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

Hydroboration of Fats. I. Positional Isomerism in the Methyl Oleate Hydroboration Reaction

SARA P. FORE AND W. G. BICKFORD

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It has been found that addition of diborane to the ethylenic bond of methyl oleate proceeds smoothly without significant reduction of the carbomethoxy group. Alkaline hydrogen peroxide oxidation of the tris(carbomethoxyalkyl)borane resulted in the formation of an equimolar mixture of 9- and 10-hydroxyoctadecanoic acids, establishing that the hydroboration reaction proceeded nonselectively. Little or no isomerization occurred on heat treatment of these substituted trialkyl boranes.

Brown and Subba Rao have reported that a variety of olefins react readily with diborane in ether solution to form trialkyl boranes[2] which can be oxidized to the corresponding alochols with alkaline hydrogen peroxide. Oxidation of the trialkyl boranes derived from 1- and 2-hexenes with alkaline hydrogen peroxide resulted in formation of the primary alcohol only from the former compound and of 2- and 3-hexanol in a ratio of 2:1 from the latter. In addition, these authors found that heating the trialkyl boranes derived from internally unsaturated olefins resulted in migration of the boron moiety to the terminal position of the olefin chain.[3]

Reaction with diborane, followed by isomerization of the resultant substituted trialkyl boranes, appears to be a possible route to the preparation of α- or ω-hydroxy acids from internally monunsaturated fatty acids. Therefore, it was desirable to ascertain whether or not such unsaturated compounds could be hydroborated without significant reduction of the carboxyl group, whether or not the boron moiety adds preferentially to either carbon of the ethylenic bond, and the extent and direction of any isomerization which may occur on heating these substituted trialkyl boranes. For this purpose methyl oleate, which would be expected to be less susceptible than oleic acid to reduction by diborane,[4] was chosen as a model compound. The procedure of Brown and Subba Rao[2] was applied to the hydroboration of methyl oleate and a portion of the reaction mixture was refluxed for 24 hr. in an attempt to effect isomerization of the resultant tris(1-carbomethoxy-8(9)-heptadecyl)-boranes. The tris(1-carbomethoxyheptadecyl)boranes recovered from the reaction mixture before and after heating were converted to the corresponding hydroxyoctadecanoic acids by treatment first with alkaline hydrogen peroxide and then with hydrochloric acid. The unsaturated materials were removed from the hydroxy acids by extraction of the crude products with petroleum ether (b.p. 30–60°). The positions of the hydroxyl groups in the two samples of hydroxyoctadecanoic acids were determined by the following series of reactions: The hydroxyoctadecanoic acids were oxidized to the corresponding keto acids which were then converted to their oximes; the oximes were subjected to Beckmann rearrangement and the resultant amides were hydrolyzed under pressure with alkali; the mixed dicarboxylic acids recovered from the hydrolyzate were analyzed by application of elution chromatography employing a modification[5] of the method of Higuchi *et al.*[6]

The analyses performed on the unheated crude tris(1-carbomethoxy-8(9)-heptadecyl)borane and its derived hydroxyoctadecanoic acids indicated that hydroboration of most of the ethylenic bonds of methyl oleate was effected without material reduction of the ester group. Heat treatment of the crude tris(1-carbomethoxy-8(9)-heptadecyl)-borane resulted in an increase in both unsaturated and neutral material.

Application of the aforementioned series of reactions to the hydroxy acids from either the original or the heat-treated substituted trialkyl boranes resulted in the isolation of only two dicarboxylic acids, azelaic and sebacic acids, and these were present in approximately equimolar proportions. It was concluded, therefore, that the boron moiety added equally to the 9- and 10-positions of methyl oleate during hydroboration, and that little or no migration of this group occurred during heating. It is not impossible, however, that some isomerization occurred and was not detected, since the yield of azelaic and sebacic acids from this sample was less than that from the unheated sample, and since the hydroxyoctadecanoic acids in the petroleum ether soluble fraction were not examined. Additional work directed toward the isomerization of trialkyl boranes of this type is now in progress in this laboratory.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).

(3) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1137 (1957).

(4) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(5) M. H. Chahine, E. R. Cousins, and R. O. Feuge, *J. Am. Oil Chemists' Soc.*, **35**, 396 (1958).

(6) T. Higuchi, N. C. Hill, and G. B. Corcoran, *Anal. Chem.*, **24**, 491 (1952).

EXPERIMENTAL

Since the structures of both the original and heat-treated tris(1-carbomethoxyheptadecyl)boranes were established by the same series of reactions, reaction conditions will be described for the former material only, pertinent data regarding the latter being given at the conclusion of each section.

Reagents. Methyl oleate (I.V., 85.5; diene, 1.5%) was prepared from the mixed methyl esters of pecan oil by low temperature fractional crystallization from acetone.[7]

Diglyme (diethylene glycol dimethyl ether) obtained from Ansul Chemical Co., Eastman's practical grade boron fluoride–ethyl ether, and Metal Hydrides' sodium borohydride were used without purification.[8]

Hydroboration of methyl oleate. The hydroboration of methyl oleate was carried out as described by Brown and Subbo Rao for 1-hexene.[2] Diborane gas (0.032 mole), generated during a period of 0.5 hr. by the dropwise addition of 2.13 g. of sodium borohydride dissolved in 50 ml. of diglyme to 11.4 ml. of boron trifluoride etherate dissolved in 21 ml. of diglyme, was bubbled through a solution of 53.3 g. (0.18 mole) of methyl oleate in 400 ml. of diglyme. The reaction was carried out in an all-glass apparatus with all joints sealed with glyptal resin. Dry nitrogen was employed as a sweep gas. Removal of the solvent from a 227 ml. portion of the reaction mixture (total volume, 470 ml.) at 35° under reduced pressure yielded 27.8 g. of a colorless viscous liquid having an iodine value of 6.9. This material began to oxidize immediately on exposure to the atmosphere.

Attempted isomerization of tris(1-carbomethoxy-8(9)-heptadecyl)borane. A 227 ml. portion of the reaction mixture was refluxed for 24 hr. Removal of the solvent under high vacuum at 60° yielded 27.2 g. of a colorless viscous oil having an iodine value of 13.8.

Hydroxyoctadecanoic acids. The substituted trialkyl boranes were subjected to oxidation with alkaline hydrogen peroxide,[9] enough alkali being used to saponify the methyl ester as well. A mixture of 26.8 g. of tris(1-carbomethoxy-8(9)-heptadecyl)borane, 8.0 g. of sodium hydroxide, 8.0 ml. of water and 120 ml. of ethanol was stirred and heated to about 60°. Heating was discontinued and 19.0 ml. of 30% hydrogen peroxide was added dropwise over a period of 0.5 hr. The reaction mixture was refluxed for 2 hr. and then was diluted with 400 ml. of distilled water containing 19.0 ml. of concentrated hydrochloric acid. Recovery of the product by the usual ether extraction procedure yielded 24.0 g. of crude hydroxy acids. An 18.0 g. sample of the hydroxy acids, upon treatment with petroleum ether (b.p. 30–60°) to remove unsaturated material, afforded 16.1 g. of hydroxyoctadecanoic acids, m.p. 78–82°.

Anal. Calcd. for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08; neut. equiv., 300.5. found: C, 72.00; H, 12.13; neut. equiv., 300.2.

The petroleum ether soluble fraction (1.86 g.) had a neutral equivalent of 310.5 and an iodine value of 38.9. Infrared analysis of this fraction indicated that approximately 66% of the ethylenic bonds were of the *trans*- configuration.

Similarly, the heat-treated sample yielded 24.2 g. of crude hydroxyoctadecanoic acids which on purification gave 15.9 g. of crystals, m.p. 77–82°.

Anal. Found: C, 72.48; H, 12.04; neut. equiv., 304.8.

The petroleum ether soluble fraction from the heat-treated sample (7.80 g.) had a neutral equivalent of 323.0 and an iodine value of 56.9. Infrared analysis of this fraction indicated that approximately 62% of the ethylenic bonds were of the *trans*- configuration.

Oxoöctadecanoic acids. A sample of the purified hydroxyoctadecanoic acids (14.0 g., 0.047 mole) in 25 ml. of glacial acetic acid was stirred and maintained at 32° during the dropwise addition of chromium trioxide (4.79 g., 0.048 mole) dissolved in 3.5 ml. of distilled water and 66 ml. of glacial acetic acid. After addition of the reagent, which required 2 hr., the sample was maintained at 35–40° for an additional 1.5 hr. The crystals which separated on dilution of the reaction mixture with water were boiled first with dilute hydrochloric acid and then with water. The keto acids thus obtained (13.84 g.) melted at 70–74°.

Anal. Calcd. for $C_{18}H_{34}O_3$: Carbonyl O, 5.36. Found: Carbonyl O, 5.3.

Oxidation of the hydroxy acid from the heat-treated sample in the same manner yielded 13.6 g. of keto acids, m.p. 66–72°.

Anal. Found: Carbonyl O, 5.3.

Oximes of oxoöctadecanoic acids. A solution of 8.73 g. (0.134 mole) of potassium hydroxide in 32 ml. of water was added to a mixture of 13.34 g. (0.0447 mole) of the keto acids, 6.21 g. (0.0894 mole) of hydroxylamine hydrochloride, and 160 ml. of ethanol. The mixture was stirred and refluxed for a period of 3 hr. After most of the ethanol had been removed at room temperature under vacuum in a rotary evaporator, the product was treated with 100 ml. of 1.5*N* hydrochloric acid. Separation of the organic material by ether extraction yielded 13.47 g. of oximes.

Anal. Calcd. for $C_{18}H_{35}NO_3$: N, 4.47. Found: N, 4.36.

Oximes (13.31 g.) were prepared as described above from keto acids (13.07 g.) derived from the heat-treated hydroboration product.

Anal. Found: N, 4.38.

The Beckmann rearrangement and hydrolysis of resultant amides. A portion of the oximes (6.56 g., 0.0209 mole) was stirred and heated at 100° for 1 hr. with 40 ml. of concentrated sulfuric acid. The reaction mixture was cooled to room temperature and poured into 400 ml. of cold distilled water which was maintained at less than 30° during this step by external cooling. The solid which separated was washed once with boiling water and then dried over sodium hydroxide in a vacuum desiccator.

The amides thus obtained (6.40 g., 0.0204 mole) were hydrolyzed by heating at 180–200° for 4 hr. with 11.9 g. of 86% potassium hydroxide in 40 ml. of water. The hydrolysis was carried out under a nitrogen atmosphere in a Parr[8] high pressure hydrogenator equipped with a glass liner.

Beckmann rearrangement of a portion of the oximes from the heat-treated sample (6.52 g., 0.0208 mole) and hydrolysis of the resultant amides (6.25 g., 0.0199 mole) were carried out as described above.

Dicarboxylic acids. The hydrolyzate was acidified with 33.5 ml. of concentrated hydrochloric acid in 50 ml. of distilled water and subjected to steam distillation for the removal of monocarboxylic acids. Ether extraction of the distillation residue yielded 2.35 g. of a light tan solid material containing the dicarboxylic acids. This fraction was extracted 5 times with 15-ml. portions of boiling water. The aqueous extract was concentrated to a volume of about 40 ml. and upon standing at room temperature deposited 1.45 g. of mixed dicarboxylic acids.

Similarly, 3.23 g. of crude and 1.15 g. of purified dicarboxylic acids were obtained from the heat-treated sample.

Chromatographic separation of the dicarboxylic acids. Duplicate samples of the mixed dicarboxylic acids (*ca.* 0.2 g., accurately weighed) were dissolved in 0.5 ml. of *t*-amyl alcohol and diluted to 10.0 ml. with chloroform. Aliquots (1.0 ml. each) of these solutions were added to a column prepared according to the procedure described by Higuchi, *et al.*[6] using 25.0 g. of dry silicic acid, 19.0 ml. of citrate buffer, *p*H 5.4, and 100 ml. of chloroform. The acids were eluted with successive 100-ml. portions of chloroform containing 0, 1.5, 3, 5, and 10% of *n*-butanol, and 10.0 ml. portions of the eluate were titrated with 0.0255*N* sodium

(7) S. P. Fore and W. G. Bickford, *J. Org. Chem.*, **24**, 620 (1959).

(8) It is not the policy of the Department to recommend the products of one company over those of any others engaged in the same business.

(9) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956).

hydroxide solution. Only two fractions were encountered and these were identified by their peak eluant volumes as azelaic acid, 50.1 mole %, and sebacic acid, 49.9 mole %.

Application of the above described procedures to the dicarboxylic acids obtained from the heat-treated sample showed the mixture to be 48.8 mole percent azelaic and 51.2 mole percent sebacic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazolopyrimidines: Their Synthesis and Structure[1]

LEONARD E. BRADY[2] AND ROBERT M. HERBST

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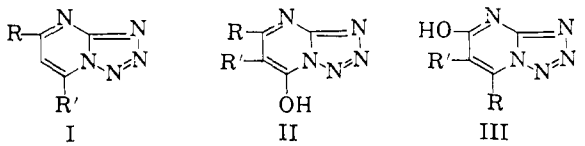
The reaction of 5-aminotetrazole with β-keto esters yields condensation products originally formulated as tetrazolo[*a*]-pyrimidines. The structure of this ring system has been substantiated through an alternative synthesis involving diazotization of 2-hydrazinopyrimidines and cyclization of the intermediate azidopyrimidines. Orientation of the substituents is supported by a study of the acylation of 5-aminotetrazole.

The formation of tetrazolopyrimidines by condensation of β-diketones and β-keto esters with 5-aminotetrazole was first described by Bülow.[3] The condensation with β-diketones in ethanol solution catalyzed with piperidine gave products assigned the structure I. With acetoacetic ester in glacial acetic acid a compound (IIa) was said to form; the possibility of formation of compounds of structure III was not considered. More recently Nachod and Steck[4] repeated Bülow's preparation of Ia for use in spectrographic studies without questioning the structure assignment. The arbitrary assignment of structures by Bülow made reinvestigation of this group of compounds desirable. Alternative methods of synthesis were devised with the object of demonstrating (1) the presence of the bicyclic system and (2) the orientation of the substituents according to II rather than III. The structural relationship of these compounds both to the purines and to bicyclic systems related to pentamethylenetetrazole made an extension of examples of this type of system attractive.



I II III

Ia. R = CH_3; R′ = CH_3
Ib. R = CH_3; R′ = C_6H_5
IIa. R = CH_3; R′ = H
IIb. R = C_6H_5; R′ = H
IIc. R = CH_3; R′ = CH_3
IId. R = CH_3; R′ = C_2H_5
IIe. R = CH_3; R′ = *n*-C_3H_7
IIf. R = CH_3; R′ = *iso*-C_3H_7
IIg. R = CH_3; R′ = *n*-C_4H_9
IIh. R—R′ = —$(CH_2)_4$—

The condensation of β-keto esters with 5-aminotetrazole was reinvestigated to determine the effect of solvents and catalysts on the reaction.It quickly became apparent that condensations in glacial acetic acid as recommended by Bülow[3] were not satisfactory. The product (IIa) obtained with acetoacetic ester was contaminated with large amounts of 5-acetamidotetrazole with which the product formed a molecular complex. The product described by Bülow as IIb, but for which no analysis was given, obtained with benzoylacetic ester under similar conditions proved to be 5-acetamidotetrazole. Using ethanol as solvent and piperidine as catalyst, as recommended for the condensation of β-diketones with 5-aminotetrazole,[3] greatly improved yields of tetrazolopyrimidines were obtained from β-keto esters. The condensation product (IIb) with benzoylacetic ester was actually obtained under these conditions. Similar condensations with a variety of alkylated acetoacetic esters gave the products IIc–IIh.

To establish the presence of a pyrimidine ring system in the products the procedure of Finnegan, Henry, and Lieber[5] for the synthesis of substituted 5-aminotetrazoles was adapted. These authors had shown that a variety of *S*-methyl thiuronium salts could be converted into 5-aminotetrazole derivatives by interaction successively with hydrazine to form aminoguanidines[6] and nitrous acid to form guanyl azides. The latter cyclized readily to form the tetrazoles. Considering 2-methylmercaptopyrimidines (IV) as cyclic *S*-

(1) Based on the doctoral thesis submitted to Michigan State University by Leonard E. Brady. Presented before the Division of Medicinal Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 7–12, 1958.

(2) Present address: Abbott Laboratories, North Chicago, Ill.

(3) C. Bülow, *Ber.*, **42**, 4429 (1909).

(4) F. C. Nachod and E. A. Steck, *J. Am. Chem. Soc.*, **70**, 2819 (1948).

(5) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

(6) G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).