Summary.

1. When prepared under carefully controlled conditions protein-free milk is variable in composition.

2. Amino nitrogen determinations before and after acid hydrolysis and the nitrogen distribution indicate that either unprecipitated protein or peptids of considerable size are present in protein-free milk.

3. By precipitation with acid mercuric nitrate or phosphotungstic acid a little less than $^1/_2$ of the nitrogenous compounds is removed. Examination of the phosphotungstic acid precipitate indicates that this reagent removes only non-amino nitrogen.

4. Further proof that conjugated amino groups are present in protein-free milk is shown by the increase in amino nitrogen after tryptic digestion.

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THE RELATIONS BETWEEN THE CHEMICAL STRUCTURES OF CARBONYL DERIVATIVES AND THEIR REACTIVITIES TOWARD SALTS OF SEMICARBAZIDE.

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Qualitative differences in the behavior of ketones and aldehydes towards reagents have been known for many years. The formation of silver mirrors from aldehydes, and the insolubility of the compounds of potassium hydrogen sulfite with aldehydes and ketones of the type R–CO–M, have long been used to detect and to separate them. According to E. Fischer,[1] α-ketonic acids react with phenylhydrazine in the presence of an excess of hydrochloric acid, while β- and γ-ketonic acids and fatty ketones do not. Von Pechmann[2] placed the reactivity of α-diketones towards phenylhydrazine and hydroxylamine between that of the monoketones and the aldehydes.

The writer[3] showed that Fischer's observations regarding the β- and γ-ketonic derivatives are inaccurate, since levulinic acid gives a hydrazone with the reagent, and also acetoacetic ester,[4] although in the latter case the product undergoes a spontaneous condensation to the salt of the corresponding pyrazolone; further, that ketones react slowly, but aldehydes quickly, which may be used to detect and

[1] *Ann.*, 236, 146 (1886).

[2] *Ber.*, 22, 2116 (1889).

[3] *J. prakt. Chem.*, [2] 44, 114 (1891).

[4] *Ibid.*, [2] 45, 587 (1892).

separate the simpler aliphatic aldehydes from ketones.[1] Subsequently, it was found that the reactivity of the carbonyl group in such compounds stands in a direct relation to the affinity constant of the acid combined with phenylhydrazine, but that for qualitative and quantitative determinations semicarbazide[2] as base is better adapted for the purpose.[3] In recent years the reaction velocities of ketones and aldehydes with various reagents have been investigated quantitatively by Petrenko-Kritschenko and collaborators, as well as by Stewart, and the results have been used as a basis for theoretical conclusions,[4] which will be discussed in a later paper. It is evident that the relative reaction velocities of such compounds with reagents should be used for theoretical speculations, and for conclusions regarding the relations to their chemical structures, only when the cause of the velocity and the difference between it and reactivity have been satisfactorily analyzed and explained.

The velocity factor in the above reactions depends mainly on the quantity and quality of the free chemical energy in the carbonyl group; that is, on its magnitude and on its affinity relations to the component parts of the addenda. If the free chemical energy is large, and the affinity factors small, or *vice versa*, then the velocity should be inconsiderable; but if both factors are large, then the velocity of the reaction should be great; and, if they are both small, it may be practically nil. A proportionality between the velocity and the above relations should exist when one of them increases while the other remains unchanged. We may, therefore, from the results of velocity determinations, using the same addendum but different keto-derivatives, draw conclusions on the effect of certain atoms in known positions to the carbonyl group on the relative change in the extent or in the nature of its free chemical energy.

In organic chemistry reactivity is often used indiscriminately with instability, which has led to confusion in chemical discussions. Stability is the result of a more or less complete neutralization of the atomic forces

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[1] According to an unpublished investigation with Mr. G. H. Shadinger, ketones of the types $CH_3—CO—C_nH_{2n+1}$, $C_2H_5—CO—C_nH_{2n+1}$, excepting ethylamyl ketone, and $C_3H_7—CO—C_nH_{2n+1}$ give phenylhydrazones even in the presence of 0.2 *N* free hydrochloric acid; some of these hydrazones, for instance, those of methylethyl-, methylpropyl-, methylbutyl- and diethyl-ketones pass over in the cold, in presence of an excess of hydrochloric acid, into the corresponding indole chlorohydrates.

[2] Thiele and Stange, *Ber.*, **29**, 31 (1894); *Ann.*, **283**, 1 (1894).

[3] Michael, *J. prakt. Chem.*, [2] **60**, 347–350 (1899); **72**, 543 (1905); *Ber.*, **34**, 4038 (1901); **39**, 2145 (1906); Michael and Turner, *Ibid.*, 2153; Michael and Hartman, *Ibid.*, **40**, 2151, 145 (1907). For the literature on other reagents for distinguishing aldehydes from ketones, see Meyer-Jacobson, *Lehrb. org. Chem.*, **1907**, pp. 674, 680 and 766. The results found in this investigation make it very doubtful whether a single one of these tests is valid for all ketones and aldehydes. This subject will be treated in a later paper.

[4] See Stewart, "Stereochemistry," **1907**, pp. 474–501.

in the molecule, *i. e.*, the conversion of their free into bound chemical energy, and should apply to the behavior of a compound to physical forces, acting separately or simultaneously. We may speak of a substance being chemically stable only in reference to a given system; thus, nitric acid, and nitromethane are stable towards chlorine, because, mainly owing to the imperfect intramolecular, atomic neutralization in $ClONO_2$, or CH_2ClNO_2, the free energy in the new systems would increase, *i. e.*, the reactions would, under ordinary conditions, only proceed with a decrease of entropy. But, these compounds are very unstable towards sodium, or an alkali, for the atomic forces in the new compounds are much better neutralized than in the old, and the reactions proceed with a great increase in the entropy.[1]

Reactivity in organic chemistry should be used only in reference to the behavior of a certain atom or group of atoms, and in a given chemical system. When we refer in general terms to the reactivity of a ketone or an acid, we usually have in mind the chemical behavior of the carbonyl or the carboxyl group toward reagents, because in most reactions the structural changes occur at these points. In reality, however, reactivity is the result of the sum total of the changes in the free and bound chemical energies in all the atoms of the system, which manifests itself at a certain atom or group of atoms in the molecule, because the quantity and quality of the energies are such, that at this point the hindrance to the chemical change is best overcome. Reactivity offers a relative measure of the relation of structure to the increase in entropy in similar chemical systems, providing the states of aggregation before and after the reactions remain the same or are strictly comparable.

The free energy shown at a carbonyl group and in the addendum, although small, may be sufficient and of a nature to induce a chemical change, while the affinity relations of the atoms that unite directly may be great, in which case the velocity of the reaction may be small but the reactivity great, and *vice versa*. It is evident that the reactivity relations of homologous keto-derivatives may be used for conclusions on the influence of certain atoms in the molecule on the relative changes in the total energy which comes into play at the carbonyl group. Furthermore, the free energy and the affinity relations may be so great that the reactions proceed too fast to allow the determination of real velocities, in which case the two relations will virtually coincide.

These investigations have, as their primary object, the arrangement of groups of carbonyl derivatives in relation to the relative reactivities

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[1] Michael, THIS JOURNAL, 32, 1001 (1910). The entropy of a chemical system can increase only by the conversion of free into bound energy. Although this energetic change is usually accompanied by the evolution of heat, the latter is not an essential condition.

of the carbonyl group towards certain reagents. We can then discuss the relations between isomers and homologs from the above points of view, and obtain an insight into the intramolecular effect of certain atoms in known positions on the reactivity of the carbonyl group; also, we may determine whether the reactivity in these reactions stands in a definite relation to the velocity factor. Finally, it may enable us to ascertain whether a connection exists between structure and reactivity; and the results may serve as a basis on which to judge the accuracy of the various hypotheses that have been proposed in this field.

After a series of preliminary experiments it was found that semicarbazide is the best reagent[1] for the purpose. It has not only a strong base, whose salts even of weak acids are only slightly hydrolyzed, but the semicarbazones are, as a rule, only sparingly soluble in water. When a base unites with an acid a certain proportion of the energy in the system is lost as heat, and to reform the original components requires the expenditure of an amount of energy at least equal to that dissipated in the formation of the salt. With a strong base the lost energy stands in a direct relation to the affinity constant of the acid, and, as the separation of the base from the acid is a preliminary phase to the formation of a semicarbazone, we may judge the capacity of a carbonyl derivative to do this work by examining its behavior toward different semicarbazide salts. In a sense, this method may be compared to the determination of the relative weights of substances, the weights in this case being the semicarbazide salts arranged in the order of increasing affinity constants of the acids. It is evident that, if the method is valid, it may be used conversely to determine the relative affinity constant of an acid by the ability of a semicarbazide salt to yield semicarbazones with ketones of known capacity.

It was found that some carbonyl derivatives form semicarbazones, even when the base is united with the strongest mineral acids; and to determine the relative reactivities between such substances, use was made of the fact that the reaction is reversible, although it is so to only a slight extent, and proceeds very slowly, under the usual conditions of the experiment. By increasing the mass of an acid in relation to that of the base, we should reach a concentration of acid, where the reverse action should be as fast as the semicarbazone formation; and, if two carbonyl derivatives react with the same salt, but not with that of the next stronger acid, we can determine the relative reactivities by ascertaining the excess of acid required to be added to the salt solutions in order to prevent the reactions.

For discussion the results are plotted as curves, the ordinates being the semicarbazide salts and the abscissas the ketones. The following figure represents the relative reactivities of the carbonyl in groups of the types:

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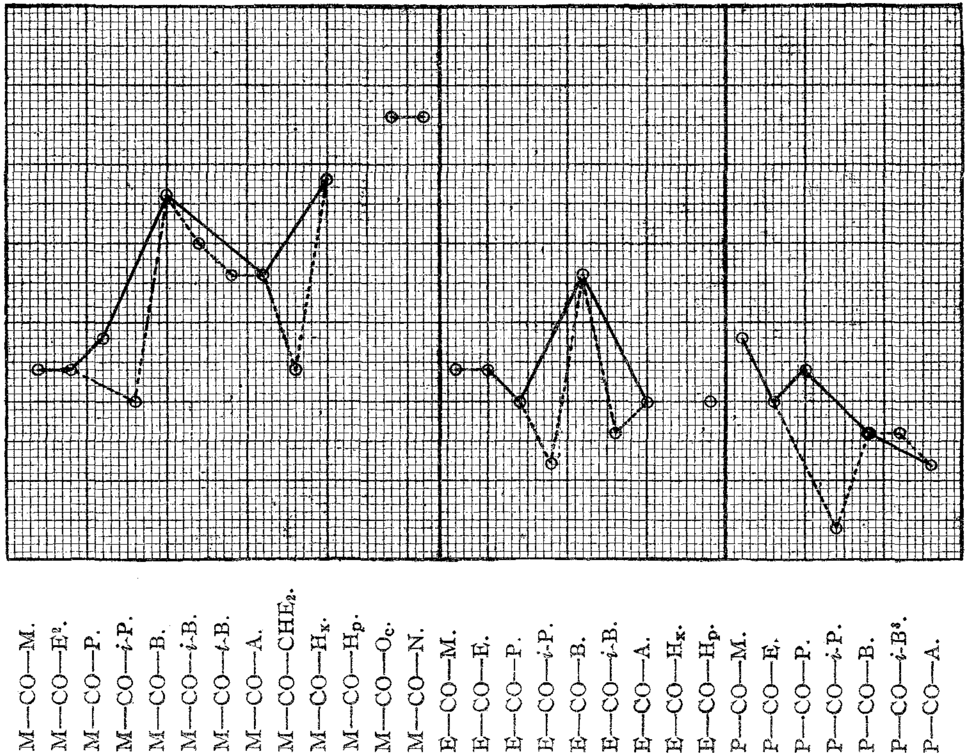
[1] Thiele and Stange, *Ann.*, 283, 1 (1894); Baeyer, *Ber.*, 27, 1918 (1894).

Fig. 1.—Reactivities of the aliphatic ketones in water.

(A) CH_3—CO—$C^nH_{2n} + 1$. (B) C_2H_5—CO—$C_nH_{2n} + 1$. (C) C_3H_7—CO—$C_nH_{2n} + 1$.



Semicarbazide salts.[1]

(15) Hydrochloride + 1.0 *N* HCl.
(13) Hydrochloride + 0.6 *N* HCl.
(12) Hydrochloride + 0.5 *N* HCl.
(10) Hydrochloride + 0.2 *N* HCl.
(9) Hydrochloride.
(8) Trichloroacetate.
(7) Dichloroacetate + 0.5 *N* Acid.
(6) Dichloroacetate.
(5) Oxalate.
(4) Chloroacetate.
(3) Formate.
(2) Acetate.
(1) Base.

[1] A numeral in a parenthesis in the text designates the reactivity according to the above scale.

[2] M—CO—E was not tried with the oxalate; its position in the scale is either (5) or (6).

[3] P—CO—*i*-B was not tried with the oxalate; its position is either (4) or (5).

(A) M-CO-C_nH_{2n+1}; (B) E-CO-C_nH_{2n+1}; (C) P-CO-C_nH_{2n+1}.[1]

To indicate the changes caused by the branching of the alkyl group, solid lines are used between those ketones containing only primary groups, and broken lines between such ketones and those containing iso- or tertiary-alkyls.

It is evident that a marked periodicity exists in the effect of the successive introductions of methyl groups in the three classes of ketones, and that the radical in different positions relative to the carbonyl shows decided and complicated differences in its influence on the reactivities. An attempt will be made to connect theory with the experimental results by the application of the principles stated above and the "scale of combined influence."[2] It should be emphasized, however, that the "scale" was deduced from the affinity constants of the normal, monobasic, fatty acids, and that the influence of the methyl group in different positions to the acidic hydrogen ($\overset{1}{H}$), as explained by it, may be applied only to the group in *cis*-positions,[3] and in compounds with similar structures; indeed, it requires some modification to be used for the iso- and tertiary-acids.[4]

In the normal, fatty acids, *cis*-$\overset{4\ 5}{CH_3}$ exercises a great (91.6%),[5] and *cis*-$\overset{5\ 6}{CH_3}$ a much less positive influence (25.5%) on the acidic hydrogen, which is due to the spacial nearness and to the number of its hydrogen atoms. The groups $\overset{6\ 7}{CH_3}$ and $\overset{7\ 8}{CH_3}$ exert, respectively, a noticeable (15.8%) and a slight negative effect, because the carbon atoms are spacially nearer to $\overset{1}{H}$ than the hydrogen atoms. The periodicity in the influence of the group is very marked upon further removal, as $\overset{8\ 9}{CH_3}$ and $\overset{9\ 10}{CH_3}$ act positively (13.2% and 5%), $\overset{10\ 11}{CH_3}$ negatively (9%), while $\overset{11\ 12}{CH_3}$ is again positive (22%).[6]

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[1] The first letter of the alkyl radical as a capital will be used to designate the series, excepting that Hx stands for hexyl, Hp for heptyl and Oc for octyl. To distinguish between secondary and tertiary radicals, *i*- and *t*- are placed before the capital letters. See THIS JOURNAL, **40,** 710, footnote 4 (1918). Numerals in parentheses are used in the text to indicate the relative order of the reactivities, for instance, after the compound, (1) denotes that it reacts only with the free base.

[2] Michael, *J. prakt. Chem.,* [2] **60,** 331 (1899); THIS JOURNAL, **32,** 999 (1910); **34,** 849 (1912).

[3] Michael, THIS JOURNAL, **40,** 708, footnote 4 (1918).

[4] Michael, *J. prakt. Chem.,* [2] **60,** 331, footnote 2 (1899).

[5] This and the following percentage relations are calculated from the affinity constants of the corresponding acids, and can only be considered approximations.

[6] The relations in the last 4 groups are calculated on the basis of Franke's (*Z. physik. Chem.,* **16,** 487 (1895)) affinity constant values. The increase in the constant in passing from normal heptylic (1.31×10^{-5}) to caprylic (1.44×10^{-5}) acid may be explained like the rise from propionic to butyric acid, *i. e.,* that the carbon atom of the introduced

In the isoalkyl acetic acids, the branched groups $\overset{5\ 6}{CH_3}$, $\overset{6\ 7}{CH_3}$ and $\overset{7\ 8}{CH_3}$ act as negative radicals; the effect of the first two groups in a branched chain is similar to that in the normal chain, when the carbon and hydrogen atoms are removed one position farther from $\overset{1}{H}$. A *change occurs again* in acids containing a tertiary alkyl, where the third $\overset{5\ 6}{CH_3}$ reverses its influence in the secondary radical and becomes decidedly positive, as before in the normal group.

The conclusions in regard to the influence of CH_3 in different positions on the acidic hydrogen in the fatty acids are applicable to its influence on the atoms of the carbonyl group in ketones of the type $C_nH_{2n+1}CO–M$, and, generally speaking, also to those of $C_nH_{2n+1}–CO–E$;[1] but in ketones in which n is greater than 3, and E is replaced by a larger alkyl radical, there is not as yet sufficient experimental data on the special relations of the atoms in two large alkyl groups to each other to explain the reactivities satisfactorily. In applying the "scale," it should be borne in mind that, in building up a homologous series, only one hydrogen at a time is replaced by CH_3, and that the influence of CH_2 on the reactivity of the carbonyl remains in the new product.

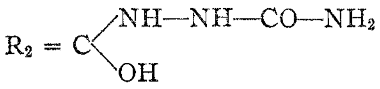
The first phase in the reaction between a ketone and a semicarbazide salt in aqueous solution consists in the formation of a "polymolecule,"[2] which may include more or less molecules of the solvent. A chemical change will take place when the free energy in the carbonyl group, and the affinity relations of its atoms to the parts of the addendum, assisted probably by that of associated solvent, are able to overcome the hindrance, which is, in the first instance, the energy required to dissociate the salt into the base and the acid, and then to overcome the bound energy between H and $HN–NH–CO–NH_2$, to the extent which it exists in the first product of the addition.[3] This primary addition product is represented by

$\overset{10\,11}{CH_3}$ is spacially nearer $\overset{1}{H}$ than the hydrogen atoms. In the original scale, 1, 2, 3, 5, 6, 4, 7 (9, 10, 11), 8, in which atoms 1 and 2 are in direct union, the relative positions of 9, 10 and 11 were left undecided. On the basis of the most trustworthy affinity constant determinations, the right end of the scale should read 7, 9, 10, 12, 11, 8, although the exact position of 8 in relation to 12 and 11 is uncertain. The periodicity in the affinity constants is another confirmation of the conclusion that the "ease of ring-formation must be a periodic function of the length of the chain" (Michael, *J. prakt. Chem.*, [2] **49**, 27 (1894)).

[1] This fact shows that the group is in cis-positions to the carbonyl group in these ketones.

[2] Michael, *Ber.*, **34**, 4028 (1901); **39**, 2140, 2570 (1906); THIS JOURNAL, **32**, 991 (1910).

[3] Michael, THIS JOURNAL, **32**, 1004 (1910); **38**, 660 (1916); *Am. Chem. J.*, **43**, 333, footnote (1910).



$$R_2 = C\begin{cases} NH—NH—CO—NH_2 \\ OH \end{cases}$$

since the affinity relations of carbon and oxygen are such that the former atom seeks to neutralize the negative, and the latter the positive component of the addendum, and by uniting in this way the maximum entropy will be realized.

The change from M–CO–M (6) to M–CO–E (6) brings the positive influences of $\overset{3\,4}{CH_3}$ on the $\overset{1}{C}$ and $\overset{4\,5}{CH_3}$ on the $\overset{1}{O}$ of the carbonyl group, whereby the free negative energy in the carbonyl and also the affinity of the oxygen for the hydrogen is decreased, while that of $\overset{1}{C}$ for the negative part of the semicarbazide addendum is increased.[1] These influences apparently approximately compensate each other, as the ketones show about the same reactivity,[2] but the effect of the loss of free energy in the carbonyl is plainly indicated by the greater reaction velocity that acetone shows towards various reagents.[3]

The step from M–CO–E (6) to M–CO–P (7) introduces the positive influences of $\overset{4\,5}{CH_3}$ on $\overset{1}{C}$, and $\overset{5\,6}{CH_3}$ on $\overset{1}{O}$, which obviously cause a smaller reduction in the free energy of the carbonyl than in the previous change. The modifications in its affinity relations to the addendum are also similar, but that caused by $\overset{4\,5}{CH_3}$ on $\overset{1}{C}$ is greater than that by $\overset{5\,6}{CH_3}$ on $\overset{1}{O}$. In accordance with theory stands the decrease in the velocity, which is, as it should be, less than that between the ketones of the lower series, and also the slight increase in the reactivity.

The new influences in M–CO–B are the positive $\overset{5\,6}{CH_3}$ on $\overset{1}{C}$, and the negative $\overset{6\,7}{CH_3}$ on $\overset{1}{O}$, which decrease the free energy in $\overset{1}{C}$ and increase that in the oxygen, while they enhance the affinities of both these atoms to the components of the addendum. We have in these changes the explanation of the sharp rise in the reactivity ((7) to (11)). Theoretically, the substitution of a hydrogen by a methyl group in no other position can change the affinity relations to favor reactivity to such an extent.

In M–CO–A (9) the new relations are the negative influence of $\overset{6\,7}{CH_3}$ on $\overset{1}{C}$, and the slighter negative influence of $\overset{7\,8}{CH_3}$ on the oxygen. This change increases the free energy in the carbonyl, and also the affinity of

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[1] The changes in the affinity relations of carbon and oxygen follow from their positions in the "Periodic System." See Michael, THIS JOURNAL, 32, 999 (1910).

[2] The exact position of M–CO–E was not ascertained, as its behavior towards the oxalate was not examined.

[3] See table of velocities given on page 404 for the relations quoted in the following pages.

the oxygen, but decreases that of $\overset{1}{C}$, for the addendum; the greater influence of $\overset{6\,7}{CH_3}$ manifests itself in the fall of the reactivity from (11) to (9).

Replacing the amyl group in M–CO–A by hexyl, introduces the negative effect of $\overset{7\,8}{CH_3}$ on $\overset{1}{C}$, and that of the positive $\overset{8\,9}{CH_3}$ on $\overset{1}{O}$; the first of these changes reduces the affinity value of $\overset{1}{C}$ very slightly, but the second increases that of the oxygen to a much greater extent. In consequence, the reactivity rises fron (9) to (12). The reactivity of M–CO–Hp was not determined; theoretically there should be an increase over M–CO–Hx, since the positive influence of $\overset{8\,9}{CH_3}$ on $\overset{1}{C}$ is greater than that of $\overset{9\,10}{CH_3}$ on $\overset{1}{O}$. This conclusion agrees with the fact, that the value for the next homolog, methyloctyl ketone (15) is larger than that of M–CO–Hx. In the first compound, $\overset{9\,10}{CH_3}$ acts positively on $\overset{1}{C}$, while $\overset{10\,11}{CH_3}$ acts negatively on $\overset{1}{O}$; *i. e.*, the affinity values of the carbonyl for the addendum in comparison to that in M–CO–Hp, is increased in both directions. Attention was directed above to the influence of a branched $\overset{5\,6}{CH_3}$ on the affinity constant of an acid being approximately the same as that of $\overset{6\,7}{CH_3}$ in a normal acid. The change, therefore, of M–CO–P (7) into M–CO–*i*-B (10), like into M–CO–B (11), should be accompanied by a marked increase in reactivity, and indeed we find that the value rises considerably.

The reactivity of M–CO–CH–M–E was not determined, and that of M–CO–CH$=E_2$ will be considered in reference to the ketone of known reactivity which is structurally the nearest related, that is, M–CO–*i*-P. The change means the introduction of the normal and the branched groups, $\overset{4\,5}{CH_3}$ to $\overset{1}{C}$ and of $\overset{5\,6}{CH_3}$ to $\overset{1}{O}$. Each of these groups should raise the reactivity, but the increase is only from (5) to (6).

The successive replacement of the hydrogens of the methyl group in acetic acid changes the affinity constant from 1.8×10^{-5} to 1.34×10^{-5}, then to 1.43×10^{-5} and finally to 1×10^{-5}; that is, the decrease first caused by $\overset{5\,6}{CH_3}$ is followed by an increase, and then by a much greater decrease in the value. From these relations, it would seem that the carbon atom in the second $\overset{5\,6}{CH_3}$ group is spacially much nearer than its hydrogen atoms to the acidic hydrogen, and that these relations are reversed in the third $\overset{5\,6}{CH_3}$ group. Besides the present experiments, no experimental data are available that can be used to ascertain the influences of the groups $\overset{3\,4}{CH_3}$ and $\overset{4\,5}{CH_3}$ in the secondary and tertiary alkyl radicals. The transition of M–CO–E (6) to M–CO–*i*-P (5) is accompanied by a decided velocity and a slight reactivity decrease; the first relation indicates a fall in the free energy of the carbonyl group, and the second, that the sum total of the positive effect of the hydrogen atoms in the branched methyl radical on the carbon of the carbonyl is greater than the negative influence of its carbon atom on the oxygen. A decided increase occurs in passing from M–CO–*i*-P (5) to M–CO–*t*-B (9), but again there is a fall in the velocity. The reactivity change is probably caused by the reversal in the spacial relations of the atoms in the tertiary methyl group, which reverse the affinity relations of the carbonyl to the addendum.

The comparison of the reactivity curves for the groups M–CO–C_nH_{2n+1} (A) and E–CO–C_nH_{2n+1} (B) shows that in the bilateral substitution of hydrogen from the fourth carbon series, a marked reduction in the reactive capacity of the ketones occurs. This downward tendency is already manifest in passing from M–CO–P (7) to E–CO–P (5), where the effect in unilateral substitution, as shown in M–CO–B (12), is reversed. Further substitution causes changes in the reactivities similar to those found and explained above in Group A. Butyl, in the place of propyl in E–CO–P, causes a rise from (5) to (9), and E–CO–A is represented by (6).

The anomalous relations in group E–CO–C_nH_{2n+1} (B) are shown also when the alkyl group becomes branched. The relation of E–CO–*i*-P (3) to E–CO–*i*-B (4) is the same as in the corresponding ketones of Class A, but that of the last ketone to E–CO–P (5) is reversed. The depression in the reactivities shown in group (B) is still more accentuated, when the alkyl groups become so large that their spacial relations to each other decidedly influence the affinity and energy conditions in the carbonyl group, and the only rise occurs in passing from E–CO–P (5) to P–CO–P (6). All the members of the group P–CO–C_nH_{2n+1} (C), when n is greater than 3, show smaller reactivities than the isomeric ketones of groups (A) and (B); and, as far as has been examined, the velocities are likewise smaller, although the decreases here are relatively less than those in the reactivities. In contrast to the large increase accompanying the replacement of propyl by butyl in (A) and (B), the reactivity decreases in (C); but, as in the first groups, the value falls somewhat in the replacement of butyl by amyl. Starting from P–CO–C_nH_{2n+1}, with n equal to three, there is a progressive decrease in the reactivity with increase in the value of n when the alkyl group remains primary. A fall likewise takes place in M–CO–C_nH_{2n+1}, when C_nH_{2n+1} changes from a primary to an isomeric secondary alkyl group; indeed, the isopropyl group in the three ketone classes depresses the reactivity to a greater extent than any of the other alkyl radicals. Thus, the change from P–CO–P to P–CO–*i*-P takes place with a reactivity fall from (7) to (1), and the latter substance is the least reactive of all the ketones that have been examined.[1] It is probable, however, that *i*-P–CO–*i*-P is still less reactive, and that it is inert to semicarbazide under ordinary conditions.

When we consider that a solvent may enter into the composition of the "polymolecule," and that it may influence the differences in the heats of solution of different substances, and the differences in the solubilities of the products formed in the reactions, it is obvious that it may also be a very decided factor in determining the reactivity and velocity.

Menschutkin[2] has shown experimentally that the solvent may have an enormous influence on the velocity of a reaction, and Petrenko-Kritschenko and Konshin[3] noticed a decided effect in the velocity of phenylhydrazone formation. Indeed, the surrounding media may alter even the chemical course in certain reactions to a greater or less extent,[4] although no change takes place in the state of aggregation.

Some preliminary experiments on the velocity and reactivity of semicarbazone formation in alcoholic solution have been made. The velocities of M–CO–M, M–CO–E, E–CO–E and P–CO–P in the experiments of Petrenko-Kritschenko and Stewart decrease in the above order, and this relation is not altered by the reagent. In striking contrast, the velocity of semicarbazone formation, using the free base in alcoholic solution, is greatest with the last, approximately the same with the first and third, and lowest with the second ketone.[5] Very noticeable, too, is the difference in the reactivity of M–CO–Hx (12) and of M–CO–M (6), M–CO–E (6) and M–CO–P (7) in water and in alcohol where the first ketone still shows a high reactivity (10), while all the other compounds only react with the free base (1). On the other hand, M–CO–CHE$_2$ shows about the same reactivity in the two media.

At first sight it would seem as if alcoholic rather than aqueous solution should favor the velocity of the formation of semicarbazones, especially with the higher ketones, which are more or less sparingly soluble in water. Besides, the tendency of the acids in the salts to esterify might be a directive force towards causing dissociation of the salt and so decrease the hindrance to the semicarbazone formation and, therefore, increase the reactivity.[6] The above results show, however, that these influences

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[1] This influence of the isopropyl group has an important theoretical bearing, which will be discussed in a paper on "Steric Hindrance."

[2] *Z. physik. Chem.*, 6, 41 (1890).

[3] *Chem. Zentr.*, 1903, II, 491.

[4] Ipatiew, *Jahrb. Chem.*, 1903, p. 738; 1904, p. 832; Michael and Zeidler, *Ann.*, 385, 245 (1911).

[5] These results are from qualitative experiments.

[6] An experiment with trichloroacetic acid in 53% alcohol, the proportion of acid to alcohol being the same as in the ketone experiments, showed that 9% of the acid was esterified in 17 hours at room temperature. The esterifying influence of the salt is probably negligible in most of the experiments.

are slight in comparison with the insolubility of the semicarbazones, through which not only one of the factors in the reaction is removed from the sphere of chemical activity, and thus prevents or retards the reverse reaction, but which facilitates the change through the loss of energy accompanying the modification in the state of aggregation. The relationship between the affinity constants of acids in water and in alcohol, where the systems remain homogeneous, also depends on the solvent.[1] We *are, therefore, quite as unjustified to attach an absolute relative value to the reactivity of a ketone, as to the affinity constant of an organic acid; in each case, we should refer to a value in a given physical and chemical system*, although with these, and with other physico-chemical constants, the relative relations are usually not changed by the media.

In the following table some of the ketones are arranged with reference to their reactivities towards semicarbazide salts in water and in alcohol, and to their velocities towards phenylhydrazine, hydroxylamine and alkali hydrogen sulfite:

TABLE.

Reactivities and Velocities.

	Reactivities with semicarbazide salts in		Velocities.				
Ketones.[2]	H_2O.	C_2H_5OH.	NH_2OH.[3] %.	$NaHSO_3$.[4] %.	$C_6H_5N_2H_3$.[5] %.	NH_2OH.[4] %.	$KHSO_3$.[7] %.
M-CO-Hx........	(12)	(10)	..	..	31	67.6	5.7
M-CO-*t*-B........	(9)	(2-7)[6]	24.5	5.6	3.6	..	..
M-CO-P..........	(7)	(1)	39.9	23.4	38	74.6	12.4
M-CO-E..........	(6)	(1)	39.2	36.4	52	59.2	14
M-CO-M..........	(6)	(1)	50	56.2	66	82	22
E-CO-E..........	(6)	(1)?	..	..	11	37.9	1.8
P-CO-P..........	(6)	(1)?	..	..	7.5	31.4	0.0
E-CO-P..........	(5)	(1)?	..	..	10	36.8	2.0
M-CO-*i*-P........	(4)	(1)	32	12.3	15	33.0	2.7
E-CO-*i*-P........	(3)	(1)	..	..	3.7	28.9	..

In comparing the reactivities of the ketones toward semicarbazide salts in water solution with the velocities, it should be borne in mind that the insolubility of the semicarbazones is a considerable factor in determining the results, and that in the velocity determinations the systems

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[1] H. Goldschmidt, *Z. Electrochem.*, 15, 4 (1909); *Z. physik. Chem.*, 70, 627 (1909); 81, 30 (1912); 89, 129 (1914).

[2] Arranged in the decreasing order of their reaction capacities to semicarbazide salts in water.

[3] Stewart, *J. Chem. Soc.*, 87, 410 (1905); 30-minute velocities.

[4] *Ibid.*, 87, 185; 60-minute velocities.

[5] Petrenko-Kritschenko, *Ann.*, 341, 150 (1905). Amount formed in 1 hour in 50% alcohol with a 0.01 *N* solution.

[6] Petrenko-Kritschenko, *Ber.*, 39, 1454 (1906). Same as in the previous statement.

[7] The exact position of this ketone, and those designated lower in the table with interrogation points, were not determined.

remained homogeneous. It is plainly evident from the figures in the table that there is no direct connection between reactivity and velocity in these reactions. Thus, with water as the solvent, M–CO–Hx (12) shows the greatest reactivity, but the velocity with phenylhydrazine is about $^1/_2$ and with potassium hydrogen sulfite $^1/_4$ of that of the much less reactive acetone (6). M–CO–*t*-B (9) comes next in reactivity, but it shows the smallest velocities of all the ketones; only about $^1/_{20}$ of that of M–CO–M (6) with phenylhydrazine. Again, M–CO–M and P–CO–P show the same reactivity (6); with phenylhydrazine and potassium hydrogen sulfite the first ketone shows the greatest velocity, while the latter has a very small velocity with the base, and does not react at all with the sulfite. Finally, unsymmetrical replacements of hydrogen in acetone by the methyl group cause at first no change in the reactivity, then a decided fall, which is followed by a considerable rise, while these structural changes with all the reagents are followed by marked decrease in the velocities.

Even when the ketone-semicarbazide system remains homogeneous during the reaction, there is no connection between reactivity and velocity. In alcoholic solution, M–CO–Hx (10) has the largest reactivity, while its velocity with phenylhydrazine is about $^1/_2$ and with potassium hydrogen sulfite $^1/_4$ of that of M–CO–M (1); M–CO–*t*-B (2–7) has a greater reactivity than M–CO–E (1), but the velocity with the base is about $^1/_{15}$ and with sodium acid sulfite about $^1/_6$ as great. Again, P–CO–P and M–CO–M are about equally reactive, but the former substance shows the smallest and the latter the greatest velocity toward the above reagents.

Although the ketones, generally speaking, do not change the order of their velocities with the reagents, it is apparent from the figures in the table that they do so in respect to the proportionality relations, which agrees with theory, since the velocity should be dependent not alone on the free energy in the carbonyl, but also on its affinity relations to the parts of the addendum, and the latter factors vary with the reagent.

These results show conclusively that velocity and reactivity are distinct relations, and that they should be invariably distinguished between in all organic investigations. This fact is of theoretical importance, as the two relations have been often confused in physico-chemical organic researches, and conclusions drawn from velocities that should have been based on reactivities. Indeed, the terms are often used indiscriminately in this field; for instance, by Petrenko-Kritschenko and Stewart in their papers.

The transition of acetone to acetoacetic ester introduces the influence of $\overset{4}{O_2}$ on the carbon and of $\overset{5}{O_2}$ on the oxygen of the keto-carbonyl group, whereby its free energy is increased and the affinity of the carbon for the addendum decreased, but less than that of the oxygen is increased. These are energy changes that indicate an augmented semicarbazone reactivity, which, indeed, increases from (6) to (10) or (11). It appears as if the reactivity of the keto-carbonyl in this class of compounds stands in a direct relation to the increase in the free energy in the group, and to the negative influence of the introduced oxygens, up to a certain degree, and that then a decrease takes place. In passing from M–CO–E (6) to CH_3–CO–CH_2–CH_2–COOE the negative influences of $\overset{5}{O}_2$ and $\overset{6}{O}_2$ on the carbon and oxygen of the carbonyl are introduced, which are greater in these respects than those of $\overset{4}{O}_2$ and $\overset{5}{O}_2$ are in going from M–CO–M (6) to CH_3–CO–CH_2–COOE; indeed, levulinic ester (12) shows the higher value. Pyruvic ester was not examined but its general behavior towards reagents indicates a high reactivity; the related oxalacetic ester gives a semicarbazone with the chlorohydrate in the presence of 10 *N* hydrochloric acid, which places its reactivity along with formic and the aromatic aldehydes.

The exact position of acetylmalonic ester was not determined, but that of diacetylmalonic ester is only between (2) and (4). This decided fall indicates that the law of maximum additive capacity[1] comes here into play, as it does in all organic addition reactions that have been thus far studied from this point of view. The accumulation of negative influence on the carbonyl may indeed become so great that its affinity values for the addendum may be even reduced to a point when addition no longer takes place.

The replacement of a hydrogen in the methylene of acetoacetic ester by alkyl causes a great fall in the reactivity; from (10) to about (2) with methyl or ethyl, and to (1) with propyl. With di-substitution, the first two alkyl derivatives react only on the free base, and dipropyl acetoacetic ester shows no reaction at room temperature on such a solution, even on long standing. A reactivity lowering takes place with acetomalonic ester (over (2)), whose methyl and ethyl derivatives also fail to act on the free base.

Benzoylacetic ester (9) reacts on the chlorohydrate; its exact position was not determined, but it probably lies higher. Very noticeable is the difference in its velocity towards the chlorohydrate solution and that of acetoacetic ester, as the reaction with the latter compound was practically complete in a few minutes, while, with the aromatic ester, it only began in two hours and was not finished in two days. This slower velocity of the keto-carbonyl in the benzoyl than in the acetyl group appears in many other substances. For instance, in the properties of the poly-benzoyl methanes, which react much slower than the corresponding acetyl de-

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[1] Michael, *Ber.*, **38**, 27 (1905); Michael and Leighton, *Ibid.*, **39**, 2792 (1906); Michael and Cobb, *Ann.*, **363**, 68 (1908); Michael and Brunel, *Am. Chem. J.*, **41**, 125 (1909); **48**, 267 (1912).

rivatives,[1] or, in the velocity of acetone (80%) and acetophenone (9.2%) on hydroxylamine.[2]

The theoretical relations between velocity and reactivity in this group of compounds cannot be satisfactorily followed from the data at hand. Stewart[3] found an increase in the velocity with sodium hydrogen sulfite in passing from acetone to acetoacetic ester, which coincides with the change in reactivity; and a further increment in acetylacetone,[4] which should also show a higher reactivity. On the other hand, Petrenko-Kritschenko and Kantscheff[5] concluded from their experiments with hydroxylamine, that the replacement of methyl in a normal fatty ketone by carbethoxyl is accompanied by a fall in the velocity, which decreases in amount the farther off the ester is from the keto-carbonyl group. In agreement with the reactivity relations, however, these chemists observed that a very decided fall in the velocities takes place when nuclear hydrogen in the keto-esters is replaced by alkyl.

The extraordinary amount of free energy in the formyl group of formic aldehyde, which is reflected in the large affinity constant of formic acid (21.4×10^{-5}), manifests itself in the unusually high velocity of its reactions, and in an enormous capacity to perform chemical work. In passing from this body to acetic aldehyde, the great positive influence of $\overset{2\ 3}{CH_3}$ to the carbon and the much less of $\overset{3\ 4}{CH_3}$ to the oxygen of the carbonyl group are introduced, which cause a great decrease in the free energy, while they increase the affinity value of the carbon for the negative part of the semicarbazide addendum more than they decrease that of the oxygen for the hydrogen. The affinity value of the carbonyl for the addendum is therefore increased, but, as this increment is small in comparison to the enormous lowering in the free energy, the chemical potential of the carbonyl group in formic is very much greater than that in acetic aldehyde.

In formic aldehyde, too, there is the unusual structural condition, that the reserve energy outside of the carbonyl is comparatively small, which accounts for the velocity and reactivity in the reactions of the compound being equally great. These energy conditions are plainly visible in the behavior of the aldehydes in the semicarbazide reactions. Formic aldehyde reacts not only with the chlorohydrate in presence of 10 *N* hydrochloric acid, but the reaction is instantaneous. Further, the great content of its free energy enables it to react on the first-formed semicarbazone to give a further condensation product. Acetic aldehyde acts on the free base, but

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[1] Michael, *Ann.*, **363**, 25, footnote (1908).

[2] Petrenko-Kritschenko, *Ber.*, **39**, 1454 (1906).

[3] *J. Chem. Soc.*, **87**, 186 (1905).

[4] *Ibid.*, **87**, 1460 (1905).

[5] *Ber.*, **39**, 1452 (1906).

not on the acetate, and its reactivity (1) is, therefore, considerably less than that of acetone (6). We have here the paradoxical relationship that the gradual replacement of the hydrogen in formic aldehyde causes at first a great decrease, and then a considerable increase in the reactivity. This is due to the enormous decrease in the free energy and comparatively slight increase in the affinity values accompanying the first step; then, since the free energy in the carbonyl has already largely disappeared, in passing over to acetone the change in the affinity factors predominates.

In *i*-B–COH and *i*-B–CO–M the semicarbazone reactivities (9) are about the same, but the chemical change is rapid with the first substance, and slow with the latter. This difference in the reaction velocities appears, too, in the behavior of acetic aldehyde and acetone towards sodium hydrogen sulfite,[1] and of *i*-P–COH and *i*-P–CO–M towards phenylhydrazine and potassium hydrogen sulfite,[2] and it is very probable that this connection between the reaction velocity of aliphatic aldehydes and of the ketones formed from them by replacing the formyl hydrogen by methyl, will hold with all, or, at least, with the great majority of reagents. Indeed, it seems that in the fatty series the velocity is always greater in an aldehyde than in any ketone, which is not the case, however, in regard to the reactivity relations, as the values in some of the ketones far transcend those of some of the aldehydes.

Benzoic, salicylic, and *o*-, *m*-, and *p*-nitrobenzoic aldehydes show a semicarbazone velocity and reactivity that appears in the fatty series only in formic aldehyde, *i. e.*, they react instantaneously with the chlorohydrate in the presence of 10 *N* hydrochloric acid. The change from C_6H_5COH to C_6H_5COM goes with a great fall in both velocity and reactivity (9), but the difference in the velocity is not in such contrast as in the experiments of Petrenko-Kritschenko[3] with phenylhydrazine and potassium hydrogen sulfite, where the aldehyde gave 90% and 77%, respectively, of derivative in an hour, while the ketone yielded only 3.7% and 0.8%, respectively.

The cause of the high reactivity of benzaldehyde may be sought in the influence of the phenyl radical, which varies with its position to the atoms in the substituting group [4] On directly joined atoms, it exerts a very strong positive influence, which characteristically appears, for instance, in the properties of the iodium bases, in those of the aromatic amines,[5] and in decreasing the affinity of carbon for carbon.[6] On the next

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[1] Stewart, *J. Chem. Soc.*, **87**, 186 (1905).

[2] Petrenko-Kritschenko, *Ann.*, **341**, 166 (1905); *Ber.*, **39**, 1454 (1906).

[3] *Ann.*, **39**, 166 (1905); *Ber.*, **341**, 1454 (1906).

[4] Michael, *J. prakt. Chem.*, [2] **60**, 436 (1899); Michael and Leighton, *Ber.*, **39**, 2792 (1906).

[5] *Ibid.*, footnote; Michael and Brunel, *Am. Chem. J.*, **41**, 126, 127, footnote 2 (1909). The persistence of Ostwald's (*J. prakt. Chem.*, [2] **33**, 352 (1886) and Bredig's

following atoms, the effect of phenyl is so decidedly negative to that of hydrogen in the same position that it increases the negativity of hydroxyl hydrogen to a greater extent than the augmented positivity of the oxygen is able to decrease it. For this reason, phenol has a much larger affinity constant than water.

There is, therefore, a fundamental difference in the effect, when a hydrogen of formic aldehyde is replaced by a phenyl or by a methyl group The methyl group, in contrast to the influence of hydrogen, greatly decreases the free energy in the carbon and oxygen of formic aldehyde, while the phenyl group decreases that in the carbon, but increases that in the oxygen. Again, the methyl group increases the affinity value of the carbon, but decreases that of the oxygen for the addenda, while the phenyl group in creases the values for both of these elements.

A theoretical deduction as to the balance of these properties in formic aldehyde and benzaldehyde is not possible at present, but there can be no doubt of the superiority of the first-named compound. This relation is not evident from semicarbazide reactions, as the velocities are too great in each case to observe a difference in speed, and the highest reactivity test is too low to distinguish between them. But the behavior of the aldehydes towards reagents with less developed affinity values leaves the question of the greater capacity of formic aldehyde out of question. This probably applies, too, to the relations of formic to salicylic, and the isomeric nitrobenzoic aldehydes, which also react instantaneously with the chlorohydrate plus 10 *N* hydrochloric acid.

Petenko-Kritschenko[1] found in the change from C_6H_5CHO to $C_6H_5CH_2$–CHO, *i. e.*, the removal of the formyl group from the nucleus, that the reaction velocity decreases. This occurs, too, in the semicarbazone formation, indeed; in this reaction both velocity and reactivity fall. The removal of the phenyl from the formyl group, as would be expected, also outbalances the acceleration in these properties, which follow from the unsaturation of the carbons in the side chain, as the values are much lower with cinnamic than with benzoic aldehyde.

(*Z. physik. Chem.*, 13, 289 (1894)) view that the basicities, or the affinity constants, of ammonia and of the amine bases, in aqueous solutions, can be determined by conductivity measurements, or by the acetic ester method (Ostwald, *Ibid.*, 16, 385 (1877)), is astonishing, in view of the so obvious fallacy in the basic assumption. Their results show only the relative stabilities of the corresponding ammonium hydroxides in dilute solutions, and confirm the law of maximum additive capacity. Phenyl influences the stabilities of the ammonium hydroxides exactly like the exceedingly strongly positive tertiary alkyl; when they are stable, as in the quaternary bases, the more strongly developed positive influence of phenyl over alkyl in this position is manifest in the experimental results (Ostwald, *Ibid.*, 16, 365 (1877)).

[6] Michael, THIS JOURNAL, 32, 997 (1910).

[1] *Ann.*, 341, 166 (1905).

The relations that have been ascertained between the affinity constants of the acids in the semicarbazide salts and the reactivities of the ketones, permit the determination of the position which an acid of unknown strength has in respect to those of the acid is used in the above experiments. Thus, from the formation of semicarbazones by standing, or continued shaking, of a very small amount of the semicarbazide salt in aqueous solution[1] with a few drops of P–CO–*i*-P (1), E–CO–*i*-P (3), M–CO–P (4), E–CO–P (5), M–CO–M (6) and M–CO–*i*-B (9) the relative position of the acid investigated towards acetic, formic, mono-, di-, and trichloroacetic and hydrochloric acids may be determined.

It is a well known fact that the laws of dilute solutions are inexact in a concentration greater than normality, and that, in many cases, there is a wide divergence between the relative strengths of strong acids as deduced in different reactions from the velocities in dilute solutions, and from their conductivities. Indeed, the latter method often leads to conclusions so incompatible with the chemical properties of strong acids, that they may be disregarded as due to errors inherent in the method. This conclusion applies, too, to the interrelations, when ascertained from the velocities of certain reactions, such as the hydrolysis of cane sugar, methyl acetate, etc., where the specific affinities of strong acids for the reagents, in contrast to those of weak ones, enter into the reactions as large disturbing factors as they are not proportional to the strengths of the acids. There can be no doubt that a correct classification of the strengths of strong acids must be based on their reactivities, and not, as has been hitherto generally done, on reaction velocities; for this reason, the relations found calorimetrically and volumetrically, since the changes are dependent on reactivity relations, are probably approximately true. From this point of view, the semicarbazide method may prove of use; especially as the relative reactivities may be determined in concentrated solutions, and the relations may be found by ascertaining the excess of acid inhibiting the semicarbazone formation. In this way, the long accepted, but chemically extremely improbable, assumption of Ostwald, that such strong acids are approximately of like strengths, and that this depends on the extent of their ionization, may be investigated, and, possibly, the method may be of use to ascertain the correct interrelations of the strengths of strong acids.

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[1] The salt may be made by neutralizing the base, or easier, by dissolving the sodium salt of the acid in an aqueous solution of semicarbazide chlorohydrate. In the latter case, it is advisable to use equivalent proportions, as the velocity of semicarbazone formation is then greater than when less sodium salt is used. For instance, acetone gave an immediate precipitate with a solution of the chlorohydrate and sodium acetate in equimolecular proportion, but when the latter salt was used to the extent of 50%, 33%, 25% and 10%, precipitates appeared only after the mixtures stood 2–3, 7, 21 and about 600 minutes, respectively.

The relations between the structure of ketones and their reactivity towards semicarbazide salts will undoubtedly be of use in characterizing, and in separating such compounds from each other, as it has already been shown to be in their separation quantitatively. In the examination of laboratory or natural products, preliminary experiments with a few drops of the liquid should be made in order to ascertain the salt of the acid of maximum strength that will yield a semicarbazone, and then the product should be allowed to stand, or, if insoluble, shaken, with a solution of that salt as long as a precipitate is formed. To ascertain whether the filtrate still contains a ketone, some sodium acetate should be dissolved in a small portion of it, and the mixture allowed to stand, or shaken if an insoluble oil is present. If a precipitate is formed, further tests should be made with fresh portions, using sodium salts of acids with smaller affinity constants than that in the semicarbazide salt first used. This method has great advantages over any that has hitherto been used for the detection and separation of ketones; it not only permits a fairly accurate quantitative analysis of mixtures in many cases, but the properties of the semicarbazones favor their characterization. There is no doubt that, with sufficient experimental data, a similar scheme is feasible for the determination and separation of aldehydes and keto-esters. Indeed, the behavior of such of these substances that have been ascertained in this paper may be of service for this purpose. For instance, the astonishing reactivity of aromatic aldehydes, in which the formyl group is directly joined to the nucleus, or the high values of several of the keto-esters, will undoubtedly be of use in this direction.

EXPERIMENTAL PART.

(The experiments with the ketones were made with Mr. G. P. Fuller, and those with the aldehydes and the keto-esters with Mr. H. J. Turner.)

Preparation of the Ketones.

All of the ketones used in this investigation were dried over fused potassium carbonate for 24 hours, then over a small amount of phosphorus pentoxide, for a few minutes only, and finally carefully fractionated.

Ketones.	Source or method of making.	Boiling point.
Acetone............	A commercially pure preparation (Kahlbaum) purified through the bisulfite compound and fractionated several times	56.5° (constant)
Methylethyl........	Kahlbaum product, repeatedly fractionated, using beads	78–78.5° (constant)
Methylpropyl.......	By decomposition of pure ethylacetoacetic ester[1]	102–102.1° (755 mm.)

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[1] The alkylacetoacetic esters were prepared by the method of Michael (*J. prakt. Chem.*, [2] **72**, 553 (1905)), and the ketones from them according to Michael and Wolgast (*Ber.*, **42**, 3176 (1909)).

Ketones.	Source or method of making.	Boiling point.
Methylisopropyl....	From zinc methyl[1] and isobutyric chloride[2]	94–95°
Methylbutyl........	Pure propylacetoacetic ester	127–127.5° (762 mm.)
Methylisobutyl.....	From zinc methyl iodide and isobutyl chloride by the Michael method	116–116.5°
Pinacoline..........	By purifying a Kahlbaum product	106–106.5°
Methylamyl........	From zinc methyl and capronyl chloride	144–145°
Unsym. diethyl acetone..............	By decomposition of pure diethylacetoacetic ester[3]	139–140°
Methylhexyl........	A Kahlbaum preparation, after drying, was repeatedly fractionated	173–173.5° (constant)
Methyloctyl........	By the decomposition of heptyl acetoacetic ester[4]	210–211° (767.4 mm.) Only 3 drops passed over from 207–210°
Methylnonyl........	A purified Kahlbaum product	231–233°
Diethyl[5]............	From zincethyl and propionyl chloride	102–102.5° (772 mm.) (constant)
Ethylpropyl........	From zinc ethyl and butyryl chloride	123–124°
Ethylisopropyl......	From zinc ethyl and isobutyryl chloride	114.5–115°
Ethylbutyl.........	From zinc ethyl and valeryl chloride	147–148° (760 mm.)

[1] In preparing the zinc alkyls the method of Lachman (*Am. Chem. J.*, **19**, 410 (1897); **21**, 446 (1899)) was found to be more convenient and to yield better results than the older methods of Frankland and of Gladstone and Tribe.

[2] In the preparation of ketones by the Freund method (*Ann.*, **118**, 1 (1861)) it was found best to drop the acid chloride (90% of two molecules) into the zinc alkyl (one molecule), the reaction flask being kept in a freezing mixture, and the addition made very slowly and accompanied by constant and vigorous shaking. The products were worked up as usual, the yield being about 70% of the theory.

[3] Michael, *Ber.*, **38**, 2096 (1905).

[4] After several unsuccessful attempts to prepare heptyl acetoacetic ester according to Jourdan (*Ann.*, **200**, 105 (1880)) by heating acetoacetic ester with heptyl iodide and sodium ethylate in alcoholic solution, it was finally made by adding the iodide to a suspension of sodium acetoacetic ester in xylene, which was obtained by granulating the sodium under hot xylene, heating with the ester, and then boiling the mixture for 5 hours. After adding water, the upper layer was washed with water, dried and distilled. The ester was not obtained as a constant boiling product, but a fraction was collected which boiled from 250–260°. The latter was decomposed by boiling for 6 hours with a strong alcoholic solution of potassium hydroxide, the alcohol distilled off on a water bath, and the residue extracted with ether. The extract was dried over fused potassium carbonate and fractionated. The fraction boiling from 200–216° was shaken with a strong aqueous solution of semicarbazide, the semicarbazone filtered and dried, and decomposed with sulfuric acid. The yield was poor, however, being only 27.5% of the theory.

[5] A 10 g. sample of a Kahlbaum product yielded on fractionation 2.7 g., boiling from 101–101.5°, and 5 g. from 101.5–102.5°, the remainder boiling from 92–150°. It was not considered advisable to use the product.

Ketones.	Source or method of making.	Boiling point.
Ethylisobutyl	From zinc ethyl iodide and isobutyryl chloride	136–137°
Ethylamyl	From zinc ethyl and capronyl chloride	162–163° (647 mm.)
Ethylheptyl	From the laboratory collection; was not dried or fractionated because there were only a few tenths of a gram of the substance available	114–115° (31 mm.) (Label on the original bottle)
Dipropyl	From zinc propyl and butyryl chloride	143.5–144.5° (755 mm.)
Propylisopropyl[1]	From zinc propyl and isobutyryl chloride	133.5–134.5°
Propylbutyl	From zinc propyl and valeryl chloride	167–169°
Propylisobutyl	From zinc propyl and isovaleryl chloride	155–157°
Propylamyl	From zinc propyl and capronyl chloride	180–181° (747 mm.)
Cyclohexane	A Kahlbaum preparation, dried over fused potassium carbonate and fractionated	156–156.5° (761.9 mm.)

Preparation of Semicarbazide and Its Salts.

Semicarbazide is best prepared from the hydrochloride, as this salt is obtainable quite pure in commerce. The salt is treated with a slight excess of a saturated sodium hydroxide solution,[2] the mixture being in a small, round-bottomed flask, which is fitted with a two-holed rubber stopper containing a capillary tube and one leading to a vacuum pump. The flask is exhausted, and heated at 100° until no more water passes off. Absolute alcohol is then added to the residue, and the flask shaken vigorously to break up the lumps. The product is then extracted repeatedly with hot absolute alcohol, and filtered, under diminished pressure, through a hot-water funnel. The crystals, which separate out of the solution on cooling, are recrystallized twice from hot absolute alcohol, and dried in a vacuum over sulfuric acid. The melting point is 95°. The base was prepared in quantities sufficient for immediate use only, as it undergoes a considerable decomposition into hydrazodicarbonamide[3] upon standing.

The best method of preparing the salts of semicarbazide is to dissolve molecular quantities of the free base and the acid in the least possible

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[1] Blaise (*Compt. rend.*, **132**, 478 (1901)) obtained this product from butyrylisobutyric ester, and gave the boiling point as 129–130°.

[2] Michael and Wolgast (*Ber.*, **42**, 3176 (footnote) (1909)) prepared the free base by heating the hydrochloride with strong potassium hydroxide solution, and evaporating in a desiccator. The method here described is better adapted for preparing it in larger quantities.

[3] Thiele, *Ann.*, **270**, 45 (1891); **271**, 127 (1892). It is also deposited when aqueous or alcoholic solution of the base or its salts are allowed to stand for a long time.

amount of cold water, mix the solutions in a small, wide crystallizing dish and concentrate them in a vacuum over sulfuric acid. Crystals soon separate, the mass usually becoming semi-solid in a day. They were then filtered under pressure and the products recrystallized from cold water.[1] The crystals are then filtered, washed with a little cold water, and dried in a vacuum.

Semicarbazide Chlorohydrate.—A Kahlbaum product, crystallized twice from hot water, melted at 175°. It is very slightly soluble in hot absolute alcohol.[2]

Acid Semicarbazide Sulfate.[3]—This substance was prepared from semicarbazide and sulfuric acid in aqueous solution; the salt separates out in fine needles which, after recrystallization from cold water and drying in a vacuum,[4] melted at 145°, with decomposition.

Neutral Semicarbazide Sulfate.—This substance was prepared by mixing alcoholic solutions of sulfuric acid and semicarbazide, and evaporating in a vacuum. The solid which separated out was filtered, washed with a little alcohol and dissolved in water. On account of its great solubility in water it could not be crystallized from that solvent, and it was, therefore, precipitated out by the addition of alcohol, filtered, washed with alcohol and dried at 105°. The salt melts at 143°, and since the melting points of the two salts are nearly the same it was analyzed.

Subst., 0.1649 g. $BaSO_4$, 0.1524.

Calc. for $NH_2CONHNH_2.H_2SO_4$: S, 18.52; calc. for $NH_2CONHNH_2.{}^1/_2H_2SO_4$: S, 12.91; Found: 12.69.

A mixture of equal parts of the acid and neutral sulfates melts at 130°, which, with the result of the sulfur determination, shows that the products are different. The neutral sulfate is extremely soluble in water, but insoluble in absolute alcohol. It reacts acid to litmus.

Semicarbazide Formate.—This substance was prepared from semicarbazide and formic acid in aqueous solution; the salt melts at 128°. Another sample, prepared in hot alcoholic solution, and the product recrystallized from the same solvent, melted at 126°.

Semicarbazide Benzenesulfonate.—This salt was prepared from benzene sulfonic acid and the base. It separates in fine plates, which melt

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[1] It is necessary to avoid crystallizing some of the salts from hot solvents, as they decompose, giving more or less of hydrazodicarbonamide.

[2] Thiele and Stange (*Ann.*, 283, 21 (1894)) state that it is insoluble in absolute alcohol.

[3] Thiele and Stange (*Loc. cit.*, pp. 19 and 23) prepared the salt by heating acetone semicarbazone with two molecules of sulfuric acid, precipitating with absolute alcohol and ether. The salt prepared in this way contains some hydrazodicarbonamide.

[4] The sulfate should not be heated, as it is readily converted into hydrazodicarbonamide. Thiele and Stange (*Loc. cit.*) stated that on heating at 120°, the latter substance was produced, while our experiments show that the sulfate cannot be dried at 100°.

at 187° (with decomposition), and is easily soluble in water and hot absolute alcohol, but is nearly insoluble in cold alcohol.

Semicarbazide Acetate.—Glacial acetic acid and a strong aqueous solution of semicarbazide were mixed and placed in a vacuum. A thick syrup formed in a day, which crystallized very slowly. The mass was pressed on a porous plate and the crystals dried *in vacuo*. The product melted at 75° (not sharp). This salt and the mono-, di- and trichloroacetates are extremely soluble in water and alcohol. The solutions in alcohol and water, on standing for several weeks, deposit hydrazodicarbonamide.

Semicarbazidemonochloroacetate.—Prepared as above in cold, aqueous solution; fine, white crystals which melt at 111 to 112°.

Semicarbazidedichloroacetate.—This substance was prepared from dichloroacetic acid and semicarbazide in aqueous solution. The crystalline product, pressed on a porous plate and vacuum dried, melted at 108°.

Semicarbazidetrichloroacetate.—Prepared by mixing hot alcoholic solutions of base and acid and evaporating in a vacuum. The syrup crystallized only after a week's standing. The product, pressed on a porous plate and vacuum dried, melted at 154° (with decomposition).

Neutral Semicarbazide Oxalate.—Prepared in aqueous solution and melted at 133° (with decomposition).

Neutral Semicarbazide Maleinate.—Prepared in aqueous solution; crystallizes in plates that melt at 100°.

Acid Semicarbazide Maleinate.—Also forms plates, melting at 133° (with decomposition).

Semicarbazide Hydrofluoride.—Made by adding hydrofluoric acid to a solution of semicarbazide in a platinum dish and evaporating *in vacuo;* the crystals were washed with cold water and vacuum dried. The substance began to melt under 100°, but decomposed so rapidly, etching the walls of the melting-point tube, that no sharp point could be determined. A portion of the product, recrystallized from cold water, began to melt at 70°, and a mixture of the crude and recrystallized products at 65° (with decomposition). The salt is evidently hydrolyzed by water very rapidly.

An attempt to prepare it by evaporating semicarbazide with dilute hydrofluoric acid on a water bath resulted in the production of hydrazodicarbonamide.

Semicarbazide Salicylate.—Semicarbazide was dissolved in water and salicylic acid in alcohol, and the solutions mixed. On evaporation a crystalline substance was deposited, which, after recrystallization from 70% alcohol and vacuum drying, melted at 153°.

Semicarbazide-*o*-nitrobenzoate.—Upon mixing cold solutions of semicarbazide in water and *o*-nitrobenzoic acid in alcohol, crystals were produced which melt at 96°, after drying.

The Aliphatic Ketones in Aqueous Solution.

The concentration of these solutions was such that 1.6 cc. contained 1.12 mg. molecules of the salt. The solutions were prepared by dissolving the weighed amounts of semicarbazide and the required acid in water and diluting to the proper concentration With the hydrochloride and the dichloroacetate, the solutions were prepared of double strength, and were then diluted with an equal volume of water or acid solution.

For the experiments, 0.5 mg. molecules of the ketones were weighed into small test-tubes, 0.8 cc. of the desired reagent solutions added, and the tubes stoppered and shaken.[1] The tubes were examined frequently, and when precipitates appeared, they were separated from the liquid, pressed on a porous plate, and washed with a mixture of ligroin and ether to free them from any absorbed ketone. After standing some hours, they were dried in a vacuum, and the melting points determined. If necessary, the substances were recrystallized from suitable solvents, again dried, and the melting points redetermined.

Acetone.—Reacted with the dichloroacetate after 24 hours, and more quickly with the acetate, formate, and monochloroacetate. With the dichloroacetate in the presence of 0.1 *N* and 0.3 *N* dichloroacetic acid and the trichloroacetate, precipitates were formed in three months which melted at 245° (hydrazodicarbonamide).

Methylethyl Ketone.—Mono- and dichloroacetates gave precipitates in 24 hours, melting at 135°.[2] The dichloroacetate in the presence of 0.3 *N* dichloroacetic acid gave hydrazodicarbonamide. There was no action with the trichloroacetate, or with the dichloroacetate in the presence of 0.1 *N* dichloroacetic acid.

Methylpropyl Ketone.—This ketone reacted in two months with the dichloroacetate in the presence of 0.5 *N* dichloroacetic acid (107°),[3] but not with 0.7 *N* acid or the trichloroacetate.

Methylisopropyl Ketone.—A precipitate was formed with the neutral oxalate at once (112°);[4] also, with the monochloroacetate, but not with the di- or the trichloroacetates.

Methylbutyl Ketone.—A reaction took place in three days with the hydrochloride in the presence of 0.5 *N* hydrochloric acid (118°).[5] No action took place with the same salt in the presence of 0.6 *N* or 1.0 *N* acid.

[1] The tubes were shaken as long as necessary. The experiments were not considered negative under 200 hours. It is also necessary to examine the supernatant liquid layer, if the ketone is not entirely soluble, as it may contain some of the semicarbazone.

[2] Stobbe, *Ann.*, **321**, 118 (1902), gives 136° as the melting point.

[3] Schultz, *Ber.*, **29**, 611 (1896), gives a melting point of 108°.

[4] Frasciatti gives melting point as 110° (*Chem. Zentr.*, **1899**, II, 801).

[5] Melting point is 122° according to Kyner (*J. prakt. Chem.*, [2] **64**, 115 (1901)).

Methylisobutyl Ketone.—The hydrochloride in the presence of 0.2 *N* hydrochloric acid gave a precipitate in one week (116°),[1] but none in the presence of 0.3 *N* acid.

Pinacoline.—Reacted in one day with the hydrochloride (157°)[2] but not in the presence of 0.1 *N* or 0.2 *N* acid.

Methylamyl Ketone.—The hydrochloride gave a precipitate in one hour (127°),[3] and, also, in the presence of 0.1 *N*, but not with 0.2 *N* or 0.3 *N* acid.

Unsym. Diethylacetone.—With the dichloroacetate a precipitate was formed in two weeks, melting at 134°,[4] and, also, with the neutral oxalate, but not with the dichloroacetate in the presence of 0.1 *N* or 0.3 *N* dichloroacetic acid, nor with the trichloroacetate.

Methylhexyl Ketone.—The hydrochloride and 0.6 *N* hydrochloric acid gave a precipitate in 24 hours (123°),[5] but was without action in the presence of 0.8 *N* acid.

Methyloctyl Ketone.—The hydrochloride and normal hydrochloric acid gave a crystalline precipitate (119°) in a week, but none with 2 *N* acid.

Subst., 0.1825 g. dried at 100°. N, 33.2 cc. at 743 mm. and 22°.

Calc. for $C_{11}H_{23}ON_3$: N, 19.7. Found: 20.1.

Methylnonyl Ketone.—Reacted with the hydrochloride and normal acid after two months (116°)[6] but not with 2 *N* hydrochloric acid.

Diethyl Ketone.—With dichloroacetate a precipitate formed in 4 days (138°);[7] in the presence of 0.1 *N* acid hydrazodicarbonamide was formed. There was no reaction with the trichloroacetate.

Ethylpropyl Ketone.—Reacted at once with the neutral oxalate (111°),[8] but not with the dichloroacetate.

Ethylisopropyl Ketone.—Reaction after two days with the formate (78°),[9] but not with the monochloroacetate or the neutral oxalate.

Ethylbutyl Ketone.—A slight precipitate with the hydrochloride after three months (111°), which was prevented by 0.1 *N* acid. A reaction also occurred with trichloroacetate.

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[1] Dilthey, *Ber.*, 34, 2123 (1901), gives 129° as the melting point.

[2] Corlinfanti, *Chem. Zentr.*, 1897, II, 1105.

[3] Walbaum and Huethig, *J. prakt. Chem.*, [2] 66, 98 (1902), give the melting point as 122° to 123°.

[4] The pure semicarbazone melts at 134°.

[5] Bouveault and Locquin, *Bull. soc. chim.*, [3] 31, 1157 (1904), give the melting point as 122°.

[6] According to Power and Lees, *J. Chem. Soc.*, 81, 1588 (1902) this semicarbazone melts at 122°.

[7] Melting point is given by Dilthey (*Loc. cit.*) as 139°.

[8] Blaise, *Loc. cit.*, gives 110°.

[9] The pure semicarbazone melts at 80°. Blaise and Herman (*Ann. chim. phys.*, [8] 17, 371 (1909)) give 92° for their product, but the ketone they used boiled between 110° and 114°, while the boiling point of our substance was 114.5° to 115°.

Ethylisobutyl Ketone.—A precipitate with the monochloroacetate in three days (not sharp at 152°).[1] No reaction with the di- or trichloroacetate.

Ethylamyl Ketone.—The neutral oxalate gave a precipitate in two months (110°).[2] The monochloroacetate also reacted, but not the dichloroacetate.

Ethylheptyl Ketone.—Reacted with the neutral oxalate after six weeks (101°);[3] also with the monochloro-, but not with the dichloroacetate.

Dipropyl Ketone.—The dichloroacetate reacted after two days (134°);[4] also, with the monochloroacetate and the neutral sulfate, but not with the dichloroacetate in the presence of 0.1 *N* dichloroacetic acid, the trichloroacetate, the acid sulfate, the benzene sulfonate, or the hydrochloride. The experiment with the trichloroacetate gave hydrazodicarbonamide on long standing.

Propylisopropyl Ketone.—With the free base a precipitate was formed in one hour which, on recrystallization, melted at 119°.[5] No reaction took place with the acetate, formate or the mono- or dichloroacetates.

Propylbutyl Ketone.—Reacted at once with the monochloroacetate (72°), but not with the dichloroacetate.

Propylisobutyl Ketone.—With monochloroacetate it reacted in three weeks (122°),[6] but not with the di- or trichloroacetates.

Propylamyl Ketone.—Reacted in 24 hours, with a strong solution of semicarbazide (67°); the formate gave a precipitate, which melted at 77°.[7] With the monochloroacetate there was no action, but with the acetate a precipitate was obtained melting at 145°, which may be a stereomeric derivative.

Cyclohexanone.—The monochloroacetate gave in one month a precipitate (160°), which, when obtained from the free base, melted at 167°.[8] The neutral oxalate, the di- and trichloroacetates and the hydrochloride yielded only hydrazodicarbonamide.

The Aliphatic Ketones in Alcoholic Solutions.

The concentration of these solutions was such that one milligram molecular weight of the ketone was contained in 1.7 cc. of solvent.[9] For

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[1] Dilthey, *Loc. cit.*, gives 143° as melting point.

[2] Bouveault and Locquin, *Loc. cit.*, give 110°.

[3] The pure semicarbazone melts at 101°.

[4] According to Dilthey, *Loc. cit.*, 133°.

[5] The pure semicarbazone melts at 119°.

[6] Bouveault and Locquin, *Loc. cit.*, give 122°.

[7] According to Bouveault and Locquin, *Loc. cit.*, 73°.

[8] Zelinsky, *Ber.*, **30**, 1541 (1897), gives 166–167°.

[9] This concentration was adopted because it is the lowest in which all of the heptanones are soluble, and it was desired to have the experiments with the lower series of ketones performed under strictly comparable conditions.

all the ketones up to and including the heptanone derivatives, the alcohol[1] used was of 0.9270 density (53.5% by volume). The octanones and the higher ketone were dissolved in alcohol of the density 0.9097 (62.5% by volume).

The salts of semicarbazide were dissolved in 53.5% alcohol, the concentration being the same as in the case of the ketones, *i. e.*, one milligram molecule in 1.7 cc.

For the individual experiments 0.85 cc. (equivalent to 0.5 milligram molecule) of the respective solutions of ketone and salt were placed in a small, stoppered test-tube and allowed to stand. After one day, three days, one week, two weeks, one month, and then each month up to five, unless otherwise stated, a few drops of the liquid were placed on a watch glass and evaporated in a vacuum. The solid residue, when dry, was washed twice with ligroin and vacuum dried. If the mass was oily, as was often the case, it was pressed on a porous plate, extracted with a mixture of equal parts of ligroin and ether, and then vacuum dried. The dry solid was then treated with a few drops of water to determine whether or not it were soluble; if wholely or partly insoluble, the liquid was sucked off and the residue examined under the microscope. When crystalline, a larger portion of the solution was treated in the same way, and the substance was recrystallized from a suitable solvent and identified by its melting point.

Dimethyl, Methylethyl, Methylpropyl and **Methylisopropyl Ketones** gave the corresponding semicarbazones with the free base, but not with any semicarbazide salt. The velocities of the reactions differed considerably; the first ketone gave a product after 24 hours (186°), the second only after 4 months (139°), and the two remaining ketones after 6 weeks (110 and 112°, respectively).

Methylbutyl and **Methylisobutyl Ketones** reacted with the acetate after 10 days and two months, respectively (120 and 131°). No change occurred with the chlorohydrate.

Pinacoline.—This ketone reacted after two months with the acetate, but not with the trichloroacetate (157°).

Methylamyl Ketone.—With the free base a reaction took place in 10 days (121°); the trichloroacetate was without effect.

Unsym. Diethylacetone.—With the monochloroacetate a product was formed in one month (131°); it also reacted with the formate, but not with the dichloroacetate.

Methylhexyl Ketone.—The ketone reacted in 4 days with the hydrochloride in the presence of 0.2 N hydrochloric acid (121°), but not with the latter in the presence of 0.3 N acid.

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[1] The alcohol employed was treated with lime, then distilled and diluted with distilled water to the desired concentration.

Diethyl Ketone.—With the free base a reaction took place in 24 hours (136°); there was no action with the *o*-nitrobenzoate, or with the di- or trichloroacetates.

Ethylpropyl Ketone.—The free base reacted in 6 weeks (109°); there was no action with the salicylate, or with the mono- or dichloroacetates.

Ethylisopropyl Ketone.—With the free base a reaction took place in 4 months (77°); there was no action with the formate or acetate.

Ethylbutyl Ketone.—A reaction took place with the acetate after 10 days (103°). With the dichloroacetate, after 5 months, hydrazodicarbonamide was formed. There was no action with the *o*-nitrobenzoate, or the di- or trichloroacetates.

Ethylisobutyl Ketone.—A reaction took place with the free base in two months (143°), but none with the mono- or dichloroacetates.

Ethylamyl Ketone.—The free base reacted in six weeks (109°), but there was no reaction with the formate.

Dipropyl Ketone.—With the free base a reaction took place at once (129°); but none with the di- or trichloroacetates.

Propylisopropyl Ketone.—With the free base a reaction took place after one month (116°); no action with the formate or di- or trichloroacetates.

Propylisobutyl Ketone.—A reaction took place with the formate after 4 months (120°).

Propylamyl Ketone.—After 4 months this ketone had reacted with the formate (70°); with the free base after two months. The mono-, di-, and trichloroacetates were without effect.

In the following experiments the reagents used were aqueous solutions of semicarbazide and its salts, the concentration being such that 0.8 cc. contained 0.56 millgram molecule. In some experiments a solution of double this concentration was employed. When solutions containing an excess of acid were desired, they were prepared by diluting a given quantity of the stronger solution of the salt with an equal volume of the acid solution of the required normality.

Aromatic Ketones.[1]

Acetophenone.—A reaction took place quickly with the hydrochloride (198°);[2] but not in 30 minutes with the latter in the presence of 0.2 *N* acid.

Propiophenone.—This ketone reacted in one day with the acetate,

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[1] The following experiments are not strictly comparable with the foregoing in aqueous solution, even when the substance is soluble in the base or in the salt solutions. The mixtures stood at room temperature with only occasional shaking, except when otherwise mentioned, and the concentrations were not the same. In some cases, the limits of the reactivity were not determined.

[2] According to Stobbe, *Ann.*, **308**, 124 (1899), the semicarbazone melts at 195 to 198°.

and in two days with the monochloroacetate (175–176°);[1] no reaction took place with the hydrochloride in a day.

Aliphatic Aldehydes.

Formic Aldehyde.—A 5% solution of the aldehyde gave at once an amorphous precipitate with the trichloroacetate, and also with the chlorohydrate, even in the presence of 10 *N* hydrochloric acid. The products dissolved on heating the solutions to 60°, but could not be obtained in a crystalline condition; they were insoluble in alcohol. A portion of the precipitate from the trichloroacetate was washed with boiling water and dried at 100° *in vacuo*. The analysis indicates a product of condensation from two molecules of semicarbazide and three molecules of the aldehyde.

Subs., 0.1296 g. CO_2, 0.1564; H_2O, 0.0744.
Calc. for $C_5H_{10}N_6O_2$: C, 32.4; H, 5.4. Found: C, 32.9; H, 6.3.

Thiele and Bailey[2] obtained a product from the hydrochloride, which, dried at 95°, analyzed approximately for this substance with $^1/_2$ a molecule of water, while Thoms[3] states that he obtained the normal condensation product of equal molecules base and aldehyde in the same manner.

Acetic Aldehyde.—Reacted at once with a 16% solution of the free base, and showed crystals (163°)[4] in two hours with the 8% reagent. There was no evidence of a reaction with the acetate after 12 days, nor with the mono-, di-, or trichloroacetates.

A solubility determination, by the Meyer method, gave 0.2120 g. substance in 6.9578 g. solution at 17°. One molecule of semicarbazone is, therefore, soluble in 180 molecules of H_2O, or one part in 33 parts.

Isovaleric Aldehyde.—The semicarbazone was formed at once with the trichloroacetate and the hydrochloride. With the latter reagent in the presence of 0.3 *N* or *N* acid thick oils were formed in 30 minutes, which were not examined.

Oenanthol.—The dichloroacetate reacted at once; the trichloroacetate yielded crystals in 15 minutes, while the chlorohydrate reacted only slightly in 30 minutes (106°).

Aromatic Aldehydes.

Benzoic Aldehyde.—Reacted at once with all the salts, including the hydrochloride, even in the presence of 10 *N* hydrochloric acid (213°).

Salicylic Aldehyde.—The hydrochloride in the presence of 10 *N* acid reacted at once (227°).[5]

***p*-Hydroxybenzoic Aldehyde.**—Reacted quickly with chlorohydrate plus 10 *N* free acid.

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[1] Stobbe and Niedenzu, *Ibid.*, **321**, 102 (1902).

[2] Thiele and Stange, *Ibid.*, **303**, 92 (1898).

[3] *Pharmaceut. Ges.*, **7**, 5.

[4] According to Thiele and Bailey, *Ann.*, **303**, 79 (1898), the semicarbazone melts at 162°.

[5] Borsche and Bolser, *Ber.*, **34**, 2098, 4299 (1901).

Anisic Aldehyde.—This body reacted with the hydrochloride in the presence of 10 *N* acid (206°).[1] A comparison of the reaction velocities of benzaldehyde and its *o*-hydroxy and *p*-methoxy derivatives with this reagent, showed that anisic aldehyde reacts somewhat slower than the other two derivatives. On heating the mixture a reverse reaction takes place, which proceeds at a somewhat lower temperature with the anisic than with the other semicarbazones.

Nitrobenzoic Aldehyde.—The hydrochloride in the presence of 10 *N* free acid reacted immediately with *o*-, *m*-, and *p*-nitrobenzoic aldehyde. The ortho compound melted at 256°, the meta at 246°, and the para at 220°.[2]

Cinnamic Aldehyde.—A reaction took place with the 8% chlorohydrate solution, but not in the presence of 0.3 *N* acid (214 to 215°).[3]

Ketonic Esters.

Acetoacetic Ethylester.—With the 16% trichloroacetate a copious precipitate of semicarbazone formed quickly and with the chlorohydrate the reaction was complete in about 4 minutes (126°). In the presence of 0.3 *N* hydrochloric acid the semicarbazone appeared in about a half hour; after concentration to 0.5 *N* hydrochloric acid no precipitate was formed in 12 hours.

Methylacetoacetic Ester.—With the 16% solution of free base pale blue crystals (183 to 187°, with decomposition) were formed in 30 minutes, in 45 the reaction was about $^2/_3$ complete, and after 18 hours no further amount was formed. Acetate in 8% solution gave a few crystals in two days, and about half of the theoretical amount was obtained after 6 days.

Subst., 0.2061 g. N, 39.1 cc. at 21° and 746 mm.
Calc. for $C_8H_{15}O_3N_3$: N, 20.9. Found: 21.1.

Ethylacetoacetic Ester.—The free base in 16% solution gave crystals in about 10 hours; the reaction was about half finished in 18 hours, and completely in two days. With the acetate about $^1/_4$ of the theoretical amount of bluish crystals (154°, with dec.) in 13 days.

Subst., 0.1641 g. N, 28.4 cc. at 19° and 754 mm.
Calc. for $C_9H_{17}O_3N_3$: N, 19.5. Found: 19.8.

Propylacetoacetic Ester.—Showed a few crystals with the 16% solution of base after 18 hours, and the reaction was almost complete in two days (145 to 147°). With the acetate a light blue, thick oil was slowly formed, which did not solidify in 13 days.

Dimethylacetoacetic Ester.—The reaction took place with the 16% solution, which was about $^1/_2$ complete in 18 of the free base, and was fin-

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[1] Walbaum, *J. prakt. Chem.*, [2] 68, 247 (1903), gives 203 to 204° as the melting point.

[2] Thiele and Stange, *Ann.*, 283, 25 (1894).

[3] Young and Witham, *J. Chem. Soc.*, 77, 230 (1900).

ished in 24 hours (183–187°, with decomposition, after recrystallization from hot water).

Subst., 0.1540 g.; H_2O, 0.1125 g.; CO_2, 0.2808.
Calc. for $C_9H_{17}O_3N_3$: C, 50.2; H, 8.0. Found: C, 49.7; H, 8.1.

Methylethylacetoacetic Ester.—Crystalline precipitate in 24 hours with the 16% solution of the base; and the reaction was nearly complete in 4 days (122°).

Diethylacetoacetic Ester.—After 4 days a few crystals were formed, using the 16% solution of the base (262°).

Dipropylacetoacetic Ester.—No crystals were formed after 11 days with the 16% solution of the base.

Allylacetoacetic Ester.—On shaking for 5 hours with the 16% solution of the free base, a good yield of semicarbazone was obtained, which, on recrystallization from hot water, melted at 125°.

Subst., 0.0863 g.; H_2O, 0.0562; CO_2, 0.1660.
Calc. for $C_{10}H_{17}O_3N_3$: C, 52.9; H, 7.5. Found: C, 52.4; H, 7.3.

Levulinic Ester.—Reacts quickly with all the salt solutions, and with the chlorohydrate plus 0.6 *N* acid. An experiment with acetoacetic and levulinic esters, using the same solution and performed under like conditions, gave a copious precipitate of semicarbazone (150°)[1] within a half hour with the latter compound, while the first substance had not reacted in a day.

Acetylmalonic Ester.—The reaction started in two hours with the 8% solution of acetate, and was complete in 10 hours upon standing and shaking at intervals. After recrystallizing from hot water it melted at 106 to 107°.

Methylacetylmalonic Ester.—No reaction occurred with the acetate on 12 days' standing, nor with the 16% solution of the base, even after 42 hours' shaking and 11 days' standing

Ethylacetylmalonic Ester.—No reaction with the 16% solution of the base after 24 hours' continuous shaking.

Diacetylmalonic Ester.—The 8% acetate solution gave a considerable precipitate in 10 hours, but none with the monochloroacetate in that time. The product is crystalline and, from the analysis, appears to be the disemicarbazone.

Subst., 0.0601 g.; H_2O, 0.0297 g.; CO_2, 0.0955 g.
Calc. for $C_{12}H_{19}O_6N_3$: C, 47.8; H, 6.3.
Calc. for $C_{13}H_{22}O_6N_6$: C, 43.3; H, 6.1. Found: C, 43.3; H, 5.5.

Acetylsuccinic Ester.—A reaction with the acetate after 7 hours. The velocity of the reaction appears to be greater with acetylmalonic than with acetylsuccinic ester, as, in several experiments performed under exactly the same conditions with equivalent amounts of the esters and 8%

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[1] Montemartin, *Gazz. chim. ital.*, **27**, II, 176 (1897).

acetate solutions, a precipitate appeared, and the reaction was also completed sooner, with the malonic derivative.

Oxaloacetic Ester.—With an 8% acetate solution the reaction began at once, and was finished in several minutes; with the chlorohydrate solution it was complete in about 5 minutes. The addition of hydrochloric acid of the concentration 0.5 *N* decreased the velocity somewhat, but a considerable precipitate had formed in 5 minutes, and, even after concentration to 10 *N* hydrochloric acid, the reaction was well advanced in a half hour.

The crystalline semicarbazone was crystallized several times from hot water, and then melted at 162°. For analysis it was dried at 100°.

Subs., 0.1546 g.; CO_2, 0.2508 g.; H_2O, 0.0885 g.
Calc. for $C_9H_{15}O_5N_3$: C, 44.1; H, 6.1. Found: C, 44.2; H, 6.4.

Benzoylacetic Ester.—Crystals appeared in about 30 minutes with an 8% acetate solution; with the monochloroacetate a slight precipitate in an hour, and the reaction was complete in 3 hours. With an 8% chlorohydrate solution a few crystals were shown in 2 hours, and, although the reaction was well advanced in 4 hours, it was not completed until 2 days.

This product was recrystallized from hot water, and then melted at 125° with dec.

Subst., 0.2661 g., dried at 100°; N, 39.1 cc. at 17° and 737 mm.
Calc. for $C_{12}H_{15}O_3N_3$: N, 16.8. Found: 16.6.

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[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF YALE UNIVERSITY.]

THE PREPARATION AND HYDROLYSIS OF ESTERS DERIVED FROM THE SUBSTITUTED ALIPHATIC ALCOHOLS.

BY GEORGE R. BANCROFT.

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In a recent paper[1] published from this laboratory an account has been given of the preparation of esters derived from the α and β substituted ethyl alcohols and of an investigation of the effect of their constitution upon the rate of hydrolysis. It was shown by a study of α-chloroethyl acetate, α-chloroethyl propionate, and α-ethoxyethyl acetate that the substitution of halogen or an alkoxyl group in the α-position of the alkyl radical of an ester accelerates the decomposition of the ester to such an extent that the reaction velocity cannot be measured. In the case of all three esters of this type that were hydrolyzed acetaldehyde formed one of the hydrolysis products. It was further observed that the substitution of hydroxyl, methoxyl, ethoxyl, chlorine and bromine, in the β-position of the ethyl radical of ethyl acetate, produces a considerable retardation of the rate of hydrolysis. The hydroxyl and ethoxyl groups, and

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[1] *Am. J. Sci.*, 44, 371–380 (1917).