## Summary

1. A micro-technique for the separation of amino acids, peptides and proteins has been developed.

2. The technique is carried out by applying an electrical potential across the ends of strips of filter paper saturated with electrolyte solution. At some intermediate position of these strips, the mixture to be separated is applied.

3. The course of separations is followed in the case of amino acids and peptides by ninhydrin treatment; in the case of protein separations by coagulation and selective dyeing *in situ* and in the case of radioactive components by autoradiography.

FORT KNOX, KENTUCKY RECEIVED JULY 28, 1949

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# Some New β-Diketones Containing the Trifluoromethyl Group[1a]

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In the course of studies on the properties of β-diketones, it was desired to investigate effects of the trifluoromethyl group in such molecules. Accordingly, a number have been prepared of the type $RCOCH(R')COCF_3$. These are described in Table I. Copper chelates and oximes which were prepared from them as characterizing derivatives, are also described there.

All the diketones but one were prepared by the Claisen condensation between ethyl trifluoroacetate[2] and a series of alkyl methyl and aryl methyl ketones, with excellent yields.

The exception, 1-acetyl-1-trifluoroacetylethane, was prepared by methylating the sodium salt of acetyltrifluoracetone with methyl iodide. The yield in this step was very low.

On four of the compounds, measurements of the rate and equilibrium constants and the heat of activation for the keto $\leftrightarrows$ enol process were made, using the bromine titration method to obtain the rate of enolization and extrapolating to zero time to obtain the equilibrium constant.

## Experimental[3]

### Synthesis of the Diketones

The Claisen condensation was carried out using standard technique.[4] To a suspension of 1.05 mole of commercial sodium methoxide in 100 cc. of dry ether[5] was added dropwise 1.00 mole of ethyl trifluoracetate with stirring, which was followed by 1.00 mole of the selected methyl ketone. The mixture was allowed to stand overnight to complete the reaction, then worked up as described below for the individual ketones.

**Acetyltrifluoroacetone.**[6]—This compound is not new; however, the procedure used for working up the reaction mixture is described here as it represents a modification of that used by Henne, *et al.*[5b] Ethyl trifluoroacetate was condensed with acetone and the reaction mixture was evaporated to dryness at reduced pressure (oil pump) then heated at 90° for twelve hours to remove alcohol from the sodium salt. If this was not done, an azeotrope was encountered in the subsequent distillation which reduced the amount of product obtained in pure form. The salt was then stirred with one mole of 10% sulfuric acid to liberate the diketone, which was drawn off. Product remaining in the water phase was extracted with ether. After drying with calcium chloride[7] and distilling, a yield of 80% of purified product was obtained. The diketone in the tailings could be recovered by making the copper chelate, purifying this and releasing the ketone either by steam distillation from 10% sulfuric acid or by treatment in ether solution with hydrogen sulfide.

**Propionyltrifluoroacetone, isovaleroyltrifluoroacetone, 1-propionyl-1-trifluoroacetylethane** and **2-naphthoyltrifluoroacetone** were prepared from ethyl methyl ketone, methyl isobutyl ketone, diethyl ketone and 2-naphthyl methyl ketone, respectively, in the same way as acetyltrifluoroacetone.

2-Naphthoyltrifluoroacetone, which is a solid was separated directly from the acidified sodium salt and purified by crystallization from dilute ethanol.

With diethyl ketone the reaction was slower than usual and forty-eight hours was allowed for completion.

That the condensation with ethyl methyl ketone occurred at the α-methyl carbon rather than at either carbon of the ethyl group was shown by demonstrating that the product formed a copper chelate and that this was different from the one obtained from the diketone formed by direct methylation of acetyltrifluoroacetone (see Table I).

**Heptoyltrifluoroacetone, benzoyltrifluoroacetone, *p*-fluorobenzoyltrifluoroacetone** and **2-furoyltrifluoroacetone** were prepared from *n*-hexyl methyl ketone, acetophenone, *p*-fluoroacetophenone and 2-furyl methyl ketone, respectively. The reaction mixture was worked up by releasing the diketone with one mole of 10% sulfuric acid and converting it to the copper chelate. After drying, the chelate was subjected to steam distillation to remove volatile impurities. Sulfuric acid was then added to bring the concentration to 10% and the diketone was obtained by further steam distillation. After separation from the water in the distillate it was dried with calcium chloride and distilled at reduced pressure if liquid or crystallized from dilute ethanol if solid.

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(1a) Work described in this paper was sponsored by the Atomic Energy Commission.

(1b) National Cancer Institute, National Institutes of Health, Bethesda 14, Maryland.

(2) (a) Henne, Alderson and Newman, THIS JOURNAL, **67**, 918 (1945); (b) Henne and Trott, *ibid.*, **69**, 1820 (1947); (c) Reid, *ibid.*, **69**, 2069 (1947).

(3) All melting points are corrected except as noted.

(4) (a) "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 266. (b) Henne, Newman, Quill and Staniforth, THIS JOURNAL, **69**, 1819 (1947).

(5) Benzene also serves well as a solvent.

(6) Only the oxime of this compound is new (see ref. 5b). The ketone and its chelate are listed for convenience.

(7) A considerable amount of water is not removed by the calcium chloride and forms a water–ketone azeotrope in the distillation, which lowers the yield of pure product. This azeotrope separates into two phases on condensation and when preparing large batches, it is advantageous to utilize this behavior to dry the product by using a separating distilling head which takes off the water-rich (upper) layer and returns the ketone-rich phase to the still.

**2-Thenoyltrifluoroacetone** and **p-phenylbenzoyltrifluoroacetone** were prepared from acetothienone and *p*-phenylacetophenone, respectively. The copper chelates of these two compounds do not dissociate satisfactorily in acid. Phenylbenzoyltrifluoroacetone was purified by treatment with hydrogen sulfide of an ether solution of the recrystallized copper chelate. After removal of copper sulfide the diketone was purified by vacuum sublimation.

In small runs, thenoyltrifluoroacetone was purified through the magnesium chelate, which was made by dissolving the ketone in benzene and stirring it vigorously for two hours in contact with a 50% excess of an aqueous solution of magnesium acetate. In order to drive the chelation reaction to completion, sufficient ammonia was added to adjust the final *p*H to 6.5. The chelate was purified and decomposed as in the case of acetyltrifluoroacetone. In runs large enough to permit the use of an efficient column it was found preferable to acidify the sodium salt, dry the liberated ketone and distil it at reduced pressure through a column with twenty-five theoretical plates.

**1-Acetyl-1-trifluoroacetylethane.**—A mixture of 37.7 g., 0.245 mole, of acetyltrifluoroacetone, 13.2 g., 0.245 mole of commercial sodium methoxide and 71.0 g., 0.50 mole, of methyl iodide in 75 cc. of dry benzene was heated sixty hours at 90° in a glass vessel placed in a steel bomb. The reaction mixture was shaken with 0.25 mole of 10% sulfuric acid and the benzene layer was drawn off and fractionally distilled at reduced pressure.

**Copper Chelates of the Diketones.**—Chelates of the diketones were easily prepared by adding an alcoholic solution of the ketone to an excess of aqueous cupric acetate solution. The chelate was obtained by filtration or extraction with ether and purified by recrystallization. Dilute alcohol was best for this purpose with the more soluble chelates. For the less soluble ones, 95% ethanol or xylene proved useful. All chelates were heated two hours at 100° *in vacuo* before analysis.

**Oximes of the Diketones.**—The conditions under which the oximes were prepared may be illustrated with acetyltrifluoroacetone. Two grams, 0.013 mole, of ketone was shaken with 25 cc. of 0.5 *N* hydrochloric acid. Alcohol was added as necessary to get the ketone into solution. Then a solution of 1.78 g., 0.026 mole of hydroxylamine hydrochloride in a little water was added. After standing overnight, the oxime was filtered off, recrystallized from hot water or dilute alcohol and dried in air. The oximes were all obtained as colorless solids, characterized by remarkable volatility and stability.

**Analyses.**—We are indebted to Mr. Charles W. Koch for the analytical work described in this paper. In order to burn these compounds completely in the micro Liebig combustion, Mr. Koch has found it necessary to use a furnace temperature of 900° with a quartz combustion tube containing Pregl universal packing followed by a silver and a lead dioxide plug. One tube will serve for about ten combustions, then falls apart from attack by the fluorine. All analyses were done in duplicate; average values are given in Table I.

## Rate Measurements

**Assay of Ketones.**—The purity of the ketones was determined by utilizing the fact that they are all acidic enough to titrate. The assay procedure consisted of dissolving a weighed amount of ketone in 3 cc. of ethanol, adding a measured excess of tenth normal alkali and back titrating with tenth normal hydrochloric acid using a glass electrode. The purity of all the ketones used was established in this way to be 99% or better.

**Reagents.**—C. P. benzene was used for measurements in that solvent.

A stock solution of 1 cc. of C. P. bromine in 39 cc. of absolute ethanol was made up before the start of each run. Solutions more than six hours old were not used as they gave a blank on aging, presumably due to the formation of bromoacetaldehyde. Higher concentrations of bromine were avoided for the same reason. A satisfactory blank was considered to be one of less than 0.05 cc. Two cubic centimeters of the solution were used for the determination

TABLE I

PHYSICAL CHARACTERISTICS OF THE DIKETONES AND THEIR DERIVATIVES[3]

| | | Diketones | | | | | Copper chelates | | | | | Oximes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Analyses, % | | | | | Analyses, % $^{j}$ | | | |
| | | B. p. (mm.) or m. p. | | | | | | Carbon | | Hydrogen | | | Carbon | | Hydrogen | |
| R | R′ | °C. | Mm | $d$ | $n_D$/°C. | Yield, % | M. p., °C. | Calcd. | Found | Calcd. | Found | M. p. | Calcd. | Found | Calcd. | Found |
| $CH_3$[4] | H | 107 | 760 | 1.27 | 1.3893/21 | 80 | 189$^{g}$ | ... | ... | .. | .. | 86–87 | 35.31 | 35.62 | 3.57 | 3.74 |
| $CH_3$ | $CH_3$ | 123 | 755 | 1.22 | 1.356 | 4.9 | 170.4–171.9$^{h}$ | 36.22 | 36.01 | 3.04 | 3.19 | ......... | ... | ... | .. | .. |
| $C_2H_5$ | H | 124 | 755 | 1.22 | 1.3951/20.5 | 84 | 154.5–155.3$^{g}$ | 36.22 | 36.46 | 3.04 | 3.20 | 64.2–65.6 | 39.35 | 39.33 | 4.40 | 4.63 |
| $C_2H_5$ | $CH_3$ | 74 | 43 | 1.22 | 1.3921/20 | 45 | 164–165$^{h}$ | 39.51 | 39.87 | 3.77 | 3.87 | 88–90 | 42.65 | 42.64 | 5.63 | 5.27 |
| *i*-$C_4H_9$ | H | 78 | 64 | 1.13 | 1.4103/19 | 87 | 124.5–125.3$^{g}$ | 42.33 | 42.32 | 4.22 | 4.51 | 90.1–91.4 | 45.50 | 45.58 | 5.58 | 5.80 |
| *n*-$C_6H_{13}$ | H | 65 | 6 | 1.09 | 1.4196/23 | 55 | 71–72$^{g}$ | 47.12 | 47.05 | 5.54 | 5.58 | ......... | ... | ... | .. | .. |
| Phenyl | H | 224 | 760 | | | | | | | | | | | | | |
| | | 39.0–40.5$^{a,b}$ | | | | 70 | 243–244$^{h}$ | 55.83 | 55.82 | 3.28 | 3.56 | 143.3–144.1 | 51.93 | 52.55 | 3.49 | 3.74 |
| *p*-Xenyl | H | 100.1–101.1$^{a,c}$ | | | | 55 | 303$^{h}$ | 59.60 | 60.59 | 3.15 | 3.49 | 191–192 | 51.95 | 52.55 | 3.94 | 4.13 |
| *p*-Fluorophenyl | H | 40–42$^{a,d}$ | | | | 75 | 263–264$^{h}$ | 45.32 | 45.35 | 1.91 | 2.43 | 119.1–119.9 | 48.17 | 48.60 | 2.84 | 3.07 |
| 2-Naphthyl | H | 70.1–71.1$^{e}$ | | | | 45 | 278.5–279.5$^{h,i}$ | 56.61 | 26.33 | 2.72 | 3.38 | 136.9–137.9 | 59.80 | 59.97 | 3.59 | 3.68 |
| 2-Furyl | H | 19–21$^{a,f}$ | | | | 70 | 226–228$^{h}$ | 40.37 | 40.74 | 2.02 | 1.96 | 152.7–153.5 | 43.46 | 43.52 | 2.74 | 2.77 |
| 2-Thenyl | H | 42.5–43.2$^{a,f}$ | | | | 80 | 242–243$^{h}$ | 37.88 | 38.92 | | | 134.3–134.7 | 42.65 | 42.64 | 5.63 | 5.27 |

[a] M. p. [b] Calcd.: C, 55.83, H, 3.28; fd. C, 55.52, H, 3.56. [c] Calcd.: C, 65.75; H, 3.79; fd. C, 65.61; H, 3.98. [d] Calcd.: C, 51.30; H, 2.58; fd. C, 50.47; H, 2.74, [e] Calcd.: C, 46.62; H, 2.48; fd. C, 47.02; H, 2.81. [f] Calcd.: C. 43.22; H, 2.27; fd. C, 43.44; H, 2.60. [g] Blue. [h] Green. [i] Uncorrected. [j] Theoretical values are calculated for the monoxime.

Table II

Heats of Activation for Enolization and Rate Constants

| R | Solvent | Ketone molarity | Aliquot volume, cc.[a] | Temp., °C. | $k_e$ sec.$^{-1}$ enolization | $k_k$ sec.$^{-1}$ ketonization | $\Delta H$ kcal. activation |
|---|---|---|---|---|---|---|---|
| $CH_3$ | Water | 0.0824 | 10 | 25.0 | 0.0149 | 1.5 | |
| $CH_3$ | Water | .0412 | 10 | 25.0 | .0149 | 1.5 | |
| $CH_3$ | 0.1 $N$ HCl | .0824 | 10 | 25.0 | .0148 | .9 | |
| $CH_3$ | 0.5 $N$ HCl | .0824 | 10 | 25.0 | .0157 | 1.9 | |
| $CH_3$ | Water | .0824 | 10 | 14.0 | .00465 | .5 | |
| $CH_3$ | Water | .0824 | 10 | 0.0 | .000899 | . . .[b] | +19.7 |
| $(CH_3)_2CHCH_2$ | Water | .0140 | 35 | 25.3 | .0118 | .6 | |
| $(CH_3)_2CHCH_2$ | Water | .0149 | 35 | 14.0 | .00342 | .3 | +19.3 |
| Phenyl | Water | .00934 | 50 | 25.0 | .00855 | .6 | |
| Phenyl | Water | .00823 | 50 | 14.0 | .00372 | .2 | +13.0 |
| 2-Thenyl | Water | .00915 | 20 | 25.0 | .0101 | .6 | |
| 2-Thenyl | Water | .0103 | 20 | 14.0 | .00296 | .2 | +19.1 |

[a] Two cubic centimeters of alcoholic bromine were added, making the solvent medium during bromination actually a dilute alcohol solution of the corresponding concentration. [b] Because it was not possible to accurately measure $p$H at this temperature, the equilibrium constant and consequently $k_k$ were not calculated.

in water. The amount was increased to 3 cc. for those in benzene, because of the larger amount of enol in the latter solvent.

A solution of 10 g. of redistilled phenol in 90 cc. of 95% ethanol was prepared. Two cubic centimeters of this were used to interrupt the bromination in the experiments in which water was the solvent. In benzene the amount was increased to 4 cc.

In the experiments in water, 5 cc. of 0.2 $N$ aqueous potassium iodide was added after the phenol. For benzene, 10 cc. of a saturated solution in 95% ethanol was used.

**Bromination Procedure.**—A number of aliquots of ketone solution, sufficient to determine a rate curve, were placed in 50-cc. glass-stoppered erlenmeyer flasks and suspended in a thermostat. The size of the aliquot used was such that in no case did it contain more than 0.8 millimole of ketone. This assured that the quantity of bromine solution specified above would always provide a good excess of bromine. Aqueous ketone solutions were aged in the thermostat at least three hours before brominations were begun; benzene solutions were aged at least forty-eight.

Before the beginning of a run, a number of vials, each containing the volume of bromine solution necessary to brominate one ketone aliquot, were prepared and thermostated. Vials of phenol solution were also made ready; it was unnecessary to thermostat these.

To carry out a bromination, a vial of bromine was dumped into a ketone aliquot and mixed as quickly as possible (0.5 second). At the expiration of a measured time interval, a vial of phenol was added and mixed quickly to arrest the reaction. Then the potassium iodide solution was added and the flask was set aside for thirty to sixty minutes at room temperature to allow the liberation of iodine to take place. The shorter interval was used for water solution, the longer for benzene. The liberated iodine was titrated with tenth normal sodium thiosulfate. The benzene layer did not interfere in the titration.

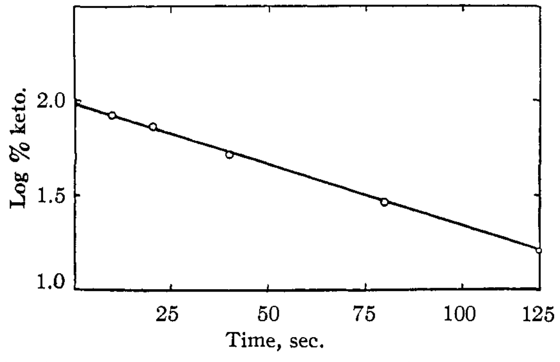

Fig. 1.—Rate of enolization of acetyltrifluoroacetone in water at 25.0°.

The liberation of iodine requires hydrogen ion, but enough is liberated by the reaction between excess bromine and phenol so that none need be added. In the benzene mixtures, however, a slight acceleration was obtained by adding a drop of 6 $N$ sulfuric acid.

The measurements in benzene solution were not rate measurements, but were confined to determination of per cent. enol in equilibrated ketone solutions. For this, a five second bromination time was used. A shorter time gave lower and unreproducible results because the enol does not brominate instantly in benzene. That five seconds was enough time to brominate all the enol present without allowing any appreciable additional enolization, was verified by observing that the same value for per cent. enol was obtained whether a five or fifteen-second interval was used.

## Results

**Kinetics.**—The rate of enolization in water fits the first order expression d(keto)/d$t$ = $-k_e$ (keto). The closeness of the fit is indicated in Fig. 1 which shows the curve for acetyltrifluoroacetone from 0.0–80% completion. Table II shows the values for the rate constants for all the ketones studied.

Doubling the bromine concentration had no effect on the rate constant; neither did decreasing the ketone concentration by half.

The effect of hydrogen ion concentration on the rate constant must be small because although the bromination liberates acid, the rate curve does not bend noticeably even at 80% reaction. This point was checked for acetyltrifluoroacetone by making rate determinations in 0.1 $N$ and 0.5 $N$ hydrochloric acid. The rate constant increases about 5% between acidities corresponding to $p$H 2.8 and 0.5 $N$.

Since the bromine was added as an alcoholic solution, the rate constants refer to dilute alcohol as solvent. It was necessary to use 2 cc. of the solution in order to have enough bromine to react with all the ketone, and since the volume of ketone aliquot varied from 10–50 ml. depending on the solubility of the particular ketone, the concentration of alcohol was appreciable and different for different ketones. However, a series of determinations on acetyltrifluoroacetone in solutions containing various concentrations of alcohol show that the effect of alcohol concentration on the rate of enolization is negligible below 30% (see Table III).

TABLE III

DEPENDENCE OF ENOLIZATION RATES AND EQUILIBRIA AT 25.0° FOR ACETYLTRIFLUOROACETONE ON ETHANOL CONCENTRATION

Molarity of ketone 0.08–0.09

| Vol. % ethanol[a] | $k_e \times 10^2$ sec.$^{-1}$ | % (enol + enolate) at equilibrium[b] | Vol. % ethanol |
|---|---|---|---|
| 16 | 1.49 | 2.5 | 0 |
| 33 | 1.37 | 4.5[c] | 20 |
| 50 | 1.37 | 3.7 | 40 |
| 67 | 1.26 | 3.1 | 60 |
| 83 | 0.927 | 8.1 | 80 |
| 95 | .644 | 20.7 | 95 |

[a] The ketone was dissolved and equilibrated in alcohol of the concentration specified in the fourth column, and the values for % (enol + enolate) refer to these concentrations. To measure the rates, 10-cc. aliquots were brominated by adding 2 cc. of alcoholic bromine solution, so the rate measurements refer to alcohol concentrations larger by the amount added with the bromine. These concentrations are listed in the first column. [b] Because of the uncertainty in relating hydrogen ion concentration to *p*H in solutions containing much alcohol, no attempt was made to correct the equilibrium values for enolate in the manner used for Table IV. [c] Probably too high.

The rate of enolization was not determined in benzene because the amount of the keto form present in this solvent is so small that accurate rate determinations could not be obtained. Rough experiments showed that enolization is very much slower in benzene than in water though, requiring some hours for completion.

**Effect of Temperature on Rate.**—The rate of enolization increases about three-fold between 14 and 25°. These were the only two temperatures systematically investigated. Heats of activation are given in Table II. A determination was also made at 0° for acetyltrifluoroacetone, so that the heat of activation for this compound rests on three points. Figure 2 shows log $k_e$ plotted against $1/T$ for acetyltrifluoroacetone. It was not considered sufficiently important for the purposes of this study to obtain measurements at three temperatures for all the ketones.

**Equilibria.**—Extrapolation of the rate curve to zero time gives a value for the sum of enol and enolate ion in the ketone solution at equilibrium. This value refers to a solution containing no alcohol, since alcohol is not added except with bromine.

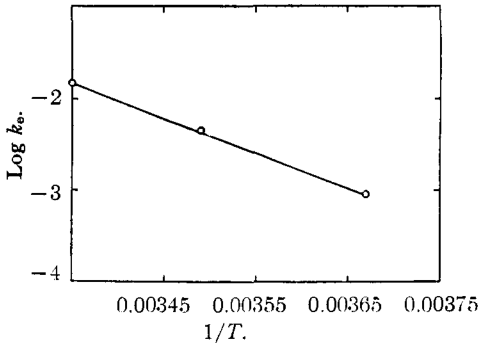

Fig. 2.—Heat of activation for enolization of acetyltrifluoroacetone in water.

That the enolate ion brominates instantly would be expected from general knowledge of the bromination of ketones in alkaline solution, where the rate of formation of enolate is found to be the rate determining step. The point was checked by adding to a water solution of acetyltrifluoroacetone enough tenth normal sodium hydroxide to neutralize half of the ketone. A rate curve (Fig. 3) was then determined on the resulting solution in the usual way. The large value for (enol + enolate) at zero time shows that the ion brominates rapidly and that the quantity obtained at zero time does include both enol and enolate. The reason the value is 22% rather than 50% is that considerable hydrolysis occurred in the hour or so between the addition of alkali, getting the solution to thermal equilibrium, and starting the brominations. This is also the reason for the curvature of the plot, as the brominations took another hour and a half.

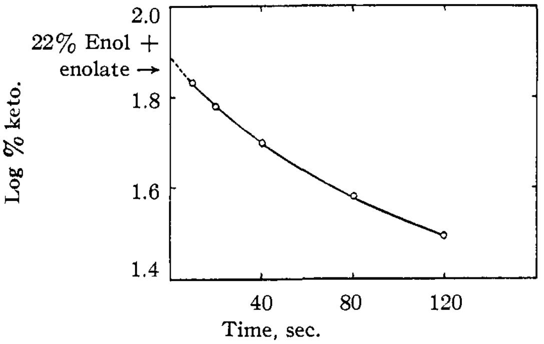

Fig. 3.—Rate of bromination of half neutralized acetyltrifluoroacetone in water.

To calculate the keto–enol equilibrium constant in water, the concentration of enolate ion was obtained by measuring the hydrogen ion concentration of an equilibrated solution and equating this to the enolate ion concentration. Then

$$K = \frac{[\text{Enol}]}{[\text{Keto}]} = \frac{[\text{Enolate}^- + \text{Enol}] - [\text{H}^+]}{[\text{Total Ketone}] - [\text{Enolate}^- + \text{Enol}]}$$

The acid dissociation constant of the enol was also calculated

$$Ka = \frac{[\text{Enolate}^-][\text{H}^+]}{[\text{Enol}]} = \frac{[\text{H}^+]^2}{[\text{Enolate}^-] + [\text{Enol}] - [\text{H}^+]}$$

The values are tabulated in Table IV. Also

TABLE IV

ACID DISSOCIATION CONSTANTS FOR WATER SOLUTIONS OF THE DIKETONES

| R | Temp., °C. | *Ka* enol | Apparent *Ka*[a] |
|---|---|---|---|
| $CH_3$ | 14 | $1 \times 10^{-3}$[b] | |
| | 25 | $2 \times 10^{-3}$[b] | $5 \times 10^{-7}$ |
| $(CH_3)_2CHCH_2$ | 14 | $4 \times 10^{-5}$ | |
| | 25 | $9 \times 10^{-6}$ | $3 \times 10^{-7}$ |
| Phenyl | 14 | $2 \times 10^{-6}$ | |
| | 25 | $1 \times 10^{-5}$ | $5 \times 10^{-7}$ |
| 2-Thenyl | 14 | $3 \times 10^{-5}$ | |
| | 25 | $5 \times 10^{-5}$ | $6 \times 10^{-7}$ |

[a] These are the values obtained by titration with alkali at room temperature. [b] These values for acetyltrifluoroacetone are probably too high. The discrepancy appears to be in the value of *p*H of the water solution which was repeatedly found to be about 2.9. The reason for the low value was not determined. A more reasonable value for *Ka* enol can be calculated from the apparent *Ka* by dividing it by 0.011, the fraction of total ketone which is enol. This leads to *Ka* enol = $5 \times 10^{-5}$.

TABLE V

THERMODYNAMIC QUANTITIES FOR THE KETO ⇄ ENOL PROCESS

| R | Solvent | Molarity | Temp., °C. | *K* = Enol/ Keto |
|---|---|---|---|---|
| $CH_3$ | Water | 0.0824 | 25.0 | 0.011[d] |
| | Water | .0824 | 14.0 | .010 |
| | Water | .0824 | 0.0 | Enol + Enolate =1.1%[a] |
| | 0.1 *N* HCl | .0824 | 25.0 | .016 |
| | 0.5 *N* HCl | .0824 | 25.0 | .008 |
| | Benzene | .0824 | 25.0 | 35[e] |
| | Benzene | .0850 | 14.0 | 37 |
| $(CH_3)_2CHCH_2$ | Water | .0140 | 25.3 | .019 |
| | Water | .0149 | 14.0 | .012[f] |
| | Benzene | .0655 | 25.0 | ..[b] |
| | Benzene | .0655 | 14.0 | 82[g] |
| Phenyl | Water | .00934 | 25.0 | .015 |
| | Water | .00823 | 14.0 | .023[h] |
| | Benzene | .102 | 25.0 | 17 |
| | Benzene | .0968 | 14.0 | ..[c] |
| 2-Thenyl | Water | .00915 | 25.0 | .016[i] |
| | Water | .0103 | 14.0 | .015 |
| | Benzene | .0669 | 25.0 | 17[j] |
| | Benzene | .100 | 14.0 | 26 |

[a] See footnote (*b*), Table II. [b] The value for (enol + enolate) obtained at 25° consistently exceeded the total amount of ketone present by about 15%. The cause of this was not determined. [c] Measurement gave just 100% enol, which makes calculation of the equilibrium constant and other thermodynamic quantities impossible. [d] The figures in this and the following footnotes (*d–j*) represent $\Delta F°$ (25°), $\Delta S°$(25°) and $\Delta H°$ in that order: +1.3, +0.7, +1.5. [e] −2.1, +4, −0.9. [f] +2.3, +16, +7. [g] −2.6, —, —. [h] +2.5, −30, −7. [i] +2.4, −3, +1. [j] −1.8, −7, −4.

included are apparent dissociation constants obtained by direct titration with sodium hydroxide of an aqueous ketone solution and taking the *p*H at the half-neutralization point as *pK*. Values for $\Delta H^0$, $\Delta F^0$ and $\Delta S^0$ appear in Table V.

**Accuracy of Measurements.**—The rate constants were reproducible to 5% and the excellent linearity of the logarithmic plot indicates that side reactions are not important. However, a test on acetyltrifluoroacetone showed that bromination in water over longer time intervals (5–10 min.) gave an iodine liberation corresponding to more than 100% bromination. This probably represents dibromination in which the second enolizable hydrogen atom is replaced. Bromination for fifteen minutes in benzene gave a titration value corresponding within 1% to the total amount of ketone present.

Extrapolating the rate curve to zero time gives the per cent. keto present. In water this has a value for all ketones of around 97%. If this is accurate to 1%, the value of per cent. enol plus enolate, obtained by subtracting from 100, will have an uncertainty of around 30%. Accordingly, the second figure in the values tabulated for equilibrium constants is rather uncertain. The values for *Ka* cannot be considered to have more than one significant figure. It will be noted that the value of *Ka* for isovaleroyltrifluoroacetone decreases at the higher temperature. It is unlikely that this is true. In calculating the heats and entropies of reaction the situation is even more difficult since the difference between logarithms is involved, and the values for these quantities cannot be regarded as more than rough estimates.

## Summary

1. By the Claisen condensation of ethyl trifluoroacetate on a series of methyl ketones, propionyltrifluoroacetone, 1-acetyl-1-trifluoroacetylethane, 1-propionyl-1-trifluoroacetylethane, isovaleroyltrifluoroacetone, *n*-heptoyltrifluoroacetone, benzoyltrifluoroacetone, *p*-phenylbenzoyltrifluoroacetone, *p*-fluorobenzoyltrifluoroacetone, 2-naphthoyltrifluoroacetone, 2-furoyltrifluoroacetone and 2-thenoyltrifluoroacetone, all hitherto unreported, have been synthesized along with copper chelates and oximes prepared from them as characterizing derivatives.

2. Kinetic and thermodynamic constants for the process Keto ⇄ Enol have been measured for acetyltrifluoroacetone, isovaleroyltrifluoroacetone, benzoyltrifluoroacetone and thenoyltrifluoroacetone.

3. The effect of the trifluoromethyl group on the keto-enol equilibrium is understandable in terms of the strong negative inductive effect of the trifluoromethyl group.

BERKELEY, CALIFORNIA RECEIVED AUGUST 3, 1949