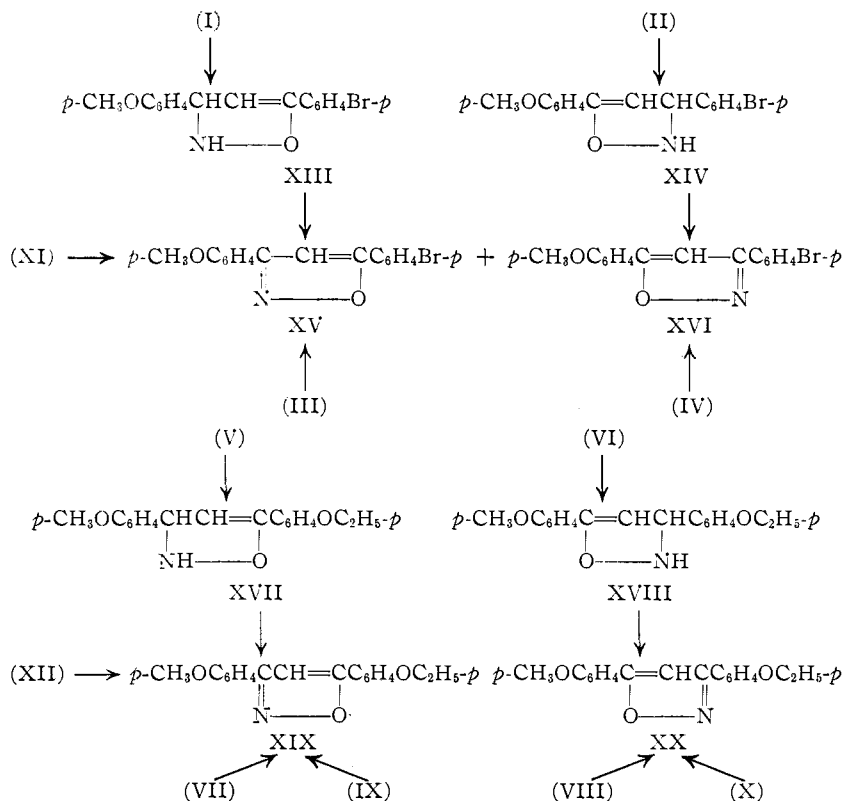


dized to the isoxazoles (XV) and (XVI), respectively. The dibromides (III) and (IV) produce the isoxazoles (XV) and (XVI), respectively.

Similarly the chalcones (V) and (VI) give the respective isoxazolines (XVII) and (XVIII) which are converted in turn to their respective isoxazoles (XIX) and (XX). The dibromide (VII) and the α -bromo-chalcone (IX) give the isoxazole (XIX) while the dibromide (VIII) and the α -bromo-chalcone (X) give the isoxazole (XX).



Experimental

The Chalcones (I), (II), (V) and (VI).—These substances were prepared by the Claisen-Schmidt condensation reaction.

The Dibromides (III), (IV), (VII) and (VIII).—The dibromides were prepared by brominating the chalcones with the calculated amount of bromine in either chloroform or carbon tetrachloride.

TABLE I

Compound	M. p., °C.	Color	Formula	Analyses, %			
				Calcd. C	Calcd. H	Found C	Found H
I	142-143	Pale yellow	C ₁₈ H ₁₈ O ₂ Br	60.6	4.1	60.6	4.1
II	152-153	Pale yellow	C ₁₈ H ₁₈ O ₂ Br	60.6	4.1	60.6	4.2
V	113	Pale yellow	C ₁₈ H ₁₈ O ₃	76.6	6.4	76.7	6.4
VI	109	Yellow	C ₁₈ H ₁₈ O ₃	76.6	6.4	76.4	6.4
III	158-159	Colorless	C ₁₈ H ₁₈ O ₂ Br ₂	40.3	2.8	40.3	2.7
IV	164-166	Colorless	C ₁₈ H ₁₈ O ₂ Br ₂	40.3	2.8	40.3	2.8
VII	100	Colorless	C ₁₈ H ₁₈ O ₃ Br ₂	48.9	4.1	48.8	4.1
VIII	124	Colorless	C ₁₈ H ₁₈ O ₃ Br ₂	48.9	4.1	48.9	4.1

The α -Bromo-chalcones (IX) and (X).—Separate solutions of each of the dibromides (VII) and (VIII) in 155 cc. of glacial acetic acid were refluxed with 27 g. of freshly fused potassium acetate for two hours. The solutions turned brownish-yellow. On pouring into large volumes

of cold water, brown oils separated. The oils were taken up in ether, freed of acetic acid by shaking with 5% sodium bicarbonate solution, washed with water, and dried over anhydrous sodium sulfate. The ether was pumped off, and the residual oils allowed to stand *in vacuo* over solid potassium hydroxide for several days. Viscous brown oils weighing 8-9 g. resulted.

Anal. Calcd. for C₁₈H₁₇O₃Br: C, 59.8; H, 4.7. Found for IX: C, 59.8; H, 4.8. Found for X: C, 59.7; H, 4.7.

Preparation of the Enolic Material (XI): A. From the Dibromide (III).—A solution of 15 g. of the dibromide (III) in 160 cc. of methanol was heated gently on a steam-bath. After refluxing had begun, a solution of 6 g. of potassium hydroxide in 30 cc. of methanol was added slowly. The mixture was colorless until over half the potassium hydroxide had been added, when it became reddish orange color. Refluxing was continued for two hours. Then the solution was chilled and acidified with dilute hydrochloric acid. The 11 g. of yellow material obtained was filtered, washed and recrystallized from 100 cc. of methanol and 200 cc. of ether, melting at 150°.

B. From the Dibromide (IV).—To a refluxing solution of 0.5 g. of the dibromide (IV) in 33 cc. of methanol was slowly added 0.25 g. of potassium hydroxide in 3 cc. of water. The colorless solution turned light yellow in color. Refluxing was continued for two hours. Then the solution was chilled and acidified with dilute hydrochloric acid with stirring. The solid obtained was filtered, washed and recrystallized from alcohol. The 0.4 g. of crystals obtained melted at 150°, and mix-melted unchanged with the material from (A) above.

Anal. Calcd. for C₁₆H₁₃O₃Br: C, 57.7; H, 3.9. Found: C, 57.6; H, 3.9.

The almost colorless crystals gave a deep red coloration with alcoholic ferric chloride. This compound is 100% enolic in methanol, as determined by the improved Kurt Meyer titration method.

Preparation of the Enolic Material (XII): A. From the Dibromide (VII).—A solution of 2.6 g. of potassium hydroxide in 20 cc. of methanol was added to a hot solution of 10 g. of the dibromide (VII) in 50 cc. of methanol while refluxing. The yellow solution was chilled and acidified with dilute hydrochloric acid. A yellow substance crystallized. It was filtered, after chilling and recrystallized from methanol to yield yellow needles weighing 4 g. and melting at 96.5°.

B. From the Dibromide (VIII).—To a hot solution of 10 g. of the dibromide (VIII) in 60 cc. of methanol was added a solution of 2.6 g. of potassium hydroxide in 20 cc. of methanol while refluxing. Upon acidification with dilute hydrochloric acid, yellow crystals immediately precipitated. These were then filtered, after chilling, and recrystallized from methanol to yield yellow needles weighing 3 g. and melting at 96°.

Anal. Calcd. for C₁₈H₁₈O₄: C, 72.5; H, 6.1. Found: C, 72.6; H, 6.1.

These products mix-melted at 96.5°. This substance gave a red coloration with alcoholic ferric chloride and was

100% enolic as determined by the improved Kurt Meyer method.

Preparation of the Isoxazoline (XIII).—To a solution of 5.9 g. of the α,β -unsaturated ketone (I) in 100 cc. of normal propyl alcohol was added 2.3 g. of hydroxylamine hydrochloride in 5 cc. of water. To this solution was added slowly 4 g. of potassium hydroxide in 20 cc. of water, causing the light yellow mixture to become a deep yellow. The solution was refluxed for two hours. On cooling, a solid separated from the orange-colored solution. The solid was filtered and washed with water and methanol. On recrystallization from methanol, 2 g. of gleaming white leaflets were obtained, melting at 170–171°. Normal propyl alcohol was used because ketone (I) was obtained unchanged with similar quantities in methanol.

Anal. Calcd. for $C_{16}H_{14}O_2BrN$: C, 60.4; H, 4.4. Found: C, 60.5; H, 4.5.

Preparation of the Isoxazoline (XIV).—To a solution of 2 g. of the α,β -unsaturated ketone (II) in 170 cc. of methanol was added 1 g. of hydroxylamine hydrochloride in 5 cc. of water. To this solution was added slowly 1.5 g. of potassium hydroxide in 5 cc. of water. The solution became slightly yellow. It was refluxed for two hours. On cooling a precipitate separated instantly. The chilled solution was filtered and the solid was washed with water and methanol; 1.4 g. of glistening colorless leaflets was obtained, melting at 148–149°.

Anal. Calcd. for $C_{16}H_{14}O_2BrN$: C, 60.4; H, 4.4. Found: C, 60.3; H, 4.4.

Preparation of the Isoxazole (XV): A. By the Oxidation of the Isoxazoline (XIII).—To a solution containing 0.4 g. of the isoxazoline (XIII) in 25 cc. of acetic acid, was added 0.2 g. of chromic oxide. The mixture became a dark reddish brown. The mixture became green when the solution was heated on the steam-bath to 60° and kept at this temperature for one half hour, with occasional stirring. The mixture was cooled and poured into 500 cc. of cold water. Instantly a light yellow solid separated from the green solution. The mixture was chilled for one half hour, filtered and washed with 50 cc. of water. On recrystallization from 275 cc. of methanol, 0.2 g. of colorless solid was obtained, melting at 193–194°.

B. From the Dibromide (III).—To a solution of 5 g. of the dibromide (III) in 100 cc. of hot ethanol was added 2.5 g. of hydroxylamine hydrochloride in 5 cc. of water. The mixture was boiled five minutes on the steam-bath, then, while still hot, 5 g. of potassium hydroxide in 5 cc. of water was added slowly. The solution turned a deep yellow in color. On cooling a solid material separated. The mixture was chilled for one hour, filtered, washed with alcohol and water and dried, yielding 0.6 g., which upon recrystallization from alcohol melted at 193–194°. It mix-melted with the isoxazole from the isoxazoline (XIII) at 193–194° with no depression.

Anal. Calcd. for $C_{16}H_{12}O_2BrN$: C, 58.2; H, 3.7. Found: C, 58.1; H, 3.6.

Preparation of the Isoxazole (XVI): A. By the Oxidation of Isoxazoline (XIV).—To a solution containing 0.4 g. of isoxazoline in 25 cc. of acetic acid, was added 0.2 g. of chromic oxide. The mixture became dark green in color. Then the solution was heated on the steam-bath to 80° and kept at this temperature for one-half hour, stirring occasionally. After cooling the mixture, it was poured into 500 cc. of cold water. Instantly a light yellow solid separated from the solution. The mixture was chilled for one-half hour, filtered with suction, and dried, yielding 0.3 g. of crude isoxazole. On recrystallization from alcohol, colorless crystals were obtained, melting at 197–198°.

B. From the Dibromide (IV).—To a solution of 5 g. of the dibromide (IV) suspended in 100 cc. of hot ethanol, was added 2.5 g. of hydroxylamine hydrochloride in 5 cc. of water. The mixture was boiled for five minutes on the steam-bath. Then, while still hot, 5 g. of potassium hydroxide in 5 cc. of water was added slowly. The solution turned a light yellow in color. On cooling a solid material separated. The mixture was chilled for one hour, filtered,

washed with alcohol and water and dried, yielding 2.5 g. of colorless crystals, which upon recrystallization melted at 197–198°. It mix-melted with the isoxazole from the isoxazoline (XIV) at 197–198°.

Anal. Calcd. for $C_{16}H_{12}O_2BrN$: C, 58.2; H, 3.7. Found: C, 58.1; H, 3.6.

Preparation of the Mixture of Isoxazoles (XV) and (XVI).—To a hot solution of 2.1 g. of the enolic material (XI) in 100 cc. of methanol was added 1.25 g. of hydroxylamine hydrochloride in 5 cc. of water. The mixture was refluxed for two hours and forty-five minutes. On cooling, a colorless solid fell out that gave a positive ferric chloride test. At this point 0.5 g. of hydroxylamine hydrochloride was added to the hot solution and refluxed for an hour. On cooling, a colorless solid separated. This solid was filtered, washed and recrystallized from methanol to yield 1.8 g. of colorless crystals melting at 194–195.5°.

Anal. Calcd. for $C_{16}H_{12}O_2BrN$: C, 58.2; H, 3.7. Found: C, 58.3; H, 3.7.

A mixture of pure (XV) and (XVI) melted at 194–195.5°.

3-Anisyl-5-phenetyl Isoxazoline (XVII).—A solution of 3.7 g. of hydroxylamine hydrochloride in 10 cc. of water was added to a hot solution of 10 g. of the unsaturated ketone (V) in 75 cc. of ethanol. A solution of 7.8 g. of potassium hydroxide in 10 cc. of water was immediately added to the mixture which was then refluxed for two hours. A dark maroon solution was formed. The product, after recrystallization from ethanol as colorless crystalline plates weighed 2.9 g. and melted at 125.5°.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.7; H, 6.4. Found: C, 72.8; H, 6.5.

3-Phenetyl-5-anisyl Isoxazoline (XVIII).—A solution of 3.7 g. of hydroxylamine hydrochloride in 10 cc. of water was added to a hot solution of 10 g. of the unsaturated ketone (VI) in 100 cc. of ethanol and a solution of 7.8 g. of potassium hydroxide in 10 cc. of water was immediately added to the mixture which was then refluxed for two hours forming a dark maroon solution. The product, after recrystallization from ethanol as colorless crystalline flakes weighed 4.35 g. and melted at 136.5°.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.7; H, 6.4. Found: C, 72.6; H, 6.4.

3-Anisyl-5-phenetyl Isoxazole (XIX): A. From the Isoxazoline (XVII).—A solution of 2 g. of the isoxazoline (XVII) in 100 cc. of glacial acetic acid was heated to 80° and 1.34 g. of chromic acid were added. The reaction mixture was stirred for forty-five minutes and then poured into 400 cc. of cold water. The resulting precipitate was filtered and washed with a little cold ethanol. It was boiled with a quantity of ethanol insufficient for complete solution and the residue remaining after quickly decanting off the hot alcoholic solution was recrystallized from ethyl acetate and subsequently from ethanol to yield colorless silky needles melting at 139°.

B. From the Dibromide (VII).—A solution of 2 g. of hydroxylamine hydrochloride in 3 cc. of water was added to a hot solution of 5 g. of the dibromide (VII) in 40 cc. of ethanol after which a solution of 4.5 g. of potassium hydroxide in 5 cc. of water was immediately added to the mixture while refluxing. The solution became reddish-brown and a precipitate was formed rapidly. It was filtered, washed with water and recrystallized from ethanol as colorless needles to yield 1.9 g. melting at 139.5°.

C. From the α -Bromocholeone (IX).—A solution of 0.57 g. of hydroxylamine hydrochloride in 5 cc. of water was added to a solution of 1.5 g. of the α -bromo ketone (IX) in 30 cc. of ethanol, after which a solution of 1.4 g. of potassium hydroxide in 5 cc. of water was added to the mixture which was then refluxed one hour forming a dark maroon solution. The product after recrystallization from methanol as colorless needles weighed 0.17 g. melting at 138.5°. The above products mix-melted at 138.5–139°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.2; H, 5.8. Found: C, 73.0; H, 5.8.

3-Phenetyl-5-anisyl Isoxazole (XX). A. From the Isoxazoline (XVIII).—A solution of 2 g. of the isoxazoline (XVIII) in 100 cc. of glacial acetic acid was heated to 80° and 1.34 g. of chromic oxide was added. The reaction mixture was stirred for 45 minutes and then poured into 400 cc. of cold water. The resulting precipitate was filtered, washed with water and then washed with a little cold ethanol. The precipitate was boiled with a quantity of ethanol insufficient for complete solution. The residue remaining after quickly decanting off the hot alcoholic solution was recrystallized from ethyl acetate and subsequently from ethanol to yield colorless needles melting at 125.5°.

B. From the Dibromide (VIII).—To a hot solution of 5 g. of the dibromide (VIII) in 40 cc. of ethanol was added a solution of 2 g. of hydroxylamine hydrochloride in 3 cc. of water after which a solution of 4.5 g. of potassium hydroxide in 5 cc. of water was immediately added to the mixture. The solution became reddish-brown and the product precipitated rapidly on refluxing. It was filtered, washed with water and recrystallized from ethanol as colorless needles weighing 2.6 g., and melting at 126°.

C. From the α -Bromochalcone (X).—A solution of 0.57 g. of hydroxylamine hydrochloride in 5 cc. of water was added to a solution of 1.5 g. of the α -bromo unsaturated ketone (X) in 30 cc. of ethanol after which a solution of 1.4 g. of potassium hydroxide in 5 cc. of water was added to the mixture. The solution turned dark red while refluxing for one hour. After cooling, the precipitate which

was formed was recrystallized from methanol as colorless needles to yield 0.18 g. melting at 126°.

Mixture of Isoxazoles (XIX) and (XX) from Diketone (XII).—To a solution of 1 g. of the enolic material (XII) in 25 cc. of ethanol was added a solution of 0.25 g. of hydroxylamine hydrochloride in 4 cc. of water and the mixture was refluxed for one hour, during which interval a colorless material precipitated. This material recrystallized from ethanol as colorless silky needles weighed 0.54 g. and melted at 131.6°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.2; H, 5.8. Found: C, 73.3; H, 5.7.

The melting points of the mixtures of varying proportions of the isoxazoles (XIX) and (XX) were found to vary irregularly between 125.6° to 138.6°. The melting point of a mixture of the isoxazoles, prepared by dissolving approximately equal quantities—about 30 mg. each—in ethanol, allowing the solvent to evaporate and then intimately mixing was 132°.

Summary

1. We have reported the preparation of two β -diketones which are 100% enolic in methanol.

2. We have shown that each β -diketone yields a mixture of two isoxazoles—each a derivative of one or the other of the resonating enol pair.

WASHINGTON, D. C.

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Hydroxylated Stearic Acids. I. Action of Prévost's Reagent on Oleic and Elaidic Esters: Evidence for Configuration of the Hydroxy Acids¹

BY HAROLD WITTCOFF AND SIDNEY E. MILLER

The Prévost reagent,² silver iodobenzoate, was applied to methyl oleate and to elaidic acid by Green and Hilditch,³ who reported that the former, after saponification, yielded a mixture of the high and low melting forms of 9,10-dihydroxystearic acids, whereas the latter yielded only the low melting form.^{3a,4} Repetition of the work in this Laboratory has shown, in contrast to the results of the English workers, that subsequent to saponification the interaction of silver iodobenzoate and methyl oleate (*cis* double bond) yields exclusively the low melting form of 9,10-dihydroxystearic acid. Likewise there results from methyl elaidate (*trans* double bond) after similar treatment the high melting form of the dihydroxy acid. Furthermore, by changing the order of the addition of the reagents, and by extending the time of reaction, it has been possible to increase the yields considerably over those reported by the previous workers.

(1) Paper No. 75, Journal Series, Research Laboratories, General Mills, Inc. Presented at the 112th meeting of the American Chemical Society, New York City, Sept. 15-19, 1947.

(2) (a) C. Prévost, *Compt. rend.*, **196**, 1129 (1933); (b) *ibid.*, **197**, 1661 (1933); (c) C. Prévost and R. Lutz, *ibid.*, **198**, 2264 (1934); (d) C. Prévost and J. Wiemann, *ibid.*, **204**, 989 (1937); (e) E. B. Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).

(3) T. G. Green and T. P. Hilditch, *Biochem. J.*, **29**, 1552 (1935).

(3a) D. Swern, G. N. Billen, T. W. Findley and J. T. Scanlan, *THIS JOURNAL*, **67**, 1786 (1945).

(4) A. Lapworth and E. N. Mottram, *J. Chem. Soc.*, 1628 (1925).

If the benzylation proceeds by *trans* addition to the double bond as Prévost contends^{2b} then it follows that low melting 9,10-dihydroxystearic acid is the *threo* form and is configurationally related to elaidic acid whereas the high melting form is the *erythro* form and represents the so-called normal or *cis* addition of the two hydroxyl groups to oleic acid.

The above conclusions reached from benzylation studies are in accord with those postulated by King⁵ from epoxidation experiments. Both our conclusions and those of King, however, are opposed to the conclusions of Atherton and Hilditch⁶ who, like King, employed epoxidation as a means of postulating configurational relationships. In reading Atherton and Hilditch's work, one is impressed with the fact that they have not taken full advantage of evidence which has accumulated relating to certain mechanisms upon which their postulations are dependent. Thus it has been shown that closure and fission of epoxide rings proceed with inversion.⁷ Likewise, modern theory proposes the *trans* addition of hypochlorous acid to olefins.⁸ Finally, hy-

(5) G. King, *ibid.*, 37 (1943).

(6) D. Atherton and T. P. Hilditch, *ibid.*, 204 (1943).

(7) See, for example, S. Winstein and H. J. Lucas, *THIS JOURNAL*, **61**, 1576 (1939).

(8) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 148.