

added to a solution of 8.4 g (0.21 mole) of sodium hydroxide in 100 ml of water cooled in ice water. This mixture was shaken in a separatory funnel with 9.9 g (0.1 mole) of methyl cyanoacetate in 100 ml of chloroform until the water layer became neutral (3 min). The layers were separated, the chloroform was evaporated, and the residue recrystallized from ethyl acetate. The yield was 23.8 g (70 %) melting at 83°C.

*Alkylation procedure.* 0.1 mole of the alkyl iodide was added to a stirred solution containing 17 g (0.05 mole) of the tetrabutylammonium salt of methyl cyanoacetate in 75 ml of chloroform. The reaction was exothermic and ended (neutral) after a few minutes. The chloroform was evaporated. Ether was added whereupon the tetrabutylammonium iodide crystallized. The iodide was filtered off. The yield of the salt was 97 %. The ether solution was evaporated and the residue analysed as described above. The relative yields of mono- and dialkylated products are given in Table 1.

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## Ion Pair Extraction in Preparative Organic Chemistry

### IV. Alkylation of Methyl Acetoacetate

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Carbon alkylation of alkyl esters of acetoacetic acid is a standard procedure in preparative organic synthesis.<sup>1</sup> With sodium ethoxide in alcohol the reaction is rather slow and the operation takes at least one day to perform. Using a base such as NaH or K<sub>2</sub>CO<sub>3</sub> in an aprotic solvent such as DMF the reaction rate is higher than in alcohol but the product is contaminated by considerable quantities of *O*-alkylation products.<sup>2</sup>

We have recently demonstrated that tetrabutylammonium salts of alkyl cyanoacetates can be obtained by ion pair extraction.<sup>3</sup> These salts were then alkylated in chloroform solution by a very rapid reaction. For preparative purposes, however, it is not necessary to prepare the pure salt separately. Instead we have found that the extraction and alkylation can be performed advantageously in one operation. This new unit operation is conveniently called extractive alkylation and can be used for many purposes. The obvious advantage of the extractive alkylation is that even compounds which are extracted as ion pair with chloroform only to a minor degree from an aqueous solution, can be quantitatively alkylated. It is thus possible to alkylate very weak acids by this procedure. Another advantage is that esters are often not hydrolysed during the conditions used in extractive alkylation.

The procedure is demonstrated by the alkylation of methyl acetoacetate. The methyl ester was chosen in order to obtain simple NMR spectra which facilitated the analysis of the products obtained. The quantitative analysis of the mixtures was carried out by VPC using a 2 m × 1/8" column containing Carbowax 20 M (5 %).

The composition of the products obtained in the extractive alkylation are given in Table 1. From this it can be seen that carbon alkylation is the main or

Table 1. Percentage composition of alkylation mixtures.

Alkylation agent	R	(R) <sub>2</sub>	OR	
	CH <sub>3</sub> COCHCOOCH <sub>3</sub>	CH <sub>3</sub> COCCOOCH <sub>3</sub>	CH <sub>3</sub> C=CHCOOCH <sub>3</sub>	CH <sub>3</sub> COCH <sub>2</sub> COOCH <sub>3</sub>
Methyl iodide	80	10	0	10
Ethyl iodide	83.5	9	0	7.5
Butyl iodide	90	5	0	5
Isopropyl iodide	70	0	23.5	6.5

exclusive reaction. The extractive alkylation procedure has thus a selectivity for carbon alkylation similar to the standard procedure in alcohol. It is, however, much more rapid than the latter. The total yields are in every case quantitative.

For identification the  $\alpha,\alpha$ -dialkylacetoacetates were prepared from the monoalkylacetoacetates by alkylation, using the same method. The identity of the *O*-alkylation product, methyl 3-isopropoxycrotonate, was proved by NMR. A compound rich in methyl 3-methoxycrotonate was obtained using dimethyl sulphate as the alkylation agent.<sup>4</sup> This compound was useful as a reference in the NMR analysis. The three components in the reaction mixture after methylation could not be completely separated. The peaks for methyl acetoacetate and methyl  $\alpha$ -methylacetoacetate were always well separated. The peak for methyl  $\alpha,\alpha$ -dimethylacetoacetate, however, coincided with that for methyl acetoacetate on a Carbowax-1500 column and with that for methyl  $\alpha$ -methylacetoacetate on a polypropyleneglycol column. A combination of the values obtained on the two different columns gave the values in the first row of Table 1.

*Experimental.* 34 g (0.1 mole) of tetrabutylammonium hydrogen sulphate was added to a cooled solution of 8 g (0.2 mole) of sodium

hydroxide in 75 ml of water. This mixture was added to a stirred solution of 11.6 g (0.1 mole) of methyl acetoacetate and 0.2 mole of the alkyl iodide in 75 ml of chloroform. The reaction was exothermic and the mixture became neutral after a few minutes. The layers were separated, the chloroform was evaporated, and the tetrabutylammonium iodide precipitated by adding ether to the residue. The iodide was filtered off and the ether evaporated. The alkylated products were analysed and the yields obtained were equal to the percentages given in Table 1.

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