Separation of the Diastereoisomers of Methyl 2,4-Dimethylheptanoate[1]

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Although the resolution of diastereoisomers by gas chromatography has been reported,[3-5] the small quantity thus separated has often prevented their isolation and the accumulation of direct evidence that separation had indeed occurred. During the course of a routine check of the purity of 2,4-dimethylheptanoic acid by gas chromatographic analysis of its methyl ester, it was noted that two components were present in comparable quantity. Evidence is presented below that these components were diastereoisomers of methyl 2,4-dimethylheptanoate.

Experimental[6]

Apparatus.—Gas chromatographic analyses were done on an instrument constructed in these laboratories employing a thermistor katharometer as detector. Two columns were used: (1) 1 m., 4 mm. i.d., 10% (w./w.) Carbowax 4000 on 60–80 mesh diatomaceous earth[7] and (2) 2 m., 4 mm. i.d., 10% (w./w.) diethyleneglycol succinate (DEGS) on 60–65 mesh, acid-washed diatomaceous earth. Helium flow rate was 50 ml./min. Column temperatures were 50 or 100°.

Infrared spectra were obtained by means of a Beckman IR-5 spectrophotometer equipped with a KBr beam condenser.

Materials.—2-Methylpentanol-1 (I) (Matheson, Coleman and Bell) was dried and distilled twice before use, n^{20}D 1.4185, b.p. 93–95° (92 mm.). Gas chromatographic analysis of I, after its purification, showed one peak on the Carbowax column at 100°.

Diethyl methylmalonate (III) (Matheson, Coleman and Bell) was distilled before use, n^{20}D 1.4129, b.p. 194–196° (760 mm.). The purity of III was studied by its saponification, decarboxylation, and esterification of the resulting free acids with diazomethane.[8] Gas chromatographic analysis of the esters on the DEGS column at 50° showed the presence of more than 99% methyl propionate and slightly less than 1% of methyl acetate. It was concluded that III had contained more than 99% diethyl methylmalonate and slightly less than 1% diethyl malonate.

Diethyl malonate (Eastman, White Label) was more than 99% pure as determined by gas chromatography on the

DEGS column at 100°. A single, minor, unidentified peak was present.

2,4-Dimethylheptanoic Acid (IV).—I was treated with phosphorus tribromide according to the procedure of Noller and Dinsmore.[9] 1-Bromo-2-methylpentane (II) was obtained in 55.6% yield, b.p. 42–43° (15.5 mm.), n^{20}D 1.4480, (n^{20}D 1.4495).[10] Gas chromatography of II on the Carbowax column at 100° showed one peak. Its infrared spectrum contained no OH bands.

Anal. Calcd. for $C_6H_{13}Br$: C, 43.65; H, 7.94; Br, 48.44. Found: C, 43.47; H, 7.82; Br, 48.73.

Sodium *t*-butoxide (1.05 moles, 24.15 g. of sodium) in 800 ml. of *t*-butyl alcohol was treated with III (1.10 moles, 191.5 g.) followed by II (1.05 moles, 173.2 g.). The resulting mixture was worked up in the conventional manner[11] to give the disubstituted malonic ester. The ester was saponified for 48 hr. with 50% potassium hydroxide. The free acid was decarboxylated by refluxing with constant boiling hydrochloric acid for 24 hr. The free acid IV was obtained in 50% yield, b.p. 82–83° (0.6 mm.), n^{20}D 1.4302.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.35; H, 11.39; neut. equiv., 158.0. Found: C, 68.34; H, 11.15; neut. equiv., 158.0 ± 0.5.

Esterification[8] of about 50 mg. of IV yielded methyl 2,4-dimethylheptanoate (V).

4-Methylheptanoic Acid (VIII).[12]—Sodium ethoxide (0.32 mole, 7.36 g. of sodium) in 150 ml. of absolute ethanol, diethyl malonate (0.34 mole, 54.5 g.), and 1-bromo-2-methylpentane (0.33 mole, 54.5 g.) reacted in the usual manner to give diethyl 2-methylpentylmalonate (VI), n^{20}D 1.4287, b.p. 110–112° (3.2 mm.), in 73% yield. Gas chromatography of VI on the Carbowax column at 100° showed one peak. Saponification of 5 g. of VI yielded 2-methylpentylmalonic acid (VII) from which was formed its bis-S-benzylthiouronium salt.

Anal. Calcd. for $C_{25}H_{36}N_4O_4S_2$: C, 57.66; H, 6.98; N, 10.78. Found: C, 58.16; H, 7.17; N, 10.42.

Decarboxylation of about 50 mg. of VII and esterification of the resulting 4-methylheptanoic acid (VIII) yielded methyl 4-methylheptanoate (IX). Gas chromatography of IX on the DEGS column at 100° showed one peak.

Separation of Diastereoisomers of V.—Chromatography of methyl 2,4-dimethylheptanoate (V) on the DEGS[13] column at 100° (flow rate 50 ml./min.) resulted in elution of two well separated peaks (A and B) within 10 min. The separation factor, β (the ratio of the retention times of peak A and peak B), was 1.09. Resolution[14] of the components was 1.07. The possibility that one of the components was methyl 4-methylheptanoate (VIII), methyl propionate, or 2,4-dimethylheptanoic acid was eliminated on the basis of the retention volumes of reference samples at the above conditions.

Peak A was collected as it was eluted from the DEGS column and rechromatographed under the same conditions. Only one peak was obtained. The infrared spectrum of peak A, as a pure liquid and in carbon tetrachloride solution, was essentially identical to the spectrum of methyl 2,4-dimethylheptanoate (V). Normalization of the area under peaks A and B showed that peak A represented 53.2% of the total mixture.

Epimerization. (a) Pure Peak A, collected from the DEGS column, was heated in a sealed tube at 110° for 18 hr. in

(1) This work was supported by Contract No. AF 33(616)-6008 with the U.S. Air Force. Mention of names of firms or trade products does not imply endorsement or recommendation by the Department of the Air Force. The authors are indebted to Dr. William R. Moore, Dept. of Chemistry, M.I.T., for his interest and advice.

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(14) As recommended by D. Ambrose in "Gas Chromatography 1960," R. P. W. Scott, ed., Butterworth Inc., Washington, D. C., 1960, p. 429.

the presence of 1 M sodium methoxide in anhydrous methanol. The reaction solution was neutralized with anhydrous methanolic hydrochloric acid, and the resulting sodium chloride removed by centrifugation. The supernatant liquid was evaporated to a small volume and chromatographed directly on the DEGS column. The resulting chromatogram showed the presence of both peak A and peak B. The area of peak A represented 41.8% of the mixture.

(b) Methyl 2,4-dimethylheptanoate was heated under reflux for 21 hr. in the presence of 1 M sodium methoxide in anhydrous methanol. The infrared spectrum of the resulting ester, as a pure liquid or in carbon tetrachloride was essentially identical with the spectrum of untreated methyl 2,4-dimethylheptanoate. Chromatography on the DEGS column showed the presence of peaks A and B. The area of peak A had decreased to 41.8% of the mixture.

(c) An approximately 10% aqueous solution of sodium 2,4-dimethylheptanoate was heated 18 hr. in a sealed tube at 115°. The free acid was isolated and esterified with diazomethane. Separation of the ester on the DEGS column showed that peak A had increased to 56.2% of the total mixture of components A and B.

Discussion

The synthesis of 2,4-dimethylheptanoic acid was accomplished in a straightforward manner. The fact that its methyl ester was separated by gas chromatography into two almost equal components (A and B) suggested that diastereoisomers had been resolved. The possible presence of impurities such as methyl 4-methylheptanoate, methyl propionate, and free 2,4-dimethylheptanoic acid was eliminated by comparison of the retention volumes of components A and B with those of the authentic reference compounds.

A and B were shown to be diastereoisomers by the fact that the infrared spectrum of A was essentially identical to the infrared spectrum of methyl 2,4-dimethylheptanoate, that A was epimerized to a mixture of A and B, that the relative quantities of A and B were changed by epimerization, and that the infrared spectrum of the epimerized mixture was the same as that of the original methyl 2,4-dimethylheptanoate.

Addition of Selenium and Sulfur Tetrachlorides to Alkenes and Alkynes

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Preparation of organic selenides and their dihalides by addition of selenium halides to an unsaturated linkage is interesting in that it produces compounds having a reactive halogen on the *beta* carbon atom.[2,5] This note describes further work

on addition to olefinic linkages and an extension of the reaction to acetylenic compounds.

Although the reaction of selenium tetrachloride with unsaturated linkages to produce selenium dichlorides is quite general, our results show that a selenide is produced with acrylonitrile. Subsequent chlorination of this selenide yields the expected selenium dichloride which reverts to the selenide on recrystallization from acrylonitrile. As the latter is not chlorinated with particular ease,[6] the presence of the nitrile group *beta* to the selenium atom must exert a labilizing influence on the selenium-chlorine linkage in this compound. Thus, selenides are to be expected whenever the selenium-chloride linkage is labilized and/or the unsaturated starting material is easily and rapidly chlorinated. In an attempt to isolate the dichloride from the addition reaction, the stoichiometric amount of acrylonitrile was reacted with selenium tetrachloride in ether. This leads to a highly colored solution, typical of solutions of alkylselenium trihalides (an almost certain intermediate of the addition reaction), from which no solid product could be obtained. This suggests that excess alkene is needed to force the reaction towards completion.

Lack of addition of selenium tetrachloride to *trans*-stilbene, even at temperatures substantially above those required for the other additions to occur, is probably due to the well documented π-electron delocalization of the carbon double bond in this type of compound. Addition occurs with diphenylacetylene, but subsequent cyclization takes place. This reaction will be reported in a separate place in the near future.

As the nearly quantitative reaction between sulfur tetrachloride and cyclohexene occurs more rapidly and at temperatures substantially lower than reported for the analogous reaction using sulfur dichloride,[7] the tetrachloride is a more active addition reagent than the dichloride. It is also a more active chlorinating agent, however, and it was found impossible to separate the sulfides from other reaction products without nearly total decomposition of the desired product in the other cases studied (see Experimental). All attempts to isolate bis-organo sulfur dichlorides of cyclohexene and hexene by separating the products from impurities at Dry Ice temperature resulted in failure.

Experimental

Sulfur and Selenium Tetrahalides.—The selenium compound was prepared by condensing dried tank chlorine onto elementary repurified selenium in a flask protected from atmospheric moisture and warming to room temperature while simultaneously passing through a slow stream of nitrogen. The sulfur compound was prepared in the same

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