

Bromination of Methyl Linoleate with N-Bromosuccinimide

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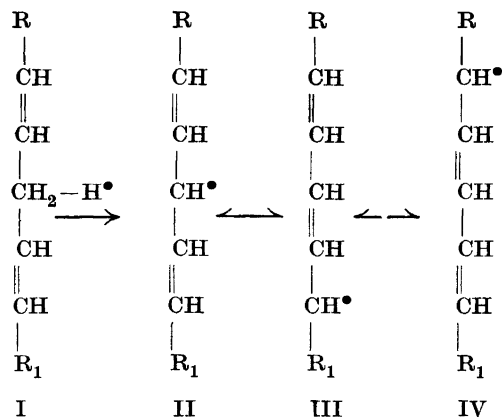
In connection with work on the autoxidation of methyl linoleate we thought it of interest to investigate the action of N-bromosuccinimide on this compound. Preliminary reports of this work have been published^{1,2}.

Ziegler *et al.*³ mentioned that methyl oleate easily formed an unstable monobromide when refluxed 40 minutes in carbon tetrachloride with one mole N-bromosuccinimide. Recently Teeter⁴ and also Sutton and Dutta⁵ have investigated the bromination of some unsaturated fatty acids with this reagent. Their results will be discussed later.

The bromination of unsaturated compounds with N-bromoimides, which has become known as the Wohl-Ziegler reaction, shows several of the characteristics of a free radical reaction⁸. It is catalysed by ultraviolet light⁶ and by added peroxides⁷, and the point of attack generally is the same as that of other reagents that are believed to react through free radicals, *i. e.* benzenediazonium chloride (Waters *et al.*^{8,9,10}; *cf.* also Karrer and Smid⁷, Howton¹⁷). An extensive review has recently been published by Djerassi¹¹.

If the assumption that this bromination is a free radical reaction is correct, the bromination of methyl linoleate with bromosuccinimide would give rise to an intermediate radical II identical with that postulated to occur in the autoxidation of this type of unsaturated fatty acids according to Farmer's theory of autoxidation^{12,13}.

This radical is formed by the removal of a hydrogen atom from carbon atom 11 and can be assumed to be a resonance hybrid with the three contributing structures II, III and IV of which two have conjugated double bonds. The reaction of the radical with a bromine atom in N-bromosuccinimide would result in the formation of a mixture of bromides of which a certain proportion would have conjugated double bonds and consequently show the characteristic light absorption in the region of 232 $m\mu$.



However, the allylic system with a bromine atom at carbon atom 11 must be expected to be so labile that a rearrangement leading to the conjugation of the double bonds could occur under the condition of the reaction (*cf.* Kharasch, Margolis and Mayo²⁰ and Bateman, Cunneen and Koch¹⁴). Thus the appearance of conjugated double bonds cannot be taken as an indication of a free radical mechanism in the same way as in the case of autoxidation. In the latter case, the hydroperoxides are more stable and less susceptible to this type of rearrangement.

RESULTS

When equimolecular amounts of methyl linoleate and N-bromosuccinimide were refluxed in dry carbon tetrachloride in ultraviolet light, the bromination reaction was complete after approximately ten minutes when practically all

Table 1.

U. V. irradi.	Time of boiling	Molar extinction				Bromine content *		Nitrogen content**
		Before evap.		After evap.		found	calc.	
		232 m μ	269 m μ	232 m μ	269 m μ			
With	10 min.	11.600	1.500	10.800	1.200	20.0—20.1%	21.4%	0
With	69 hrs	5.700	26.600	4.800	22.100	6.5—6.7 »	—	0
Without	94 hrs 15 min.	4.800	25.000	4.400	21.700	7.3—7.7 »	—	—

* Micro-Carius

** Micro-Kjeldahl

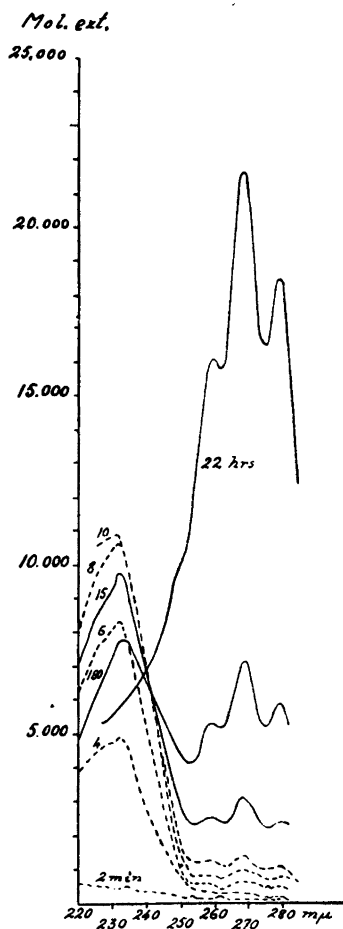


Fig. 1. Absorption spectra of methyl linoleate refluxed in carbon tetrachloride with one mole *N*-bromosuccinimide during times indicated.

bromine was bound in the fatty acid molecule (see Table 1). The ultraviolet absorption spectra of samples taken out after different times are shown in Fig. 1.

As the bromination proceeded a strong absorption band with a maximum at 232 $m\mu$ appeared and increased up to ten minutes when all *N*-bromosuccinimide had reacted. Three very weak maxima at 259, 269 and 279 were also present. If the reflux was stopped at this time, the spectrum of the reaction mixture stayed unchanged if stored in the cold. The results were similar if the reaction mixture was refluxed in an atmosphere of nitrogen or in air.

If the refluxing was continued, however, the absorption at 232 $m\mu$ decreased, whereas the low bands at 259, 269 and 279 increased (Fig. 1). After

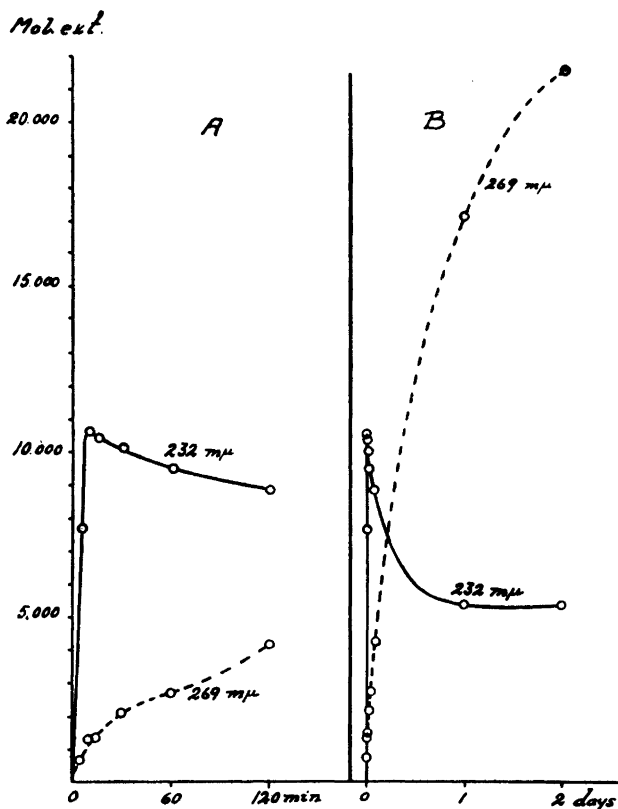


Fig. 2. Change of absorption at 232 $m\mu$ and 269 $m\mu$ with time of methyl linoleates when refluxed with *N*-bromosuccinimide. Illumination of the reaction mixture with ultraviolet light during the first fifteen minutes.

22 hours the former band could no longer be distinguished and only the latter absorption with three maxima characteristic for a conjugated triene was found. Simultaneously with these spectral changes during the prolonged reflux the main part of the bromine was progressively split off as hydrogen bromide from the brominated fatty acid. However, about 30 per cent remained even after very prolonged reflux and appears to be in a more stable position. The change of the absorption maxima at 232 and 269 $m\mu$ with time is shown in Fig. 2.

When the bromination was carried out under the same conditions as the experiment shown in Figs. 1 and 2 except that the illumination with U. V. light was omitted, the reaction was much slower although the curves followed the same general pattern (Fig. 3). All *N*-bromosuccinimide had reacted after

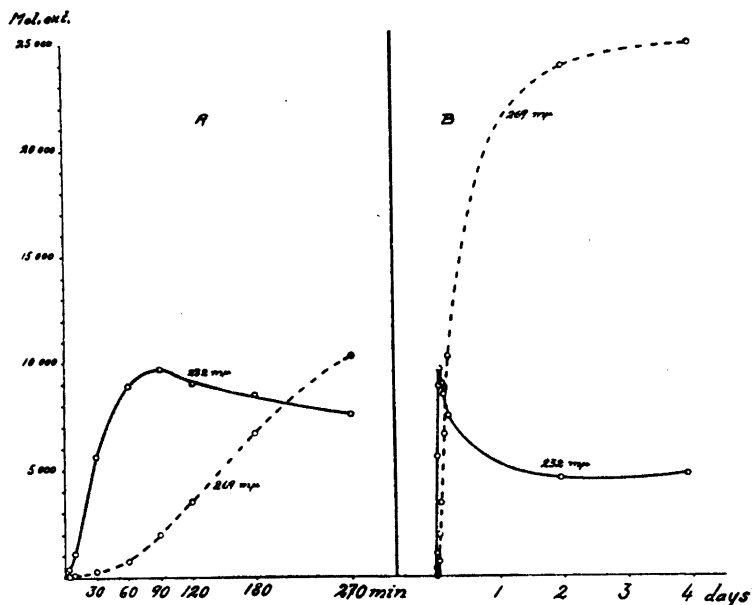


Fig. 3. Identical with fig. 2 except that the ultraviolet illumination was omitted.

about 90 minutes, whereas when the mixture was illuminated this reaction was completed in less than ten minutes.

The appearance of the band at $232\text{ m}\mu$ in the initial bromination is very similar to the earlier phases of the autoxidation of methyl linoleate. In order to compare the two reactions, samples of linoleate were treated with different amounts of N-bromosuccinimide in U. V. light and the maximum absorption at $232\text{ m}\mu$ recorded when all N-bromosuccinimide had reacted. The results of these experiments are plotted in Fig. 4. The earlier parts of the curve corresponds to a molar absorption of the reacted molecules of about 15,000 whereas in the autoxidation at 37° generally about 20,000 has been recorded. As the reaction proceeds, the molar absorption gradually falls off (Fig. 4). If one mole of conjugated diene is formed per molecule that has reacted, an absorption about 30,000 would be expected, as has also been recorded in the quick enzymatic oxidation of sodium linoleate with pure lipoxidase at 0° ^{15,16}. However, at higher temperatures and with longer reaction times the enzymatic as well as the ordinary autoxidation yields products with lower molar absorptions. This has been ascribed to the fact that only a certain part of the primary peroxide has conjugated double bonds and to the destruction of the newly formed conjugated system by further oxidation.

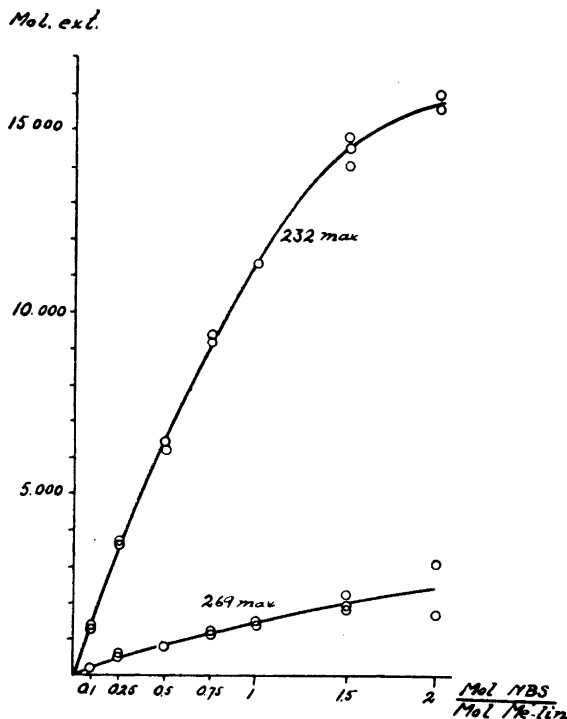


Fig. 4. Maximum absorption at 232 $m\mu$ of linoleate brominated with different amounts of *N*-bromosuccinimide.

In the case of bromination with *N*-bromosuccinimide it seems improbable that addition of the reagent to conjugated double bonds takes place as the reaction product was practically nitrogen free, as was also found by Teeter⁴. However, assuming that a free radical mechanism operates, the decreasing absorption might have several explanations. The progressively lower molar absorption at 232 $m\mu$ with more reagent might to some degree depend on bromination in the α -position to the newly formed conjugated system. Furthermore some 1 : 2 addition of bromine might have taken place as has recently been found by Howton¹⁷ and others^{18,19}. Some addition of secondarily formed hydrobromic acid might also take place²⁰.

Teeter⁴ has tested the influence of various solvents and reaction times on the bromination. Dilution with carbon tetrachloride caused a progressively lower halogen transfer with 25 min. reaction time. 3.5 ml carbon tetrachloride with 10 g methyl esters of soy bean fat acids stirred at 70° reacted to 99 per cent after 40 minutes but as the bromine content was only 18.03 instead

of the calculated value of 21.4 %, some dehydrobromination may have taken place.

Teeter does not seem to have made any observation on the spectral properties of the reaction products. However, he reacted the bromides obtained with sodium methoxide and sodium cyanide to yield products which were apparently very complex mixtures.

Sutton and Dutta⁵ recently investigated the bromination of a number of pure esters of unsaturated fatty acids with N-bromosuccinimide. They found that the bromide of oleate could be subjected to molecular distillation without decomposition, whereas corresponding products from linoleate and linolenate were less stable and decomposed under these conditions.

In our investigation we have used dilute solutions so that all N-bromosuccinimide was dissolved soon after the carbon tetrachloride began to boil and the succinimide formed also remained in solution until the reaction mixture had cooled to room temperature.

Sutton and Dutta, however, refluxed for example 8.4 g ethyl linoleate with 5.1 g N-bromosuccinimide in 50 ml carbon tetrachloride for 4 ½ hours with frequent shaking. The isolated product had a bromine content of 13.6 % (calc. for a monobromide 20.7 %) and an absorption corresponding to a content of 10.2 % triene.

They consider their results as indication that the bromination does not proceed via a free radical mechanism. In their experiments, reaction mixtures have been used more than 50 times more concentrated than ours. In our experiments a clear solution is obtained within 3—4 minutes after the reflux is started. In Sutton and Dutta's experiments a clear solution is probably never obtained and as they have not recorded the time required until all N-bromosuccinimide had reacted, or followed the change in the U. V. spectrum during the earlier stages of the reaction, it is difficult to compare our result with theirs. The secondary reactions might completely obscure the changes during the primary bromination.

The marked catalytic effect observed in our experiment by ultraviolet light, in accordance with earlier investigations, seems to indicate that the bromination under our conditions is a free radical reaction.

The observed spectral changes in the earliest stages during the actual bromination, showing that a considerable formation of conjugated double bonds takes place, do not necessarily imply that a free radical mechanism was causing these changes as is probable in the autoxidation. They could be explained by allylic rearrangements of the primary bromides^{14,20}. The later changes are all caused by the secondary splitting off of hydrobromic acid and perhaps some addition of this acid. However, our results on the bromination

of linoleate with N-bromosuccinimide can all be explained if the primary bromination product is a free radical reaction as proposed by Waters⁸, although they do not furnish conclusive proofs. Further work on the structure of the products and the kinetics of the reaction is needed to clarify this question.

EXPERIMENTAL

Methyl linoleate was prepared essentially according to McCutcheon²¹, N-bromosuccinimide according to Bredt and Hof²². All brominations were done in dry, redistilled carbon tetrachloride. A mercury arc lamp (Orig. Hanau STU 500) was placed 43 cm from the reaction flask (Pyrex).

Example of bromination with one mole N-bromosuccinimide per mole linoleate:

165.6 mg N-bromosuccinimide, 100 ml carbon tetra chloride and 274.2 mg methyl linoleate was rapidly brought to boiling under reflux on a sand bath in ultraviolet light under an atmosphere of nitrogen or air. The reaction mixture became homogeneous after boiling 3–4 minutes. Samples of approx. 2 ml were withdrawn at different times and immediately cooled to room temperature in water. They were used for the starch-iodide reaction to follow the disappearance of the N-bromosuccinimide and for spectrophotometry. For the latter determination 1 ml was blown to dryness with CO₂, and this was repeated twice after the addition of 0.5 ml abs. alcohol to ensure that no carbon tetrachloride remained. This procedure takes at most 25–30 minutes and the sample is most of the time below 10° C. It was then immediately dissolved in ethanol and the spectrum examined at a suitable dilution in the Beckman spectrophotometer. The molar extinctions were calculated on the original linoleate content of the aliquot taken.

For determining the bromine content of the reaction products the bromination was carried out in the following way.

151.9 mg N-bromosuccinimide (100 %) + 75 ml CCl₄ + 250.4 mg methyl linoleate in 25 ml CCl₄ were boiled under reflux in ultraviolet light for 10 min. Then the mixture was cooled and 50 ml were withdrawn. The rest (50 ml) was boiled for 69 hours without illumination and treated as the first fraction.

The first fraction removed gave a negative starchiodide reaction. 1 ml was withdrawn for spectrophotometry. When the succinimide in the fraction had precipitated, the mixture was filtered through a sintered glass filter. The clear solution was evaporated in vacuo at about 35° C, twice dissolved in a little cyclohexane and again taken to dryness. The substance was then dissolved in ether, washed with a buffer solution of pH 7 and then with water. The ether solution was dried with anhydrous sodium sulphate, filtered through a sintered glass filter and partially evaporated with the aid of a current of CO₂. The ether solution was made up to exactly 10 ml. 0.5 ml samples were taken for the following determinations.

- a. Spectrophotometry.
- b. Bromine determination (Carius-micro-method).
- c. Nitrogen determination (Kjeldahl-micro-method).

The results are given in Table 1 (p. 436).

SUMMARY

The bromination of methyl linoleate with N-bromosuccinimide in refluxing carbon tetrachloride has been investigated.

Ultraviolet light strongly catalyzed the reaction.

During the bromination a strong absorption at $232\text{ m}\mu$ appears due to conjugation of the double bonds. On prolonged reflux of the bromide hydrobromic acid is split off with triene formation.

The reaction mechanism is discussed.

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