from materials obtained directly from the living matter. They are of interest as showing possibilities of increases in enzyme activities, at present uncontrolled, which have been assumed, perhaps tacitly, to occur only during life processes. Decreases in enzyme actions are too common to consider in this connection, but such increases as are described compel attention. The selective increases in the lipase and protease actions indicate that the characters of the enzymes are changing and may perhaps parallel or correspond to changes in substances in the growth of living organisms. In general, the bearing of these relations upon the mechanism of the chemical transformations which occur in life processes is of interest.[4]

Summary

Spontaneous increases in the lipase and protease actions of a number of tissue and tumor extracts are described. These increases were selective in character, taking place with certain substrates and not with others under the same conditions. The possible significance of such changes in action in connection with phenomena occurring in life processes is indicated.

New York, N. Y.

[Contribution from the Chemical Laboratory of the University of Illinois]

THE USE OF ALIPHATIC ACID ANHYDRIDES IN THE PREPARATION OF KETONES BY THE FRIEDEL AND CRAFTS REACTION

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The use of acid anhydrides in the Friedel and Crafts reaction has been limited very largely to phthalic anhydride or its substitution products. This has come about because of the ease of conversion of the benzoylbenzoic acids obtained into anthraquinones in such yields as to make the process of practical importance. The details which have been developed in connection with the synthesis have shown that two or more mols. of anhydrous aluminum chloride must be employed if a high yield of benzoylbenzoic acid is to be obtained.

Considerably less study has been devoted to the condensation of succinic anhydride and maleic anhydride with aromatic compounds by means of anhydrous aluminum chloride. Here also, however, two or more mols. of condensing agent must be used in order to produce satisfactory yields.

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[4] Compare Falk, "Catalytic Action," The Chemical Catalog Co., Inc., New York, 1922; Chapter VII, "A Chemical Interpretation of Life Processes."

[1] This communication is an abstract of a portion of a thesis submitted by C. R. Noller in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

Previous study of the use of the anhydrides of simple aliphatic monobasic acids in the Friedel and Crafts reaction has been neglected. This is undoubtedly due to the fact that satisfactory yields of ketones are, in general, obtained when acid chlorides are used and only one mole of aluminum chloride is ordinarily necessary. At the time of the discovery of the Friedel and Crafts reaction, two or three investigators[2] attempted to use the simple aliphatic acid anhydrides in place of acid chlorides. They obtained poor results as compared with the use of the acid chlorides. A survey of their results, however, indicates that, in all cases, only one mole or less of aluminum chloride was used.

The smoothness of reaction and good yields of products, when phthalic anhydride and succinic anhydride are condensed with aromatic compounds provided at least two moles of aluminum chloride are used, led to the prediction that the failure of these early investigators in the use of simple aliphatic acid anhydrides was due to the too small proportion of aluminum chloride. In this paper are described the results of a study of the condensation of several aliphatic monobasic acid anhydrides with various aromatic compounds using two moles of anhydrous aluminum chloride.

A systematic study has been made of the condensation, first of acetic anhydride and then of other simple anhydrides with benzene, anisole and a variety of their homologs and derivatives. It has been found that the reactions take place with surprising regularity and smoothness, and with very good yields of exceptionally pure products. A single distillation of the crude material gives a constant-boiling ketone. A study of the literature has shown that in the preparation of ketones from acid chlorides and aromatic compounds, a considerably modified procedure must frequently be used with change of acid chloride or more particularly with change of aromatic compound; it is surprising to see how often the temperature, the amount of solvent, the order of addition of reagents, etc., have been varied in the different syntheses. With the use of acid anhydrides, on the other hand, identically the same procedure may be used in all cases. The only variations which have been employed in 19 different preparations are the occasional change of the temperature of the condensation and of the time of heating in order to complete the reaction. Excellent results are obtained when the acid anhydride is allowed to run into a well-stirred mixture of anhydrous aluminum chloride and aromatic compound with or without a solvent, preferably carbon disulfide; heating for a short time completes the reaction.

The advantages and disadvantages of the acid anhydrides, especially acetic anhydride, should be pointed out. The handling of acid chlorides,

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[2] (a) Friedel and Crafts, *Compt. rend.*, **86**, 1368 (1878); (b) *Ann. chim. phys.*, [6] **14**, 455 (1888). (c) Michaelis, *Ber.*, **15**, 185 (1882). (d) Roux, *Ann. chim. phys.*, [6] **12**, 334 (1887).

particularly acetyl chloride, is disagreeable and is avoided by the use of acetic anhydride. Moreover, the grade of acetyl chloride purchased commercially is generally variable in purity, while a C. P. grade of acetic anhydride of commerce is standard and may be used directly in the synthesis of ketones.

The ketones made from acid chlorides frequently boil over a wide range. The occurrence of by-products is common; thus in the condensation of anisole with acetyl chloride, Gattermann and others[3] observed the formation of dianisyl ethylene, and in the condensation of anisole with propionyl chloride, the formation of dianisyl propylene. No such by-products were ever obtained when acid anhydrides were used. It is reported very often[4] in the descriptions of the syntheses of ketones from acid chlorides, that care must be taken to follow the specific directions given or else resinous substances would form. Under none of the conditions used in this research were resinous substances produced.

In the condensation of phenol ethers with acid chlorides, a splitting of the ether linkage takes place to a certain extent along with the formation of the ketone. In some cases where no particular precautions were observed, this amounted to a large proportion of the total yield.[5] The splitting takes place to a less extent with the acid chlorides of higher molecular weight than with acetyl chloride.[6] With the acid anhydrides, the splitting of the ethers was small, seldom amounting to more than 5% of the total reaction mixture. In many cases, no splitting was found and never when any of the acid anhydrides other than acetic anhydride was used.

One argument which might be used against the substitution of acid anhydrides for acid chlorides in the Friedel and Crafts reaction would be the greater expense due to the larger amount of aluminum chloride necessary and to the fact that two moles of aliphatic acid are necessary for the preparation of an acid anhydride, whereas only one is necessary for the preparation of the acid chlorides. This latter point is of negligible importance in the case of acetic anhydride. The smoothness of reaction and purity of product greatly overweigh any additional expense on account of the acetic anhydride and aluminum chloride used. At the present time, the use of acid anhydrides of higher molecular weight than acetic anhydride would, in general, be impractical because of their cost. The acids themselves, from which the anhydrides are prepared, are not cheap sub-

[3] (a) Gattermann, *Ber.*, **22**, 1129 (1889). (b) Gattermann, Ehrhardt and Maisch, *Ber.*, **23**, 1199 (1890). (c) Klages, *Ber.*, **35**, 2262 (1902).

[4] (a) Claus, *J. prakt. Chem.*, [2] **41**, 400 (1890). (b) Holleman, *Rec. trav. chim.*, **10**, 215 (1891). (c) Verley, *Bull. soc. chim.*, [3] **17**, 909 (1897). (d) Willgerodt and Hambrecht, *J. prakt. Chem.*, [2] **81**, 78 (1910).

[5] (a) Auwers, *Ann.*, **364**, 164 (1909); (b) **408**, 248 (1915). (c) Hill and Graf, This Journal, **37**, 1839 (1915).

[6] Auwers and Lämmerhirt, *Ber.*, **53**, 428 (1920).

stances so that whether one or two moles of acid are used for the reaction is an important consideration. With these acids gradually becoming cheaper, however, and with new and cheaper methods available for the preparation of anhydrides,[7] the use of these other anhydrides for producing various ketones in preference to the use of acid chlorides would be practical. In the experiments carried out with butyric acid anhydride and valeric acid anhydride, butyric acid and valeric acid are readily recovered after the condensation reaction mixture has been decomposed with water merely by extracting the insoluble layer with alkali and reacidifying the alkaline solution. The actual amount of acid, therefore, employed in a ketone synthesis is only slightly over one molecular equivalent.

In conclusion, it may be said that acetic anhydride may conveniently be used in place of acetyl chloride in the Friedel and Crafts reaction and may be relied upon to give better and more consistent results. The acid anhydrides of higher molecular weight are also convenient reagents for use in the synthesis of ketones.

The possible application of the use of anhydrides in the preparation of ketones where acid chlorides give poor results is now being studied.

Experimental Part

As exactly the same procedure was followed in the preparation of all the ketones, only a table is given representing the yields and constants of the compounds. Slight changes in individual experiments are given after the general directions. The yield of ketone given in the table is that obtained on the first distillation of the crude mixture and, in all cases, was collected over a range of 3° or less. Where two figures for the yield are given, these represent the maximum and minimum in a number of experiments. The boiling points are those obtained on redistillation of the ketone and the densities and indices of refraction are those of the redistilled product.

General Procedure

A solution of 0.5 mole of the aromatic hydrocarbon or derivative in 200 cc. of carbon disulfide (in special experiments, benzene or toluene; see below) is placed in a 1-liter three-neck flask, fitted with a mercury-sealed mechanical stirrer, a dropping funnel, and a reflux condenser bearing a tube to carry off the hydrogen chloride evolved. To this solution is added 1.1 mole of powdered anhydrous aluminum chloride ($AlCl_3$) and then, with rapid stirring, 0.5 mole of the acid anhydride is slowly added through the dropping funnel. This addition requires about 15 minutes during which time the temperature of the mixture comes to the boiling point of the carbon disulfide and a rapid evolution of hydrogen chloride takes place. After all the acid anhydride has been added, the mixture is heated on the

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[7] Société chimique des usines des Rhône, Ger. pat. 334,554; 346,236.

TABLE I

RESULTS

Compound	Yield of ketone %	Melting point (corr.) °C.	Boiling point in a vacuum (corr.)		Boiling point at Atm. press. (corr.)		d_4^{20}	n_D^{20}
			°C.	Mm. of Hg	°C.	Mm. of Hg		
Acetophenone	76–83	19.5–20	88.5	16	201.0	736	....	....
p-Methyl-acetophenone[8]	85–89	.....	93.5	7	225.0	736	1.0051	1.5335
p-Methoxy-acetophenone[9]	94–96	36–37.5	139.0	15	264.0	736	....	....
p-Chloro-acetophenone[10]	66–68	20–21	99.0	7	236.5	740	....	....
p-Bromo-acetophenone[11]	68–69	49–50.5	117.0	7	255.5	736	....	....
2,4-Dimethoxy-acetophenone[12]	77–80	39–40	157.5	7	298.5	736	....	....
3-Methyl-4-methoxy-acetophenone[a]	73	26–26.5	116.0	3	273.5	744	....	....
2-Methyl-4-methoxy-acetophenone[13]	87	.....	116.5	3	267.0	735	1.0796	1.5510
5-Methyl-2-methoxy-acetophenone[14]	64–70	.....	120.5	7	260.5	740	1.0652	1.5370
2,4,6-Trimethyl-acetophenone[15]	87–88	.....	90.0	3	240.5	735	0.9754	1.5175
p-Methyl-propiophenone[16]	86	.....	106.0	8	239.0	739	.9926	1.5278
p-Methoxy-propiophenone[17]	87	24–26	125.0	4	275.0	739	....	....
5-Methyl-2-methoxy-propiophenone[18]	86	.....	118.5	3	270.0	735	1.0490	1.5323
p-Methyl-butyrophenone[4d]	86	.....	114.0	6	252.0	739	0.9745	1.5215
5-Methyl-2-methoxy-butyrophenone[b]	84	.....	123.0	3	276.5	739	1.0258	1.5250
p-Methoxy-valerophenone[19]	85	22–23.5	150.5	6	300.0	739	....	....
3-Methyl-4-methoxy-valerophenone[c]	83	31–33	151.5	4	308.7	744	....	....
p-Methyl-ω-chloro-acetophenone[20]	46–59	54.5–55	113.0	4	...	...	....	....
2-Methoxy-1-acetonaphthone[21]	69–70	57–58	158.0	2	...	...	....	....

[a] *Anal.* Subs., 0.1998: CO_2, 0.5330; H_2O, 0.1323. Calc. for $C_{10}H_{12}O_2$: C, 73.13; H, 7.37. Found: C, 72.77; H, 7.41.

[b] *Anal.* Subs., 0.1811: CO_2, 0.4999; H_2O, 0.1356. Calc. for $C_{12}H_{16}O_2$; C, 74.96; H, 8.38. Found: C 75.28; H 8.38.

[c] *Anal.* Subs., 0.1914: CO_2, 0.5317; H_2O, 0.1532. Calc. for $C_{13}H_{18}O_2$: C, 75.69; H 8.78. Found: C, 75.76; H, 8.96.

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[8] Ref. 2c. Essner and Gossin, *Bull. soc. chim.*, **42**, 95 (1884). Claus, *Ber.*, **19**, 234 (1886). Ref. 4c. Boeseken, *Rec. trav. chim.*, **16**, 313 (1897). Sorge, *Ber.*, **35** 1069 (1902). Auwers and Kolligs, *Ber.*, **55**, 42 (1922).

[9] Ref. 3a. Ref. 3b, p. 1201. Ref. 4b. Straus, *Ann.*, **374**, 139 (1910).

[10] Gautier, *Ann. chim. phys.*, [6] **14**, 373 (1888). Collet, *Bull. soc. chim.*, [3] **21**, 69 (1899). Straus and Ackermann, *Ber.*, **42**, 1812 (1909).

[11] Schweitzer, *Ber.*, **24**, 550 (1891). Schöpff, *Ber.*, **24**, 3766 (1891). Hale and Thorp, THIS JOURNAL, **35**, 266 (1913).

[12] Tahara, *Ber.*, **24**, 2461 (1891). Sachs and Herold, *Ber.*, **40**, 2724 (1907).

[13] Eykmann, *Chem. Weekblad*, **1**, 457 (1904).

[14] Auwers, *Ber.*, **45**, 988 (1912); Ref. 5b.

[15] Ref. 4a, p. 504. Klages and Allendorff, *Ber.*, **31**, 1008 (1898). Noyes and Hufferd, THIS JOURNAL, **43**, 928 (1921).

[16] Errara, *Gazz. chim. ital.*, **21**, 95 (1891). Ref. 3c, p. 2252. Ref. 5b, p. 243.

[17] Ref. 3b, p. 1203. Ref. 3c.

[18] Klages, *Ber.*, **37**, 3994 (1904). Ref. 5b, p. 249.

[19] Layraud, *Bull. soc. chim.*, [3] **35**, 233 (1906).

[20] Kunckell, *Ber.*, **30**, 578 (1897). Collet, *Bull. soc. chim.*, [3] **17**, 507 (1897). Ryan, *Ber.*, **31**, 2132 (1898).

[21] (a) Ref. 3b, p. 1209 (1890). (b) Rousset, *Bull. soc. chim.*, [3] **17**, 312 (1897). (c) Witt and Braun, *Ber.*, **47**, 3216 (1914). (d) Fries, *Ber.*, **54**, 709 (1921). (e) Schneider and Kunau, *Ber.*, **54**, 2305 (1921).

water-bath and stirred for 30 minutes at the end of which time there is practically no more evolution of gas. The reaction mixture is then cooled to room temperature and decomposed by pouring into ice and water. It is convenient to allow the carbon disulfide to evaporate under the hood during the decomposition, although it might be recovered by distillation from a water-bath before decomposing with water. After decomposition, the mixture is cooled and extracted with a little ether, and the ether layer washed first with water, then with 10% sodium hydroxide solution, and finally with water. It is then dried over calcium chloride, the solvent distilled and the residue subjected to distillation in a vacuum from a modified Claissen flask.[22]

Notes on the Procedure

In some cases a very small amount of unchanged aromatic hydrocarbon came over as a low-boiling fraction, but this was in each instance so much lower boiling than the ketone that it did not interfere in obtaining a pure ketone by distillation.

In preparing the derivatives of benzene and toluene, 200 cc. of the hydrocarbon was used as a solvent instead of carbon disulfide. The temperature of the mixture rose to the boiling point of the benzene during the addition of the anhydride, or to about 90° when toluene was used.

Although the acid anhydrides are, in general, not so reactive as the acid chlorides, the reactions, when phenol ethers were used, were rather vigorous so that the mixtures were cooled to about 5° before the addition of aluminum chloride and were kept in an ice- and water-bath during the addition of the acid anhydride, thus causing less splitting of the ether. Only a few of the phenol ether condensations yielded phenolic ketones as by-products. From the alkaline extraction liquors by acidification, there was obtained 7 to 10% of 2-hydroxy-4-methoxy-acetophenone (peonol) in the preparation of 2,4-dimethoxy-acetophenone, 2% of 2-methyl-4-hydroxy-acetophenone in the preparation of 2-methyl-4-methoxy-acetophenone, 1 to 7% of 5-methyl-2-hydroxy-acetophenone in the preparation of 5-methyl-2-methoxy-acetophenone, and 14 to 17% of 2-hydroxy-1-acetonaphthone in the preparation of 2-methoxy-1-acetonaphthone.

In preparing the aceto derivatives of the halogen-substituted hydrocarbons and the chloro-acetyl derivative of toluene, the best yields were obtained when the mixtures were heated on the water-bath before and during the addition of the acid anhydride and the heating was continued for one hour after all the anhydride had been added.

The low yield of *p*-methyl-ω-chloro-acetophenone from toluene and chloro-acetic anhydride is probably due to the fact that the chlorine atom enters into the reaction and gives by-products. Since chloro-acetyl

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[22] Noyes and Skinner, THIS JOURNAL, 39, 2718 (1917).

chloride reacts more rapidly than the anhydride, better yields and less by-products are obtained when the chloride is used.

Occasionally, especially when using *p*-cresol methyl ether and resorcinol dimethyl ether, the reaction mixtures solidified during the heating on the water-bath, thus making it necessary to finish the heating without stirring.

With β-naphthol methyl ether, the mixture solidified before all of the anhydride could be added. This probably accounts for the higher percentage of the hydroxy compounds which are formed.

About 60% of the butyric acid and about 70% of the valeric acid, formed when their anhydrides are used, can be recovered by acidifying the sodium hydroxide washings and then salting out.

The majority of all the ketones made in this investigation had been previously prepared and their structures reasonably well established. The position of the aceto group in the methoxy-acetonaphthone from β-naphthol methyl ether was in doubt. Fries[21d] obtained a compound (m. p., 64°) by heating β-naphthol acetate with aluminum chloride to which he assigned the structure 2-hydroxy-1-acetonaphthone and stated that this compound was different from that obtained by splitting with aluminum chloride the methoxy-acetonaphthone prepared from β-naphthol methyl ether, acetyl chloride and aluminum chloride, as determined by mixed melting points. To the latter compound (m. p., 64°) he assigned the structure 2-hydroxy-3-acetonaphthone. The melting point of 2-methoxy-1-acetonaphthone was given as 59° and that of 2-methoxy-3-acetonaphthone as 57.5°.

In determining the structure of the methoxy-acetonaphthone (m. p., 57–58°) obtained when β-naphthol methyl ether, acetic anhydride and aluminum chloride reacted, it was found that the hydroxy-acetonaphthone (m. p., 63–64°) prepared by splitting the methoxy-acetonaphthone mentioned above with aluminum chloride is identical with the compound (m. p., 63–64°) obtained by the rearrangement of β-naphthol acetate. Moreover, on methylating an alkaline solution of the hydroxy-acetonaphthone prepared from β-naphthol acetate with dimethyl sulfate, the methoxy-acetonaphthone (m. p., 57–58°) is identical with that prepared from β-naphthol methyl ether, acetic anhydride and aluminum chloride. Both were found to be identical with the compound (m. p., 57–58°) prepared according to Gattermann's directions from β-naphthol methyl ether, acetyl chloride and aluminum chloride, so that in all cases the aceto group enters the same position. This has been shown by Fries to be the 1 position. The identity of the different compounds was established by taking mixed melting points.

Summary

1. Aliphatic acid anhydrides may very conveniently be used in place of acid chlorides in the Friedel and Crafts reaction, provided that slightly

over two moles of anhydrous aluminum chloride are used for each mole of acid anhydride that is allowed to react.

2. The ketones are obtained in good yields and boil almost constant on the first distillation.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

SULFONEFLUORESCEIN AND DIHYDROXYBENZOYL-BENZENE-ORTHO-SULFONIC ACID, AND SOME OF THEIR DERIVATIVES[1]

BY W. R. ORNDORFF AND R. S. VOSE

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In 1884 Remsen[2] discovered sulfonefluorescein and called this class of compounds the sulfonephthaleins. Remsen and Hayes[3] in 1887 attempted to isolate sulfonefluorescein, but obtained the ammonium salt of dihydroxybenzoyl-benzene-*o*-sulfonic acid, as shown in 1889 by Remsen and Linn[4] who prepared sulfonefluorescein by heating dihydroxybenzoyl-benzene-*o*-sulfonic acid at 185°. Their analyses of the *amorphous* material showed it to contain a molecule of water. Fahlberg and Barge[5] in 1889 state that instead of the reaction between resorcinol and *o*-sulfobenzoic acid being analogous to that of the formation of fluorescein, it gave a product resulting from the condensation of four molecules of resorcinol with one of *o*-sulfobenzoic acid. Blackshear[6] in 1892 made sulfonefluorescein by the method of Remsen and Linn and his analyses of the *amorphous* product agreed with those of these authors. White[7] in 1895 made sulfonefluorescein by the same method and attempted to prepare a bromine derivative. He repeated the work of Fahlberg and Barge and obtained similar results. Remsen and McKee[8] in 1896 found that both chlorides of *o*-sulfobenzoic acid gave sulfonefluorescein when heated with resorcinol. They state that when dried in the air their product contained a molecule of water. Sisley[9] in 1897 made sulfonefluorescein by heating "saccharin" with resorcinol and sulfuric acid and states that he obtained a tetrabromo compound. Sohon[10] in 1898 made sulfonefluorescein from resorcinol and the

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[1] From a dissertation presented by R. S. Vose in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Remsen, *Am. Chem. J.*, **6**, 180 (1884).

[3] Remsen and Hayes, *ibid.*, 9, 372 (1887).

[4] Remsen and Linn, *ibid.*, **11**, 73 (1889).

[5] Fahlberg and Barge, *Ber.*, **22**, 754 (1889).

[6] Blackshear, *Am. Chem. J.*, **14**, 455 (1892).

[7] White, *ibid.*, **17**, 545 (1895).

[8] Remsen and McKee, *ibid.*, **18**, 802 (1896).

[9] Sisley, *Bull. soc. chim. Paris*, [3] **17**, 822 (1897).

[10] Sohon, *Am. Chem. J.*, **20**, 257 (1898).