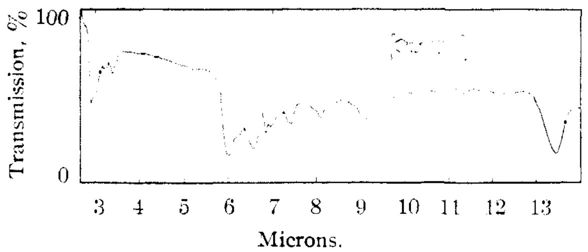

Fig. 11.—Infrared spectrum of polytryptophan from the rearrangement[5] of sodium α-carboxy-β-3-indolylpropiono-(benzoylhydroxamate) in water, the film being cast from ethanol.

of the α-form, has a peak at 6.58 μ ascribed[7] to the β-configuration. Likewise, poly-α-aminobutyric acid, polynorleucine and poly-5-aminovaleric acid, with bands at 6.12 ± 0.01 μ, show N–H peaks at the unexpected positions of 6.48, 6.50 and 6.45 μ, respectively. Absorption near 6.8 μ due to CH_2 groups has also been found consistently. Above 7 μ, characteristic double-bond absorption was observed at 10.88 μ with poly-2-amino-4-pentenoic acid, and a typical band for the benzene ring is present in the spectra of polyphenylalanine between 13.33–13.41 μ, and in that for polytryptophan at 13.46 μ. Consistent absorption appears in all of the polypeptides in the regions near 7 and near 8 μ, but no unequivocal assignments could be made for these peaks.

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EVANSTON, ILLINOIS

[CONTRIBUTION NO. 874 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

A Study of Acid Catalysis in Ketone Acylations

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Six Lewis acids have been investigated as possible catalysts for the acylation of ketones with anhydrides to give β-diketones. Of these reagents, only two, anhydrous ferric chloride and anhydrous zinc chloride, are satisfactory. In the attempted acylation of acetophenone with acetic anhydride in the presence of aluminum chloride, only dypnone was obtained; while the use of either iodine or anhydrous stannic chloride as the catalyst gave benzoic acid instead of the expected benzoylacetone.

The Claisen acylation of ketones to give β-diketones has been effected by both acidic and basic condensing agents. Although the use of a number of bases such as sodium metal,[2] alkali alkoxides,[3] alkali amides,[4] substituted alkali amides[5] and sodium triphenylmethide[4] has been investigated, apparently only one acid, gaseous boron fluoride[6–8] has been studied.

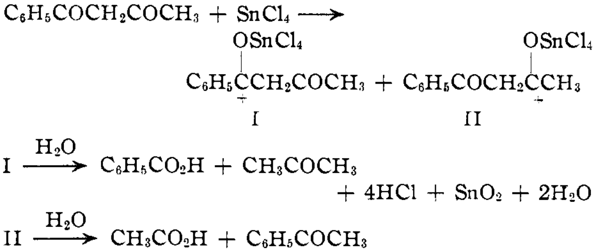
Since Friedel–Crafts acylations have been effected not only by aluminum chloride,[9] but by a number of other Lewis acids such as iodine,[10] phosphorus pentoxide[11] and anhydrous ferric[12] and zinc chlorides,[13] it was of interest to determine whether general acid catalysis was applicable in the Claisen acylation of ketones with anhydrides.

To study the relative effectiveness of the various catalysts, the acylation of acetophenone with acetic anhydride, as shown in the following equation, was investigated in the presence of six Lewis acids.

$$C_6H_5COCH_3 + (CH_3CO)_2O \xrightarrow{\text{Lewis acid}} CH_3CO_2H + C_6H_5COCH_2COCH_3$$

No benzoylacetone was obtained using aluminum chloride. The isolation of the dehydrated ketol, dypnone (11.5%) in this experiment, confirms the earlier work of Calloway and Green,[14] who found that acetophenone is self-condensed by aluminum chloride. Phosphorus pentoxide was a poor catalyst for the reaction since it gave only a 7.5% yield of the product.

The use of either iodine or stannic chloride to effect the reaction gave none of the desired β-diketone. Instead, benzoic acid, in yields of 18 and 38%, respectively, and acetophenone were isolated from these attempted acylations. It is possible, as shown in the following scheme, that the benzoic acid arose from the iodine or stannic chloride-induced cleavage of benzoylacetone which was probably formed but not isolated.



$$C_6H_5COCH_2COCH_3 + SnCl_4 \longrightarrow \underset{\text{I}}{C_6H_5\overset{\overset{OSnCl_4}{|}}{\underset{+}{C}}CH_2COCH_3} + \underset{\text{II}}{C_6H_5COCH_2\overset{\overset{OSnCl_4}{|}}{\underset{+}{C}}CH_3}$$

$$\text{I} \xrightarrow{H_2O} C_6H_5CO_2H + CH_3COCH_3 + 4HCl + SnO_2 + 2H_2O$$

$$\text{II} \xrightarrow{H_2O} CH_3CO_2H + C_6H_5COCH_3$$

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[1] This paper is based on a thesis presented by Bruno M. Perfetti to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Master of Science degree.

[2] J. M. Sprague, J. J. Beckham and H. Adkins, THIS JOURNAL, **56**, 2665 (1934).

[3] H. Adkins and J. L. Rainey, *Org. Syntheses*, **20**, 6 (1940).

[4] R. Levine, J. A. Conroy, J. T. Adams and C. R. Hauser, THIS JOURNAL, **67**, 1510 (1945).

[5] M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).

[6] H. Meerwein and J. Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

[7] C. R. Hauser and J. T. Adams, THIS JOURNAL, **66**, 345 (1944).

[8] J. T. Adams and C. R. Hauser, *ibid.*, **67**, 284 (1945).

[9] See "Anhydrous Aluminum Chloride in Organic Chemistry," by C. A. Thomas, Reinhold Publishing Corp., New York, N. Y., 1941.

[10] H. D. Hartough and A. I. Kosak, THIS JOURNAL, **68**, 2639 (1946).

[11] H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3098 (1947).

[12] M. W. Farrar and R. Levine, *ibid.*, **72**, 4435 (1950).

[13] H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 1012 (1947).

[14] N. O. Calloway and L. D. Green, *ibid.*, **59**, 809 (1937).

TABLE I

ACYLATION OF KETONES WITH ANHYDRIDES

Ketone	Acylation by anhydrides, % Acetic	Propionic	*n*-Butyric	Reaction conditions
Methyl isopropyl	47.5[a](28)[b]	38.8[c]	20.5[d,e]	1 hr., 110°
Methyl isobutyl	26.5[e,f](41)[g]	18.5[e,h](43)[i]	19.1[e,j](44)[k]	1 hr., 110°
Diethyl	4.7[l](62)[m]	7.3[n]	9.9[o](46)[i]	1 hr., 110°
Diisobutyl	19.1[p](45)[i]	17.2[q]	22.3[r]	1 hr., 110°
Cyclohexanone	13.5[i,s](35)[i]	11.7[i,t](35)[i]	12.3[i,u](34)[i]	1 hr., 80°
Acetophenone	43.5[i,v,w](50)[i]	11.8[i,x](30)[i]	19.7[i,y](15)[i]	1 hr., 110°
2-Acetylthiophene	21.4[z]	13.0[aa,bb]	11.3[aa,cc]	1 hr., 100°
2-Acetylfuran	4.6[dd]	3.0[ee]	2.5[ff,gg]	0.5 hr., at 50° then 0.5 hr., at 90°

[a] α,α-Dimethylacetylacetone, b.p. 70–74° (20 mm.) (see ref. 7). [b] The numbers in parentheses are yields obtained by other workers using boron fluoride. [c] Acetylpropionyldimethylmethane, b.p. 81–82° (20 mm.). *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.58; H, 9.92. Found: C, 67.56; H, 9.41. [d] Consisted of 98% acetylbutyryldimethylmethane, b.p. 91–93° (20 mm.). (*Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.87; H, 10.10) and 2% dibutyrylmethane, b.p. 96–99° (20 mm.), blue copper salt, m.p. 157–158° (see ref. 17). [e] The mixture of β-diketones was separated by the alkali extraction method (see ref. 7). [f] Consisted of 65% α-isopropylacetylacetone, b.p. 80–82 (20 mm.) (see ref. 7) and 35% isovalerylacetone, b.p. 82–83° (20 mm.); copper salt, m.p. 154–155° (see ref. 7). [g] See ref. 7. [h] Consisted of 65% α-isopropylpropionylacetone, b.p. 91–93° (20 mm.) (see ref. 8) and 35% propionylisovalerylmethane, b.p. 92–94° (20 mm.); copper salt, m.p. 128.5–129.5° (see ref. 8). [i] See ref. 8. [j] Consisted of 94% α-isopropylbutyrylacetone, b.p. 102–105° (20 mm.) (see ref. 8) and 4% dibutyrylmethane, b.p. 96–99° (20 mm.); copper salt, m.p. 157–158° (see ref. in footnote *d*). [k] See ref. 7 and 8. [l] α-Methylpropionylacetone, b.p. 92–93° (30 mm.); gray copper salt, m.p. 176–178° (G. T. Morgan, H. D. Drew and C. R. Porter, *Ber.*, **58**, 333 (1925)). [m] See ref. 6. [n] Methyldipropionylmethane, b.p. 94–97° (20 mm.); gray copper salt, m.p. 171–173° (see ref. in footnote *l*). [o] Methylpropionylbutyrylmethane, b.p. 105–108° (20 mm.); gray copper salt, m.p. 150–151° (see ref. 8). [p] α-Isopropylisobutyrylacetone, b.p. 112–116° (20 mm.) (see ref. 8). [q] Isopropylpropionylisobutyrylmethane, b.p. 120–121° (20 mm.). *Anal.* Calcd. for $C_{12}H_{22}O_2$: C, 72.66; H, 11.18. Found: C, 72.45; H, 11.19. [r] Isopropylbutyrylisobutyrylmethane, b.p. 128–129° (20 mm.). *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.55; H, 11.39. Found: C, 73.37; H, 11.72. [s] 2-Acetylcyclohexanone, b.p. 62–64° (2.5 mm.). [t] 2-Propionylcyclohexanone, b.p. 78–80° (2.0 mm.); gray copper salt, m.p. 185–186°. [u] 2-Butyrylcyclohexanone, b.p. 84–87° (2.5 mm.); gray copper salt, m.p. 157–158°. [v] Benzoylacetone, b.p. 103–105° (1.8 mm.); m.p. 57–58° from petroleum ether, b.p. 30–60°. [w] See ref. 15. [x] ω-Propionylacetophenone, b.p. 125–128° (5.0 mm.); green copper salt, m.p. 152–153°. [y] ω-Butyrylacetophenone. b.p. 116–118° (1.8 mm.); green copper salt, m.p. 137–138°. [z] 2-Thenoylacetone, b.p. 128–131° (8.0 mm.); green copper salt, m.p. 227–229° (S. R. Harris and R. Levine, THIS JOURNAL, **70**, 3360 (1948)). [aa] See ref. in footnote *z*. [bb] 2-Thenoylpropionylmethane, b.p. 118–122° (2 mm.); green copper salt, m.p. 193–194°. [cc] 2-Thenoylbutyrylmethane, b.p. 139–142° (4.0 mm.); green copper salt, m.p. 138–139°. [dd] 2-Furoylacetone, isolated as its copper salt, m.p. 216–219° (S. R. Harris and R. Levine, *ibid.*, **71**, 1120 (1949)). [ee] 2-Furoylpropionylmethane, b.p. 93–96° (1.5 mm.). *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.04; H, 6.07. Found: C, 65.32; H, 6.02. [ff] 2-Furoylbutyrylmethane, b.p. 123–125° (6.5 mm.). *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.71. Found: C, 66.32; H, 6.79. [gg] Of the β-diketones listed in this table, those which have an isopropyl group on the carbon atom between the two carbonyl groups give no color test with alcoholic iron(III) chloride solution; those which carry a methyl group on that carbon atom give a violet color and those which are unsubstituted give a red color.

In order to test this idea, two experiments were performed. First, stannic chloride was added to an equivalent of benzoylacetone in benzene solution and the mixture refluxed for 1.5 hours. In this way, benzoic acid (27%), acetophenone (12%) and recovered β-diketone (55%) were obtained. From a similar experiment involving a benzene solution of 0.2 mole of β-diketone and 0.01 mole of iodine, there were isolated benzoic acid (18%), acetophenone (5%) and recovered benzoylacetone (71%). Thus, it is possible for both iodine and stannic chloride to effect the cleavage of the β-diketone at both carbonyl groups. In this connection, it is of interest to note that Adkins and coworkers[15] have cleaved benzoylacetone with alcoholic hydrogen chloride to give acetophenone and ethyl acetate. Apparently neither acetone nor ethyl benzoate was obtained.

Both ferric and zinc chloride gave fair yields of the β-diketone. The 43.5% yield obtained with zinc chloride compares favorably with that obtained with boron fluoride (50%).[6] Furthermore, an attempt to acylate acetophenone with acetyl chloride in the presence of zinc chloride gave none of the desired β-diketone, but an 11.5% yield of dypnone was isolated. Since zinc chloride gave the best yield of benzoylacetone, it was used for the acylations listed in Table I. It was found that in several cases the yields of products isolated using zinc chloride as the catalyst were considerably lower than those obtained with boron fluoride. In spite of the low yields obtained with zinc chloride, it should be pointed out that considerably less time and condensing agent are required when it is employed as compared with boron fluoride.

Two of the acylations, *i.e.*, the butyrylation of methyl isopropyl and methyl isobutyl ketone are of particular interest. While the boron fluoride-effected butyrylations of these ketones gave a mixture of the expected β-diketones,[7,16] the same acylations, when effected by zinc chloride, gave in each case one of the expected β-diketones (V or VIII) and dibutyrylmethane.

$$\underset{\text{III}}{CH_3COCH(CH_3)_2} + \underset{\text{IV}}{(n\text{-}C_3H_7CO)_2O} \xrightarrow{BF_3}$$

$$\underset{\text{V}}{CH_3COC(CH_3)_2COC_3H_7\text{-}n} + \underset{\text{VI}}{n\text{-}C_3H_7COCH_2COCH(CH_3)_2}$$

$$\underset{\text{VII}}{CH_3COCH_2CH(CH_3)_2} + \text{IV} \xrightarrow{BF_3}$$

$$\underset{\text{VIII}}{CH_3COCH(CH(CH_3)_2)COC_3H_7\text{-}n} +$$

$$\underset{\text{IX}}{n\text{-}C_3H_7COCH_2COCH_2CH(CH_3)_2}$$

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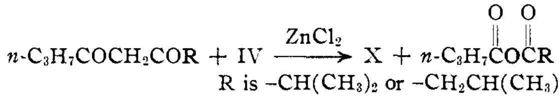
(15) H. Adkins, W. Kutz and D. B. Coffman, THIS JOURNAL, **52**, 3212 (1930).

(16) J. T. Adams and C. R. Hauser, *ibid.*, **67**, 284 (1945).

$$\mathrm{III} + \mathrm{IV} \xrightarrow{\mathrm{ZnCl_2}} \mathrm{V} + \underset{\mathrm{X}}{n\text{-}C_3H_7COCH_2COC_3H_7\text{-}n}$$

$$\mathrm{VII} + \mathrm{IV} \xrightarrow{\mathrm{ZnCl_2}} \mathrm{VIII} + \mathrm{X}$$

It appeared that the dibutyrylmethane might have been formed from the β-diketones VI and IX (methyl derivatives, which were not isolated) by acyl exchange with IV. To test this hypothesis, an authentic sample of IX was prepared and treated with *n*-butyric anhydride in the presence of zinc chloride. Considerable resinification took place and from the reaction mixture none of IX was recovered but 12% of X was obtained. Thus, it appears that acyl exchange is possible in the reaction of VII and IV in the presence of zinc chloride.



$$n\text{-}C_3H_7COCH_2COR + \mathrm{IV} \xrightarrow{\mathrm{ZnCl_2}} \mathrm{X} + n\text{-}C_3H_7\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R$$

R is $-CH(CH_3)_2$ or $-CH_2CH(CH_3)_2$

Experimental

General Method for the Acylation of Ketones with Anhydrides in the Presence of Lewis Acids.—To a stirred mixture of 0.5 mole of ketone and 1.0–2.0 moles of anhydride was added the appropriate amount of the Lewis acid and the reaction mixture was then stirred and heated for the appropriate period of time at 75–110°. The contents of the reaction flask was allowed to cool to room temperature, poured onto 250 ml. of ice and water and the phases separated, the aqueous phase was extracted with several 100-ml. portions of ether or chloroform and the combined organic phases dried over Drierite. The solvent was removed and the residue then fractionated in vacuum to give the reaction products. In most reactions, considerable quantities of non-distillable resinous materials remained in the distillation pot. In those cases where the products consisted of a mixture of β-diketones, these were separated by the alkali extraction method.[7] Thus, from a mixture of 0.5 mole (60.5 g.) of acetophenone, 115 ml. of 95% acetic anhydride and 0.5 mole (68 g.) of anhydrous zinc chloride, there was obtained 35.2 g. (43.5%) of benzoylacetone, b.p. 103–105° (1.8 mm.), m.p. 57–58° cor.[15]

Cleavage of Benzoylacetone. (a) By Stannic Chloride.—To a stirred solution of 0.10 mole (16.2 g.) of benzoylacetone and 100 ml. of dry benzene was added dropwise 0.10 mole (12.0 g.) of stannic chloride over a five-minute period and the mixture refluxed for 1.5 hours on a steam-bath. The mixture was then poured onto water and extracted with several portions of ether. The ether extracts were then extracted with several portions of 10% sodium carbonate solution. Acidification of the basic extracts gave 3.3 g. (27%) of benzoic acid, m.p. 121.5–122.5° alone and when mixed with an authentic sample. The ether extracts were dried and distilled to give 9.0 g. (55%) of benzoylacetone, b.p. 104–105° (2.0 mm.), and 1.4 g. (11.6%) of acetophenone, b.p. 62–65° (3.5 mm.), 2,4-dinitrophenylhydrazone, m.p. 249–250° alone and when mixed with an authentic sample. **(b) By Iodine.**—A mixture of 0.10 mole (16.2 g.) of benzoylacetone, 100 ml. of dry benzene and 0.01 mole (2.5 g.) of iodine was refluxed for 1.5 hours and worked up as described in part (a) to give 2.2 g. (18%) of benzoic acid, m.p. 121.5–122.5°, 0.6 g. (5%) of acetophenone, b.p. 92–95° (20 mm.), and 11.5 g. (71%) of benzoylacetone, b.p. 104–105° (2.0 mm.).

Acyl Exchange between Butyrylisovalerylmethane and *n*-Butyric Anhydride in the Presence of Anhydrous Zinc Chloride.—A mixture of 0.8 mole of butyrylisovalerylmethane, prepared by the method of Adams and Hauser,[17] 0.85 mole (116 g.) of zinc chloride and 1.6 moles (253 g.) of *n*-butyric anhydride was heated at 125° for 1.5 hours. When the reaction mixture was worked up using the general method outlined above, there was obtained 15.0 g. (12.2%) of dibutyrylmethane, b.p. 101–103° (20 mm.)[17]; copper salt, m.p. 156–157°. None of the starting β-diketone was recovered and a large amount of non-distillable resinous material remained in the distilling flask.

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(17) J. T. Adams and C. R. Hauser, THIS JOURNAL, **66**, 1220 (1944).

PITTSBURGH, PENNSYLVANIA