

and 3-methylpentanol-2, respectively: heats of vaporization, 9901 and 10,014 cal.; boiling points,  $118.70 \pm 0.02$  and  $134.32 \pm 0.02^\circ$ ; Trouton constants, 25.3 and 24.6. These last values are considerably greater than the normal value of 21. This characterization is typical of all the hexanols thus far studied.

The viscosity data were found to be in very poor agreement with the values calculated from the equations of Andrade<sup>3</sup> and Raman.<sup>4</sup>

From the surface tension data the Eötvös constants were calculated and it can be seen that as the temperature is raised, they approach the normal value of 2.12, indicating decreasing association with increasing temperature. It can also be seen that the values of the parachor approach, although somewhat less closely, the normal value of 288.2.

The data for the refractive indices, substituted in the Lorenz-Lorentz formula, give for the molecular refractive power of the two alcohols, 31.26 and 31.19, respectively, which is in close agree-

(3) Andrade, *Phil. Mag.*, **17**, 497 (1934).

(4) Raman, *Nature*, **III**, 532 (1923).

ment with the molecular refractive power as calculated from the atomic refractive constants of carbon, hydrogen and oxygen as given by Eisenlohr,<sup>5</sup> namely, 31.44 and 31.44, respectively.

### Summary

The various thermodynamic properties of 2,3-dimethylbutanol-2 and 3-methylpentanol-2 have been measured carefully. The vapor pressures follow the Rankine equation accurately. The values of Trouton's constant derived from these data are considerably greater than the normal value of 21, a behavior which is typical of all the hexanols thus far studied. The measured viscosities are in poor agreement with the values calculated from the equations of Andrade and Raman. The molecular refractions agree closely with the values calculated from the recognized atomic refractive constants. The values of the parachor and the Eötvös constants suggest that both alcohols are associated and that the degree of association decreases with increasing temperature.

(5) Eisenlohr, *Z. physik. Chem.*, **75**, 585 (1911).

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RECEIVED DECEMBER 23, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FURMAN UNIVERSITY]

## Photochemical Bromination of Aryl Methyl Ketones

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While sunlight and artificial irradiation have been employed in the preparation of individual  $\omega$ -bromo ketones,<sup>1</sup> little quantitative study has been made of the photochemical bromination of aryl methyl ketones in spite of much current interest in the mechanism of ketone bromination.<sup>2</sup> Altschul and Bartlett<sup>3</sup> record a few results on the rate of bromination of diphenylacetophenone in acetic acid in "daylight" and "dark" but no data are given on the intensity of the illumination during the experiments which ranged in time from forty-six hours to twenty-eight days. In the present investigation a study has been made of the

photochemical bromination of several aryl methyl ketones under varying intensities of irradiation and in the presence of different concentrations of water, sulfur and acid, three catalysts which profoundly influence the rates of bromination. Interesting observations are made also on the rates of formation and disappearance of the intermediate addition compounds between the ketones and the bromine.

### Negative Catalytic Effect of Water

The marked negative catalytic effect of water on the photochemical bromination in carbon tetrachloride became apparent when acetophenone was found so hygroscopic that it was not possible to weigh samples in the air; the rates of bromination were found to vary as much as 15%, and when one sample was exposed to the air for several hours there was actually no bromination within the five-minute period that gave 100% bromination on a dry sample.

(1) (a) Lazennec, *Bull. soc. chim.*, [4] **5**, 501-508 (1909); (b) Evans, *THIS JOURNAL*, **35**, 1770-1774 (1913); (c) Ruggli and Reichwein, *Helv. Chim. Acta.*, **20**, 913-918 (1937).

(2) (a) Nathan and Watson, *J. Chem. Soc.*, 217-220 (1933); (b) Morgan and Watson, *ibid.*, 1173-1174 (1935); (c) Evans, *et al.*, *ibid.*, 1167-1173 (1935); 785-789 (1936); 1434-1439 (1938); (d) Paul and Hammett, *THIS JOURNAL*, **58**, 2182-2187 (1936); (e) Kröhnke, *Ber.*, **69B**, 614-621 (1936); 921-935 (1936); (f) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Chapter 8.

(3) Altschul and Bartlett, *J. Org. Chem.*, **5**, 623-636 (1940).

The method of bromination was to measure rapidly with a 1.0 cc. pipet the 0.01 molar quantities of the ketones into a 300-cc. Pyrex Erlenmeyer flask; 20.0 cc. of c. p. carbon tetrachloride containing 1 mg. of sulfur to slow down the rate of bromination (see Table II below) was added, and the flask, attached to a return condenser by a ground-glass joint, was placed in a thermostat at 30°; 1.6 g. (0.01 *m*) of bromine in 10.0 cc. of c. p. carbon tetrachloride was added and the photochemical bromination carried out with a 300-watt clear-glass Mazda lamp supported exactly three inches above the flask. At the end of a definite period of time the light was cut off and 20 cc. of a 20% potassium iodide solution containing 0.8 g. of sodium acetate buffer<sup>2a</sup> added; the liberated iodine was removed with excess thiosulfate solution, and the excess thiosulfate determined by titration with standard iodine solution, using starch-iodide indicator. The results with and without the addition of water are given in Table I.

TABLE I  
NEGATIVE CATALYTIC EFFECTS OF WATER ON KETONE  
BROMINATION  
30°, 300 watts, 3-inches, CCl<sub>4</sub> + 1 mg. S

Ketone	Water added, cc.	Time, min.	% Bromination
1 Acetophenone	None	5	100.0
2 Acetophenone	0.5	15	0.0
3 <i>p</i> -Chloroacetophenone	None	5	91.0
4 <i>p</i> -Chloroacetophenone	None	5	90.2
5 <i>p</i> -Chloroacetophenone	None	5	92.1
6 <i>p</i> -Chloroacetophenone	0.1	5	0.0
7 <i>p</i> -Chloroacetophenone	0.1	9½	29.7
8 <i>p</i> -Bromoacetophenone	None	5	97.9
9 <i>p</i> -Bromoacetophenone	None	5	97.3
10 <i>p</i> -Bromoacetophenone	0.1	5	0.0
11 $\beta$ -Naphthylacetophenone	None	5	32.5
12 $\beta$ -Naphthylacetophenone	None	5	35.6
13 $\beta$ -Naphthylacetophenone	0.1	5	4.9
14 <i>o</i> -Hydroxyacetophenone	None	5	44.5
15 <i>o</i> -Hydroxyacetophenone	None	5	44.9
16 <i>o</i> -Hydroxyacetophenone	0.1	5	50.0
17 <i>o</i> -Methoxyacetophenone	None	5	1.0
18 <i>o</i> -Methoxyacetophenone	None	5	1.1

The striking negative catalytic effect of water on all the brominations except that of *o*-hydroxyacetophenone led to the supposition that the latter was being brominated in the nucleus rather than in the methyl group; when this ketone was brominated in the dark a value of 44.0% was obtained, whereas none of the other ketones in Table I showed any bromination in the dark within five minutes.

The 0.5 cc. of water added to the acetophenone in the first run of Table I proved immiscible in the 30 cc. of carbon tetrachloride present, but when an attempt was made to use acetic acid as the solvent, in order to permit larger amounts of water to be added, there was no photochemical bromination of acetophenone in five minutes in this solvent even with 600 watts at 2 inches. The 0.1 cc. of water added to the carbon tetrachloride solutions of Table I seemed to form clear miscible solutions.

**Effect of Sulfur on the Photochemical Bromination.**—The strong negative catalytic effect of

sulfur on side-chain bromination reported previously,<sup>4</sup> led to an investigation of this phenomenon in the photochemical bromination of ketones. The results are summarized in Table II.

TABLE II  
SULFUR EFFECT ON THE BROMINATION OF *p*-CHLORO-  
ACETOPHENONE  
30°, 300 watts, 3 inches, 5 minutes

Sulfur added, mg.	Solvent	% Bromination
None	CCl <sub>4</sub>	100.0
1	CCl <sub>4</sub>	91.0
1	CCl <sub>4</sub>	90.2
1	CCl <sub>4</sub>	92.1
10	CCl <sub>4</sub>	73.7
100	CCl <sub>4</sub>	52.0
1000	CS <sub>2</sub>	72.3
1000	CS <sub>2</sub>	73.1
2000	CS <sub>2</sub>	68.0
2000	CS <sub>2</sub>	65.5

The striking difference in the negative catalytic effects of sulfur and moisture on the photochemical bromination of ketones as compared with side-chain brominations, suggests the interesting possibility of directed bromination in a molecule containing both groups (*e. g.*, methyl *p*-tolyl ketone). Side-chain bromination was blocked by 100 mg. of sulfur<sup>4</sup> while 2000 mg. of sulfur slowed down the bromination of *p*-chloroacetophenone only about one-third. On the other hand, 0.1 cc. of water prevented any bromination of ketones in carbon tetrachloride in five minutes (Table I); adding 0.1 cc. of water to toluene (0.01 *m*) in the same solvent caused a slight increase in the rate of bromination (36.5% in five minutes at 300 watts, 3 inches, as contrasted with 32.4 in dry carbon tetrachloride. The possibilities of such directed bromination into the side-chain or the ketone group are now being investigated.

**Irradiation Effects.**—The influence of different intensities of irradiation are shown in Table III. The brominations were carried out on 0.01 molar quantities of *p*-chloroacetophenone in pure

TABLE III  
IRRADIATION EFFECTS ON THE BROMINATION OF *p*-CHLORO-  
ACETOPHENONE IN CARBON TETRACHLORIDE AT 30°

Watts	Distance, inches	Time, min.	% Bromination
300	1	3	58.5
300	6	3	0.0
300	6	4.5	42.0
60	6	5	0.0
60	6	7	15.6
60	1	5	1.0

(4) Sampsey and Hicks, THIS JOURNAL, 68, 3252-3253 (1940).

carbon tetrachloride. In all the brominations the interesting observation was made that the bromine color first began to fade around the edges of the solution, and then gradually extended toward the center. Care was taken not to shake the flask during the brominations.

**Intermediate Compound Formation.**—Another intriguing phase of the photochemical bromination of ketones was the study of conditions affecting the formation and decomposition of intermediate addition compounds formed between one mole of bromine and one mole of ketone.<sup>5</sup> Acid is known to increase the rate of formation of these intermediate compounds in the non-photochemical brominations reported in the literature. We found a decided acceleration also in the photochemical bromination. In one experiment dry hydrogen chloride was bubbled into c. p. carbon tetrachloride for two minutes; 20.0 cc. of this solution was then used in the bromination of *p*-chloroacetophenone (0.01 *m*), using 60 watts at 3 inches; when 1.6 g. of bromine in 10.0 cc. of carbon tetrachloride was added there was 83.5% bromination in two minutes; on cutting the hydrogen chloride concentration in half by using 10.0 cc. only of the former solution, mixed with 10.0 cc. of solvent containing no acid, the rate was cut to 41.1% under the same conditions of irradiation.

Irradiation shortened the time required for the separation of the bromo-ketone intermediate compound. When a dry sample of acetophenone (0.01 *m*) in 20.0 cc. of c. p. carbon tetrachloride and 1.6 g. of bromine in the same solvent

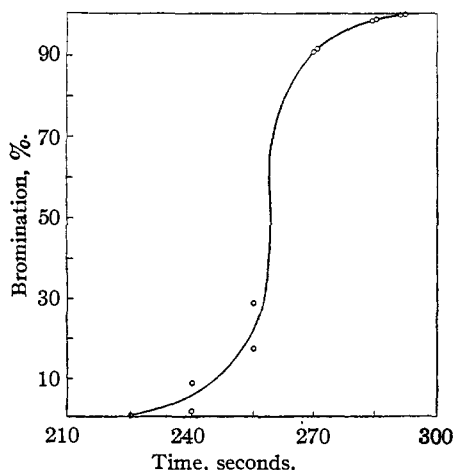


Fig. 1.—Rate of decomposition of bromine-acetophenone intermediate.

<sup>5</sup> Hahn, *Ber.*, **44**, 1552-1553 (1911).

were exposed for two minutes to 300 watts at 6 inches, the orange colored intermediate compound began separating after twenty-three minutes at room temperature (about 18°), and the bromination was complete four and one-half minutes later; a sample of acetophenone treated similarly but not exposed to the lamp required forty minutes for the intermediate to appear, and the reaction went to completion five minutes later.

In order to follow more closely the rate of decomposition of the intermediate bromo-ketone compound, 6.0 cc. of dry acetophenone was dissolved in 100.0 cc. of c. p. carbon tetrachloride in a 300-cc. Pyrex Erlenmeyer flask equipped with a siphon and atomizer bulb for the quick withdrawal of samples; the solution was placed in a thermostat at 30° under a 200-watt Mazda bulb at 6 inches; 50.0 cc. of a carbon tetrachloride solution of bromine (0.01 *m*) was run in and samples withdrawn at the intervals noted in Table IV; the samples withdrawn were run into weighed flasks containing 20 cc. of 20% potassium iodide solution and 0.8 g. of sodium acetate buffer, and the amount siphoned out was determined by reweighing the flasks; excess thiosulfate was then added and the excess determined by an iodine titration. The results of two such runs are recorded in Table IV.

TABLE IV  
RATE OF DECOMPOSITION OF BROMINE-ACETOPHENONE INTERMEDIATE

6.0 cc. Ketone + 100.0 cc. CCl<sub>4</sub> + 50.0 cc. Br<sub>2</sub> Soln. (0.01 *m*), 30°, 200 watts, 6 inches

min.	Time sec.	% Bromination	min.	Time sec.	% Bromination
1	00	0.0	3	45	0.0
4	00	0.6	4	00	8.7
4	15	17.0	4	15	28.8
4	30	90.0	4	30	90.4
4	45	97.9	4	45	98.2
4	52	100.0	4	51	100.0

The most striking phenomenon about Table IV is that practically no bromination took place until the intermediate compound began to separate at about four minutes, but that then the bromination proceeded at a rapid rate, more than 60% taking place in the fifteen-second period of 4:15 and 4:30. Figure 1 shows this effect graphically. This delayed formation of the intermediate, followed by its rapid decomposition with the liberation of hydrogen bromide, was observed frequently in the runs of Table I. *p*-Chloroacetophenone, however, did not form an insoluble in-

intermediate, but expt. no. 7 of Table I was stopped when a vigorous evolution of hydrogen bromide was observed after nine and one-half minutes.

While irradiation shortens the time of formation of the intermediate compound, it does not seem to noticeably influence the rate of its decomposition, for in Table V the 200-watt light was turned off at the first appearance of the orange-red precipitate after about three minutes and forty-five seconds, but the decomposition followed the same course as in Table IV.

TABLE V

DECOMPOSITION OF BROMINE-ACETOPHENONE INTERMEDIATE AFTER THE IRRADIATION WAS SHUT OFF

6.0 cc. Ketone + 100.0 cc. CCl<sub>4</sub> + 50.0 cc. Br<sub>2</sub> soln. (0.01 *m*), 30°, 200 watts, 6 inches for 3 min. 45 sec.

Time		% Bro- mination	Time		% Bro- mination
min.	sec.		min.	sec.	
1	00	0.0	4	30	88.0
4	00	1.5	4	45	98.5

TABLE VI

DECOMPOSITION OF BROMINE-ACETOPHENONE INTERMEDIATE IN WATER

6.0 cc. Ketone + 0.5 cc. Water + 100.0 cc. CCl<sub>4</sub> + 50.0 cc. Br<sub>2</sub> soln. (0.01 *m*), 30°, 200 watts, 6 inches

Time		% Bro- mination	Time		% Bro- mination
min.	sec.		min.	sec.	
1	00	0.0	39	15	98.6
27	00	1.0	39	50	100.0
35	45	2.2			

Water, on the other hand, not only delayed the time of formation of the intermediate but it prolonged the period of decomposition. In Table VI 0.5 cc. of water was added to the 6.0 cc. of acetophenone in 100.0 cc. of c. p. carbon tetrachloride; the intermediate compound was not observed until thirty-five minutes and forty-five seconds after the 50.0 cc. of bromine solution (0.01 *m*) was added, and it persisted for four minutes and five seconds.

**Acknowledgment.**—The authors wish to express appreciation for the active interest of Dr. E. Emmet Reid in this research.

### Summary

1. Rates are given for the photochemical bromination of acetophenone, *p*-chloroacetophenone, *p*-bromoacetophenone,  $\beta$ -naphthylacetophenone, *o*-hydroxyacetophenone and *o*-methoxyacetophenone.

2. Water and sulfur are shown to be negative catalysts, while irradiation and hydrogen chloride shorten the time of bromination in carbon tetrachloride.

3. Factors influencing the rates of formation and decomposition of the intermediate bromo-ketone compounds have been studied.

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RECEIVED JANUARY 9, 1941

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

## Some Normal and Alkamine Esters of *m*-Aminomandelic Acid and Related Compounds

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The problem of the relation between chemical constitution and physiological activity has been widely studied. In the field of local anesthetics, much of the work has centered on variations of the procaine molecule. The amino alcohol<sup>1</sup> used to esterify the carboxyl group of *p*-aminobenzoic acid has been varied, and the amino group has been replaced by various substituents.<sup>2</sup> These studies have produced hundreds of compounds possessing local anesthetic action to a greater or lesser degree than procaine.

In nearly all instances the para substituted compounds have been prepared and their local

anesthetic efficiency studied, but only a small amount of work has been done on the ortho and meta substituted compounds of each type of compound prepared. Some studies along this line have been the preparation of the esters of *o*- and *m*-aminobenzoic acids<sup>3</sup> and cinnamic acids.<sup>4,5</sup>

In 1938 Shriner and Keyser<sup>6</sup> suggested that a carbonyl group conjugated with double bonds in an aromatic nucleus enhanced anesthetic activity. On the basis of this consideration it was thought that the esters of *p*-aminomandelic should

(1) Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).

(2) Coles and Lott, *THIS JOURNAL*, **58**, 1989 (1936).

(3) German Patent 170,587 (1906).

(4) Wildman and Thorp, U. S. Patent 1,193,649 (1916).

(5) Kamm, *THIS JOURNAL*, **42**, 1030 (1920).

(6) Shriner and Keyser, *ibid.*, **60**, 286 (1938).