[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Positional Isomerism in the Formoxylation of Petroselinic Acid

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Pure *cis*-6-octadecenoic acid has been formoxylated employing perchloric acid as a catalyst and reaction times of fifteen and ninety minutes. The reaction products were subjected to a series of syntheses to produce a mixture of dicarboxylic acids which were analyzed by chromatographic separation. The dibasic acids consisted of glutaric, adipic, pimelic, suberic, azelaic, and sebacic acids. The results obtained indicated that the addition of formic acid took place chiefly at the 5-, 6-, 7-, and 8-carbon positions with minor amounts occurring at the 9- and 10-carbon positions when the reaction time was extended to ninety minutes. The process appears to be essentially a migration of the carbonium ion in which perchloric acid is a participant.

Prior investigations into the formoxylation of certain monoethenoid compounds have shown that perchloric acid catalyzed reactions proceed smoothly resulting in relatively high yields of the corresponding formoxy derivatives.[2] Certain observations made during the former investigation are of particular interest. First, the formoxylation of 1-hexene resulted in a mixture of the 2- and 3-hexyl formates to the exclusion of the 1-formoxy derivative,[2] attributed to the enhanced stability of the secondary carbonium ion. Second, the reaction product from the formoxylation reaction of ethylenic compounds invariably contained some unsaturation. Third, the treatment of pure 10-hydroxyoctadecanoic acid by the perchloric acid catalyzed formoxylation procedure resulted in an equilibrium mixture of formoxyoctadecanoic acids as well as unsaturated material. More recently, a reinvestigation of the perchloric acid catalyzed formoxylation of *cis*-9-octadecenoic acid was conducted for the purpose of establishing the exact nature of the positional isomers formed during the reactions.[3] It was concluded that an equimolar mixture of the 9- and 10-formoxyoctadecanoic acids was produced in the reaction, and furthermore, it was claimed that perchloric acid induced no wandering of the secondary carbonium ion. It appeared of importance therefore, to investigate the perchloric acid catalyzed addition of formic acid to petroselinic, *cis*-6-octadecenoic, acid and to ascertain whether 6- and 7-formoxyoctadecanoic acids were the sole isomers present in the product or if wandering of the carbonium ion occurred.

Formoxylation of *cis*-6-octadecenoic acid was achieved by the addition of anhydrous formic acid employing perchloric acid as a catalyst.[2] In order to obtain information regarding the influence of reaction time on the positional isomers formed, two experiments were carried out during which the *cis*-6-octadecenoic acid was subjected to formoxylation for fifteen-minute and ninety-minute periods. The formoxy derivatives were then hydrolyzed to the mixed hydroxyoctadecanoic acids, and oxidized to the corresponding oxo acids whose oximes were subjected to the Beckmann rearrangement. The resulting amides were hydrolyzed under pressure with strong alkali and then converted to the free acids. The fraction containing the mixed dibasic acids was analyzed by elution chromatography employing a Marvel and Rands silicic acid column[4] which had been modified. Application of this procedure to the mixed dibasic acids of both runs resulted in the separation of four major peaks which were identified as glutaric, adipic, pimelic, and suberic acids. Two considerably smaller peaks were also encountered in the ninety-minute run which were attributed to the presence of azelaic and sebacic acids. The distribution of the component dibasic acids in mole percent was as follows: 11.2 of glutaric, 35.6 of adipic, 34.0 of pimelic, and 19.2 of suberic in the fifteen-minute run, and 19.2 of glutaric, 25.1 of adipic, 27.5 of pimelic, 18.9 of suberic, 6.8 of azelaic, and 4.3 of sebacic in the ninety-minute run. These results indicate that the addition of formic acid takes place at the 5- to 10-carbon positions inclusive, and that the number and amount of the different positional isomers formed depends on the length of the reaction time. It does not appear entirely reasonable that the migration of the point of attachment toward the carboxyl group should have progressed no further than the 5-carbon position. It is possible that a carbonium ion on the 4-carbon position may have been internally stabilized by the formation of the lactone of 4-hydroxyoctadecanoic acid.

On the basis of the foregoing observations it is evident that there has been a wandering of the point of attachment of the addendum from the original position of the double bond of the *cis*-6-octadecenoic acid. These results are in marked contrast to those previously reported for the formoxylation of *cis*-9-octadecenoic acid,[3] even though essentially the same conditions including the reaction time were

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(4) C. S. Marvel and R. D. Rands, Jr., *J. Am. Chem. Soc.*, **72**, 2642 (1950).

employed in both instances. If in fact, in the former work[3] there was no migration of the carbonum ion from the 9- and 10-positions, it must be concluded that the position of the ethylenic bond along the carbon chain is the factor which influences the migration of the carbonium ion. The progressive formation of the positional isomers outside the original site of the double bond may be accounted for either by a simple migration of the secondary carbonium ion or by a more complex mechanism involving a shift of the ethylenic bond. It is significant that perchloric acid induces a migration of the double bond in 1- and 2-butene by an addition-elimination sequence of the catalyst.[5] Of equal importance is the observation already mentioned that unsaturated compounds are formed when 10-formoxyoctadecanoic acid is subjected to the formoxylation conditions. This may be interpreted as indicating that equilibrium conditions are established in the reaction whereby formic acid is eliminated from the formoxy derivative thereby producing a new ethylenic bond in the original or an adjacent position. This newly formed ethylenic bond is attacked by a proton and the addition product rearranges into a carbonium ion which again participates in the formoxylation reaction. Thus a sequence of reactions is established whereby positional isomers can be formed. The process is essentially a migration of the carbonium ion in which perchloric acid is a participant.

EXPERIMENTAL

Materials. Pure *cis*-6-octadecenoic acid (m.p. 29.2–29.7°, I.V. 89.4) was prepared by low temperature fractional crystallization of the mixed fatty acids obtained from parsley seed oil.[6] Ozonolysis of this acid and chromatography of the degradation products yielded adipic acid as a sole dibasic acid, indicating that no other unsaturated acids were present as impurities.

The anhydrous formic acid, 98+% Eastman Kodak white label grade,[7] was used without further purification.

Formoxyoctadecanoic acids. A mixture of 40.5 g. (0.14 mole) of *cis*-6-octadecenoic acid, 100 ml. (2.6 moles) of anhydrous formic acid, and 0.6 ml. of 60–62% perchloric acid was magnetically stirred and refluxed under an atmosphere of nitrogen for 15 min. The reaction mixture was then poured into 1000 ml. of water and the oily layer separated. The aqueous layer was extracted with three 250-ml. portions of ether. The ether extracts and the oily layer were combined and washed with water until free of acid and then dried over anhydrous sodium sulfate. From the ether were recovered 40.7 g. of crude formoxyoctadecanoic acids which were not further purified.

In another experiment in which approximately the same amount of materials was employed, the reaction time was extended to 90 min. yielding 43.7 g. of the crude product.

Following is a description of a series of reactions which was applied to the products obtained from both formoxylation procedures:

Hydroxyoctadecanoic acids. The formoxyoctadecanoic acids were hydrolyzed with 220 ml. of 6*N* ethanolic potassium hydroxide. Most of the ethanol was distilled and the remaining portion was poured into 1000 ml. of water which contained 135 ml. of concd. hydrochloric acid. The solid hydroxyoctadecanoic acids which formed after 2 hr. standing were filtered off, washed with water, and dried in a vacuum desiccator over potassium hydroxide. Thus 38.5 g. of a crude mixture of hydroxyoctadecanoic acids were obtained from the 15-min. run and 40.5 g. from the 90-min. run.

Anal. Calcd. for $C_{17}H_{34}(OH)COOH$: OH, 5.32; neut. equiv., 300.46; I.V., 0. Found for the 15-min. run: OH, 4.69; neut. equiv., 344.48; I.V., 13.09. For the 90-min. run: OH, 4.47; neut. equiv., 306.20; I.V., 12.25.

Oxo-octadecanoic acids. In a flask equipped with a magnetic stirrer were placed 30.5 g. (0.10 mole) of the mixed hydroxyoctadecanoic acids dissolved in 70 ml. of glacial acetic acid. The mixture was stirred and its temperature maintained at 32° while a solution of 10 g. of chromium trioxide in 10 ml. of water and 140 ml. of glacial acetic acid was added dropwise during a period of 1 hr. After the addition, the temperature of the solution was raised to 35–40° and stirring continued for an additional 2 hr. The dark green solution was poured into 500 ml. of water and the resulting fine precipitate filtered off. The solid was washed once in 300 ml. of boiling 1:1 hydrochloric acid solution and once in 300 ml. of boiling water. On drying in a vacuum desiccator over potassium hydroxide 25.1 g. of solid oxo-octadecanoic acids was obtained from the 15-min. run and 29.6 g. from the 90-min. run.

Anal. Calcd. for $C_{17}H_{33}(O)COOH$: carbonyl O, 5.35. Found for the 15-min. run: carbonyl O, 4.82. For the 90-min. run: carbonyl O, 5.04.

Oximes of oxo-octadecanoic acids. A mixture of 18.3 g. of the oxo-octadecanoic acids, 7.0 g. of hydroxylamine hydrochloride, 13.0 g. of potassium hydroxide in 46 ml. of water, and 240 ml. of absolute ethanol was refluxed for 6 hr. Ethanol was removed by vacuum stripping at room temperature employing nitrogen as a sweep gas. The remaining mixture was acidified with 100 ml. of 1.5*N* hydrochloric acid and extracted with three 75-ml. portions of ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. The ether was then removed yielding 17.2 g. of liquid oximes from the 15-min. run and 16.7 g. from the 90-min. run.

Anal. Calcd. for $C_{17}H_{33}(NOH)COOH$: N, 4.50. Found for the 15-min. run: N, 4.09. For the 90-min. run: N, 3.67.

The Beckmann rearrangement. A 9.4-g. sample of the crude oximes was dissolved in 60 ml. of concd. sulfuric acid and heated at 100° for 1 hr. The reaction mixture was then cooled and poured into 600 ml. of ice water containing crushed ice and allowed to crystallize. The solid was filtered off, washed twice by boiling in 100-ml. portions of water and then crystallized by addition of ice. The brown, semisolid material was dried in a vacuum desiccator over potassium hydroxide producing 7.1 g. of amides from each run.

Hydrolysis of the amides. The mixture of amides was dissolved in 60 ml. of 25% potassium hydroxide and heated in an autoclave at 180–200° for 4 hr. The cooled contents of the autoclave was acidified with 80 ml. of 1:1 hydrochloric acid and extracted with five 50-ml. portions of ether. On evaporation of the ether, there remained 4.8 g. and 4.6 g. of a brown residue from the 15-min. and 90-min. runs respectively, which was mainly composed of a mixture of monobasic and dibasic acids.

Dibasic acids. The residue obtained from hydrolysis of the amides was extracted five times with 20-ml. portions of boiling water. The combined extracts were evaporated and the solid dried to constant weight in a vacuum desiccator over potassium hydroxide. There was obtained 1.7 g. of a

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(7) The mention of this or other commercial products does not constitute an endorsement of them by the U. S. Department of Agriculture.

mixture of dibasic acids from the 15-min. run and 1.2 g. from the 90-min. run.

Chromatographic separation. A column was prepared similar to that of Marvel and Rands[4] with some modification. A 25-g. portion of dry silicic acid was thoroughly mixed in a mortar with 13 ml. of water and 1 ml. of 0.02% aqueous bromocresol green indicator. Two drops of concentrated ammonium hydroxide were added to impart a green color to the column. The mixture was slurried with 100 ml. of chloroform and packed into a chromatographic tube (23 mm. O.D. × 600 mm. long). Five pounds pressure of nitrogen was applied to the top throughout the packing and elution of the column. From each run, duplicate samples of the mixed dibasic acids (*ca.* 52 mg., weighed accurately) dissolved in 0.25 ml. of *t*-amyl alcohol and diluted to 2.5 ml. with chloroform, were added to separate columns and each washed down with 5 ml. of chloroform. The columns were eluted with 100-ml. portions of 1, 2, 3, 4, 5, 7½, 10, 20, 30, and 40% of *n*-butyl alcohol in chloroform. The percolate was collected in 10-ml. fractions, diluted with 20 ml. of absolute ethanol, and titrated with 0.0254*N* sodium hydroxide solution to the end point of *m*-cresol purple indicator. In all the runs four major peaks were encountered which were identified as suberic, pimelic, adipic, and glutaric acids by chromatographing a sample of the mixed dibasic acids to which known quantities of pure suberic, pimelic, adipic, and glutaric acids had been added. In addition there also appeared two small peaks at the beginning of the chromatograms from the 90-min. run, and the nature of the elution curves indicated these to be azelaic and sebacic acids. The mixture of the dibasic acids obtained from the 15-min. run consisted of 11.2 mole % glutaric, 35.6 mole % adipic, 34.0 mole % pimelic, and 19.2 mole % suberic acids, while the dibasic acids from the 90-min. run consisted of 19.2 mole % glutaric, 25.1 mole % adipic, 25.7 mole % pimelic, 18.9 mole % suberic, 6.8 mole % azelaic, and 4.3 mole % sebacic acids. The recovery of the dibasic acids during the elution process was nearly 100% of the amount introduced on the column.

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[CONTRIBUTION FROM THE NATURAL PRODUCTS RESEARCH DEPARTMENT OF SCHERING CORPORATION]

Halogenated Progesterones. II.[1] 17α-Oxygenated 9α,11β-Dihaloprogesterones

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The synthesis of some 9α,11β-dichloro-, 9α-chloro-11β-fluoro-, 9α-bromo-11β-fluoro- and 9α-bromo-11β-chloro-17α-acyloxyprogesterones is described. Some of these compounds show progestational activity when tested in rabbits.

Recent research on the synthesis of active progestational compounds has concentrated to a large extent on the preparation of various analogs of 17α-acetoxyprogesterone[2] in view of the enhanced and particularly the oral activity of the latter.[3]

Among derivatives of 17α-acetoxyprogesterone which have been reported are included 6α-methyl-17α-acetoxyprogesterone[4] and the corresponding 1-dehydro, 6-dehydro and 1,6-bisdehydro analogs,[4c] 6α - fluoro - 17α - acetoxyprogesterone[5] and the corresponding 1-dehydro, 6-dehydro and 1,6-bisdehydro analogs,[5b] 6α-chloro-17α-acetoxyprogesterone[6] and the corresponding 1-dehydro, 6-dehydro and 1,6-bisdehydro analogs,[6] 6α-bromo- and 1 - dehydro - 6α - bromo - 17α - acetoxyprogesterone,[6] 21 - fluoro - 17α - acetoxyprogesterone,[7] and the corresponding 6α - methyl[7] and 6 - dehydro-6-methyl[8] analogs, 21-chloro-,[7] 21-chloro-6α-methyl-[7], 21-bromo-,[7] 21-iodo-,[7] 6α-cyano-[9] 6α-nitro-[10], 1-dehydro-[6,11], 11β-acetoxy-[12], 9α-bromo-11β-hydroxy-[13] and 9α-fluoro-11-oxygenated-17α-acetoxyprogesterone[13].

In contrast to 17α-acetoxyprogesterone, 17α-hydroxyprogesterone caproate[3] is orally inactive

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