Although the *p*-nitrobenzoate could not be made, these authors successfully esterified the alcohol with acetic anhydride and with *p*-diphenylyl *iso*cyanate; these reagents are regarded as powerful dehydrating agents, but strong acidity is not developed during esterifications with them. Kenyon and Young also found that a hydrogen phthalate could be made from the alcohol through the potassium derivative, but the free acid ester soon decomposed spontaneously. It is improbable that the readily-dehydrated alcohols mentioned above could be successfully purified through the hydrogen phthalates (cf. Blumann and Zeitschel, *loc. cit.*), and the (−)-pulegol which Paolini claimed to have isolated in this way (*Atti R. Accad. Lincei*, 1919, **28**, II, 190, 236) may well have some other structure.

p-Nitrobenzoates and 3 : 5-dinitrobenzoates of allylic alcohols usually decompose on being heated to temperatures not much above 100°, and this thermal instability is a disadvantage in the usual procedure for isolating terpene alcohols, as steam-distillation of the ester to remove terpenes may cause serious losses of ester from thermal decomposition and from the action of the acids produced. By conducting the steam-distillation in the presence of a little sodium carbonate the autocatalytic effect of free acid is prevented, but the thermal decomposition of the crude esters may still occur. It was thought that esters having greater thermal stability might be obtained from acids which differed from *p*-nitro- and 3 : 5-dinitro-benzoic acids in having the carboxyl group isolated from electronic interaction with an aromatic nucleus carrying strongly electronegative groups, but the results obtained with several substituted acetic acids


(IV.)


(V.)


(VI.)

were not encouraging. *p*-Nitrophenoxyacetic (IV; $R = NO_2$), *p*-phenylazophenoxyacetic (IV; $R = N{:}N{\cdot}C_6H_5$), 1-nitro-2-naphthoxyacetic (V), and phthalimidoacetic (VI) acids could all be converted into chlorides and thence into suitably crystalline esters with 4-methylpent-3-en-2-ol, but the thermal stability of these esters, as judged by their behaviour in the melting-point tube, was not significantly greater than that of the nitrobenzoic esters. These acids may be of use in the characterisation of alcohols, and the *p*-phenylazophenoxyacetates are sufficiently coloured to be potentially useful in chromatographic separations.

EXPERIMENTAL.

(±)-4-*Methylpent*-3-*en*-2-*ol*.—Commercial mesityl oxide was distilled through a 100-cm. column of single-turn Fenske helices and the fraction with b. p. 128·5—129° was used. The apparatus and general procedure for the Meerwein–Ponndorf reduction have been described previously (Macbeth and Mills, *J.*, 1949, 2646). From mesityl oxide (86 g.), dissolved in dry *iso*propanol (200 ml.) and added dropwise during 4·5 hours to a refluxing solution of distilled aluminium *iso*propoxide (104 g.) in *iso*propanol (600 ml.) and heated for a further 2 hours until the 2 : 4-dinitrophenylhydrazine test for ketone became negative, a crude product (75 g.) was obtained with b. p. 55—58°/15 mm. This was redistilled through the 100-cm. column, and the fraction (60 g.) with constant b. p. of 56·5°/15 mm. was used for the esterifications. The alcohol remained colourless when stored in a brown-glass bottle for a year.

Acid Chlorides.—*p*-Nitrophenoxyacetic acid (Fritzsche, *J. pr. Chem.*, 1879, **20**, 267), *p*-phenylazophenoxyacetic acid (Mai and Schwabacher, *Ber.*, 1901, **34**, 3936), and 1-nitro-2-naphthoxyacetic acid (Lees and Shedden, *J.*, 1903, **83**, 750) were made by published procedures.

Each of the foregoing acids was converted smoothly into the chloride by warming it with pure thionyl chloride (3—5 moles) on the steam-bath for 1—2 hours. After removal of thionyl chloride under reduced pressure, followed by the evaporation of small portions of dry carbon tetrachloride, the *p*-nitrophenoxyacetyl chloride (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2418) was recrystallised from light petroleum, and the 1-nitro-2-naphthoxyacetyl chloride (Spitzer, *Ber.*, 1901, **34**, 3191) from carbon tetrachloride. The latter chloride crystallised directly from the excess of thionyl chloride in large crystals of high purity, but was recrystallised before use.

p-Phenylazophenoxyacetyl chloride is new, but was not obtained analytically pure. It crystallised from carbon tetrachloride containing light petroleum as small orange scales, m. p. 88—90°, but contained traces of anhydride or free acid which could not readily be removed. This material was quite suitable for esterifications; when added to absolute ethanol containing pyridine, it gave the known ethyl ester as shining orange scales, m. p. 70—71°; Mai and Schwabacher described this ester as greenish crystals with m. p. 70°.

Procedure for Esterification.—The esterification of 4-methylpent-3-en-2-ol with *p*-nitrobenzoyl chloride is typical of the procedure followed for the other esters. The chloride (0·02 mole), dissolved in dry benzene (25 ml.), was added to a stirred ice-cold solution of the alcohol (0·02 mole) and pyridine (0·022 mole) in light petroleum (40 ml.; b. p. 60—90°), and the mixture placed in the refrigerator overnight. Crystalline pyridine hydrochloride separated at once. The filtered solution of ester was washed several times with 1% aqueous sodium carbonate solution, then several times with water, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left the ester as yellowish needles (82% yield). Recrystallisation from light petroleum (b. p. 60—90°) gave the pure ester with the properties recorded in the table.

Esters of (±)-4-*methylpent*-3-*en*-2-*ol*.

Ester.	Form.	M. p.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
p-Nitrobenzoate	Needles	71—72°	$C_{13}H_{15}O_4N$	62·9	5·8	62·7	6·1
p-Nitrophenoxyacetate	Scales	41—42	$C_{14}H_{17}O_5N$	60·3	6·3	60·2	6·1
1-Nitro-2-naphthoxyacetate	Plates	90—91	$C_{18}H_{19}O_5N$	65·9	6·1	65·6	5·8
p-Phenylazophenoxyacetate	Scales	59—60	$C_{20}H_{22}O_3N_2$	70·7	6·5	71·0	6·6

The other esters recorded were obtained in similar yields. The 3 : 5-dinitrobenzoate (Macbeth and Mills, *loc. cit.*) and phthalimidoacetate (Barnes, Jackman, and Macbeth, *loc. cit.*), prepared by this method, have already been described. All could be recrystallised without decomposition from light petroleum or aqueous methanol, and gave sharp, reproducible m. p.s, but when heated above the m. p. in capillary tubes they decomposed suddenly between 110° and 150°. The decomposition temperature varied somewhat with different samples of ester, but the phthalimidoacetate was the most stable, and the 3 : 5-dinitrobenzoate the least stable to heat. The *p*-phenylazophenoxyacetate was orange, and the other esters faintly yellow.

We acknowledge financial assistance provided through the Commonwealth Science Fund.

JOHNSON CHEMICAL LABORATORIES,
UNIVERSITY OF ADELAIDE, AUSTRALIA.

[*Received, May 7th,* 1951.]