[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Peroxide Effect in the Rearrangement of α-Bromoacetoacetic Ester

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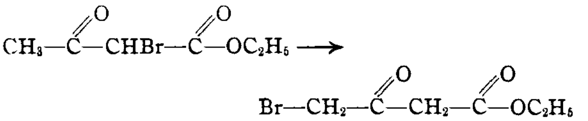
Introduction

It was observed by Epprecht[1] that ethyl α-bromoacetoacetate rearranges upon standing for several months to ethyl γ-bromoacetoacetate.



$$CH_3-C(=O)-CHBr-C(=O)-OC_2H_5 \longrightarrow Br-CH_2-C(=O)-CH_2-C(=O)-OC_2H_5$$

Later, Hantzsch[2] showed that this rearrangement presumably is brought about by hydrogen bromide. The experimental proof of Hantzsch's statement rests upon the observations that pure α-bromoacetoacetic ester could be distilled repeatedly *in vacuo* without undergoing any change, while the ester containing hydrogen bromide rearranged within the time required for a single distillation. Hantzsch further claims that the rate of rearrangement of α-bromoacetoacetic ester in carbon disulfide is proportional to the concentration of hydrogen bromide.

There is some dispute regarding the nature of the products formed by chlorination of acetoacetic ester. Haller and Held[3] claim that both the α- and γ-chloro esters are formed, while Epprecht[4] and Hantzsch and Schiffer[5] were able to isolate only the α-chloro ester.[6] Neither of the investigators noted any rearrangement with the α-chloroacetoacetic ester.

We have observed that hydrogen chloride will not cause the rearrangement of α-bromoacetoacetic ester to the γ-bromo ester. This fact in conjunction wth the difference in stability of the α-chloro and α-bromoacetoacetic esters suggested to us that the reagent responsible for the rearrangement in the case of hydrogen bromide and the α-bromo ester is not hydrogen bromide alone, but hydrogen bromide and a peroxide (and/or oxygen). The experiments described in this article amply confirm this assumption. Our present hypothesis[7] is that the effect of peroxides (and/or oxygen) and hydrogen bromide is due to a chain mechanism involving bromine atoms. The absence of a similar effect with hydrogen chloride is predicted readily upon the above basis, for the latter does not yield chlorine atoms when treated with a peroxide.

Discussion of Results

Our work was facilitated greatly by the fact that the α-bromoacetoacetic ester liberates iodine quantitatively from a potassium iodide solution, while the γ-ester liberates only a negligible amount of iodine. Consequently, the course of the rearrangement could be followed iodometrically.

The experiments in Table I were carried out in a glacial acetic acid solution which was 0.25 *N* with respect to both α-bromoacetoacetic ester and hydrogen bromide. Table I shows that in the absence of air and light the rearrangement is slow, unless a peroxide (such as ascaridole) is added. Furthermore, a peroxide by itself will not cause the rearrangement of the α- to γ-bromo ester but requires the assistance of hydrogen bromide. We are inclined to regard the slow transformation by hydrogen bromide of the α-bromo ester in an evacuated system and in the dark, to traces of peroxides present in the ester. This assumption finds justification in the high speed of transformation in the presence of peroxides, and the ineffectiveness of hydrogen

TABLE I

THE REARRANGEMENT OF ETHYL α-BROMOACETOACETATE BY HYDROGEN BROMIDE IN GLACIAL ACETIC ACID[a]

Conditions Air	Conditions Illumination	Added peroxide	Reaction time, hours	% Rearrangement	Remarks
Absent	None	None	2	20	
Absent	None	None	3	20	
Absent	200-w. lamp	None	2	80	
Absent	200-w. lamp	None	3	88	
Absent	None	Ascaridole	2	86	
Present	None	None	2	73	
Present	None	None	3	79	
Present	200-w. lamp	None	2	72	
Present	200-w. lamp	None	3	79	
Present	200-w. lamp	Ascaridole	16	0	HBr absent
Present	200-w. lamp	Ascaridole	5	0	HCl used instead of HBr
Present	200-w. lamp	None	72	0	
Present	None	None	0.5	95	Solvent benzene
Absent	None	None	0.5	5	

[a] The results recorded in the tables (I, II, III) have been duplicated many times in our laboratory.

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[1] Epprecht, *Ber.*, **27**, 355 (1894).

[2] Hantzsch, *ibid.*, 355, 3168.

[3] Haller and Held, *ibid.*, **22**, ref. 255 (1889).

[4] Epprecht, *Ann.*, **278**, 64 (1893).

[5] Hantzsch and Schiffer, *ibid.*, **25**, 728 (1892).

[6] The γ-chloroacetoacetic ester was prepared by Hamel [*Bull. soc. chim.*, [4] **29**, 390 (1921)].

[7] Kharasch, Englemann and Mayo, *J. Org. Chem.*, **2**, in press. (1937).

chloride as a rearranging agent in the presence or absence of peroxides.

The above conclusions are further confirmed by the experiments described in Table II. It was reasoned that it might be easier to free ethyl acetoacetate from peroxides than ethyl α-bromoacetoacetate and that the bromination of the former with one mole of bromine should yield a pure α-bromo ester and hydrogen bromide in equivalent quantities. The experiments in Table II were carried out in a glacial acetic acid solution which was 0.20 M with respect to both ethyl acetoacetate and bromine. Bromination was complete in five minutes in the light. Similar experiments were performed in the absence of light. The solutions were colorless when the tubes were opened. The rate of disappearance of bromine, however, was not followed. The results show that *in vacuo* and in darkness the α-bromo ester is distinctly more stable than one might conclude from the experiments recorded in Table I, except (as before) in the presence of added peroxides. In the presence of air or under illumination, rearrangement is fast.

TABLE II

THE REARRANGEMENT OF ETHYL α-BROMOACETOACETATE IN ITS PREPARATION FROM ETHYL ACETOACETATE AND BROMINE IN GLACIAL ACETIC ACID

Conditions		Added	Reaction time,	% Re-	
Air	Illumination	peroxide	hours	arrangement	Remarks
Absent	None	None	5.5	9	
Absent	None	None	14	10	
Absent	200-w. lamp	None	3.5	74	
Absent	None	Ascaridole	3.5	81	
Present	None	None	3.5	91	
Present	None	None	14	97	
Present	None	None	21	96	Solvent carbon disulfide
Absent	None	None	21	35	

Somewhat similar results were obtained in the study of this rearrangement in the dark in non-polar solvents. Thus, in benzene as a solvent, and in air, α-bromoacetoacetic ester rearranges in the presence of hydrogen bromide to the γ-form to the extent of 95% in thirty minutes, but practically no rearrangement occurs in that period of time in an evacuated system. In carbon disulfide as a solvent, the α-bromoacetoacetic ester reacts to the extent of 96% in twenty-one hours (actually the rearrangement took place in a few hours, but the tube was examined at the end of that period), while under identical conditions in an evacuated system only 35% rearrangement was observed. It is our belief that the slow rearrangement noted in the evacuated tubes is due to minute traces of oxygen or peroxides in the reaction mixture, and not to a distinctly different mechanism.

Table III shows that ethyl α-methylacetoacetate and bromine (*i. e.*, ethyl α-bromo-α-methylacetoacetate and hydrogen bromide) behave in the same manner as ethyl acetoacetate and bromine (shown in Table II) but the rearrangement is much faster under all conditions. This is not surprising in view of the fact that we were unable to isolate α-bromo-α-methylacetoacetic ester containing more than 60% of the theoretical titratable bromine, and that after vacuum distillation of such a sample it contained only 20% of active bromine. The greater instability of α-bromo-α-methylacetoacetic ester is probably associated with the greater activity of the bromine atom attached to a tertiary, rather than to a secondary, carbon atom.

TABLE III

THE REARRANGEMENT OF ETHYL α-BROMO-α-METHYLACETOACETATE IN ITS PREPARATION FROM ETHYL α-METHYLACETOACETATE AND BROMINE

Conditions		Added	Reaction time,	% Re-
Air	Illumination	peroxide	min.	arrangement
Absent	None	None	25	46
Absent	200-w. lamp	None	25	95
Absent	None	Ascaridole	25	97
Present	None	Ascaridole	25	95

The above experiments show beyond a reasonable doubt that the rapid rearrangement of α-bromoacetoacetic esters is due to the combined effect of hydrogen bromide and oxygen or peroxides. By analogy with the effect of peroxides in the addition of hydrogen bromide to unsaturated compounds, it seems likely that this effect is due to chain reactions involving bromine atoms. We hope to elaborate upon this mechanism more fully in a future publication.

Experimental Part

α-Bromoacetoacetic ester and its α-methyl derivatives were prepared by the method of Conrad and Schmidt.[8] The theoretical quantity of bromine was added to the ester, mixed with twice its volume of ice and water, over a period of one to two hours. Stirring was continued until the mixture was colorless. The ester was separated, washed thoroughly with water, dried over anhydrous sodium sulfate in the cold, and fractionally distilled *in vacuo;* b. p. 98–99° (10 mm.).

α-Bromoacetoacetic ester was prepared in carbon disulfide solution by a similar method also described by Conrad and Schmidt.[8] It was required for testing for the absence of titratable halogen. The best sample had a b. p.

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(8) Conrad and Schmidt, *Ber.*, **29**, 1044 (1896).

116–119° (8 mm.) and contained 3.7% active bromine. It seems likely that this product before fractional distillation may represent an equilibrium mixture of α- and γ-bromo esters rather than pure γ-ester.

Vacuum runs were made essentially according to a procedure which already has been described.[9] Two bomb tubes were connected to a vacuum line by means of a T-tube. One contained the appropriate ester (usually about 1 millimole) dissolved in acetic acid, the other, hydrogen bromide or bromine in acetic acid. Each solution was of twice the concentration desired after mixing. It was important to use fresh, colorless hydrogen bromide solution to eliminate any effects due to bromine molecules. Each tube was cooled sufficiently so that the system could be evacuated to 10^{-4} mm. (or better). The system was then sealed off and the acetic acid and bromine or hydrogen bromide were distilled *in vacuo* into the other bomb tube, which was sealed off while strongly cooled. The reaction mixture was then allowed to stand at room temperature for the desired time, after which it was opened under potassium iodide solution (80% water and 20% alcohol to facilitate solution and titration), acidified with a little acetic acid. After shaking for a minute or two, the solution was titrated with standard thiosulfate solution, using starch as an indicator.

For air runs, similar solutions in Pyrex Erlenmeyer flasks with ground glass stoppers usually were used, preliminary experiments having shown that this method gave the same results as the method described above when air was admitted before sealing off the bomb tubes.

For illumination, a 200-watt incandescent lamp with a silvered reflector, and at a distance of 30 cm. from the reaction vessel, was employed. An electric fan was used to prevent overheating.

Summary

1. Ethyl α-bromoacetoacetate and α-bromo-α-methylacetoacetate are rearranged slowly by hydrogen bromide in darkness, and in evacuated tubes, to the corresponding γ-bromo esters.

2. The above rearrangements are accelerated by either added peroxides, air (oxygen), or illumination.

3. Preparation of the α-bromo esters in the absence of air gives products which are usually stable toward rearrangement by hydrogen bromide in the absence of illumination and air.

4. It is concluded that the observed peroxide effect is due to bromine atoms formed by the action of air or peroxides on hydrogen bromide.

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[9] Kharasch and Mayo, THIS JOURNAL, **55**, 2468 (1933).

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The Biuret Reaction of Sarcosyldiglycine and Glycylsarcosyldiglycine[1]

BY JULIUS FELDMAN

The investigation of the biuret reaction by Schiff,[2] Tschugaeff,[3] Ley and Werner,[4,5] Tomita,[6] and Rising and co-workers[7] has led to the postulation of certain hypotheses concerning the atomic groups requisite for occurrence of the biuret reaction. Briefly, these criteria are (1) an ionizable hydrogen atom and (2) a nitrogen atom capable of forming a cupri-ammonium complex. For the fulfilment of these conditions, it is necessary, in most cases, to postulate a tautomeric form in which a hydrogen atom has migrated from an amide nitrogen atom to a carbonyl oxygen atom. Further, the relative strength of the acidic and basic groups seems to play an important role in determining whether or not a given substance will exhibit the biuret reaction. Thus, glycine anhydride forms a complex copper salt, yet glycylglycine does not. Again, N-monoethylmalonamide, monoethyloxamide, and symmetrical diethyloxamide form complex copper salts, yet unsymmetrical diethyloxamide and triethyloxamide do not show the biuret reaction under any known experimental conditions.

The object of the present investigation was (1) to adduce further evidence for the tautomeric structure of the complex copper salts, and (2) to study the effect of increasing the basicity of a polypeptide molecule upon the ease of biuret formation. For this purpose, the complex cop-

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[1] Abstract of a dissertation presented by the author in partial fulfilment for the degree of Doctor of Philosophy at the University of Chicago. The investigation was carried out under the supervision of the late Dr. Julius Stieglitz.

[2] H. Schiff, *Ber.*, **29**, 298 (1896); *Ann.*, **299**, 236 (1898); **318**, 287 (1901); **352**, 73 (1907).

[3] L. Tschugaeff, *Ber.*, **38**, 2899 (1905); **39**, 3190 (1906); **40**, 1973 (1907).

[4] H. Ley, *Z. Elektrochem.*, **10**, 954 (1904).

[5] H. Ley and F. Werner, *Ber.*, **40**, 705 (1907).

[6] M. Tomita, *Z. physiol. Chem.*, **201**, 38 (1931).

[7] M. M. Rising and C. Johnson, *J. Biol. Chem.*, **80**, 709 (1928); M. M. Rising, J. Hicks and G. Moerke, *ibid.*, **89**, 1 (1930); M. M. Rising and P. S. Yang, *ibid.*, **99**, 755 (1933); M. M. Rising, F. M. Parker and D. Gaston, THIS JOURNAL, **56**, 1178 (1934); P. S. Yang, *J. Chinese Chem. Soc.*, **4**, 27 (1936); C. Li, Master's Thesis, University of Chicago, 1930; L. Jeffries, Thesis, 1930; P. Wenaas, THIS JOURNAL, **59**, 1353 (1937); J. E. Saurwein, unpublished data.