

were decomposed by the Umhoefer<sup>13</sup> method to obtain the vinylic chlorine atom as chloride ion for radioactivity assay.

1,3-Dichloropropene isomer hydrolyzed and conditions	<i>cis</i> isomer 5 hr., 40°	<i>cis</i> isomer 8 hr., 40°	<i>trans</i> 10.5 hr., 40°
Calcd. specific activity of allylic chlorine of 1,3-dichloropropene	120	120	116
Specific activity of chlorine in 3-chloro-2-propenyl 3,5-dinitrobenzoates	4.7	9.8	7.5

**Radioactivity Assays.**—The radiochemical assays of the various materials containing chlorine were made by determination of the amount of radiation from silver chloride spread on 25.0-mm. watch glasses of uniform curvature. The silver chloride counting plates were prepared in the following manner. A quantity of chloride ion solution, calculated from titration data to contain 6.3 mg. of chlorine, was measured accurately into a 15-ml. graduated centrifuge tube, acidified with 6 *N* nitric acid, and the chloride ion precipitated by addition of 2–3 ml. of 1 *N* silver nitrate solution. The mixture was centrifuged, the supernatant liquid removed, the precipitate washed with water, centrifuged and

(13) R. R. Umhoefer, *Ind. Eng. Chem., Anal. Ed.*, **15**, 383 (1943).

the washings discarded. The silver chloride was then peptized in 3 ml. of 0.02% gelatin solution using a motor driven platinum wire stirrer. The peptized silver chloride was transferred quantitatively in small portions to a 25.0 mm. watch glass, previously brought to constant weight, and dried in an oven at 100–105°. After cooling, the spread of silver chloride was covered with a collodion film, weighed, and stored in darkness until counted.

This technique of plate preparation has given reproducible results within 1–2%. Losses in radioactivity resulting from deterioration of the sample by light over a period of several days were negligible. The distribution of silver chloride on the plate appeared to be the primary factor influencing the precision of counting. The specific activities of various samples as determined from counting rates were found to vary directly, within the limits of experimental error, with the isotopic composition of the sample and were not influenced by variation of 20% in the total weight of the sample.

A Tracerlab TGC-2 Geiger tube with a mica end-window of less than 2 mg./cm.<sup>2</sup> thickness, mounted in a lead shield, was used with a Tracerlab "64" Scaler (Tracerlab, Inc., Boston, Mass.) for all radioactivity measurements. The relative counting rates of all samples were determined in exactly the same position with respect to the Geiger tube, which gave a counting geometry of approximately 9%. The expected instrumental and standard statistical error under these conditions was less than 1%.

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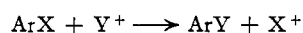
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

## The Aromatic Elimination Reaction. II. The Mechanism of the Acid-catalyzed Deacylation of Aromatic Ketones<sup>1</sup>

BY W. M. SCHUBERT AND H. K. LATOURETTE<sup>2</sup>

The rate-determining step in the reaction of 2,6-dimethylacetophenone and acetomesitylene with strong sulfuric acid to yield the aromatic hydrocarbon and acetic acid was found to be a first order decomposition of the conjugate acid of the ketone. Taking into account the appreciable ionization of the ketone, the expression,  $\log k + H_0 - \log \frac{[B]}{[B] + [BH^+]}$  = const., was derived and found to hold over a wide range of acid concentration. The *pK*<sub>a</sub> of 2,6-dimethylacetophenone was found to be –7.8. The deacylation step for acetomesitylene was 66 times as fast as that for 2,6-dimethylacetophenone.

The aromatic elimination reaction, which can be looked upon as an example of electrophilic aromatic substitution, may be represented crudely by the equation



A common example of the aromatic elimination reaction is aromatic deacylation, in which X is an acyl group and Y<sup>+</sup> is a proton. The deacylation reaction was discovered by Louise,<sup>3</sup> who found that benzoylmesitylene upon treatment with hot phosphoric acid yielded mesitylene and benzoic acid. In a more extensive study, Klages and Lickroth<sup>4</sup> found that acylbenzenes having at least one ortho alkyl substituent were cleaved in boiling sirupy phosphoric acid to the aromatic hydrocarbon and the fatty acid. If no bulky ortho alkyl substituent were present, cleavage of the acylbenzene did not occur. More recently, Arnold and Rondstedt<sup>5</sup> were able to bring about deacetylation of 9-acetyloctahydroanthracene and 4-acetylhydrindane in boiling sirupy phosphoric acid.

In order to elucidate the mechanism of deacyla-

tion and gain further insight into electrophilic aromatic elimination and substitution, the deacylation was quantitatively studied. The ketones used were 2,6-dimethylacetophenone and acetomesitylene (2,4,6-trimethylacetophenone). They were found to deacetylate readily in strong sulfuric acid at or near room temperature. The formation of acetic acid in the deacylation afforded a ready means of measuring the rate of reaction, since a method of determining concentration of acetic acid in the presence of a large excess of sulfuric acid had already been reported.<sup>6</sup>

### Experimental

**Preparation of Materials.**—Acetomesitylene prepared by the method of Adams and Noller<sup>7</sup> was purified by fractional distillation, b.p. 100–102° (7 mm.), *n*<sub>D</sub><sup>20</sup> 1.5155. The method of De Jong<sup>8</sup> was used to convert 2,6-dimethylbenzoyl chloride to 2,6-dimethylacetophenone, b.p. 117–118° (26 mm.), *n*<sub>D</sub><sup>20</sup> 1.5120.

Solutions of 72.5 to 96% sulfuric acid were prepared by dilution of C.P. concentrated sulfuric acid. The 100% sulfuric acid was prepared by mixing appropriate amounts of concentrated and fuming sulfuric acid. The strength of each acid solution was determined by titration against standard alkali of an aliquot portion of a diluted sample of the acid.

Technical grade methanesulfonic acid was dried by continuous azeotropic distillation with a mixture of equal parts

(1) For paper I in this series see *THIS JOURNAL*, **71**, 2639 (1949).

(2) Abstracted in part from the Ph.D. thesis of H. K. Latourette, University of Washington, 1951.

(3) E. Louise, *Ann. chim. phys.*, [6] **6**, 206 (1885).

(4) A. Klages and G. Lickroth, *Ber.*, **32**, 1549 (1899).

(5) R. T. Arnold and E. Rondstedt, *THIS JOURNAL*, **68**, 2177 (1946).

(6) D. N. Craig, *Bur. Standards J. Research*, **6**, 169 (1931).

(7) R. Adams and C. R. Noller, *THIS JOURNAL*, **46**, 1892 (1924).

(8) P. De Jong, *Rec. trav. chim.*, **61**, 539 (1942).

of benzene and toluene. It then was distilled, b.p. 134.5–135° (3 mm.), and further purified by crystallization. The purified acid was found to be 99.0% pure by titration against standard alkali. A portion of the 99.0% methanesulfonic acid was diluted to 90.4%.

**Products of the Deacylation.**—Acetomesitylene (10 g.) when dissolved in 83% sulfuric acid (50 cc.) at room temperature for several hours yielded 7.30 g. (91% yield) of an upper layer of mesitylene, b.p. 162–164°. The dinitro derivative melted at 84–86.5° and showed no depression in melting point when mixed with authentic dinitromesitylene. In 85% sulfuric acid the product was mesitylenesulfonic acid which separated as white crystals. These were isolated as reported in the previous article,<sup>1</sup> m.p. 75–76°. The dihydrate is reported<sup>9</sup> as melting at 77°.

The upper layer formed in the reaction of 2,6-dimethylacetophenone (1.9 g.) with 85% sulfuric acid (15 ml.) at 40° for two days was identified as *m*-xylene, since it formed a dinitro derivative, m.p. 91–92°, identical with an authentic sample. In greater than 85% sulfuric acid the product was assumed to be xylenesulfonic acid, since no upper layer formed.

**Kinetic Method.**—The rate of deacylation of the aromatic ketone at a particular temperature in a particular concentration of sulfuric acid was determined by the running of four or more simultaneous reactions each at the same initial concentration, but for differing time intervals. A duplicate run, again with four or more simultaneous reactions was made from one day to six months later.

For each reaction mixture, a sample (about 0.3 g.) of the ketone was weighed out in a thin-walled glass ampule. Sulfuric acid (10 ml.) of appropriate concentration contained in a 25-ml. glass stoppered erlenmeyer flask was brought to temperature in a Sargent constant temperature water-bath. The ampule was dropped into the solution at zero time and the flask was withdrawn momentarily from the bath, briefly shaken to break the ampule and cause solution of the ketone, then quickly replaced in the bath. Since the runs were made near room temperature and the flask was withdrawn from the bath for a period of less than three seconds, little error was introduced by use of this procedure. After a suitable time interval the reaction was quenched by a rapid transfer of the reaction mixture onto 20 g. of ice contained in a 1-l. three-necked flask.

The amount of acetic acid formed was determined by a method similar to that of Craig.<sup>6</sup> One and one-half molar equivalents of 5 *N* sodium hydroxide was added to the diluted reaction mixture. The three-necked flask was fitted with a dropping funnel, a capillary and a double-Hopkins

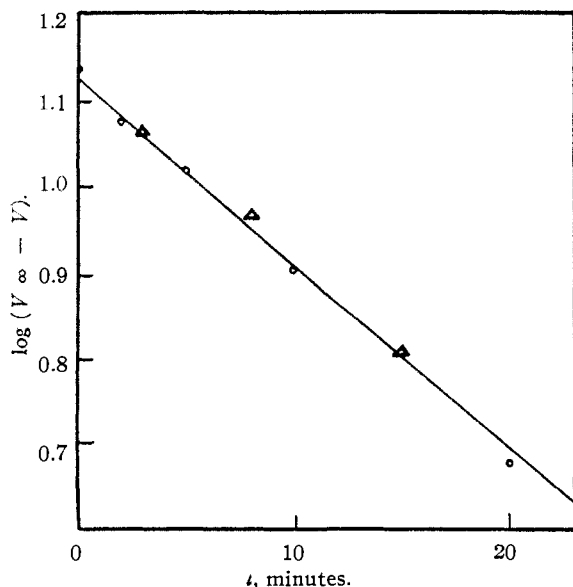


Fig. 1.—First order plot of rate of acetic acid formation from acetomesitylene in 80.4% sulfuric acid at 20.0° (class b precision):  $\Delta$ , first run;  $\circ$ , second run.

(9) H. Rose, *Ann.*, **164**, 55 (1872).

head attached to a downward condenser. The solution was distilled to near dryness under 35 mm. pressure. Twice, about 8 ml. of water was added through the dropping funnel and the solution again distilled to near dryness. The pressure then was reduced to 15 ml. and the residue evaporated to dryness. The total distillate was titrated against 0.1 *N* sodium hydroxide, phenolphthalein being the indicator. The method was found by blank runs without ketone to be accurate within the experimental error of titration.

In a few runs in which methanesulfonic acid rather than sulfuric acid was used, the procedure was the same except that to neutralize the acid, 1.2 molar equivalents of sodium hydroxide and 0.5 molar equivalents of sodium bisulfate were added per molar equivalent methanesulfonic acid.

In general, excellent first order plots of  $t$  against  $\ln(V_{\infty} - V)$  were obtained, in which  $V$  is the volume of standard sodium hydroxide required to titrate volatile acid formed at time  $t$  and  $V_{\infty}$  is the volume required at complete reaction. The slope of the best straight line estimated by eye was taken as the value of  $k$ . The rate constants obtained were arbitrarily assigned three classes of precision based on an inspection of points about the straight line. In class a constants, deviations were less than 2%, in class b, less than 5%, and class c, less than 10%. Most of the rate constants for 2,6-dimethylacetophenone are of class a. The rate constants for acetomesitylene are somewhat less reliable because the reaction is extremely rapid at the temperature studied, and because many of the runs were made before the technique was perfected. However, the distribution of points about a straight line was random, showing no drift. An example of the first order plot is shown in Fig. 1. The rate constant from this plot was estimated to be of class b precision.

**The Sulfonation of 2,6-Dimethylacetophenone.**—The yields of acetic acid obtained in the kinetic runs on the deacylation of 2,6-dimethylacetophenone were found by titration to be 99 to 100% in concentrations of sulfuric acid up to 85%. In greater than 85% sulfuric acid the yield of acetic acid fell off on a smooth curve (see Table I). The yields of acetic acid obtained from acetomesitylene were quantitative in up to 87.1% sulfuric acid.

TABLE I

YIELD OF ACETIC ACID OBTAINED IN THE DEACYLATION OF 2,6-DIMETHYLACETOPHENONE

H <sub>2</sub> SO <sub>4</sub> , %	Yield acetic acid, %
85.0	99.4
90.0	91.1
93.0	85.6
96.0	72.5
100.0	8.9

Reductions in the yield of acetic acid were attributed to sulfonation of 2,6-dimethylacetophenone yielding 2,4-dimethyl-3-acetylbenzene-1-sulfonic acid. The sodium, lead and *S*-benzylthiuronium salts of this sulfonic acid were isolated from a large scale run in the following manner. A solution of 2,6-dimethylacetophenone (10.2 g., 0.069 mole) in 100% sulfuric acid (40 cc.) was maintained at 40° for four hours. About one third of the solution was saved for preparation of the lead salt (below) and the remainder was poured into 200 cc. of cold saturated aqueous sodium chloride. The white crystalline precipitate was collected by suction filtration and then dissolved in 70 cc. of warm water. The solution was neutralized with 10% sodium hydroxide and cooled. The cream-colored precipitate was collected by suction filtration, yield 5.68 g. About 5 g. of this was recrystallized twice from water and dried over phosphorus pentoxide, yielding 1.5 g. of chloride-free, sulfate-free white platelets.

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>O<sub>4</sub>SNa: C, 47.99; H, 4.43; S, 12.81; Na, 9.19. Found: C, 47.73; H, 4.15; S, 12.57; Na, 8.88.<sup>10</sup>

A third of the sulfuric acid solution prepared above was poured over 50 g. of ice. To the resulting solution was added 40 g. of basic lead carbonate. The precipitated lead sulfate was removed by suction filtration and then digested

(10) Most of the analyses reported in this paper are by Dr. O. H. Schwarzkopf, Middle Village, Long Island, New York.

twice with 50 cc. of water and the mixture refiltered. The combined filtrates were evaporated to dryness on the steam-bath to yield 4.6 g. of the lead sulfonate. Recrystallization from water and thorough drying over phosphorus pentoxide gave 1.4 g. of shining white crystals.

*Anal.* Calcd. for  $C_{10}H_{11}O_4SPb$ : C, 36.30; H, 3.35; S, 9.69; Pb, 31.31. Found: C, 36.09; H, 3.32; S, 9.30; Pb, 31.51.

The S-benzylthiuronium sulfonate (0.7 g.) prepared from the sodium salt (1.5 g.)<sup>11</sup> melted at 151–154°.

*Anal.* Calcd. for  $C_{13}H_{22}N_2O_4S_2$ : C, 54.80; H, 5.62; S, 16.25; N, 7.10. Found: C, 54.81; H, 5.38; S, 16.35; N, 7.25.

**Measurement of the  $pK_a$  of 2,6-Dimethylacetophenone.**—The method of Hammett, Flexser and Dingwall<sup>12</sup> was used. The spectrum of various sulfuric acid solutions about  $1.2 \times 10^{-4}$  molar in ketone was measured repeatedly at recorded time intervals, since the spectrum changed with time due to the deacylation reaction. In 70 and 75% sulfuric acid the reaction was sufficiently slow (the time for half-reaction was a day or two) so that optical density measurements made quickly were insignificantly different from readings extrapolated back to zero time. It was necessary to extrapolate readings in 80 and 85% sulfuric acid back to zero time. This was done with the aid of the first order rate constant obtained by following the change in  $\ln I$  with time at wave lengths in which a third species, e.g., xylene or xylene sulfonic acid, did not absorb appreciably. The rate constants are significant only for the extrapolation since the temperature of the room (25–27°) was not accurately measured. Measurements in 90 and 100% sulfuric acid were discarded because of the increased reaction rate and because competing sulfonation of the ketone increased the number of species contributing to the spectrum.

In Fig. 2 is plotted the measured absorption at various times as well as the extrapolated zero-time absorption,  $\epsilon_0$ , in 85% sulfuric acid. Absorption by the free base is in the region of 250  $m\mu$ . The low maxima around 275  $m\mu$  appearing after 260 minutes are attributed to the xylene sulfonic acid. In Table II are summarized all the useful spectral measurements, the  $\epsilon_0$  values, and values calculated for  $pK_a$ .

TABLE II

EXTINCTION COEFFICIENTS AND  $pK_a$  VALUES FOR 2,6-DIMETHYLACETOPHENONE IN  $H_2SO_4 + H_2O$  MIXTURES

Wave length, $m\mu$	$H_2SO_4$ , %								$\epsilon_0^a$	$pK_a$
	75.0		80.0		85.0		85.0			
$H_2O$	$\epsilon$	$\epsilon_t$	$t$ , min.	$\epsilon_0^b$	$\epsilon_t$	$t$ , min.	$\epsilon_0^b$	$\epsilon_0^b$		
290	339	1286	1850	8	1870	3140	24	3560	-7.71	
300	201	1079	2024	9	2050	4350	25	4980	-7.73	
310	108	772	1840	10	1860	4600	27	5320	-7.79	
320	45	470	1329	11	1340	3580	28	4140	-7.80	
330	15	270	825	12	834	2298	30	2680	-7.84	
								Avg.	-7.8	

<sup>a</sup> Based on a rate constant of  $1.19 \times 10^{-3} \text{min.}^{-1}$ . <sup>b</sup> Based on a rate constant of  $5.70 \times 10^{-3} \text{min.}^{-1}$ .

The first method of Hammett, Flexser and Dingwall<sup>12</sup> was used to calculate  $pK_a$ . Values of  $K_a$  and  $\epsilon_{BH^+}$  at various wave lengths in solutions with known  $h_0$  values were obtained by simultaneous solutions of the equation

$$K_a + \epsilon_{BH^+} \left( \frac{h_0}{\epsilon_{BH^+} - \epsilon} \right) - \left( \frac{h_0}{\epsilon_{BH^+} - \epsilon} \right) = 0 \quad (1)$$

The wave lengths chosen were in the region in which the  $\epsilon_0$  curve (the reference curve in 75% sulfuric acid) was relatively flat, and hence the medium effect of a lateral shift in spectrum small. The two values of  $\epsilon$ , the observed extinction coefficient at a particular wave length, which were used in each simultaneous solution of equation (1), were those measured in 80.0 and 85.0% sulfuric acid. The value, -7.8, was obtained for  $pK_a$ .

(11) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Ed. III, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 215.

(12) L. A. Flexser, L. P. Hammett and A. Dingwall, *THIS JOURNAL*, **57**, 2103 (1935).

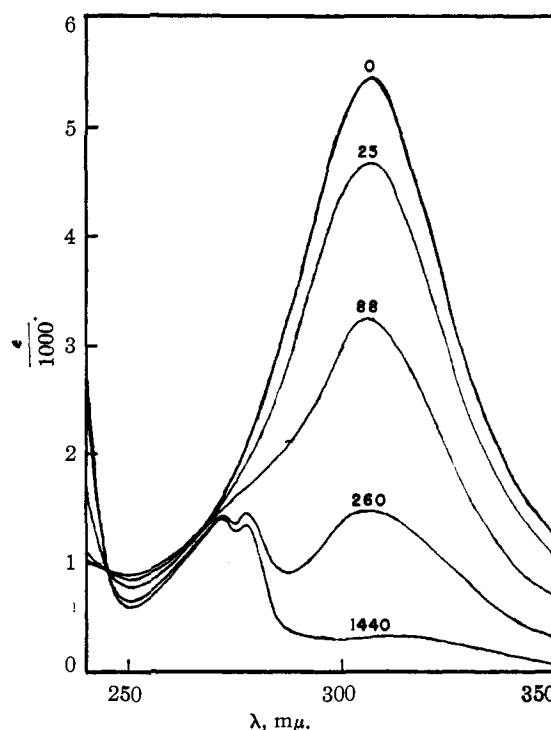


Fig. 2.—Change in absorption spectrum with time of 2,6-dimethylacetophenone ( $1.128 \times 10^{-4}$  molar) in 85.0% sulfuric acid. Number above each curve is the time in minutes.

### Kinetic Results and Calculations

#### Change in $k$ with Sulfuric Acid Concentration.

The observed rate constant for the reaction of acetomesitylene and 2,6-dimethylacetophenone with strong sulfuric acid was a first order constant in any particular concentration of sulfuric acid, but increased very rapidly with increasing sulfuric acid concentration. The yield of acetic acid obtained from acetomesitylene was quantitative in the range of sulfuric acid concentrations used, 80.4 to 87.1%. The yield of acetic acid obtained from 2,6-dimethylacetophenone was quantitative in 72.5 to 85.0% sulfuric acid, but diminished in higher concentrations. It was shown that the side reaction responsible for the lower yield of acetic acid was at least in major part sulfonation of the aromatic ketone to yield 2,4-dimethyl-3-acetylbenzene-1-sulfonic acid. This sulfonic acid was the only product isolated (as the sodium and lead salts) from a large scale reaction of 2,6-dimethylacetophenone with 100% sulfuric acid.

Despite the reduction in yield of acetic acid from 2,6-dimethylacetophenone in greater than 85% sulfuric acid, the rate of acetic acid formation was still in very good agreement with a first order process. This can be explained if the reasonable assumption is made that the competing sulfonation is a first order reaction in excess sulfuric acid. From the well known property of parallel reactions of the same order

$$k_{\text{observed}} = k + k_s \quad (2)$$

where  $k$  and  $k_s$  are the rate constants for deacylation and sulfonation, respectively. Since

$$\frac{k}{k_s} = \frac{\% \text{ yield of HOAc}}{100 - \% \text{ yield HOAc}} \quad (3)$$

the value of  $k$  can be obtained by simultaneous solution of (2) and (3).

In Table III are summarized the values of  $k_{\text{observed}}$ ,  $k$  and  $k_s$  obtained for 2,6-dimethylacetophenone in various concentrations of sulfuric acid. Rate constants for the deacylation of acetomesitylene, in which  $k_{\text{observed}} = k$  in all concentrations of sulfuric acid studied, are given in Table IV.

TABLE III

THE REACTION OF 2,6-DIMETHYLACETOPHENONE WITH SULFURIC ACID AT 40.0°

Acid, %	$k_{\text{obs.}} \times 10^6$ sec. <sup>-1</sup>	(Deacylation) $k \times 10^3$ sec. <sup>-1</sup>	(Sulfonation) $k_s \times 10^3$ sec. <sup>-1</sup>
72.5	0.348 <sup>a</sup>	0.348	..
75.0	0.926 <sup>a</sup>	0.926	..
77.5	2.35 <sup>a</sup>	2.35	..
80.0	5.25 <sup>a</sup>	5.25	..
82.5	11.32 <sup>a</sup>	11.32	..
85.0	21.8 <sup>a</sup>	21.8	..
87.5	38.7 <sup>a</sup>	36.8	1.9
90.0	56.0 <sup>a</sup>	51.0	5.0
93.0	73.0 <sup>a</sup>	62.0	11.0
96.0	95.0 <sup>a</sup>	68.0	26.1

<sup>a</sup>, <sup>b</sup>, <sup>c</sup> refer to precision of rate constant as defined in the experimental section.

TABLE IV

THE REACTION OF ACETOMESITYLENE WITH SULFURIC ACID AT 30.0°

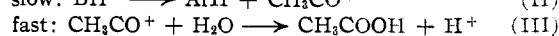
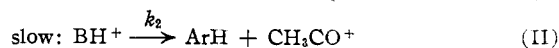
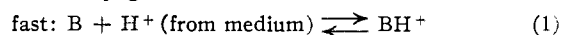
H <sub>2</sub> SO <sub>4</sub> , %	$k \times 10^3$ sec. <sup>-1</sup>
80.4	2.78 <sup>a</sup>
83.5	5.16 <sup>c</sup>
84.8	6.78 <sup>b</sup>
87.1	8.02 <sup>c</sup>
80.4	6.33 <sup>c</sup>

<sup>a</sup>, <sup>b</sup>, <sup>c</sup> refer to precision of rate constant as defined in the experimental section. <sup>z</sup> Measured at 40.0°.

**The Deacylation of Acetomesitylene in Methanesulfonic Acid.**—The rate constant for the deacylation of acetomesitylene at 20.0° was found to be  $5.46 \times 10^{-5}$  sec.<sup>-1</sup> in 90.4% methanesulfonic acid and  $46.0 \times 10^{-5}$  sec.<sup>-1</sup> in 99.0% methanesulfonic acid. Both constants are of precision *a* as defined in the experimental section. An upper layer, presumably mesitylene, was formed in both solutions. The rapid rise in rate in the non-sulfonating medium, methanesulfonic acid, supports the view that the rapid rise in rate in sulfuric acid is not due to direct replacement of COCH<sub>3</sub> by SO<sub>2</sub>OH.

### Discussion

The value of the first order constant for deacylation,  $k$ , rises very rapidly with increasing sulfuric acid concentration as can be seen in Tables II and III. For example, the deacylation rate at 40° for 2,6-dimethylacetophenone increases nearly two hundred-fold from 72.5 to 96.0% sulfuric acid. The change in  $k$  with sulfuric acid concentration is interpreted by means of the following mechanism, in which a fast acid-base equilibrium step is followed by the rate determining first order decomposition of the conjugate acid of the ketone, BH<sup>+</sup>.



According to Hammett and Deyrup,<sup>13</sup> if the rate-controlling step of an acid-catalyzed reaction is a first order decomposition of a conjugate acid of type BH<sup>+</sup> then the equation

$$H_0 + \log k = \text{constant} \quad (4)$$

should hold, if "the ratio of the concentration of this ion to the total concentration of substrate is small." In the deacylation reaction this condition is fulfilled only in the lower percentages of sulfuric acid, and thus equation (4) does not hold throughout the entire range of acid concentration studied. However, the rate constant can be expressed in terms of  $H_0$  if the appreciable ionization to BH<sup>+</sup> is taken into account.

A derivation similar to that of Hammett<sup>14</sup> is used. The Brönsted rate equation for the rate-controlling step is

$$v = k_2[BH^+] \frac{f_{BH^+}}{f_{tr^+}} \quad (5)$$

where  $f$  is the activity coefficient and  $tr^+$  refers to the transition complex. From the equilibrium of equation I

$$a_{BH^+} = K_a a_B a_{H^+} \quad (6)$$

hence

$$v = k_2 K_a [B] a_{H^+} \frac{f_B}{f_{tr^+}} \quad (7)$$

also

$$v = k[B]_{\text{stoichiometric}} = k([B] + [BH^+]) \quad (8)$$

Equation (8) holds true in the absence of the side reaction of sulfonation because the rate of appearance of acetic acid is equal to the rate of disappearance of stoichiometric B. Equation (8) also holds true in the presence of the sulfonation reaction because the rate of deacylation is still a function of the rate of disappearance of stoichiometric B, since

$$v_{\text{observed}} = k[B]_{\text{stolch.}} + k_s[B]_{\text{stolch.}} = v + v_s \quad (9)$$

where  $v$  is the velocity of deacylation and  $v_s$  the velocity of sulfonation. From (7) and (8) it follows that

$$k \doteq \frac{v}{[B] + [BH^+]} = k_2 K_a \frac{[B]}{[B] + [BH^+]} a_{H^+} \frac{f_B}{f_{tr^+}} \quad (10)$$

If, as assumed by Hammett<sup>11</sup>

$$f_B f_{CH^+} / f_{tr^+} f_C = \text{constant} \quad (11)$$

and remembering

$$H_0 = -\log a_{H^+} \frac{f_C}{f_{CH^+}} \quad (12)$$

where C is an indicator base of neutral charge type, then

$$\log k + H_0 - \log \left( \frac{[B]}{[B] + [BH^+]} \right) = \text{constant} \quad (13)$$

In order that the validity of expression (13) could be tested it was necessary that values of  $\log ([B]/([B] + [BH^+]))$  be known. These values were calculated for 2,6-dimethylacetophenone from the experimentally determined  $pK_a$  with the aid of the equation<sup>14</sup>

$$\log \frac{[B]}{[BH^+]} = H_0 - pK_a \quad (14)$$

(13) L. P. Hammett and A. L. Deyrup, *THIS JOURNAL*, **54**, 2738 (1932).

(14) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX.

The value found for the  $pK_a$ ,  $-7.8$ , is undoubtedly not as reliable as values obtained by Hammett<sup>12</sup> for similar bases. Spectral data had to be extrapolated to zero time because of the change in the absorption spectrum with time due to reaction of the ketone. The  $pK_a$  calculations were based of necessity on extrapolated absorption curves in only two concentrations of sulfuric acid in addition to the reference concentration.

In Table V are shown the results of testing the validity of equation (13) and hence the mechanism proposed. The assumption was made that the  $pK_a$  of 2,6-dimethylacetophenone is essentially the same at  $40^\circ$ , the temperature of the kinetic measurements, as at  $25^\circ$ , the temperature at which  $pK_a$  was determined.

TABLE V  
TEST OF EQUATION (13) AND REACTION II FOR  
2,6-DIMETHYLACETOPHENONE

$H_2SO_4$ , %	$H_0$	$\log k$	Sum:	
			$\frac{\log \frac{[B]}{[B] + [BH^+]}}{[B] + [BH^+]}$	$\frac{\log k + H_0}{[B] + [BH^+]}$
72.5	-5.85	-5.46	0.004	-11.31
75.0	-6.16	-5.03	.01	-11.18
77.5	-6.48	-4.63	.02	-11.09
80.0	-6.82	-4.28	.04	-11.06
82.5	-7.19	-3.95	.09	-11.05
85.0	-7.62	-3.64	.22	-11.04
87.5	-7.92	-3.43	.37	-10.98
90.0	-8.17	-3.29	.52	-10.94
93.0	-8.50	-3.21	.78	-10.93
96.0	-8.86	-3.16	1.10	-10.92

The constancy of these sums over such a wide range of sulfuric acid strength is impressive and compares favorably with results of other rate studies, generally over more narrow ranges of acid strength, in which a relationship between  $\log k$  and  $H_0$  was observed.<sup>13,14</sup>

In order to determine if equation (13) holds for the deacylation of acetomesitylene it was necessary to assume a value for  $pK_a$ . The  $pK_a$  of acetomesitylene could not reliably be measured at room temperature because of the speed of its reaction with sulfuric acid. An estimate that  $pK_a = -7.6$  was made on the following basis. Firstly, the markedly lower basicity of 2,6-dimethylacetophenone as compared to acetophenone ( $pK_a = -6.03$ )<sup>12</sup> is apparently due to decreased stability of the conjugate acid (relative to the free base) brought about by the ortho methyl substituents, which sterically dampen resonance distribution of the positive charge to the ring and the methyl substituents. Consequently, the added para methyl substituent of acetomesitylene cannot exert its full hyperconjugative effect in helping distribute the positive

TABLE VI  
TEST OF EQUATION (13) AND REACTION II FOR ACETO-  
MESITYLENE

$H_2SO_4$ , %	$\log k$	$H_0$	Sum:	
			$\frac{-\log \frac{[B]}{[B] + [BH^+]}}{[B] + [BH^+]}$	$\frac{\log k + H_0}{[B] + [BH^+]}$
80.4	-2.56	-6.88	0.08	-9.36
83.5	-2.29	-7.39	.21	-9.47
84.8	-2.17	-7.58	.29	-9.46
87.1	-2.10	-7.88	.46	-9.52

charge of the conjugate acid. Thus, the  $pK_a$  of acetomesitylene should differ less from that of 2,6-dimethylacetophenone than does the  $pK_a$  of *p*-methylacetophenone ( $pK_a = -5.35$ ) differ from that of acetophenone. Hence the estimate was made that acetomesitylene has a  $pK_a$  of about 0.2 unit more than has 2,6-dimethylacetophenone. On the basis of this estimate, equation (13) was found to hold quite well.

Equation (13) could not be tested against the rate measurements made in two concentrations of methanesulfonic acid since  $H_0$  is known for 100% methanesulfonic acid only ( $H_0 =$  about  $-6.0$ ).<sup>15</sup> However, the deacylation reaction could be used as a measure of  $H_0$  of various concentrations of this acid.

A marked activating effect by para methyl is shown by a comparison of the two ketones studied. The rate constant,  $k$ , for the deacylation of acetomesitylene at  $40.0^\circ$  in 80.4% sulfuric acid ( $633 \times 10^{-5} \text{ sec.}^{-1}$ ) is 102 times that of 2,6-dimethylacetophenone under the same conditions. The deacylation rate constant for 2,6-dimethylacetophenone was not measured in 80.4% sulfuric acid but was estimated from a plot of  $k$  against per cent. sulfuric acid to be  $6.2 \times 10^{-5} \text{ sec.}^{-1}$ . Since the basicity of the ketones is a factor in the value of  $k$ , more valid for comparative purposes are probably values of  $k_2$ , the rate constant for the rate controlling step. If the constant of equation (13) is  $\log k_2 K_a$ , then  $k_2$  can be evaluated. This involves the assumption that the constant of equation (11) is unity, and also the intrinsic assumption made in deriving (13), that  $k_2$  does not change with changing medium. Thus

$$\log k_2 = \log k + H_0 - \log \left( \frac{[B]}{[B] + [BH^+]} \right) + pK_a \quad (15)$$

The same values of  $k_2$  can be calculated from the expression

$$k_2 = k \frac{[B] + [BH^+]}{[BH^+]} \quad (16)$$

which is obtained by combining equations (5) and (8), and assuming  $f_{BH^+}/f_{tr^+} = 1$ . This means assuming that the conjugate acid in an activated form has the same activity coefficient as the conjugate acid itself. The variations in  $\log k_2$  calculated with the aid of equation (15) or (16) are, of course, the same as the variation in the sum of equation (13). An average value of  $k_2$  of  $6.03 \times 10^{-4} \text{ sec.}^{-1}$  at  $40^\circ$  was calculated for 2,6-dimethylacetophenone, the value in 72.5% sulfuric acid being discarded because of its abnormal deviation. The value of  $k_2$  at  $40^\circ$  for acetomesitylene was calculated, from the one value of  $k$  measured, to be  $398 \times 10^{-4} \text{ sec.}^{-1}$ . The rate-controlling step is thus 66 times as rapid for acetomesitylene as for 2,6-dimethylacetophenone. This activating effect of methyl is greater than shown in nitration, in which toluene is substituted 24 times as fast as benzene,<sup>16</sup> but less than that shown in chlorination, in which toluene is substituted about 350 times as fast as benzene.<sup>17</sup> The deacylation reaction differs from these, of

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course, in that electrophilic displacement occurs at but a single site.

Experiments are underway which definitely indicate a steric factor also operative in the reaction.

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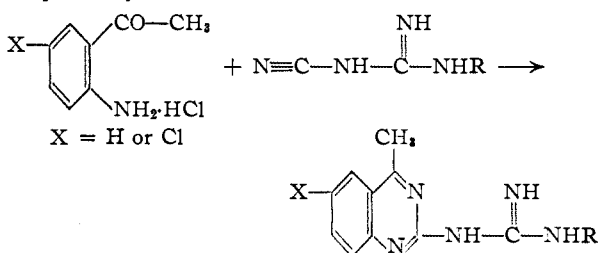
## 2-Guanidinoquinazolines

By L. F. THEILING AND R. L. MCKEE

A series of 2-guanidinoquinazolines has been prepared for pharmacological evaluation. The compounds were formed by condensation of *o*-aminoacetophenones with appropriate cyanoguanidines.

A study of the preparation of numerous heterocyclic compounds carrying guanidine substituents has been initiated in this Laboratory. The 2-guanidinoquinazolines are felt to be of special interest since, when appropriately substituted, they embody the skeleton present in Paludrine.

Initial attempts at preparation from 2-aminoquinazolines were abandoned when these compounds were found to resist the action of cyanogen bromide, cyanamides, substituted cyanamides and alkyl isothiocyanates. A convenient synthesis was finally developed by interaction of *o*-aminoacetophenone hydrochloride and dicyandiamide or its alkyl or aryl derivatives



The nitration of acetophenone<sup>1</sup> produced about 85% of the theoretical of mixed nitroacetophenones which consisted of approximately 65% of the meta-isomer and 35% of the ortho. After separation, *o*-nitroacetophenone was hydrogenated to form *o*-aminoacetophenone.<sup>1</sup> The *m*-nitroacetophenone was converted in 72% yield by an adaptation of the procedure of reference 2 into *m*-chloroacetophenone which was nitrated<sup>3</sup> in 39% yield to give 2-nitro-5-chloroacetophenone. This was in turn reduced over platinum oxide (96% yield) or with iron and acetic acid (87% yield) to 2-amino-5-chloroacetophenone.<sup>3</sup>

1-Alkyl-3-cyanoguanidines, 1,1-dialkyl-3-cyanoguanidines, and 1-aryl-3-cyanoguanidines were prepared from sodium dicyandiamide and amine hydrochlorides.<sup>4</sup>

Interaction of the aminoacetophenone hydrochlorides with the cyanoguanidines was brought about by refluxing in rather concentrated aqueous

solution or by fusion in the absence of a solvent. Although the products from the former procedure were more easily purified, the yields from the latter procedure occasionally were higher. During the vigorous reaction accompanying the fusion method, hydrogen chloride and the amino ketone were evolved from the reaction mixture. After this was observed, it was found possible to minimize this loss by inclusion of pyridine hydrochloride in the fusion mixture with a significant increase in yield.

The 2-guanidinoquinazolines form monohydrochlorides of varying solubility in cold water, while their nitrates are quite sparingly soluble in cold water, especially in the presence of a slight excess of nitrate ion. They are quite stable to boiling aqueous mineral acids and are only slowly degraded to 2-aminoquinazolines by alkali. In contrast to the behavior of 2-guanidinobenzimidazole<sup>5</sup> the guanidinoquinazolines were found to be inert to nitrous acid both in the cold and at 55°. Finally, an attempt to alkylate 2-guanidino-4-methylquinazoline with butyl iodide in propanol-2 resulted in recovery of starting materials.

### Experimental

**2-Amino-4-methylquinazoline** was prepared by warming a mixture of *o*-aminoacetophenone hydrochloride (5.0 g.) and cyanamide (1.5 g.). At 50°, a vigorous reaction occurred as indicated by evolution of vapor and a rapid rise in temperature. After cooling, the reaction mixture was dissolved in 50 cc. of hot water containing 5 drops of hydrochloric acid, treated with Norite, and made alkaline with ammonia. The resulting oil was separated by decantation and crystallized from hot water. Further recrystallization from water or from benzene-petroleum ether mixtures did not alter the initial melting point, 159–159.8°, of the pale-yellow needles obtained in 65% yield.

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>: C, 67.9; H, 5.7; N, 26.4. Found: C, 67.7; H, 5.8; N, 26.3.

The monohydrochloride was prepared in benzene solution with dry hydrogen chloride and, after crystallization from 95% alcohol, appeared as pale yellow needles melting at 239–240° (dec.). Calcd. for monohydrochloride, neut. equiv., 196. Found: neut. equiv. (by titration), 204.

**2-(6-Methoxy-1,2,3,4-tetrahydroquinolyl-1)-4-methylquinazoline** was similarly prepared in 19% yield from 2 g. of 1-cyano-6-methoxy-1,2,3,4-tetrahydroquinoline<sup>6</sup> and 1.8 g. of *o*-aminoacetophenone hydrochloride at 200° in diphenyl ether. The acid-soluble material was recrystallized from benzene-petroleum ether to afford a yellow, crystalline material melting at 86.5–88°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O: N, 13.8; CH<sub>3</sub>O, 10.2. Found: N, 13.8; CH<sub>3</sub>O, 10.4.

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