

dicarboxylic acid by hydrolysis of the corresponding barbituric acid.<sup>7</sup> Hydrolysis by refluxing in aqueous alkali yielded an acid, m.p. 180° dec., after recrystallization from water.

*Anal.* Calcd. for C<sub>9</sub>H<sub>14</sub>O<sub>4</sub>: C, 58.06; H, 7.57. Found: C, 58.15; H, 7.79.

This may correspond to the acid, m.p. 185°, reported by Desai and Hunter,<sup>2</sup> but which we were unable to obtain by their procedure.

TABLE I  
INFRARED ABSORPTION, 2 TO 12 μ<sup>a</sup>

IA (m.p. 173°)	IB (m.p. 134°)	III (m.p. 176°)	IV (m.p. 177.5°)
		2.96 st.	
3.4-3.5 v. st.	3.4-3.5 v. st.	3.4-3.55 v. st.	3.4-3.5 v. st.
		3.90 st.	
5.90 st.	5.90 st.	5.92 v. st.	5.93 st.
6.83 v. st.	6.86 st.	6.87 v. st.	6.85 v. st.
7.06 v. w.			
7.23 med.	7.26 med.	7.28 st.	7.22 st.
7.40 v. w.	7.50 med.	7.55 med.	
7.70 med. -	7.70 med.	7.64 med. -	7.75 med.
7.90 med.	7.85 med.	7.93 med.	7.95 w.
8.18 med. +	8.02 med. +	7.99 med. +	8.14 med.
8.47 v. w.	8.12 med. +	8.10 med.	8.59 v. w.
8.62 w.	8.33 med. +	8.38 med.	
8.78 w.	8.77 med.	8.80 med. +	8.72 med.
9.08 med. -		8.90 w.	9.10 w.
9.45 w.		9.66 w.	
9.92 w.	9.85 w.	9.90 med.	
10.70 st.	10.70 st.	10.30 med.	10.90 v. st.
		10.62 st.	
		11.25 med.	
		11.64 med.	

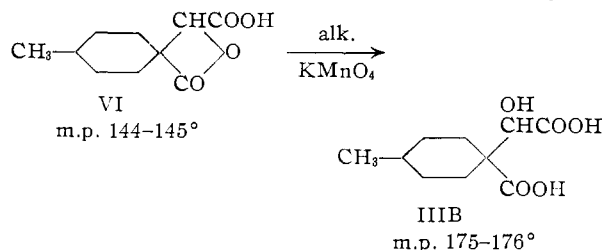
<sup>a</sup> st. = strong; med. = medium; w. = weak; v. = very.

### Discussion

The agreement in melting point between the products we isolated and those of Desai and Hunter<sup>2</sup>

(7) This acid was kindly supplied to us by Dr. E. H. Van Heyning of the Eli Lilly Laboratories, m.p. 248-250°, dec. *Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: N, 13.32. Found: N, 13.43 (private communication).

are excellent for every case except that of the acid, m.p. 138°, to which they assigned the structure of the glycolic acid IIIB. Our sample of acid isolated at this stage proved to be a lactone. It seems likely that their acid, m.p. 138°, was actually an



impure sample of the lactone VI since, like our sample of VI, "oxidation" with alkaline permanganate gave an acid, m.p. 175-176°. Our identification of this material as the glycolic acid IIIB and not the malonic acid IVB is based not only on analysis but on the strong hydroxyl bands in the infrared spectra, a sharp band at 2.96 μ for the free hydroxyl group and a broad band at 3.90 μ for the associated hydroxyl group (see Table I).

It would appear from our experience that permanganate oxidation of the glycolic acids IIIA or IIIB leads to their complete degradation to water-soluble fragments which we did not isolate by simple extractive procedures, leaving behind traces of starting acid IA or unreacted glycolic acid IIIB.

It would therefore appear that the evidence offered by Desai and Hunter cannot be accepted as demonstrating the existence of stable "chair" and "boat" isomers in a cyclohexane ring compound.

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## Addition of Hydrogen Bromide to *trans*-4-Heptenoic Acid

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*trans*-4-Heptenoic, 4-bromoheptanoic and 5-bromoheptanoic acids have been synthesized in high purity. The addition of anhydrous hydrogen bromide to *trans*-4-heptenoic acid gives an equal mixture of 4- and 5-bromoheptanoic acids. This addition appears to be the first to give a statistical ratio of products from an olefinic acid in which the double bond is closer to the carboxyl group than the 9,10-position.

The influence of the carboxyl group on the mode of addition of unsymmetrical reagents to a double bond in several remote positions in a carbon chain is still an unsettled question. When the double bond is in the terminal position, CH<sub>2</sub>=CH(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H, addition of hydrogen bromide according to the Markownikoff rule and reverse addition in the presence of peroxides are well established.<sup>2</sup> Non-ter-

minal double bonds in the β,γ-position, RCH=CHCH<sub>2</sub>CO<sub>2</sub>H, appear to add the negative parts of hydrogen halides,<sup>3,4</sup> sulfuric acid<sup>4</sup> and hypochlorous acid<sup>5</sup> predominately to the γ-carbon atom, although the evidence in all cases is not convincing. This mode of addition is predicted by the strong positive inductive effect of the carboxyl group. Finally, although the randomness of additions of hydrogen

(1) This work was taken from the Ph.D. thesis of James A. Knight, Procter and Gamble Fellow, The Pennsylvania State College, 1948-1949.

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John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 444-450, and K. S. Markley, "Fatty Acids," Interscience Publishers, Inc., New York, N. Y., 1947, pp. 340-342.

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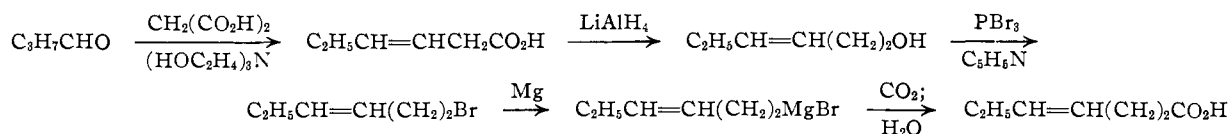
(4) R. Fittig and co-workers, *Ann.*, 255, 30, 77 (1889).

(5) G. F. Bloomfield and E. H. Farmer, *J. Chem. Soc.*, 2062 (1932).

bromide to 9,10-undecenoic acid<sup>6</sup> and sulfuric acid to 9,10-octadecenoic acid<sup>7</sup> has been demonstrated, surprising and unexplained results are reported for additions to non-terminal double bonds in less remote positions. Thus, 4-hexenoic acid is reported to add hypochlorous acid to give almost exclusively the 5-chloro-4-hydroxy derivative,<sup>8</sup> and 6-octadecenoic acid is believed to form 7-hydroxystearic acid in 93% yield upon hydration by the sulfuric acid method.<sup>8</sup>

In this investigation, the statistically random addition of hydrogen bromide to *trans*-4-heptenoic acid is described. The acid is the simplest one having a non-terminal double bond in a remote position and in which any effect of hyperconjugation is minimized by methylene groups on each side of the double bond. Hydrogen bromide was chosen as the addend, for it reacts readily at reasonable temperatures to give a stable product free of diastereoisomers such as might result from the addition of hypohalous acids. Furthermore, the two possible bromoheptanoic acids could be synthesized in high purity from the corresponding lactones, and their methyl esters differed sufficiently in refractive index to permit an analysis based on this property.

The *trans*-4-heptenoic acid was synthesized by the following series of reactions



The position of the double bond was established by the synthesis and demonstrated by ozonolysis. The *trans* configuration was assigned on the basis that the Knoevenagel condensation produces the *trans* form of crotonic acid from acetaldehyde<sup>9</sup> and by comparison of the infrared spectrum with those of elaidic and vaccenic acids. The absorption at 10.25  $\mu$  has been associated with the *trans* configuration.<sup>10</sup>

Addition of dry hydrogen bromide to the heptenoic acid occurred readily at 70° without solvent to give a mixture of equal amounts of 4- and 5-bromoheptanoic acids. The mixture was analyzed by converting to the corresponding methyl esters at 0° with diazomethane followed by fractional distillation and determination of the refractive indices of the fractions. Refractive indices were determined to  $\pm 0.0002$  corresponding to a precision of  $\pm 5\%$  in the composition of the mixture. Attempts to add hydrogen bromide at room temperature or in ether or hexane solvents were unsuccessful. Addition was incomplete as was evidenced by a low bromine content for the product.

(6) E. P. Abraham, E. L. R. Mowat and J. C. Smith, *J. Chem. Soc.*, 948 (1937).

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### Experimental

**3-Hexen-1-ol.**—3-Hexenoic acid was prepared from 4.77 moles of freshly distilled *n*-butyraldehyde and 3.5 moles of malonic acid in 3.5 moles of triethanolamine.<sup>11</sup> Fractionation through an 18-plate column gave a 40% yield boiling at 81–82° at 2 mm., m.p. 14°,  $n_D^{20}$  1.4395, *p*-phenylphenacyl ester, m.p. 65°. Quantitative microhydrogenation over platinum in acetic acid: calcd. H<sub>2</sub> uptake, 1.00 mole; found, 1.03 moles.

To 57 g. of lithium aluminum hydride and 1500 ml. of dry ether was added with stirring 143 g. (1.25 moles) of 3-hexenoic acid at a rate sufficient to produce gentle refluxing. Stirring was continued for six hours, the mixture then cooled and decomposed by the addition of 1 l. of 20% sulfuric acid. The aqueous layer was extracted with two 100-ml. portions of ether, and the combined ethereal solution concentrated to 500 ml. and dried over anhydrous sodium sulfate. Fractionation gave 113 g. (90%) of 3-hexen-1-ol, b.p. 95° at 84 mm.,  $n_D^{20}$  1.4380–1.4382.

**3-Bromo-1-hexene.**—To 107 g. of 3-hexen-1-ol and 30 g. of dry pyridine cooled in a salt-ice-bath was added 115 g. of freshly distilled phosphorus tribromide over a period of five hours. The temperature of the mixture did not exceed 0° during the addition. After standing for four hours at room temperature, the crude bromide was diluted with ether, washed with three 25-ml. portions of water and dried

over calcium chloride. Fractionation gave 100 g. (58%) of 1-bromo-3-hexene, b.p. 69° at 42 mm.,  $n_D^{20}$  1.4690–1.4696.

***trans*-4-Heptenoic Acid.**—The Grignard reagent from 1-bromo-3-hexene was prepared in the usual way from 95 g. of the bromide, 14.2 g. of magnesium and 200 ml. of ether. Carbonation was effected at –10° by bubbling carbon dioxide into the cooled solution over a period of three hours. The mixture was decomposed by 3 *N* sulfuric acid. The organic acid was separated from 10 g. of neutral oil by extraction with 6% sodium hydroxide solution. Fractionation of the product gave 59 g. (79%) of 4-heptenoic acid, b.p. 95° at 3 mm.  $n_D^{20}$  1.4413, neut. equiv. calcd., 128, found, 128, *p*-phenylphenacyl ester, m.p. 77–78°. This derivative was homogeneous; the m.p. was unchanged after two recrystallizations. The *trans* configuration was confirmed by a comparison of the infrared spectrum with those of other *cis-trans* compounds.<sup>10</sup> The 4-heptenoic acid has a sharp maximum at 10.3  $\mu$ . Quantitative microhydrogenation over platinum in acetic acid: calcd. H<sub>2</sub> absorption, 1.00 mole; found, 1.02 moles.

The location of the double bond in this acid was confirmed by ozonolysis of a 6.84-g. sample in 80 ml. of chloroform. The ozonide was decomposed and oxidized by the procedure of Henne and Hill<sup>12</sup> with a mixture of 18 g. of sulfuric acid and 12.5 g. of 30% hydrogen peroxide in 80 ml. of water. The volatile acid was separated in 57% yield by steam distillation and identified as propionic acid by the method of Dyer.<sup>13</sup> Succinic acid, m.p. and mixed m.p. 184–185, was isolated in 78% yield by continuous ether extraction of the residue.

**Methyl Hydrogen Esters.**—Glutaric acid, m.p. 97–98°, was prepared as described.<sup>14</sup> A mixture of 502 g. of the acid and 900 g. of acetyl chloride was refluxed for three

(11) R. P. Linstead, E. G. Noble and E. J. Boorman, *ibid.*, 557 (1933).

(12) A. L. Henne and P. Hill, *This Journal*, **65**, 753 (1943).

(13) D. C. Dyer, *J. Biol. Chem.*, **28**, 445 (1917).

(14) C. S. Marvel and W. F. Tuley, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 289.

hours and fractionated through a 6-plate column. The distilled anhydride, b.p. 144° at 8 mm., solidified immediately, m.p. 52–55°. The yield was 410 g. (92%). Methyl hydrogen succinate and methyl hydrogen glutarate were prepared from the corresponding anhydrides by a modification of the method described for ethyl hydrogen 2,3-dimethylsuccinate.<sup>15</sup> For the succinic ester, 7.2 moles of the anhydride and 30 moles of methanol were refluxed for nine hours. For the glutaric ester, 3.6 moles of the anhydride and 7.3 moles of methanol were refluxed for three hours. Methyl hydrogen succinate was separated from dimethyl succinate by dissolving in dilute aqueous sodium bicarbonate. The ester obtained upon acidification was fractionated through a 6-plate column to give 539 g. (57%), b.p. 119° at 4 mm., m.p. 51–52°. The crude methyl hydrogen glutarate was distilled directly through this column to give 364 g. (70%), b.p. 111° at 1 mm.,  $n_D^{20}$  1.4390–1.4392.

**Carbomethoxyacyl Chlorides.**—Thionyl chloride was purified by distillation from linseed oil followed by fractional distillation. Each of the methyl hydrogen esters was allowed to stand for 15 hours with a 30% excess of thionyl chloride and then fractionated to give the following products: 3-carbomethoxypropionyl chloride, 290 g., 47%, b.p. 102° at 35 mm.,  $n_D^{20}$  1.4412–1.4413 and 4-carbomethoxybutyryl chloride, 387 g., 94%, b.p. 107° at 18 mm.,  $n_D^{20}$  1.4438–1.4440. The former compound was much less stable and more difficult to purify.

**Aldo Esters.**—The acyl chlorides were reduced in one-mole quantities to the corresponding aldehydes by the Rosenmund catalytic hydrogenation procedure described for  $\beta$ -naphthaldehyde.<sup>16</sup> In the reduction of 3-carbomethoxypropionyl chloride, 89% of the hydrogen chloride was evolved upon heating for five hours at 112–114°. From the 4-carbomethoxybutyryl chloride only 84% of the hydrogen chloride was obtained upon heating for six hours at 116–122°. The xylene solutions were washed with 5% sodium bicarbonate solution and fractionated at a pressure of 10 mm. Hydrogen chloride was evolved during the distillations, and the products polymerized upon standing as was shown by an increase in the refractive indices. By rewashing the distillates with 5% sodium bicarbonate solution and refractionating through a 6-plate column, stable products were obtained in addition to polymers, which in each case decomposed smoothly at 220° to give more monomeric product. In this way, there was obtained 3-carbomethoxypropionaldehyde, 88 g., 24% b.p. 69–71° at 15 mm.,  $n_D^{20}$  1.4212–1.4220, 2,4-dinitrophenylhydrazone, m.p. 131–132°, and 4-carbomethoxybutyraldehyde, 101 g., 33%, b.p. 80–83° at 8 mm.,  $n_D^{20}$  1.4265–1.4268, 2,4-dinitrophenylhydrazone, m.p. 106–107°.

**4- and 5-Heptanolactones.**—A solution of 101 g. (0.78 mole) of 4-carbomethoxybutyraldehyde in 300 ml. of dry ether was cooled to  $-10^\circ$  and 0.68 mole of ethylmagnesium bromide in 200 ml. of ether was added over a period of two hours.<sup>17</sup> Stirring was continued for five days at room temperature. The mixture was decomposed by 15% aqueous ammonium chloride. The crude hydroxy ester (91 g.) was saponified by heating for one hour with 28 g. of sodium hydroxide in 130 ml. of ethanol and 150 ml. of water. Ethanol was removed under reduced pressure as an azeotrope with water and benzene. Neutral oil (17.5 g.) was separated by ether extraction of the aqueous solution of the sodium salt which, in turn, was acidified with sulfuric acid and extracted with ether to give 70 g. (71%) of 5-hydroxyheptanoic acid.

In a similar manner, 36 g. (43%) of 4-hydroxyheptanoic

acid was obtained from 70.5 g. (0.60 mole) of 3-carbomethoxypropionaldehyde and 0.58 mole of *n*-propylmagnesium bromide at  $-30^\circ$ . The reaction in this case was much more vigorous despite the lower temperature.

The hydroxy acids were not washed free of sulfuric acid, and were lactonized directly by boiling for two hours with benzene. Additional benzene was added occasionally to keep the volume constant. The products were taken up in 250-ml. portions of ether and washed with two 70-ml. portions of 5% sodium carbonate solution and two 10-ml. portions of water. Aqueous layers were re-extracted with 300 ml. of ether. Fractionation gave 4-heptanolactone, 29 g. (91%), b.p. 72–73° at 1 mm.,  $n_D^{20}$  1.4410 and 5-heptanolactone, 21 g. (34%), b.p. 68–69° at 1 mm.,  $n_D^{20}$  1.4545.

**Methyl 4-Bromoheptanoate and Methyl 5-Bromoheptanoate.**—The lactones were converted to the corresponding bromo acids by treatment with dry hydrogen bromide at room temperature for one hour after evolution of heat could no longer be detected. The hydrogen bromide was introduced from a cylinder (Matheson Co.) through a fritted glass filter stick in an all-glass apparatus. The bromo acid was then diluted with 50 ml. of dry ether, cooled to 0°, and treated with a 5% excess of an ethereal solution of diazomethane. For the 4-bromoheptanoate, it was necessary to repeat the treatment with hydrogen bromide at 75° and the esterification, which required a small additional amount of diazomethane, in order to obtain a product analyzing correctly for bromine. A yield of 90% was obtained for each bromo ester upon fractionation through a short column.

Methyl 4-bromoheptanoate,  $n_D^{20}$  1.4610.

*Anal.* Calcd. for  $C_8H_{15}O_2Br$ : Br, 35.8. Found: Br (Stepanoff), 35.8.

Methyl 5-bromoheptanoate,  $n_D^{20}$  1.4639.

*Anal.* Calcd. for  $C_8H_{15}O_2Br$ : Br, 35.8. Found: Br (Stepanoff), 35.7.

Mixtures of the two esters of known composition were prepared. A plot of the refractive index versus the composition of these mixtures was a straight line.

**Addition of Hydrogen Bromide to 4-Heptenoic Acid.**—The following procedure was typical. The acid (2.95 g.) was placed in an all-glass apparatus under nitrogen. Hydrogen bromide was bubbled into the acid through a fritted glass filter stick for two hours at 25° and 1.5 hours at 70°. The product was extracted into 50 ml. of dry ether, cooled at 0°, and treated with an excess of diazomethane in ether. Fractionation of the ester was effected by extremely slow distillation at 1 mm. pressure through a 30 × 0.3 cm. micro column. An attempt was made in each experiment to collect only 1–3 drops of the distillate in the first fraction to ensure removal of any olefinic ester from the major portion of the distillate. In this case, the first fraction weighed 0.38 g. and had  $n_D^{20}$  1.4605, almost that of pure methyl 4-bromoheptanoate. The remainder of the distillate was collected in three fractions totaling 4.27 g. (89%),  $n_D^{20}$  1.4613–1.4633 (1.4625 when combined).

*Anal.* Calcd. for  $C_8H_{15}O_2Br$ : Br, 35.8. Found: Br (Stepanoff), 35.6. On the refractive index-composition curve, this represents 52–56% of methyl 4-bromoheptanoate depending upon whether the first fraction is ignored or included.

A second experiment carried out under the same conditions gave essentially the same results: namely, a 97% yield of product containing 35.5% bromine and  $n_D^{20}$  1.4625 corresponding to 52% methyl 4-bromoheptanoate.

Experiments carried out for five hours without solvent at room temperature, for four hours in hexane (7 ml.) at room temperature, and for 12 hours in ether (7 ml.) at room temperature all resulted in incomplete addition.

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