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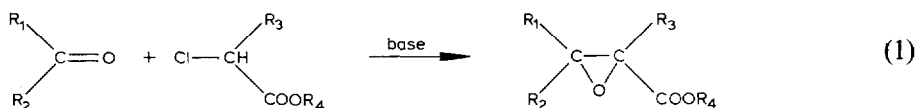
Application of gas-liquid chromatography to the investigation of crude Darzens reaction products

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One of the important synthetic procedures available for the homologation of carbonyl compounds is the Darzens synthesis. The first step of the process consists in the Darzens reaction itself, *i.e.*, the condensation of a carbonyl compound and an α -halogenated ester anion affording esters of substituted 2,3-epoxycarboxylic acids (eqn. 1).



In pharmaceutical chemistry, the Darzens condensation is an important step in the synthesis of retinol (vitamin A). Further, the condensation products of benzaldehyde, *p*-tolualdehyde, *p*-methylacetophenone and particularly of acetophenone with ethyl chloroacetate are widely used as flavour compounds, imitating the aroma of strawberries.

In spite of these practical examples, no paper has yet been published describing the composition of the crude reaction mixtures formed by Darzens condensation of substituted benzaldehydes and acetophenones with α -halogenated esters. This may be due to the relative complexity of such mixtures, making difficult a quantitative determination of their individual components. A peculiar point is that the major reaction products, *e.g.*, ethyl 2,3-epoxy-3-phenylbutanoate, have two chiral carbon atoms and consequently exist as *Z*- and *E*-isomers. In this respect, for organoleptic reasons, it is advantageous that the reaction mixtures contain as high a proportion of *Z*-isomers as possible, and this can be checked only by 100 MHz ^1H NMR spectroscopy or gas-liquid chromatography (GLC).

The use of GLC for the analysis of pure products formed (as mixtures of *E*- and *Z*-isomers) by the reaction of acetophenone with ethyl chloroacetate, and for assessing the quality of commercial "strawberry aldehyde C_{16} "¹ has been reported earlier^{2,3}. Both medium-polar (4% XE-60 on Chromosorb G AW DMCS²) and low-polarity stationary phases (3.8% SE-30 on Chromosorb W AW DMCS³ or 5%

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OV-101 on Chromosorb W AW DMCS¹) were used for this purpose. For similar compounds formed from substituted benzaldehydes and ethyl chloroacetate, a highly polar phase (15% ethylene glycol succinate on Chromosorb) has been recommended⁴.

This study was aimed at finding a suitable analytical method to investigate the outcome of Darzens reaction between substituted benzaldehydes and acetophenones on the one hand and ethyl chloroacetate on the other.

The highly or medium-polar phases mentioned above are not convenient for this purpose, because several minor components of the reaction mixtures (*e.g.*, methyl cinnamate, cinnamyl butenoate, phenacyl acetate¹ and ethyl 2-hydroxy-3-phenyl-3-butenate⁵) have the same retention times as the principal products on these phases; moreover, the latter show considerable tailing, preventing their accurate, quantitative determination. Polymeric carriers such as Porapak Q and Tenax are unsatisfactory for the same reason, and no convenient internal standard is available for use with the low-polarity phases mentioned above (SE-30, OV-101). Apiezon L seems to be the stationary phase best suited for the intended purpose.

EXPERIMENTAL

The reaction mixtures were analysed using a glass column (4 m × 3 mm I.D.), packed with 15% Apiezon L on Chromaton N AW DMCS (grain size 0.160–0.200 mm) under the following conditions: column, temperature programmed from 100 to 290°C at a rate of 5°C/min; injection port temperature, 270°C; carrier gas (nitrogen)

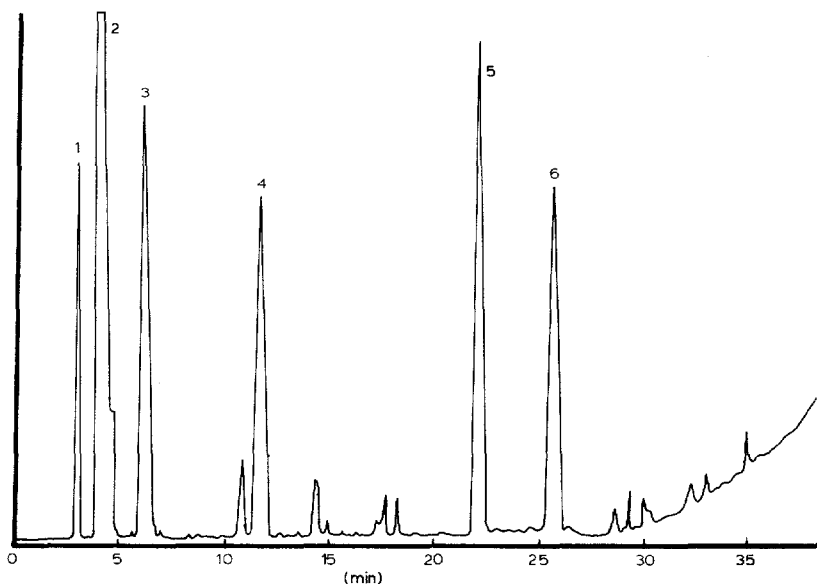


Fig. 1. Typical chromatogram of a Darzens reaction mixture (condensation product of acetophenone with ethyl chloroacetate in the presence of metallic sodium, with added ethylbenzene as internal standard). Peaks: 1 = ethyl chloroacetate; 2 = toluene; 3 = ethylbenzene; 4 = acetophenone; 5 = ethyl (*Z*)-2,3-epoxy-3-phenylbutanoate; 6 = ethyl (*E*)-2,3-epoxy-3-phenylbutanoate.

flow-rate 150 ml/min (corresponding to an overpressure of 250 kPa at 100°C); and flame-ionization detector.

The analyses were performed on a Model Chrom-5 gas chromatograph (Laboratory Instruments, Prague, Czechoslovakia) fitted with a digital integrator.

RESULTS AND DISCUSSION

Under the conditions described, a good separation of both the initial compounds and minor by-products was achieved. The ratio found between the *Z*- and *E*-isomers of ethyl 2,3-epoxy-3-phenylbutanoate was in good agreement with that determined by ¹H NMR spectroscopy (66.1% of *Z*-isomer found by GLC versus 67.4% by NMR analysis using a Tesla 100-MHz apparatus and deuteriochloroform as solvent; in another instance, values of 91.0% and 90.0% of *E*-isomers were found by GLC and NMR, respectively; these determinations were carried out on fractions resulting from vacuum distillation of the reaction mixtures).

For the stationary phase and conditions mentioned above, two internal standards were found to be suitable were ethylbenzene and dibutyl ether, which, being unreactive, can be conveniently added to the reaction mixtures at the beginning of the condensation. A typical chromatogram of the reaction mixture resulting from the condensation of acetophenone with ethyl chloroacetate (reaction carried out with metallic sodium in toluene, using ethylbenzene as internal standard) is shown in Fig. 1.

With the internal standards mentioned above (ethylbenzene for work with weakly polar solvents and dibutyl ether with more polar ones), the outcome of the Darzens reaction of substituted acetophenones and benzaldehydes with ethyl chloroacetate can be studied by GLC without any overlapping of the various peaks corresponding to starting materials, internal standards or products formed.

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