tensity of the S–H band at 3.97 μ was reduced by half and that of the C=O band at 5.8 μ was also considerably reduced. There was no further spectral change in 5 days. A mixture that had stood several hours at 25° was more viscous than a fresh mixture.

Similar behavior was observed when 1-butanethiol or 1,1-cyclohexanedithiol was mixed with 3,5,5-trimethylhexanal or when 3,5,5-trimethyl-1,1-hexanedithiol was mixed with propionaldehyde, but not when *gem*-dithiols were mixed with cyclohexanone.

(b).—Boron fluoride etherate (1.1 ml.) was added dropwise with swirling to an equimolar mixture of 20.0 g. of 3,5,5-trimethyl-1,1-hexanedithiol and 6.06 g. of propionaldehyde at 0–10°. The mixture at once became cloudy because of water formation. After 24 hours, water and ether were added and the ether layer was distilled to give 21.2 g. of a complex mixture of b.p. 39–168° (0.7 mm.).

Similar results were obtained when boron fluoride etherate was added to an equimolar mixture of 1,1-propanedithiol and either acetone or propionaldehyde. In each case, a high yield of a complex liquid, b.p. 70–140° (0.5 mm.), was obtained.

In a control experiment, a solution of 5.00 g. of boron fluoride etherate, 5.00 g. of 3,5,5-trimethyl-1,1-hexanedithiol and 5.00 g. of methanol was kept at 25° for 48 hours and then poured into ice-water. Extraction with ether followed by distillation of the extract gave 4.5 g. (90% recovery) of the dithiol.

Oxidation of 3,5,5-Trimethyl-1,1-hexanedithiol by Nitric Acid.—The *gem*-dithiol (37.4 g.) was added dropwise to 520 ml. of well-stirred, 16 *N* nitric acid at such a rate that a temperature of 95–105° was maintained. After an additional 1.5 hours at this temperature, the mixture was diluted with 600 ml. of water and extracted with ether. Treatment of the aqueous layer with barium hydroxide precipitated 38.2 g. (84% yield) of barium sulfate. Distillation of the ether extract through a 36-inch spinning-band column showed that it contained about 10 g. (36% yield) of acid A, b.p. 93–97° (6 mm.), $n^{25}\text{D}$ 1.4212, and 15 g. (49% yield) of acid B, b.p. 103–104° (6 mm.), $n^{25}\text{D}$ 1.4275, neut. equiv. 158. The infrared absorption spectrum of acid B was identical with that of a sample of 3,5,5-trimethylhexanoic acid.[18] Acid A had the composition of 2,4,4-trimethylpentanoic acid.[19]

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.6; H, 11.1; neut. equiv., 144. Found: C, 66.8; H, 11.4; neut. equiv., 146.

Acknowledgments.—This work was done with the help of many people in our laboratories, among whom should be mentioned J. R. Downing and D. M. Huck, who interpreted the spectra, and H. S. Young, who made many valuable suggestions.

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[18] A. A. Pavlic (to E. I. du Pont de Nemours and Co.), U. S. Patent 2,470,859 (1949); W. M. Bruner, *Ind. Eng. Chem.*, **41**, 2860 (1949).

[19] F. C. Whitmore, C. I. Noll, J. W. Heyd and J. D. Surmatis, THIS JOURNAL, **63**, 2028 (1941).

WILMINGTON, DELAWARE

[CONTRIBUTION NO. 308 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

Synthesis of Pyrimidines and Pyridines from Acetylene and Nitriles

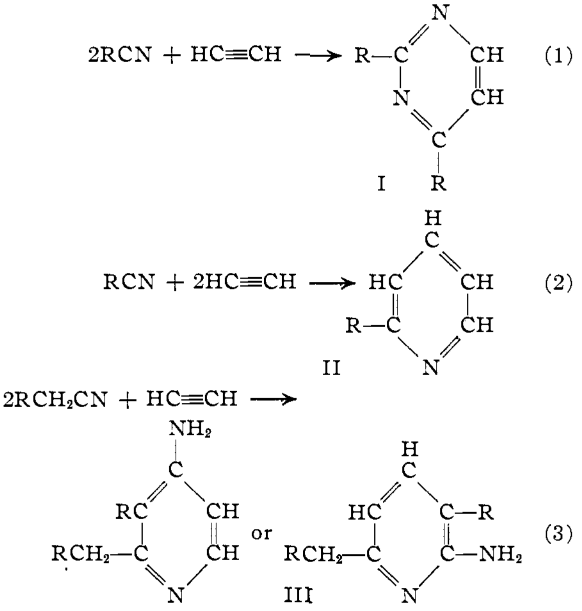
BY T. L. CAIRNS, J. C. SAUER AND W. K. WILKINSON

RECEIVED JANUARY 30, 1952

Discovery of a new reaction of acetylene with nitriles has led to synthesis of 2,4-disubstituted pyrimidines in yields up to 51%. In the propionitrile/acetylene reaction, 2,4-diethylpyrimidine and an isomeric aminopyridine were both obtained. In the benzonitrile/acetylene reaction, 2-phenylpyridine was obtained as a minor by-product.

A new reaction between acetylene and nitriles yielding principally pyrimidines and in some cases pyridines, has been discovered. Previously, pyrimidines have frequently been made by adding amidines to β-diketones or β-ketonic acids.[1] Certain alkylated pyridines have been synthesized by allowing acetylene (or acetaldehyde) to react with ammonia or hydrogen cyanide.[2,3]

It has now been found that 2,4-disubstituted pyrimidines can be prepared in yields of up to 51%[4] from a mononitrile such as acetonitrile, propionitrile, isobutyronitrile or benzonitrile with acetylene in the presence of an alkali metal catalyst. From propionitrile, an aminopyridine isomeric with the pyrimidine was obtained in about the same yield as the pyrimidine. In the case of benzonitrile, small amounts of 2-phenylpyridine were isolated, in addition to the 2,4-diphenylpyrimidine. The reactions are illustrated by the equations



The formation of these products can perhaps be best explained by means of a carbanion mechanism. Under the reaction conditions, the following ions

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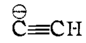
[1] P. Karrer, "Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1950, pp. 818–819.

[2] J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., Waverly Press, Baltimore, Maryland, 1949, p. 60.

[3] R. C. Elderfield, "Heterocyclic Compounds," Volume I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 455.

[4] J. C. Sauer and W. K. Wilkinson, U. S. Patent 2,524,479 (1950).

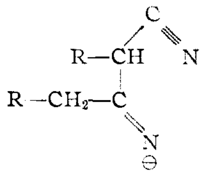
may initially be present for inducing subsequent reactions leading to pyrimidines and pyridines.


$\overset{\ominus}{C}\equiv CH$

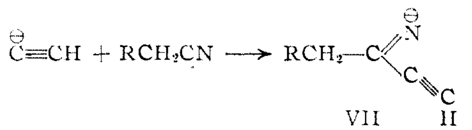
IV


$R\overset{\ominus}{C}HCN$

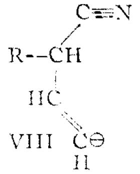
V


VI

Thus, it is visualized that the acetylide ion (IV) can react with the nitrile to give the intermediate ion (VII) which in turn reacts with more nitrile to give the pyrimidine (I) or with more acetylene to give the pyridine (II). In the formation of the


VII

4-aminopyridine (III) it is postulated that the ion (VI)[5] reacts with acetylene. The isomeric 2-aminopyridine (III) could be formed by the interaction of carbanion (V) with acetylene to give (VIII) which reacts with a second molecule of nitrile.


VIII

A convenient procedure for carrying out the synthesis involved injecting acetylene at 13–17 atmospheres pressure into a rocker bomb containing the nitrile and alkali metal heated to 175–200°. Acetylene was repressured as required. After the bomb was cooled and excess acetylene vented, the reaction mixture was purified by distillation, and the products were characterized by spectral and elemental analyses, neutral equivalent, suitable derivatives and in some cases by comparison with authentic samples.

Experimental

Source and Purification of the Materials.—The nitriles were commercial or Eastman Kodak chemicals and were purified by distillation. Commercial grade acetylene obtained from the Air Reduction Sales Company was passed through a series of scrubbers containing, in order, Fieser solution, calcium chloride, activated alumina and sodium hydroxide pellets. The ultraviolet absorption spectra were determined on a Cary Recording Spectrophotometer Model No. 11. All determinations were in chloroform solvent and the *k* values are expressed as specific absorption coefficients. Yields were based on the amount of nitrile consumed.

Acetonitrile/Acetylene Reaction.—To 156 g. of chilled acetonitrile was cautiously added 2 g. of potassium in small portions. After the reaction between the nitrile and the potassium was complete, the mixture was transferred to a 500-ml. stainless steel rocker bomb which had been previously flushed with nitrogen. The bomb was pressure-tested with nitrogen at 36 atmospheres pressure, then cooled in a "Dry Ice"/methanol cooling bath and evacuated to about 10 mm. pressure. The equipment was installed behind a heavy barricade and all operations with acetylene were controlled from the outside. With a bomb temperature slightly under 0°, acetylene under 8 atmospheres pressure was applied and the reaction mixture was heated to 175°. When this temperature was reached, additional acetylene pressure was applied until the bomb gage reached 16 atmospheres. The pressure was maintained at 16–17 atmospheres by periodic repressuring with acetylene for 7 hours while the temperature was slowly increased to 200°. The bomb was then cooled to room temperature, pressure released and the contents removed. The brownish reaction mixture was filtered and the filtrate distilled. There was recovered 71 g. of acetonitrile. The liquid distilling at 43–135° (9–12 mm.) was refractionated and 9 g. of 2,4-dimethylpyrimidine (I, R = CH_3) distilling at 37–41° (13 mm.) was isolated (8.2% yield). A larger sample of 2,4-dimethylpyrimidine, composited from several runs, was further characterized as follows: b.p. 150–151°; m.p. −4°; $n^{25}D$ 1.4880. *Anal.* Calcd. for $C_6H_8N_2$: C, 66.5; H, 7.4; N, 25.9; neut. equiv., 108. Found: C, 66.3; H, 7.6; N, 25.8; neut. equiv., 112.

The picrate, prepared under the usual conditions, was recrystallized from alcohol, m.p. 137–140.5°. A mixed m.p. with a sample from the 2,4-dimethylpyrimidine prepared by the literature[6] method was 140–141°. *Anal.* Calcd. for $C_{12}H_{11}O_7N_5$: C, 42.8; H, 3.3; N, 20.8. Found: C, 43.3; H, 3.3; N, 20.9.

The dibenzal derivative was prepared by the literature[6] method, m.p. 142–143°. A mixed m.p. with the authentic sample was 141–143°. *Anal.* Calcd. for $C_{20}H_{16}N_2$: C, 84.4; H, 5.6; N, 9.9. Found: C, 84.0; H, 5.6; N, 10.4.

Samples prepared by the literature and the acetylene methods had identical odors strongly resembling the characteristic odor of acetamide.

Spectral data are shown in Fig. 1. This accumulation of data eliminates the possibility of the formation of the isomeric 3,6-dimethylpyridazine or 2,3-dimethylpyrazine.

Propionitrile/Acetylene Reaction.—Using the procedure outlined above 250 g. of propionitrile and 4 g. of potassium were treated with acetylene for 8 hours at 180° and a gage pressure of 14–20 atmospheres. Distillation of the reaction mixture gave two products. These products have been characterized as 2,4-diethylpyrimidine (I, R = C_2H_5) and an isomeric higher-boiling product assigned the aminopyridine structure III (R = CH_3).

(a) **2,4-Diethylpyrimidine** (I, R = C_2H_5).—By distillation there was obtained 29.8 g. of this compound, b.p. 68–72° (15 mm.) (9.7% yield). A redistilled sample had a boiling point of 85-86° (28 mm.), $n^{25}D$ 1.4829. This compound had the expected ultraviolet absorption spectrum (see Fig. 1) and neutral equivalent. Unexpectedly, a solid picrate could not be prepared. *Anal.* Calcd. for $C_8H_{12}N_2$: C, 70.5; H, 8.9; N, 20.5; neut. equiv., 136. Found: C, 70.65; H, 8.99; N, 20.3; neut. equiv., 139.

(b) **High-boiling Fraction** (postulated to be either 2-ethyl-3-methyl-4-aminopyridine or 2-amino-3-methyl-6-ethylpyridine (III, R = CH_3)).—From the reaction mixture mentioned above was also obtained 38.6 g. of an isomeric liquid, b.p. 116° (15 mm.), $n^{25}D$ 1.5531 (12.5% yield). The compound slowly crystallized at room temperature, m.p. 55–60°. *Anal.* Calcd. for $C_8H_{12}N_2$: C, 70.5; H, 8.9; N, 20.5; neut. equiv., 136. Found: C, 70.96; H, 9.17; N, 20.5; neut. equiv., 141.9.

The acetyl derivative of III, prepared by weighing a sample into excess acetic anhydride and refluxing for one hour, also contained one basic group (perchloric acid titration). This is in keeping with the fact that amino groups in 2- or 4-aminopyridines are actually amide-like in character.[7]

Van Slyke Amino Determination.—The reaction in this determination proceeded rather sluggishly, indicating a weak primary amino group. *Anal.* Calcd. for $C_8H_{12}N_2$: primary amino group, 11.7. Found: primary amino group, 10.56 in 90 min. and 9.83 in 60 min.

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(5) For an analogous mechanism involving the dimerization of nitriles, see G. A. Reynolds, W. J. Humphlett, F. W. Swamer and C. R. Hauser, *J. Org. Chem.*, **16**, 165 (1951).

(6) J. Schmidt, *Ber.*, **35**, 1577 (1902).

(7) A control experiment with an authentic sample of 2-aminopyridine (Reilly Tar and Chemical Corp.) also contained one basic group according to the perchloric acid titration procedure. *Anal.* Calcd. for $C_5H_6N_2$: neut. equiv., 94, 94.8. An authentic sample of the acetyl derivative (R. Camps, *Arch. Pharm.*, **240**, 349 (1902); *Chem. Zentr.*, **73**, II, 647 (1902)), also contained one basic group according to the perchloric acid titration procedure. *Anal.* Calcd. for $C_7H_8ON_2$: neut. equiv., 136. Found: neut. equiv., 143.7.

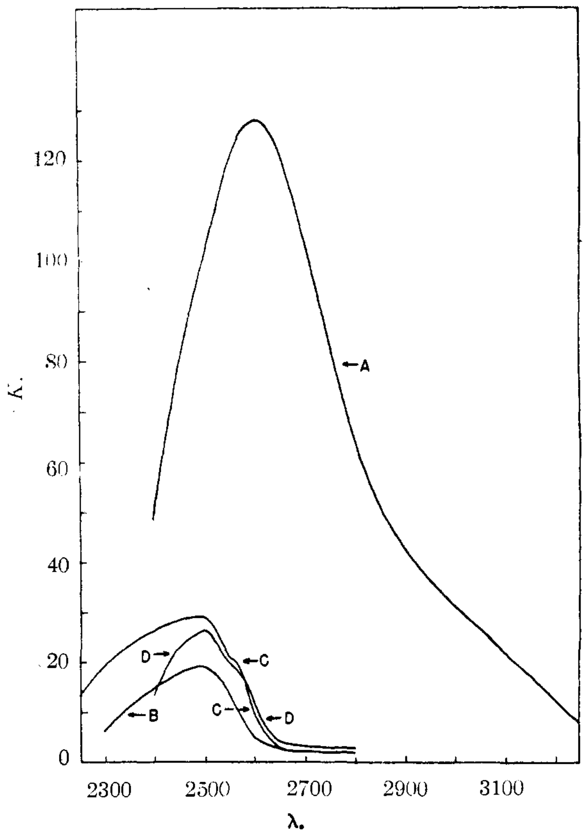

Fig. 1.—A, 2,4-diphenylpyrimidine; B, 2,4-diisopropylpyrimidine; C, 2,4-dimethylpyrimidine; D, 2,4-diethylpyrimidine.

Picrate.—A picrate was prepared by adding 0.10 g. of this compound to 10 ml. of a saturated solution of picric acid in alcohol. Recrystallization from alcohol gave a yellow picrate melting at 196.5°. *Anal.* Calcd. for $C_{14}H_{15}N_5O_7$: N, 19.1. Found: N, 19.11.

Acetyl Derivative.—The aminopyridine (III, 15 g.) was mixed with 30 g. of acetic anhydride. Some heat was evolved and the solution was set aside at 4° for one hour. After subsequent standing for 3 days at room temperature the reaction mixture was dissolved in 100 ml. of ether, washed with aqueous sodium carbonate, and the ether layer dried over anhydrous sodium carbonate. After stripping the ether, the residual liquid was distilled and the fraction distilling at 167–170° (15 mm.) was saved. This fraction slowly crystallized at room temperature, m.p. 93–96°. *Anal.* Calcd. for $C_{10}H_{14}N_2O$: C, 67.7; H, 7.9; N, 15.7. Found: C, 67.17; H, 8.27; N, 15.62.

Ultraviolet Spectral Data.—The ultraviolet spectrum for III is shown in comparison with 2-aminopyridine in Fig. 2. It will be noted that maxima occur at about 2400 and 2900 Å. for both III and 2-aminopyridine. Worth mentioning (but not shown in Fig. 2) is a comparison of pyridine: aminopyridine (III) with benzene:aniline. In going from pyridine to III, the *k* values increase from about 3.0 to 43 with a shift of about 375 Å. to the longer wave lengths. Similarly, in going from benzene to aniline, the *k* values increase from about 2.2 to 19.5 with a shift of about 285 Å. to the longer wave lengths.[8]

Isobutyronitrile/Acetylene Reaction.—Using the procedure outlined above, 150 g. of isobutyronitrile and 1 g. of potassium were treated with acetylene for 6 hours at 200° at a gage pressure of 15–20 atmospheres. By distillation there was recovered 90 g. of isobutyronitrile. The diisopropylpyrimidine (I, R = $(CH_3)_2CH$) distilled at 77–84° (15 mm.), n^{25}_D 1.4721 (21 g., 29.4% yield). *Anal.* Calcd. for $C_{10}H_{16}N_2$; C, 73.2; H, 9.8; N, 17.0; neut. equiv., 164. Found: C, 73.03, 73.03; H, 9.86, 9.76; N, 16.48, 16.33; neut. equiv., 167.2, 167.5.

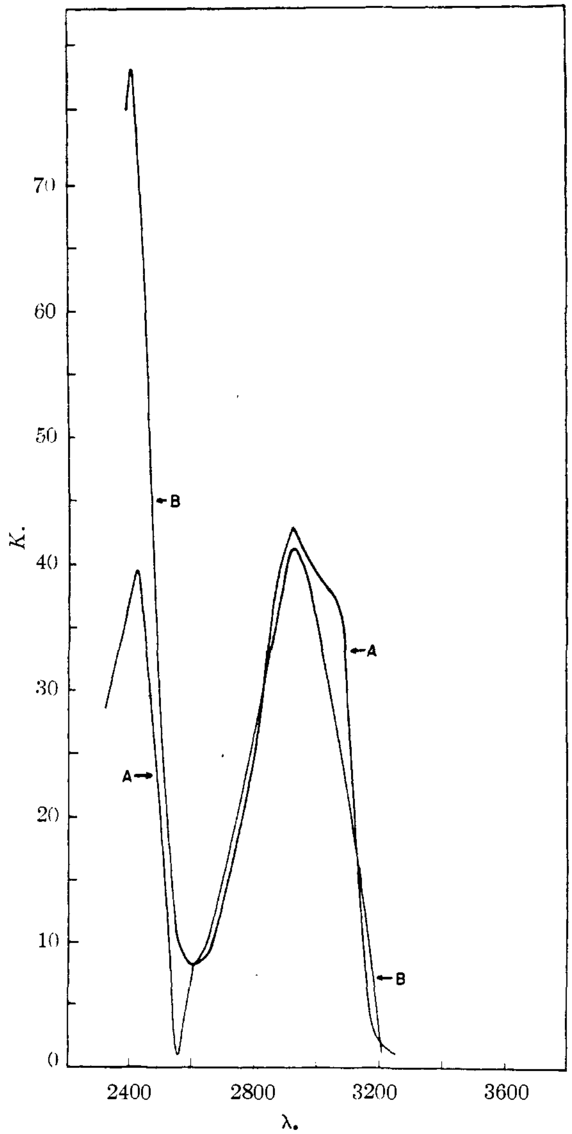

Fig. 2.—A, 2-methyl-3-ethyl-4-aminopyridine; B, 2-aminopyridine.

The pyrimidine formed a picrate readily. *Anal.* Calcd. for $C_{16}H_{19}N_5O_7$: C, 48.8; H, 4.8; N, 17.8. Found: C, 49.1, 49.2; H, 4.9, 4.9; N, 18.03, 18.09.

The ultraviolet absorption spectrum is very similar to the spectrum of dimethylpyrimidine (Fig. 1).

Benzonitrile/Acetylene Reaction.—Using the procedure outlined above, benzonitrile (200 g.) and potassium (2 g.) were treated with acetylene at a gage pressure of 13–16 atmospheres for 6.2 hours, while the temperature was maintained at 170–180°. From the crude products of two duplicate runs there were obtained 2-phenylpyridine (II, R = C_6H_5, 11 g., 1.8% yield) distilling at 142–145.5° (13 mm.), n^{25}_D 1.6147, and 2,4-diphenylpyrimidine (I, R = C_6H_5, 130 g., 29% yield) distilling at 195–200° (2–4 mm., n^{25}_D 1.6543).

Characterization of 2-Phenylpyridine.—*Anal.* Calcd. for $C_{11}H_9N$: C, 85.1; H, 5.8; N, 9.1. Found: C, 84.0; H, 6.0; N, 10.5.

The picrate was recrystallized from alcohol, m.p. 172–172.5°. A mixed m.p. with an authentic[9] sample melted at 171–172°. *Anal.* Calcd. for $C_{17}H_{12}O_7N_4$: C, 53.2; H, 3.1; N, 14.6. Found: C, 53.3; H, 3.5; N, 14.8.

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(8) API Ultraviolet Absorption Spectra Curve No. 1 for Benzene and Curve No. 106 for Aniline.

(9) F. W. Bergstrom and S. H. McAllister, THIS JOURNAL, **52**, 2845 (1930).

Characterization of 2,4-Diphenylpyrimidine.—The viscous distillate, $n^{25}D$ 1.6543, slowly crystallized to a yellow solid, m.p. 58–59°. *Anal.* Calcd. for $C_{16}H_{12}N_2$: C, 82.8; H, 5.2; N, 12.0; neut. equiv., 232. Found: C, 83.0; H, 5.3; N, 11.7; neut. equiv., 249.

In comparing the ultraviolet spectrum of 2,4-diphenylpyrimidine with the spectra of the aliphatic pyrimidines, the former was found to have a greater absorption coefficient and the peak was shifted slightly to the longer wave length.

In another run, benzonitrile (125 g.) and potassium (2 g.) were treated with acetylene at a gage pressure of 10–15 atmospheres for 14 hours, while the temperature was maintained at 180–200°. There was recovered 25 g. of benzonitrile (b.p. 62–70° (7 mm.)). The 2,4-diphenylpyrimidine distilled at 190–194° (3 mm.) (57 g., 51% yield).

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

Transesterification. II. Esters of Strong Organic Acids

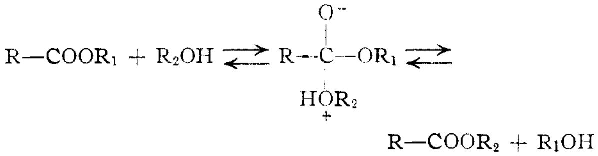
BY ALFRED R. BADER AND HENRY A. VOGEL

RECEIVED FEBRUARY 22, 1952

The transesterification of β-keto esters has been compared with that of esters of other strong organic acids. Malonates and oxalates, like acetoacetates, are transesterified under mild conditions, and it is suggested that the ease of transesterification of β-keto esters is due mainly to special structural features inherent in these esters, while that of oxalates is due to the inductive effect of the neighboring group.

In our first communication[1] we reported on the transesterification of β-keto esters which proceeds at steam-bath temperatures in the absence of catalysts. We have now completed a qualitative study of transesterifications of acids of strength similar and greater than that of acetoacetic acid to determine whether this facile transesterification is due to the inductive effect of the acetyl group, to intermolecular catalysis by active hydrogen or to structural features unique in β-keto esters. Table I lists the acids investigated, their ionization constants and the products obtained after heating representative primary and secondary alcohols with excess ester on the steam-bath without catalysts for 16 hours.

In any ester interchange one has the equilibria



$$R{-}COOR_1 + R_2OH \rightleftharpoons R{-}\overset{\overset{\large O^-}{|}}{\underset{\underset{+}{HOR_2}}{\underset{|}{C}}}{-}OR_1 \rightleftharpoons R{-}COOR_2 + R_1OH$$

the equilibrium constants of which are probably not greatly different from 1[2] and the reason for the ease of transesterification of acetoacetates at first considered most likely was the inductive effect of the acetyl group which removes electrons from the ester carbonyl, increases its electrophilic reactivity and thus the speed with which the equilibria are set up. A correlation is that acetoacetic acid is over ten times as strong an acid as acetic. Our qualitative data indicate, however, that the inductive effect can only be a mildly contributory factor in the ease of transesterification of β-keto esters because esters of some stronger acids do not react under our experimental conditions. Nor does it seem likely that the ease of transesterification of β-keto esters is due to an active hydrogen catalysis because we have found that when alcohols are heated in unreactive esters such as ethyl butyrate containing ethyl acetoacetate in a molar ratio of 10:1, the higher acetoacetate is the sole reaction product. Such experiments are, however, not entirely conclusive because one would expect the acetoacetate to be the more basic ester and its reaction might be the only one catalyzed.

TABLE I

Acid	$10^5 K_1$ at 25°	Products
Caprylic	1.44[a]	None
Butyric	1.50[b]	None
Crotonic	2.03[b]	None
Levulinic	......	None
Benzoic	6.27[b]	None
Lactic	13.9[c]	None
Acetoacetic	26[d]	Acetoacetates
Benzoylacetic	......	Benzoylacetates
Furoic	68[e]	None
Fumaric	95.7[f]	Small amt. fumarates
Tartaric	104[g]	None
Phthalic	112[h]	None
Malonic	177[f]	Mixed and symm. malonates
Ethyl-*n*-butylmalonic	......	None
Maleic	1200[f]	None
Oxalic	5900[i]	Mixed and symm. oxalates

[a] C. G. Derrick, THIS JOURNAL, **33**, 1152 (1911). [b] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939). [c] A. W. Martin and H. V. Tartar, THIS JOURNAL, **59**, 2672 (1937). [d] K. J. Pedersen, *J. Phys. Chem.*, **38**, 993 (1934). [e] W. L. German, G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1604 (1937). [f] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 201. [g] I. Jones and F. G. Soper, *J. Chem. Soc.*, 1836 (1934). [h] W. J. Hamer, G. D. Pinching and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 539 (1945); *C.A.*, **40**, 3044 (1946). [i] R. Gane and C. K. Ingold, *J. Chem. Soc.*, 2153 (1931).

After the completion of this work, our attention was drawn to a paper by Carroll[3] which independently describes the facile alcoholysis of acetoacetic and related esters. Carroll attempted to determine the rates of transesterification of acetoacetates by measuring the rates of distillation of lower alcohols evolved, and on the basis of these possibly inaccurate data concluded that the rate determining step is first order with respect to the ester when pri-

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[1] A. R. Bader, L. O. Cummings and H. A. Vogel, THIS JOURNAL, **73**, 4195 (1951).

[2] P. R. Fehlandt and H. Adkins, *ibid.*, **57**, 193 (1935).

[3] M. F. Carroll, *Proc. XIth. Intern. Congr. Pure and Applied Chem.*, **2**, 39 (1947); *C. A.*, **45**, 7015 (1951).