[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Mechanism of the Sulfonation Process

BY ARTHUR MICHAEL AND NATHAN WEINER

The action of sulfuric acid, the anhydride and fuming sulfuric acid on olefinic and aromatic hydrocarbons has been the subject of many researches, dating back almost to the beginning of modern organic chemistry. In all that time no rational theory for the mechanism of these reactions has been proposed and even today many of the experimental facts are wrongly or imperfectly interpreted. Regnault,[1] in 1838, studied the instantaneous and vigorous reaction between ethylene and sulfuric anhydride and Berthelot,[2] in 1854, showed that concentrated sulfuric acid absorbed ethylene comparatively slowly, with the formation of ethylsulfuric acid. It has long been known that fuming sulfuric acid absorbs ethylene rapidly, but the reaction products have not been experimentally established, although it is assumed that ethionic acid or carbyl sulfate is formed. On the other hand, the reaction between alkenes and sulfuric acid of various concentrations, up to 100%, has been investigated frequently,[3] usually for the purpose of determining the optimum conditions for the synthesis of the corresponding acid sulfuric esters. It has always been found that the presence of the anhydride in the sulfuric acid reduces the yield of alcohol obtained by hydrolysis of the addition product, although at first it makes the absorption more rapid, which is ascribed to the formation of ethionic acid or carbyl sulfate.

As a result of his researches on the action of nitric acid on alkenes, Wieland[4] concluded that the nitration process with alkenes takes place by the acid adding basically as HO– and $-NO_2$. Without any experimental support, Wieland[4] assumed that fuming sulfuric acid acts upon ethylene similarly to nitric acid; in the first step, functioning as a basic addendum, HO– and SO_3H, and thus directly forming isethionic acid. This compound is esterified to ethionic acid, which then loses water, to form the corresponding anhydride, carbyl sulfate.

The generally accepted speculations are opposed to long-established, experimental facts on the behavior of sulfuric acid, its anhydride and oleum with ethylene. In Wieland's mechanism, the anhydride functions in no apparent way to determine the course of the reaction, although it is well known that it reacts instantaneously and vigorously with ethylene, while even 100% sulfuric acid acts relatively slowly. The formation of ethionic acid is written as taking place by the interaction of ethylene and sulfuric acid, notwithstanding that the reaction actually results in the formation of the acid sulfuric ethyl ester.[3] No investigator had observed the formation of carbyl sulfate in the reaction of ethylene with oleum, even of considerable anhydride content. Plant and Sidgwick[3] studied the rate of absorption of ethylene in sulfuric acid of various concentrations, up to 100%, at different temperatures, and the absorption of the gas in 14% oleum at 70°. In contrast to the markedly autocatalytic character of the absorption, as shown by the absorption curves with the other concentrations of acid, they found that the absorption in the oleum was extremely rapid in the early stages. This was ascribed, without futher investigation, to the combination of supposedly free sulfuric anhydride with ethylene to form carbyl sulfate. However, from their data on the rate of absorption, it is obvious that the anhydride, contained as pyrosulfuric acid, plays the dominant role in the rapid reaction of the oleum with ethylene, which is opposed to Wieland's assumption. Further, there is no experimental support to his extraordinary assumption that sulfuric acid, as an addendum, can function as a base, *i. e.*, add as HO– and $-SO_3H$. The individual steps in Wieland's proposed carbyl sulfate mechanism have not been experimentally established, and, finally, the theoretical support from his nitration scheme is futile, since it has been shown recently[5] that Wieland's experimental results on nitration are irrelevant and his theoretical speculations fallacious.

The theoretical considerations which induced Michael and Carlson[5] to reëxamine the action of nitric acid on alkenes, led us to reinvestigate the

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[1] Regnault, *Ann.*, **25**, 32 (1838).

[2] Berthelot, *Ann. chim.*, [3] **43**, 385 (1854).

[3] See Plant and Sidgwick, *J. Soc. Chem. Ind.*, **40**, 14T (1921); Brooks and Humphrey, THIS JOURNAL, **40**, 822 (1918).

[4] Wieland and Sakellarios, *Ber.*, **53**, 203 (1920). The primitive, give-and-take, interpretation of nitration and sulfonation, which is still advanced in many textbooks, is so obviously impossible, that a refutation should be unnecessary.

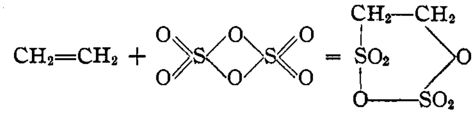
[5] Michael and Carlson, THIS JOURNAL, **57**, 1268 (1935).

course of the reaction between ethylene and fuming sulfuric acid. A semi-quantitative examination of the relationship between the ethylene absorbed, the amount of sulfuric anhydride present and the quantity of ethionic acid formed, showed that, when the concentration of anhydride was not in excess of that necessary to form pyrosulfuric acid, one mole of ethionic acid was formed for each mole of pyrosulfuric acid present. When the amount of anhydride was in excess, carbyl sulfate crystallized from the reaction mixture. It was also found that the amount of ethionic acid formed in these reactions corresponded to the quantity of pyrosulfuric acid plus one-half the quantity of the excess of anhydride as SO_3. These relationships held even when 50% excess of ethylene was absorbed. On the basis of Wieland's mechanism, there is no reason why all the ethylene absorbed should not have been converted into ethionic acid.

The above experimental results demonstrate clearly why fuming sulfuric acid differs from ordinary acid in its action on ethylene. Since the reaction between ethylene and pyrosulfuric acid leads to ethionic acid, it is obvious that the first acid does not add to ethylene as other strong acids do, *i. e.*, as the electrolytic components, H– and $-S_2O_6OH$. The pyrosulfuric acid adds, like other inorganic acid anhydrides, to ethylene, with fission between the anhydride oxygen and sulfur, thus directly forming ethionic acid:[6]

$$CH_2{=}CH_2 + HOSO_2OSO_2OH \longrightarrow HO_3SCH_2CH_2OSO_3H$$

When the anhydride is in excess, this acts to form carbyl sulfate, in the ratio of one mole to two of sulfur trioxide or to one of S_2O_6. The action of the SO_3 on ethylene should lead primarily to vinylsulfonic acid,[7] and, on further action, this should yield vinyl disulfonic acid, but not carbyl sulfate. In the discussion of this reaction, it has been overlooked that sulfur trioxide exists in the reagent in balanced equilibrium with S_2O_6. To favor the functioning of the anhydride as SO_3, we brought the compounds together in a gaseous condition, maintaining ethylene in excess. Although the gaseous anhydride consisted mainly of SO_3, the product was likewise carbyl sulfate. Since carbyl sulfate cannot be formed by the action of sulfur trioxide on ethylene, it must be the product of a reaction involving S_2O_6, the other component of the balanced chemical system



That, notwithstanding the greater free chemical energy content of SO_3, the reaction proceeds through S_2O_6, must be because the reaction product, carbyl sulfate, is intramolecularly better neutralized than the possible alternative product, vinyl disulfonic acid. Since the loss of energy in the polymerization of SO_3 to S_2O_6 is slight, the formation of carbyl sulfate probably represents the maximum possible degradation of chemical energy.

We have also examined the reaction of isethionic acid with (1) one mole of 100% sulfuric acid, (2) one mole of 100% sulfuric acid followed by one mole of anhydride, considered as SO_3, (3) one mole of anhydride alone, and, finally, (4) two moles of anhydride. In the first three reactions, the product was ethionic acid and only in the last relationship was carbyl sulfate formed. Wieland[4] was, therefore, correct when he assumed that isethionic acid can be converted to ethionic acid by fuming sulfuric acid, but he failed to take into consideration that, even if pyrosulfuric acid were used, isethionic acid would be formed first and that water would appear in the following step to ethionic acid, which would hydrate an equivalent quantity of pyrosulfuric to sulfuric acid. Apparently, Wieland assigned a catalytic influence to the anhydride present in the fuming acid, but enough water would be liberated to hydrate completely all the available anhydride, unless pyrosulfuric acid with a considerable excess of free anhydride were used. With even strong oleum, only sulfuric acid would be present finally to act upon the ethylene. Evidently, Wieland's mechanism is based on an erroneous understanding of the experimental facts. Recalculation of the data of Plant and Sidgwick,[3] in the above-mentioned experiment with 14% oleum, shows that the absorbing acid should have increased in weight by 4.9% during the rapid absorption, if that reaction were due to the addition of pyrosulfuric acid; whereas, the formation of carbyl sulfate, assumed by them, should have required an increase of only 2.45%. Their first measurement, made after two hours, showed an increase of 7.47%. After this

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(6) An alternate mechanism, based on the formation of ethyl sulfate, and it then reacting with the anhydride, is improbable since it assumes that the acid could react before the anhydride. Also improbable, and far more complicated, is the assumption of the primary formation of ethylene sulfonic-sulfuric anhydride ester, which decomposes into two moles of ethionic acid.

(7) Kohler, *Am. Chem. J.*, **19**, 738 (1897).

initially rapid absorption, the rate fell off to one approximately one-third as great and one comparable to that found for 100% acid, which, at 70°, absorbed 3.83% of its weight of ethylene after two and one-half hours. Assuming a proportional increase for the first two hours, the absorption due to the 100% acid in the oleum must be 3.1% and the absorption due to the fuming acid must therefore be 4.3%, which is in agreement with our views. These results point unambiguously to the scheme of addition here formulated.

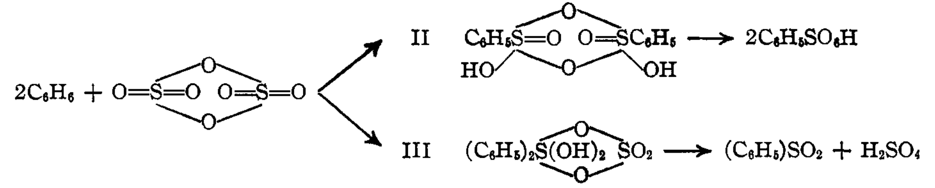
It is now obvious that sulfuric acid cannot function as a base, *i. e.*, with HO- and SO_3H as addendum components and, therefore, that Wieland's mechanism of aromatic sulfonation is untenable. Mitscherlich[8] found that fuming sulfuric acid acted upon benzene in the cold with formation of benzenesulfonic acid and a small amount of diphenyl sulfone. The same products were obtained, with a slightly better yield of the sulfone, by using sulfuric anhydride. Michael and Adair[9] showed that no diphenyl sulfone was formed in the action of sulfuric acid upon benzene and that benzene and benzenesulfonic acid do not interact, except with use of a drastic dehydrating agent, thus proving that the appearance of the sulfone in Mitscherlich's experiment could not result from sulfuric acid without anhydride. In an attempt to show experimentally that the sulfonation of benzene can be brought about through a pseudo-substitution reaction, we treated benzene with dimethyl sulfate in the presence of aluminum chloride, similarly as nitrobenzene was obtained from ethyl nitrate.[10] Regardless of the order of mixing the reagents, methylated benzenes were formed. However, it was found that aluminum chloride and the sulfuric ester interacted vigorously, with gas evolution. This must have been methyl chloride, which was undoubtedly the alkylating reagent.

Wieland's mechanism of the sulfonation process with alkenes and sulfuric acid was shown above to be untenable, and, evidently, it is inapplicable to the sulfonation of alkanes with sulfuric anhydride and, also, to the formation of aromatic sulfonic acids with that reagent. All discrepancies disappear if alkane and aromatic sulfonation, by sulfuric acid, or anhydride, is considered a pseudo-substitution, or an aldolization reaction, respectively, involving, with the acid, primarily an aldolization between a nuclear hydrogen of a hydrocarbon and a sulfonyl group. From this point of view, the sulfonation of benzene by sulfuric acid goes through the following stages

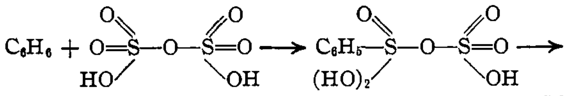
$$C_6H_6 + H_2SO_4 \longrightarrow C_6H_5SO(OH)_3 \longrightarrow C_6H_5SO_3H + H_2O$$

Since the reaction takes place slowly, and only on heating, this implies that the chemical potential between the addendum atoms and sulfur and oxygen is insufficient to induce the primary addition phase at room temperature; it could not be expected, therefore, that the better neutralized and less energetic sulfonyl group of benzene sulfonic acid could react with benzene, except under far more drastic conditions. On the other hand, the Δ-atoms of that group in $SO_3 \rightleftharpoons S_2O_6$ are more energetic, and show stronger affinity relations for the addendum components, than in sulfuric acid. Sulfonation with the anhydride can proceed simultaneously through SO_3 (I) and S_2O_6 (II), while the formation of diphenyl sulfone must take place through S_2O_6 (III)

I $C_6H_6 + .O_2S{=}O = C_6H_5SO_3OH$



Similarly, the sulfonation of benzene by pyrosulfuric acid must proceed as follows



$$C_6H_6 + O{=}\overset{O}{\underset{HO}{S}}{-}O{-}\overset{O}{\underset{OH}{S}}{=}O \longrightarrow C_6H_5{-}\overset{O}{\underset{(HO)_2}{S}}{-}O{-}\overset{O}{\underset{OH}{S}}{=}O \longrightarrow C_6H_5SO_2OH + H_2SO_4$$

The smaller yield of the sulfone in the reaction between benzene and oleum and that with sulfuric anhydride is thus accounted for; the concentration of S_2O_6 in oleum is smaller than in the anhydride and the chemical potential of the SO_2 groups in the pyrosulfuric acid present in oleum decidedly less.

Experimental

General Procedure.—The apparatus for absorbing ethylene in fuming sulfuric acid was constructed much

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[8] Mitscherlich, *Ann.*, **12**, 305 (1834).

[9] Michael and Adair, *Ber.*, **10**, 585 (1877).

[10] For literature, see Michael and Carlson,[5] p. 1273, footnote 23.

after the same design as that used by Plant and Sidgwick[3] in their investigation. The apparatus was about 20 cm. long with an internal diameter of 12 mm., and indented at the bottom over about 2.5 cm. of its length to increase the length of liquid column through which the ethylene would have to pass. The inlet tube was sealed into a ground joint, the matching member of which was the top of the absorption tube. The inlet and exit tubes were supplied by stopcocks, lubricated by sirupy phosphoric acid. The end of the inlet tube dipped into the acid and was drawn out to a small opening. The absorption tube was constricted at its middle, to break up froth carried up by the gas. The exit tube was connected to a glass-stoppered U-tube, containing glass pearls and sufficient 100% sulfuric acid to seal the bend. This acted as a trap for any sulfuric anhydride that might be vaporized by the passage of gas.

Between 1-2 cc. of 100% sulfuric acid was placed in the previously weighed absorber by means of a small pipet, and the weight of the acid determined. Then sulfuric anhydride was distilled into the acid, by heating 65% fuming sulfuric acid in an all glass distilling apparatus with a delivery tube, equipped with a ground joint, that fitted the top of the absorption tube. The weight of the sulfuric anhydride added was determined.

Ethylene was bubbled through the absorber, by displacement with water from a 20-liter bottle, at a rate of approximately one liter per hour. The gas was dried by passage through two towers of potassium hydroxide and three U-tubes filled with Dehydrite. The initial run was started at room temperature, but after approximately 75% of one mole of gas had been absorbed, the rate of absorption became extremely slow. To speed it up, the absorber was immersed in a water-bath, kept between 70-80°, until the end of the run. Runs 1-7 were made in this manner. However, it was observed that heating caused the mixture to darken. Therefore, runs 8-12 were made over a period of twenty-one to twenty-four hours at room temperature. Under these conditions our analytical method indicated that apparently more ethionic acid was formed than could be accounted for theoretically. Investigation of the products formed under identical conditions in a large scale run, and checked by analytical procedure, showed the high results of runs 8-12 were due to insufficient hydrolysis of the reaction products.

When sufficient ethylene was absorbed, as determined by the increase in the weight of the absorber, the total contents of the absorber and U-tube were washed quantitatively into a flask, diluted to about 250 cc., and refluxed for one hour. This was done in order to hydrolyze any organic sulfates, such as diethyl sulfate and ethyl sulfuric acid, to sulfuric acid and the ethionic acid to isethionic acid, leaving it as the only acid which does not form an insoluble barium salt. When the solution was cool, it was diluted to one liter, and the total acidity determined by titration with 0.1 N potassium hydroxide; 25-cc. portions of the solution were analyzed gravimetrically for sulfate. The difference between the total acidity and that due to sulfuric acid was used to calculate the amount of isethionic acid. In runs 13-15, the entire absorption was carried out at room temperature and the mixture heated in the absorber at 80° for three to four hours, without passage of gas. These runs are in complete agreement with theory. The results are tabulated.

Expt.	H_2SO_4, g.	SO_3, g.	Ratio $\frac{\text{Moles } SO_3}{\text{Moles } H_2SO_4}$	G. C_2H_4 Absorbed	Ratio $\frac{\text{Moles } C_2H_4 \text{ abs.}}{\text{Moles } H_2S_2O_7}$	Normality of soln. in isethionic acid	Ratio $\frac{\text{Moles isethionic acid found}}{\text{Moles } H_2S_2O_7}$
1[a]	1.801	2.628	1.787			0.0251	1.367[b]
2	1.864	1.424	0.936	0.408	0.819	.0143	0.960[c]
3	2.847	2.285	.983	.840	1.050	.0291	1.020
4	2.717	1.377	.621	.502	1.040	.0167	0.971
5	4.924	3.597	.895	1.165	0.926	.0401	.968[c]
6	3.031	1.740	.703	0.794	1.304	.0219	1.009
7	2.980	1.329	.546	.723	1.555	.0169	1.019
13[d]	2.648	1.557	.720	1.023	1.877	.0198	1.016
14	2.424	1.466	.741	1.121	2.185	.0182	0.995
15	2.292	1.647	.880	0.940	1.631	.0205	.996

[a] The calculations are based on the anhydride as SO_3. Expts. 1-7, absorption up to 75% carried out at room temperature and then at 80°. [b] SO_3 in excess of that necessary to form $H_2S_2O_7$. Carbyl sulfate crystallized out. Calculated: isethionic acid formed on hydrolysis equivalent to $H_2S_2O_7$, (0.0184 mol) + one-half excess SO_3, (0.0072 mol) = 0.0256 mol. Found 0.0251. [c] Insufficient ethylene absorbed. Ratio, C_2H_4 absorbed: Isethionic acid found. [d] Absorption carried out at room temperature, and product heated in absorber for three to four hours at 80°, after completion of absorption. Expts. 8-12 were insufficiently hydrolyzed, as mentioned in the experimental part.

Experiments with Isethionic Acid

Action of Equal Moles of 100% Sulfuric Acid.—Five grams of isethionic acid, previously dried in a vacuum desiccator over phosphoric anhydride, was placed in a small glass-stoppered flask, and 4.5 g. of sulfuric acid was added. The mixture warmed up considerably. The reaction mixture stood overnight in a desiccator. It was poured into about 300 cc. of ice water, the cold solution was then neutralized with barium carbonate, and the solid filtered off. The solution was evaporated to about 40 cc. on a water-bath, and the small amount of precipitate was removed. The solution was diluted with alcohol to about 70 cc. and allowed to stand. The white salt of ethionic acid that crystallized out was filtered and recrystallized from 50% alcohol.

Anal. Calcd. for $C_2H_4S_2O_7Ba \cdot {}^1/_2H_2O$: Ba, 39.2. Found: Ba, 39.1.

Action of One Mole of Sulfuric Anhydride.—Five grams of isethionic acid was placed in a glass-stoppered flask, and 3.1 g. of anhydride was distilled into the ice-cooled flask. The mixture was allowed to stand overnight in a desiccator. No solid formed on standing nor upon cooling. The product was poured into ice water and worked up as above. The salt was dried over phosphoric anhydride in a vacuum desiccator, and analyzed for barium.

Anal. Calcd. for $C_2H_4S_2O_7Ba$: Ba, 40.24. Found: Ba, 39.96.

Action of One Mole of 100% Sulfuric Acid and One Mole of Sulfuric Anhydride.—Six grams of isethionic acid was mixed with 5.4 g. of 100% sulfuric acid, and 4.4 g. of anhydride was distilled into the cooled mixture, which was placed overnight in a desiccator. No solid formed nor did any appear upon cooling. The product was worked up as described above and the barium salt was found to contain 39.6% barium. Calcd. for $C_2H_4S_2O_7$-$Ba \cdot {}^1/_2H_2O$: Ba, 39.2.

Action of Two Moles of Anhydride on Isethionic Acid.—Eight and eight-tenths grams of sulfuric anhydride was distilled into an ice-cooled flask containing 5 g. of isethionic acid. When the anhydride was added, a large amount of solid appeared in the flask. The product stood overnight in a desiccator, and the solid was then filtered, in an apparatus which precluded exposure to moisture. It was brought onto a porous plate and placed in a desiccator over phosphoric anhydride. The solid then became white upon standing. On exposure to the air, it fumed and liquefied. It melted at 80–85°, and thus showed the properties of carbyl sulfate.

Action of Anhydride on Ethylene in Gas Phase.—To ensure a reaction between ethylene and anhydride in the presence of ethylene in excess, the reaction was carried out in a mixing chamber in which the concentrations of the gaseous reagents could be controlled by the rate of inflow of the gases. The mixer was provided with three stopcocks, pointing in the same direction. Ethylene was passed in through one, the anhydride in a current of dry carbon dioxide by the second, and carbon dioxide alone was admitted through the third, to dilute the reaction mixture when the reaction became too vigorous. In general, it was necessary to use the third inlet only at the end of a run, when residual gases were entirely displaced by carbon dioxide. The dry ethylene was passed in at the rate of 20 liters per hour, while the carbon dioxide was allowed to pass through the chamber containing anhydride at a rate which caused it to vaporize about 4 g. per hour. The ethylene, therefore, was present in a *sixteen-fold excess.* Solid began to appear at the point of mixing, immediately upon starting the passage of the gases and continued to form during the run. When the experiment was completed, the solid was scraped out and placed on a porous plate in a desiccator. It fumed and liquefied in the air. The dry solid melted at 80–85° and was identical in all other respects with carbyl sulfate. This compound was also formed in the dark and at varying temperatures, *e. g.*, from −20° to ordinary temperature.

Summary

1. Contrary to Wieland, the action of fuming sulfuric acid on ethylene does not proceed by addition of H_2SO_4, functioning as the assumed basic addendum parts, HO– and $-SO_3H$, to form isethionic acid. It adds by direct addition of the pyrosulfuric acid present, each mole of the acid yielding one mole of ethionic acid. The reaction takes place by the acid acting directly as an addendum, whose parts are formed by fission at the anhydride oxygen, similar to the addition process with the anhydrides of other mineral acids.

2. All inorganic and organic acids, that do not contain an anhydride group, function as electrolytic addenda in additions to unsaturated carbon, or carbonyl, systems. The extremely weak, amphoteric, hypochlorous acid could not add in this manner and probably acts primarily by oxidation at the unsaturated carbons.[11]

3. All sulfonic acid syntheses with the use of sulfuric acid proceed by pseudo-substitution, involving, primarily, the addition of a hydrogen and carbon of a hydrocarbon group in the organic compound to the unsaturated oxygen and the attached sulfur, respectively, of a sulfonyl group. The orientation of the sulfonic radical, thus introduced into fatty hydrocarbons and of several radicals into aromatic hydrocarbons, follow the rules proved for substitution in the aliphatic series.[12] From this standpoint, the chemical structures of aliphatic derivatives, based upon incomplete and inexact experimental data, are largely erroneous, and many, supposedly, homogeneous compounds consist of a mixture of isomers.

4. The formation of carbyl sulfate, in the action of sulfuric anhydride on ethylene, has been explained by addition of the alkene to the S_2O_6 component of the balanced anhydride system, $SO_3 \rightleftharpoons S_2O_6$.

5. Isethionic acid is converted into carbyl sulfate in the action of two moles of SO_3, or one of S_2O_6. With sulfuric acid, or only one mole of SO_3, ethionic acid is formed.

6. Wieland's generally accepted mechanism of aromatic sulfonation, which postulates the primary, basic addition of sulfuric acid as HO– and $-SO_3H$, has been shown untenable. The pseudo-substitution mechanism, proposed recently for aromatic nitration,[5] has been extended to sulfonation by sulfuric acid, and sulfonation with sulfuric anhydride interpreted as an aldolization reaction.

7. The formation of aromatic sulfones from hydrocarbons and anhydride has been explained

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[11] Michael and Carlson,[5] p. 1268, footnote 4.

[12] Michael, *Ber.*, **34**, 4028, 4035, footnote 1 (1901); **39**, 2138, 2151 (1906).

on the basis of two moles of hydrocarbon reacting upon an SO_2 of the S_2O_6 component of the reversible $SO_3 \rightleftharpoons S_2O_6$ system of the anhydride.

CAMBRIDGE, MASS. RECEIVED NOVEMBER 19, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXLIX. The Synthesis of Aryl Substituted Dihydrouracils and their Conversion to Uracil Derivatives[1]

BY TREAT B. JOHNSON AND JOHN E. LIVAK

In laying out the program of pyrimidine research to be discussed in this paper the authors had three major objectives in mind, namely:

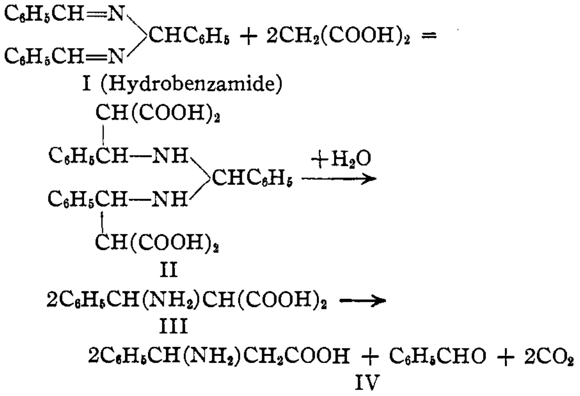
(1) To develop a convenient and practical method for preparing aromatic β-amino acids of the type $RCH(NH_2)CH_2COOH$ (R = an aryl group C_6H_5, $NO_2C_6H_4$, C_7H_7, $C_{10}H_7$, etc.) to be used for the synthesis of a series of substituted β-ureido acids.

(2) To make a study of the factors influencing and limiting the cyclization of these β-ureido acids to hexahydropyrimidines or 4,5-dihydrouracils.

(3) To determine the general utility of Fischer's[2] method for converting 4,5-dihydrouracils into their corresponding uracil derivatives.

1. Synthesis of β-Amino Acids

In order to obtain the β-amino acids desired for our research, we utilized a method of preparation which the Russian chemist, Rodionov,[3] developed as a result of a critical study of the well-known Knoevenagel reaction.[4] He found that the reaction between an aromatic aldehyde, like benzaldehyde, for example, and malonic acid in alcoholic ammonia solution, gives not only cinnamic acid (Knoevenagel) as a reaction product, but that in addition a β-amino acid $C_6H_5CH(NH_2)CH_2COOH$ is produced in practically equal amount. Rodionov demonstrated this reaction to be one of general application,[5] and later carried out a corresponding condensation with malonic ester, thereby obtaining a β-aminodicarboxylic ester which yielded after saponification and partial decarboxylation the same β-amino acid as was obtained directly by condensation of benzaldehyde with malonic acid. In our work we modified the procedure applied by Rodionov by using in place of the aldehyde and ammonia the corresponding hydrobenzamide formed by interaction of the aldehyde with ammonia. The reactions involved in this method of synthesizing β-phenyl-β-aminopropionic acid IV may be explained as follows



Starting with anishydramide β-(*p*-methoxyphenyl)-β-aminopropionic acid[6] is prepared according to the same technique.

2. Cyclization of β-Ureido Acids to 4,5-Dihydrouracils

β-Ureido acids are easily prepared by interaction of β-amino acids with cyanic acid and alkyl and aryl isocyanates. All the ureido- and thioureido-constructions prepared by the authors in their research from β-phenyl-β-aminopropionic acid and β-(*p*-methoxyphenyl)-β-aminopropionic acids are well-defined crystalline substances and were all easily purified by crystallization from hot water or alcohol. For conversion of this type of acids into 4,5-dihydrouracils various methods have been used: (1) cyclization by treatment with acetyl chloride;[7] (2) by the application of heat;[8] (3) cyclization by digestion with acetic anhy-

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[1] From a dissertation presented by John E. Livak to the Graduate Faculty of Yale University in June, 1935, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Fischer and Roeder, *Ber.*, **34**, 3751 (1901).

[3] Rodionov and Malewinskaja, *ibid.*, **59**, 2952 (1926).

[4] Knoevenagel, *ibid.*, **31**, 2596 (1898).

[5] (a) Rodionov and Vyazkova, *J. Gen. Chem.* (U. S. S. R.), **3**, 628 (1933); (b) Rodionov and Postovskaja, THIS JOURNAL, **51**, 841 (1929); (c) Rodionov, *ibid.*, **51**, 851 (1929); (d) Rodionov and Federowa, *Arch. Pharm.*, **266**, 121 (1928).

[6] Posner, *Ann.*, **389**, 62 (1912).

[7] Hoogewerf and Van Dorp, *Rec. trav. chim.*, **9**, 57 (1876); Fischer and Leuchs, *Ber.*, **35**, 3797 (1902).

[8] Posner and Rohde, *ibid.*, **42**, 2791 (1909).