Nevertheless, it must be born in mind that the oxidases of the echinoderm egg and of yeast or mammalian heart were found to resemble each other very much. It is probable that the oxidase will have a different protein for each species (cf. hemoglobin), and that the proteins of the oxidases from heart and yeast may differ from each other just as much as either differs from that of echinoderm eggs. Furthermore, cytochrome c has been demonstrated in sea-urchin spermatozoa, and has been found to catalyze oxidations through the echinoderm egg oxidase. A small amount of cytochrome c (apparently less than $5 \times 10^{-4}$ µg per mg dry matter) is thus quite possible in the sea-urchin egg. In such a case the mammalian and the echinoderm cytochrome systems differ not in fundamental composition, but merely in concentration of their components.

My gratitude is due to the Director and Staff of the Scottish Marine Biological Station, Millport, where this investigation was carried out.


Received January 11, 1951.

An Improved Method for Selfcondensations of Esters by means of Alkali Ethoxides

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A general method for the preparation of $\beta$-ketoesters of the formula $RCH_2COCH(R)CO_2CH_2$ is the forced selfcondensation of esters with sodium ethoxide, as described by Mc Elvain. The yields of the $\beta$-ketoesters obtained by this method are usually very good, but the practical procedure can be somewhat simplified.

The preparation of dry, powdered sodium or potassium ethoxide is a rather cumbersome process, but the preparation of a suspension of the same reagent is easily performed in an inert solvent whose boiling point is higher than the melting point of the metal, which can then be very finely divided and hence is very reactive.

The choice of the solvent is dependent upon the boiling point of the ester used. In order not to remove some of the ester by azetropic distillation with the alcohol formed in the reaction, the boiling point of the ester should be some degrees higher than that of the solvent. For esters with high boiling points, over $140^\circ$, xylene b. p. 135-140$^\circ$ is a useful solvent; for those in the region 115-140$^\circ$ toluene b. p. 111$^\circ$ can be used; and for those with a low boiling point, below 115$^\circ$, the best solvent seems to be benzene, b. p. 81$^\circ$, but in this case sodium m. p. 97.8$^\circ$ is preferably replaced by potassium m. p. 63.8$^\circ$. Of course sodium may be used if it is first powdered
under xylene, and then the solvent replaced by benzene, but the time for the preparation of the ethoxide suspension is then increased to about 12 hours.

The alcohol formed is continuously removed by careful distillation through an efficient column, and the end of the reaction, which is reached when no more alcohol is formed, is indicated by a rise in temperature until near the boiling point of the solvent. In this way, the end-point is much more readily determined than by the method of Mc Elvain 1, who for the low boiling esters, followed the progress of the reaction by measuring the refractive index of the distillate. For the high boiling esters 2, he removed the alcohol under reduced pressure and the end of the reaction was taken to be the point when the boiling of the mixture ceased.

By this modification the same yields are obtained as by the old method, but the reactions are more easily controlled and the operations need very little attention. For the low-boiling esters, only the theoretical amount of ester is used, whereas Mc Elvain had to use a considerable excess much of which was lost in the isolation process 3.

**EXPERIMENTAL**

**Ethyl propionyl-propionate.** In a 1-l three-necked flask fitted with a mercury seal stirrer, a dropping funnel and a 30 cm Widmer column with a total reflux variable take-off still head, were placed 500 ml of dry benzene and 19.5 g (0.5 atom) of potassium. The flask was heated in an oil bath and refluxed for some minutes in order to expel the air, and then the stirrer was started. To the boiling suspension, 23 g (0.5 mole) of absolute alcohol were added carefully from the dropping funnel. After the addition of about 1 ml, the oil bath was removed and the addition continued at such a rate that rapid refluxing was secured. When all the alcohol had been added, the oil bath was replaced and the mixture refluxed for half an hour to complete the reaction.

If the procedure above is not followed and air is allowed to enter the flask with the finely powdered potassium, an explosion may occur when the alcohol is added.

102 g of dry ethyl propionate (1 mole) were added and the alcohol formed removed by careful fractionating. The take-off was so regulated, that the temperature at the top of the column did not exceed 70°. When no more alcohol could be obtained, about 100 ml of benzene were distilled off, and the mixture allowed to cool.

These operations take about 15 hours, and as the reaction needs very little attention, the distillation of the alcohol can be made overnight after careful adjustment of the take-off.

The clear, deeply coloured solution thus obtained was poured over 20 ml of conc. sulphuric acid and an excess of ice. The organic layer was separated, and the water extracted with ether. The combined organic layers were washed with water and then with a solution of sodium bicarbonate. After drying over a little anhydrous sodium sulphate, the ether and benzene were removed under reduced pressure, and the residue fractionated in vacuo. Yield 59 g (75 %) of ethyl propionyl-propionate boiling at 88–90°/12 mm.

**Ethyl n-butyryl-n-butyrate.** In the same apparatus as above were placed 400 ml of dry toluene and 11.5 g (0.5 atom) of sodium. The flask was heated in a wax bath until the sodium melted. The stirrer was started, the wax bath removed, and 23 g of absolute alcohol were carefully added through the dropping funnel.

The procedure after this was the same as that above except that 118 g of dry ethyl n-butyrate (1 mole) were added instead of the ethyl propionate, and the alcohol removed below 90°. Yield 70 g (75 %) of ethyl n-butyryl-n-butyrate boiling at 103°/11 mm.
Ethyl n-valeryl-n-valerate. The same procedure as above was used, except that 400 ml of xylene was used instead of the toluene and 130 g (1 mole) of dry ethyl n-valerate instead of the ethyl n-butylate. Yield 80 g (75 %) of pure ethyl n-valeryl-n-valerate boiling at 124–126°/10 mm.


Received January 19, 1951.

Quaternary Derivatives of 2-Benzylphenoxyethylamines

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In the search for new adrenergic blocking agents related to the basic ethers of phenol1 several quaternary ammonium compounds derived from o- and p-benzylphenol were prepared. The physical and chemical data for four such compounds are presented below (see table).

Because of the incidental relation to 2-benzylphenoxydimethylaminoethane HCl which was found by Cheney et al.2 to be a potent histamine antagonist it was of interest to investigate the above mentioned quaternary compounds in this respect.

The pharmacological results, the details of which will be dealt with by others elsewhere, indicate that all these compounds are considerably less active than the hydrobromide of 2-benzylphenoxydimethylaminoethane which is as active as the corresponding hydrochloride described by Cheney et al.2, and approximately twice as active as Benadryl.

The quaternaries are somewhat less active than Benadryl.

The ammonium compounds were prepared by refluxing for three hours two moles of the appropriate tertiary amine with one mole of crude 2-benzylphenoxyethylhalide and removing excess volatile amine in vacuo, or, more conveniently, by refluxing the free tertiary benzylphenoxyethylamine prepared according to ref. 2 with an excess of the appropriate halide in ethanol. The yields were from 85 to 90 % of the theoretical.


Received January 4, 1951.

Table 1. 2-Benzylphenoxyethylammonium halides.

<table>
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<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>X</th>
<th>m.p. °C</th>
<th>% X calc. found</th>
<th>cryst. from</th>
<th>solubility in water</th>
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<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>I</td>
<td>150</td>
<td>32.17 32.04</td>
<td>abs. ethanol</td>
<td>sl. soluble</td>
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<tr>
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<td>C₂H₅</td>
<td>C₂H₅</td>
<td>Br</td>
<td>151</td>
<td>20.38 20.28</td>
<td>abs. ethanol-ether (1 : 1)</td>
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<td>C₇H₅</td>
<td>Br</td>
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<td>C₂H₅ COOC₂H₅</td>
<td>Cl</td>
<td>154</td>
<td>9.40 9.72</td>
<td>ethylacetate: alcohol (1 : 1)</td>
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